Congenital Heart Disease in Adolescents and Adults
Series Editors: Massimo Chessa · Helmut Baumgartner
Andreas Eicken · Alessandro Giamberti

Konstantinos Dimopoulos
Gerhard-Paul Diller *Editors*

Pulmonary Hypertension in Adult Congenital Heart Disease

Springer

Congenital Heart Disease in Adolescents and Adults

Endorsed by
The ESC Working Group on Grown-up Congenital Heart Disease
AEPC Adult with Congenital Heart Disease Working Group

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The aim of this series is to cast light on the most significant aspects – whether still debated or already established – of congenital heart disease in adolescents and adults and its management. Advances in the medical and surgical management of congenital heart disease have revolutionized the prognosis of infants and children with cardiac defects, so that an increasing number of patients, including those with complex problems, can reach adolescence and adult life. The profile of the adult population with congenital heart disease (ACHD) is consequently changing, and in future many adult patients will present different hemodynamic and cardiac problems from those currently seen. A cure is rarely achieved, and provision of optimal care is therefore dependent on ongoing surveillance and management in conjunction with experts in this highly specialized field. Specialists in ACHD management need to have a deep knowledge not only of congenital cardiac malformations and their treatment in infancy and childhood, but of general medicine, too. A training in adult cardiology, including coronary artery disease, is also essential. Similarly, surgeons need to acquire expertise and good training in both adult and pediatric cardiosurgery. Readers will find this series to be a rich source of information highly relevant to daily clinical practice.

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We would like to thank our colleagues, those who have contributed to this book and those who have helped shape our practice over the years in this difficult, but rewarding field of medicine. We would especially want to thank our amazing patients who inspire us every day with their strength and resilience.

To my wife Alessia and my sons Alexandros and Adriano for their unconditional love, support and infinite patience.

Konstantinos Dimopoulos

For Astrid, Liv and Carlotta.

Gerhard-Paul Diller

Preface to the Series

In Europe, we are currently faced with an estimated ACHD population of 4.2 million; adults with congenital heart disease now outnumber children (approximately 2.3 million). The vast majority cannot be considered cured but rather having a chronic heart condition that requires further surveillance and timely re-intervention for residual or consequent anatomical and/or functional abnormalities. ACHD patients have very special needs and the physicians taking care of them need expert training. Special health care organization and training programs for those involved in ACHD care are therefore required to meet the needs of this special population.

ACHD problems remain a small part of general cardiology training curricula around the world, and pediatric cardiologists are trained to manage children with CHD and may, out of necessity, continue to look after these patients when they outgrow pediatric age.

There are clearly other health issues concerning the adult with CHD, beyond the scope of pediatric medicine, that our patients now routinely face. Adult physicians with a non-CHD background are therefore increasingly involved in the day-to-day management of patients with CHD.

Experts in congenital heart disease should work to improve the health care system, so that teens and young adults have an easier time making the transition from receiving health care in pediatric cardiology centers to receiving care from specialists in adult cardiology.

The aim of this series is to cast light on the most significant aspects of congenital heart disease in adolescents and adults and its management, such as transition from pediatric to adulthood, pregnancy and contraception, sport and physical activities, pulmonary hypertension, burning issues related to surgery, interventional catheterization, electrophysiology, intensive care management, and heart failure.

This series wishes to attract the interest of cardiologists, anesthesiologists, cardiac surgeons, electrophysiologists, psychologists, GPs, undergraduate and postgraduate students, and residents, and would like to become relevant for courses of cardiology, pediatric cardiology, cardiothoracic surgery, and anesthesiology.

We thank both the wonderful groups of leading cardiovascular experts from around the world, for donating their precious time, producing excellent textbooks

and making this book series a reality, and the members of the two Working Groups (ESC and AEPC ACHD/GUCH Working Group) for the invaluable suggestions and support without which this work would not be possible.

San Donato, Italy — Massimo Chessa
Münster, Germany — Helmut Baumgartner
Munich, Germany — Andreas Eicken
San Donato, Italy — Alessandro Giamberti

Foreword

Pulmonary arterial hypertension (PAH) is a common complication of adult congenital heart disease (ACHD), affecting up to 10% of patients. PAH, in turn, impacts on quality of life and survival of these patients. This area used to be a medical orphan; there were very limited therapeutic options for these patients. In fact, some of the medical interventions of the past have been harmful to patients, namely routine venesections for patients with chronic cyanosis and secondary erythrocytosis, i.e. patients with Eisenmenger syndrome (ES). It is these very patients (with ES), who represent the extreme end of the spectrum of PAH-ACHD, that have particularly benefited from recent advances in our understanding of late pathophysiology, prognostication, and advanced therapy for PAH in the context of ACHD. This follows if not mirrors recent advances in the management and treatment of PAH of other etiologies. As a result, the lives of patients with ES have been transformed, with improved quality of life, functional capacity, and survival prospects following the introduction of advanced PAH therapy. Most ES patients are now cared for in tertiary centers, where other needs such as contraception, iron supplementation, noncardiac surgery, and physical conditioning can all be met. More work is, nevertheless, needed for these patients and for the broader group of patients with PAH-ACHD who may have not yet developed ES.

I am delighted to write the foreword for this concise book, providing essential and easily accessible information for the tertiary and nontertiary healthcare professional who is interested in ACHD and/or PAH. The editors of the book, Drs. Dimopoulos and Diller, from the Royal Brompton Hospital and the University Hospital Muenster, respectively, have compiled a comprehensive text, inviting experts from the UK and Germany, as well as other world authorities in the PAH-ACHD field. The book outlines the key points with regard to the current classification, pathophysiology, diagnostics, and treatment. There are specific chapters addressing hematological issues, different imaging modalities, cardiac catheterization, cardiopulmonary exercise testing and the six-minute walk test, physical conditioning, and the evidence for a "treat and repair approach," if any. Furthermore, the book addresses patients with the Fontan operation and complex underlying congenital heart disease, who may not have PAH in the strict sense but some have pulmonary vascular disease. The data for advanced PAH therapy for this patient subgroup is sparse at present, but there is rationale for it and more research is clearly needed. Last but not least, the book addresses counseling, contraception, and the

latest in the management of pregnancy and PAH-ACHD, which is still associated with a high mortality/morbidity risk.

The key objective of the book is to increase awareness of PAH-ACHD, describe recent advances in the field, and suggest appropriate diagnostic work up and timely specialist referral so that effective, state-of-the-art therapy is made available for every patient with PAH-ACHD. This book will serve as an invaluable resource for healthcare professionals in the care of ACHD and PAH patients, but also for cardiologists, obstetricians, and other disciplines outside of ACHD centers—senior or junior—who may also be called upon to care for these patients.

London, UK Michael A. Gatzoulis, M.D., Ph.D.

Preface

Pulmonary hypertension (PH) is a hemodynamic condition associated with a wide variety of diseases. The various types of PH differ significantly in their management, and expertise in both PH and the underlying condition is essential for improving outcomes. In no other area of PH is this more true than in pulmonary arterial hypertension (PAH) related to congenital heart disease (PAH-CHD).

CHD is the most common inborn defect in humans. Almost 1 in 100 children born presents with a mild or more complex form of CHD. PH is one of the most common and devastating complications of CHD, first described by Victor Eisenmenger in 1897. Subsequent landmark work by authors, including Paul Wood and Heath and Edwards, have shed light on the pathophysiology of PAH-CHD, with observations that apply not only to PAH-CHD but also most other types of PAH. The introduction of cardiac surgery in the 1950s and subsequent advances in the surgical and interventional management, paired with the evolution of diagnostic modalities, both invasive and non-invasive, have resulted in early diagnosis and treatment of CHD, allowing for the majority of children with CHD to reach adult life and beyond and reducing the risk of developing PH, especially Eisenmenger syndrome. Despite this, the prevalence of PAH-CHD remains high, as ever more patients with repaired defects present with residual or newly developed PAH-CHD.

Recent national PH databases have demonstrated that PAH-CHD is one of the most common types of PAH, with a prevalence similar to that of idiopathic PAH. Within PAH-CHD, a wide variety in anatomy and pathophysiology exists and, thus, requires significant expertise in both PAH and CHD. In most developed countries, the routine care of PH and CHD patients is indeed concentrated in tertiary centres with specific expertise in either or, ideally, both of these areas. Despite significant similarities in lung pathophysiology to other types of PAH, such as idiopathic PAH and PAH related to connective tissue disease, the mechanism of onset, natural history and management of PAH-CHD differ significantly to that of other types of PAH. Mistakes and pitfalls in the management of such patients are often related to lack of knowledge or expertise in this condition, and old practices.

Huge leaps have also been made in the treatment of PAH in the last three decades. Prior to 1995, no therapies were available, while nowadays several drugs are available, supported by robust evidence on their safety and efficacy. Increased awareness of PAH has also resulted in earlier diagnosis and timely treatment, improving the quality of life and outcome of many PAH patients, including those with

PAH-CHD. Despite the above, PAH still remains an incurable disease, with significant morbidity and mortality.

This book, *Pulmonary Hypertension in Adult Congenital Heart Disease*, is part of Springer's new book series *The Congenital Heart Disease in Adolescents and Adults*. In this book, international experts in the field of ACHD and PH provide a detailed description of all aspects of this condition based on available evidence and expert opinion. The book is divided into three sections, with chapters on the pathophysiology and classification of PH in ACHD, the diagnosis of PH in ACHD, and its management. Novel topics, such as segmental PH, post-capillary PH in ACHD, PAH in patients with persistent systemic-pulmonary shunts and PAH in patients with small cardiac defects or previous reparative surgery, are covered in dedicated chapters written by major experts in their respective fields. The section on the diagnosis of PH in CHD covers every step, from physical examination and ECG, to sophisticated modalities such as CMR and advanced CT, to invasive assessment. The final section on treatment describes all aspects of the pharmacological treatment and non-pharmacological management of PAH-CHD. It also includes chapters on special topics, such as the management of PAH-CHD in pregnancy and in special populations such as patients with Fontan circulation and those with Down syndrome. Finally, the novel topic of palliative care in PAH-CHD is reviewed.

This book is aimed at providing the reader with a complete but user-friendly overview of the topic of PH in ACHD. It is a comprehensive manual and a guide in the management of adults with PAH-CHD and will be essential for all ACHD and PH healthcare professionals (senior and junior physicians, nurse specialists) in tertiary practice, as well as physicians and healthcare workers in general cardiology and emergency services, where patients often present acutely. It provides an overview of current state-of-the art practice in this field, and we hope it will prove useful in improving the day-to-day care of this complex group of patients.

London, UK — Konstantinos Dimopoulos
Münster, Germany — Gerhard-Paul Diller

Contents

Part I

Pathophysiology and Classification of Pulmonary Hypertension in Adult Congenital Heart Disease

Congenital Heart Defects and Pulmonary Hypertension: The Heath–Edwards Paradigm

1

Konstantinos Dimopoulos, Elizabeth Orchard, and Annalisa Angelini

Abbreviations

ANG	angiotensin
ASD	atrial septal defect
AVSD	atrioventricular septal defect
CHD	congenital heart disease
CO	cardiac output
CTEPH	chronic thromboembolic pulmonary hypertension
ECG	electrocardiogram
ET	endothelin
LA	left atrium
LV	left ventricle
NO	nitric oxide
PA	pulmonary artery
PAH–CHD	pulmonary arterial hypertension related to congenital heart disease
PAH	pulmonary arterial hypertension
PAP	pulmonary arterial pressure
PDA	patent ductus arteriosus

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PGI2	prostacyclin
PH	pulmonary hypertension
PVD	pulmonary vascular disease
PVR	pulmonary vascular resistance
PVRi	pulmonary vascular resistance indexed
RA	right atrium
Rp/Rs	ratio of pulmonary-to-systemic resistance
RV	right ventricle
RVEDP	right ventricular end-diastolic pressure
TCPC	total cavopulmonary connection
VSD	ventricular septal defect
WU	Wood units

1.1 Introduction

Pulmonary hypertension (PH) is a haemodynamic and pathophysiological disorder associated with a variety of cardiovascular and respiratory conditions, including congenital heart disease (CHD) [1]. PH is defined by international guidelines as an increase in mean pulmonary arterial pressure (meanPAP) ≥25 mmHg at rest, assessed by cardiac catheterization. The normal values of resting mean PAP are 14 ± 3 mmHg, with an upper limit of 20 mmHg. The significance of values in the "grey zone" of 21–24 mmHg is unclear, and currently, due to lack of data, there is no reliable definition of PH occurring with exercise.

A comprehensive international clinical classification for PH categorizes the multiple conditions in which PH may be present according to similarities in clinical presentation, pathology, haemodynamics and treatment (Table 1.1). Haemodynamically, PH can be distinguished into precapillary and post-capillary based on the absence or presence of a rise in mean left atrial/mean pulmonary wedge/left ventricular end-diastolic pressure (≤15 mmHg). Patients in group 1, pulmonary *arterial* hypertension (PAH), have precapillary PH with a pulmonary vascular resistance (PVR) >3 Wood units (WU) in the absence of other causes of precapillary PH such as lung disease (belonging to group 3), chronic thromboembolic PH (CTEPH group 4) or other rare diseases (group 5).

CHD can result in both precapillary and post-capillary PH. The latter can be the result of systemic ventricular dysfunction (e.g. a failing systemic right ventricle (RV)), congenital left-sided outflow tract obstruction, left-sided valve disease or pulmonary vein stenosis, i.e. any condition that can cause a rise in left atrial and/or pulmonary venous pressures. Post-capillary PH is divided by international PH guidelines - depending on the pulmonary wedge pressure (PWP), left ventricular end-diastolic pressure (LVEDP) or left atrial pressure - into isolated and combined post- and precapillary PH, based on the presence of a PVR ≤3 or >3 WU, respectively, and/or a diastolic pressure gradient (diastolicPAP–meanPWP) < or ≥7 mmHg, respectively. This is to distinguish between PH that is purely a reflection of the rise in left-sided (post-capillary) pressures and PH which appears to be "out of proportion" to the left-sided pressure. The latter can occur in patients with long-standing post-capillary PH (e.g. long-standing haemodynamically significant mitral stenosis or long-standing

Table 1.1 The clinical classification of pulmonary hypertension according to international pulmonary hypertension guidelines [1]

Clinical classification of pulmonary hypertension
1. Pulmonary arterial hypertension
1.1 Idiopathic
1.2 Heritable
1.2.1 BMPR2 mutation
1.2.2 Other mutations
1.3 Drugs and toxins induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 Human Immunodeficiency virus (HIV) infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1′. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
1′.1 Idiopathic
1′.2 Heritable
1′.2.1 EIF2AK4 mutation
1′.2.2 Other mutations
1′.3 Drugs, toxins and radiation induced
1′.4 Associated with:
1′.4.1 Connective tissue disease
1′.4.2 HIV infection
1″. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital or acquired left heart inflow or outflow tract obstruction and congenital cardiomyopathies
2.5 Congenital or acquired pulmonary veins stenosis
3. Pulmonary hypertension due to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases
4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
4.1 Chronic thromboembolic pulmonary hypertension
4.2 Other pulmonary artery obstructions
4.2.1 Angiosarcoma
4.2.2 Other intravascular tumours
4.2.3 Arteritis
4.2.4 Congenital pulmonary arteries stenoses
4.2.5 Parasites (hydatidosis)

(continued)

Table 1.1 (continued)

Clinical classification of pulmonary hypertension
5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
5.1 Haematological disorders
Chronic haemolytic anaemia
Myeloproliferative disorders
Splenectomy
5.2 Systemic disorders
Sarcoidosis
Pulmonary histiocytosis
Lymphangioleiomyomatosis
Neurofibromatosis
5.3 Metabolic disorders
Glycogen storage disease
Gaucher disease
Thyroid disorders
5.4 Others
Pulmonary tumoral thrombothic microangiopathy
Fibrosing mediastinitis
Chronic renal failure (with/without dialysis)
Segmental pulmonary hypertension

In *bold*, pulmonary hypertension that can be encountered in congenital heart disease
BMPR2 bone morphogenetic protein receptor, type 2, *EIF2AK4* eukaryotic translation initiation factor 2 alpha kinase 4, *HIV* human immunodeficiency virus

systemic ventricular dysfunction) and significantly affects management (see Chap. 8). For example, patients with atrial switch repair for transposition of great arteries (Mustard or Senning) often present with systemic ventricular dysfunction and tricuspid (systemic atrioventricular valve) regurgitation, which typically progresses in severity over time. The rise in pressure within the pulmonary venous pathways is often due to the rise in right ventricular end-diastolic pressure (RVEDP) and significant tricuspid regurgitation and is transmitted backwards to the lungs, resulting in PH which is purely (isolated) post-capillary. Over time, a precapillary component to the PH can develop, transforming the isolated post-capillary PH to combined pre- and post-capillary PH. This further affects cardiac haemodynamics and may also preclude heart transplantation if not reversible. PAH therapies should not be used in such cases as, despite the existence of precapillary component, this is not PAH.

PAH related to congenital heart disease (PAH–CHD) is precapillary PH and is characterized by a rise in PVR with normal left atrial pressure. It is typically the result of pulmonary vascular disease (PVD) caused by chronically elevated pulmonary arterial pressures in patients with large post-tricuspid defects: a large ventricular septal defect (VSD), patent ductus arteriosus (PDA) or aortopulmonary window. The chronic pressure and volume load cause fibrotic and proliferative lesions in small muscular arteries (Fig. 1.1).

PAH–CHD is classified by the international PH guidelines into four groups according to the severity of the disease, direction of shunt, defect size and previous

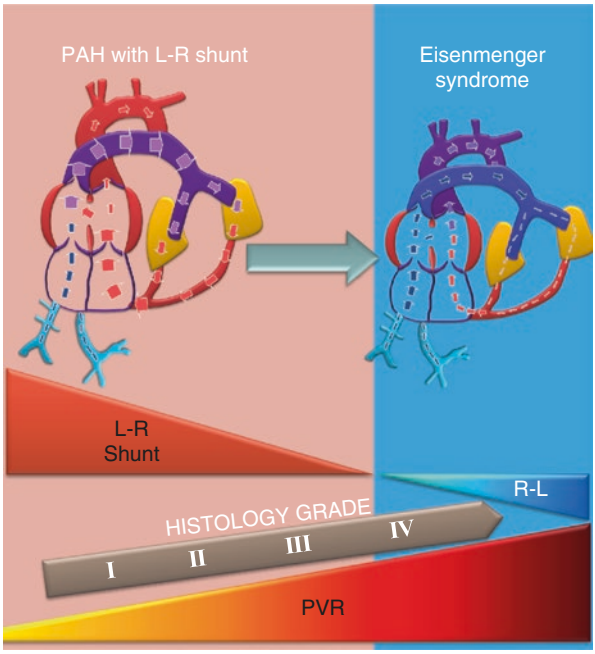

Fig. 1.1 The pathogenesis of pulmonary arterial hypertension in congenital heart disease in a patient born with a large ventricular septal defect. As soon as the baby is born and starts breathing, pulmonary vascular resistance (PVR) drops and significant left-to-right (L–R) shunting occurs through the VSD. Pressure and volume overload of the pulmonary circulation over time causes pulmonary vascular disease of increasing severity, which results in a progressive rise in PVR and reduction in L–R shunting. Eventually, the PVR reaches systemic levels, and the shunt becomes bidirectional, with right-to-left (R–L) shunting causing cyanosis (Eisenmenger syndrome). The timing and severity of the development of PVD vary greatly between individuals

repair (Table 1.2). Group 1 of this classification is the extreme end of the spectrum and the best known type of PAH–CHD: Eisenmenger syndrome.

There are an additional two types of PH related to CHD the guidelines do not focus upon: segmental PH and PH in patients with a previous Fontan-type operation [2]. All types of PH and PAH related to CHD are described in detail in the various chapters of this book.

1.2 The Morphology of PAH Related to CHD: Pulmonary Vascular Disease

Heath and Edwards were the first to provide a detailed histological classification of "hypertensive PVD" [3]. This was based on the study of 67 cases of CHD and 2 cases of idiopathic PH, of which 64 cases had proven PH (n = 55) or inferred from clinical or pathologic findings (n = 9), while 5 cases had a mean

Table 1.2 The four types of PAH–CHD and two additional types of CHD that may develop pulmonary vascular disease (precapillary component) [1, 2]

A. Eisenmenger syndrome	Includes all systemic-to-pulmonary shunts due to large defects leading to a severe increase in PVR and a reversed (pulmonary-to-systemic) or bidirectional shunt. Cyanosis, erythrocytosis and multiple organ involvement are present
B. Pulmonary arterial hypertension associated with systemic-to-pulmonary shunts	Patients with moderate to large defects, in which the increase in PVR is mild to moderate, left–right shunt is still largely present, and no cyanosis is present at rest
C. Pulmonary arterial hypertension with small defects.	Patients with a clinical picture very similar to idiopathic PAH, who have (coincidental?) small defects
	–ventricular septal defects <1 cm
	–atrial septal defects <2 cm
D. Pulmonary arterial hypertension after corrective cardiac surgery	Congenital heart disease has been corrected but PAH:
	–is still present immediately after surgery or
	–has recurred several months or years after surgery in the absence of significant postoperative residual congenital lesions or defect sequela of previous surgery
Additional types of pulmonary vascular disease related to CHD	
Segmental pulmonary hypertension	In these cases, part of the lung vasculature develops pulmonary vascular disease, while other areas may be normally perfused or hypoperfused
Raised PVR in Fontan patients	Patients with a previous Fontan-type operation can develop a rise in PVR, despite low pulmonary arterial pressure

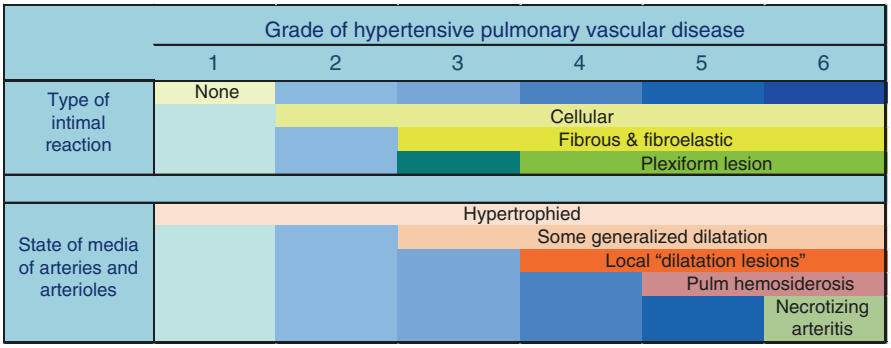

Fig. 1.2 The six histological grades of pulmonary vascular disease, according to Heath and Edwards [3]

PAP <30 mmHg (atrial septal defects, ASDs) and were used as controls. They provide a classification with six classes based on the type of intimal reaction (none/cellular/fibrous and fibroelastic/plexiform lesion) and the state of the media or arteries and arterioles (hypertrophied/some generalized dilatation/local "dilatation lesions"/pulmonary haemosiderosis/necrotizing arteritis, Fig. 1.2). They went on to apply this classification in 32 patients who underwent reparative surgery, demonstrating that all patients with a histologic grade ≤3 had an immediate postoperative systolic PAP <55 mmHg [4]. Arterial muscular hypertrophy, arteriolar muscularization and subintimal fibrosis were, therefore, categorized as potentially reversible (histological grade 3 or below), while angiomatoid and plexiform ("dilatation") lesions and

necrotizing arteritis were deemed irreversible (histological grade 4 or above). Heath and Edwards highlight, however, the fact that some degree of reversibility may also be encountered in grade 4 lesions, with some drop in PAP seen after repair, but never below a systolic PAP of 50 mmHg. They recognized that there is a gradual change from one grade to another and that structural changes in PH are not uniform in individual arteries throughout the lung [5]. They also pointed out the potential differences between PAH–CHD due to post-tricuspid shunts, which develops from birth, to instances of PAH developing in later life in patients with ASDs.

The Heath–Edwards classification, while being groundbreaking and still largely in use in a modified version (Figs. 1.3 and 1.4), did not provide a definitive solution to the clinical dilemma of reversibility and operability of congenital defects with associated PH

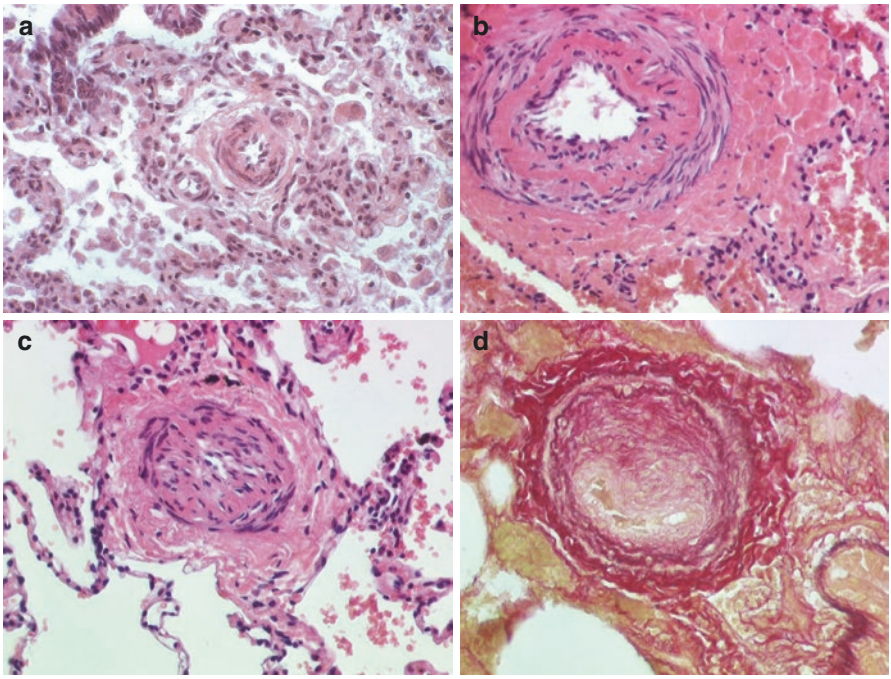

Fig. 1.3 The modified Heath–Edwards classification of hypertensive pulmonary vascular disease used in current practice: grades I–III. Histology of III of the IV grades of the modified Heath–Edwards classification of hypertensive pulmonary vascular disease used currently. Note the old grades IV, V and VI are now grouped in the new grade IV of the modified classification. In (**a**), histology of a grade I lung biopsy showing small arteries with hypertrophy of the media, in the absence of intimal hyperplasia, in a newborn baby with a ventricular septal defect. Haematoxylin eosin staining, original magnification ×10. In (**b**), histology of a grade II lung biopsy, showing an artery with intimal smooth muscle cell proliferation and medial hypertrophy. Increased adventitia fibrosis. Haematoxylin eosin staining, original magnification ×20. In (**c**), histology of a grade III lung biopsy with sub-occlusive concentric intimal proliferation and thinning of the media and fibrosis of the adventitia. Haematoxylin eosin staining, original magnification ×20. In (**d**), histology of a grade III lung biopsy with obstructive eccentric fibrocellular intimal proliferation of an artery in a 4-month-old boy with an atrioventricular septal defect. Note the two-stage lesion, with fibrous thickening (*red* fibrous staining) at the base closer to the media and a more cellular component adjacent to the lumen (smooth muscle cells in *yellow*). The media is thinned and dilated, and the adventitia is fibrotic. Elastic fibre Van Gieson staining, original magnification ×20

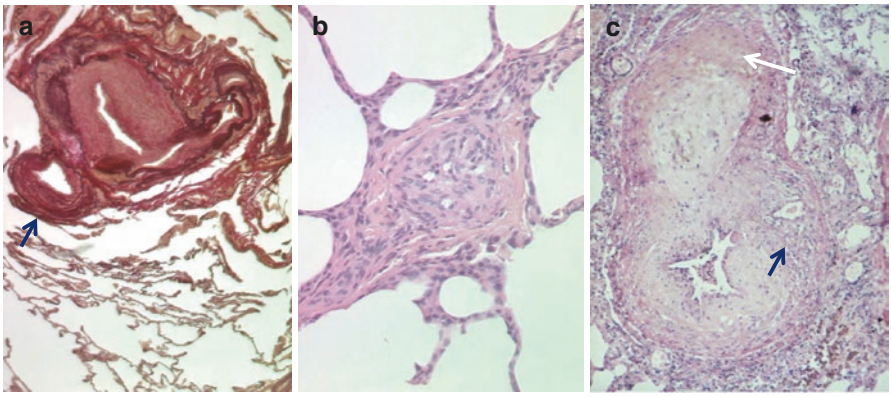

Fig. 1.4 The modified Heath–Edwards classification of hypertensive pulmonary vascular disease used in current practice: grade IV. In (**a**), histology of a grade IV lung biopsy with severe dilatation and sub-occlusive fibrosis of an artery. Note the onion-like appearance of the small artery on the *left* (*black arrow*). Elastic fibre Van Gieson staining, original magnification ×10. In (**b**), histology of a grade IV lung biopsy with a typical plexiform lesion. Haematoxylin eosin staining, original magnification ×20. In (**c**), histology of a grade IV lung biopsy with a typical aneurysmatic lesion, with occlusion of the lumen and fibrinoid necrosis (*white arrow*) of the parietal wall and neo-angiogenetic proliferative aspect (*black arrow*) in a patient with an (ASD), who died after repetitive pulmonary hypertensive crises

[6]. Beyond the risks associated with lung biopsy in patients with PH, a close relation between structural alterations in the pulmonary arteries and the change in PAP after closure of the cardiac defect was not confirmed. Moreover, even in their cohort, some patients with a favourable fall in PAP had residual PH, which could regress or progress over the years (see group 4 of the PAH–CHD classification) [2, 4].

Other more recent classifications for PVD have been proposed [6, 7]. Rabinovitch et al. used quantitative methods of analysis of histological specimens and focused on the extension of muscle (size and position of small arteries in which it is present), thickness of arterial medial muscular coat and concentration of small peripheral arteries per unit area in relation to the alveolar concentration [5]. When correlated to haemodynamic data, three new grades of PVD were observed:

- Grade A: Abnormal (for the patient's age) extension of muscle into peripheral arteries. In this group, all patents had increased pulmonary blood flow but normal PAP, and it is likely to be, at least in part, a reversible process.
- Grade B: Increased percentage of arterial wall thickness (medial muscular coat, assessed quantitatively in the small intra-acinar arteries 50–100 μm), which, when severe, correlated with an elevation in PA pressure. This was always seen together with abnormal extension of muscle into small arteries (grade A). Cases with mild increase in medial hypertrophy were felt to be potentially reversible. More severe forms of medial hypertrophy are likely to be associated with a rise in PVR and may not be reversible.

- Grade C: Reduction in the number of small peripheral arteries. This was always associated with features of grades A and B and always observed in Heath–Edwards 3 or higher and could be a loss of arteries through occlusion or lack of adequate pulmonary blood flow. It was, however, also observed in less severe forms (perhaps due to insufficient growth of new arteries compared to alveoli in young children). Most patients in group C had a raised PVR indexed (>3.5 WU × m^2). This stage was felt to precede obliterative PVD and could identify patients in whom PVD will progress after repair. The authors felt that reversibility depended on the ability of the pulmonary vascular bed to generate new arteries.

Grades A and B were felt by the authors to be refinements of the Heath–Edwards grade 1, while grade C reflected the failure of the arteries to proliferate normally, a novel finding compared to Heath and Edwards. This classification focuses, therefore, on early structural changes, before the appearance of fibrotic intimal damage.

No classification is perfect, and biopsy findings should be interpreted in the light of the clinical picture when assessing reversibility. Wagenvoort et al. reported on 28 patients with CHD and PH in whom lung biopsy was performed at the time of PA banding and after repair of the defect [8]. While earlier lesions showed regression, more severe concentric-laminar intimal fibrosis showed no tendency towards regression and often even progressed. Fibrinoid necrosis and plexiform lesions were always irreversible, even when only occasional arteries were affected by these changes. Wagenvoort later talked about a "point of no return" as far as reversibility was concerned, which lies somewhere between mild and severe concentric-laminar intimal fibrosis and can be frustrating for the pathologist if the preoperative lung biopsy shows moderate to fairly severe intimal fibrosis [9]. In all cases, but especially those in which the histology is in the "grey zone", require consideration of clinical and haemodynamic findings to decide whether corrective cardiac surgery is advisable. In practice, most patients do tend to fall between the two extremes of mild medial hypertrophy and extensive dilatation lesions [10]. Therefore, routine lung biopsies have been abandoned in recent years.

1.3 The Evolution of Pulmonary Vascular Disease in Common Types of CHD

PAH typically develops in CHD in the presence of a large post-tricuspid shunt, which causes both volume and especially pressure overload to the pulmonary circulation. The endothelium plays an important role in the interface between haemodynamics and the vessel wall as well as providing an antithrombogenic semipermeable barrier and fulfilling metabolic functions [11]. Endothelial cells influence vascular tone, smooth muscle cell growth and differentiation and the response to vascular injury, be it hypoxia, altered shear stress, inflammation or toxins. Injury to the endothelium leads to impaired endothelial-dependent relaxation, defective levels of von Willebrand factor and

fibrinolysis, in situ thrombosis, programmed cell death and loss of small vessels [10, 12]. Activated endothelial cells also produce more vasoconstrictive and proliferative factors such as endothelin-1 (ET-1), angiotensin II (ANG II), thromboxane A2 and lower amounts of vasodilating antiproliferative agents such as NO and prostacyclin (PGI2). Indeed, plasma ET and thromboxane B2 concentrations are elevated in patients with PAH–CHD due to congenital heart defects [13, 14]. The thickening of the wall of more proximal intra-acinar and pre-acinar muscular arteries and neointimal formation has been related to excessive proliferation and migration of cells that have markers of smooth muscle cells because they are positive for α-smooth muscle actin. This may be a specialized subpopulation, may have originated as stem cells or fibrocytes, may be transformed fibroblasts or endothelial cells or all of the above.

Plexiform lesions are characteristic of advanced PVD. These were first described in CHD, but are also seen in other types of PAH, including idiopathic PAH. While the exact pathogenesis of these lesions remains uncertain, it has been postulated that the increase in pulmonary blood flow in CHD elicits reflex vasoconstriction and endothelial dysfunction. Intense vasospasm may cause vascular necrosis and arteritis, and plexiform lesions develop in areas of focal fibrinoid necrosis, by active cell reorganization and recanalization of thrombus [15]. It has been postulated that plexiform lesions are a failed attempt of the pulmonary vasculature to bypass obstructive lesions [16, 17]. The only animal model of plexiform lesions is in dogs, after the creation of a systemic-to-pulmonary shunt, leading to severe PH [18]. Interestingly, monoclonal endothelial cell proliferation was encountered in plexiform lesions of patients with idiopathic, but not PAH secondary to CHD or connective tissue disease [19].

The size and location of the shunt dictate the rate of development and ultimate severity of the PAH. In patients with pre-tricuspid shunts (ASDs), there can be significant volume but no significant pressure overload of the pulmonary circulation. Recruitment of previously underperfused vessels allows the lungs to accommodate larger volumes of blood, and PAH may occur later in life, with significant PVD developing only in rare cases [20]. In fact, it appears that the volume overload imposed by ASDs can only lead to a significant rise in PVR when accompanied by a sort of intrinsic predisposition of the pulmonary vasculature towards PVD [2, 21]. The importance of genetics in the development of PAH is supported by the now numerous genes identified as responsible for the development of hereditary PAH and the well-established predisposition of patients with Down syndrome to the early development of severe PVD [22–25]. Children with ASDs who develop severe PVD usually have inoperable disease with severe intimal fibrosis and vessel obstruction, resembling that of patients with large VSDs [10]. Some call this idiopathic PAH with an associated atrial communication, especially when the latter is small (<2 cm in diameter), underlining the importance of an underlying predisposition of the pulmonary vasculature.

In post-tricuspid shunts, the combined effect of volume and pressure overload results in early development of PVD, with a high PVR that becomes largely irreversible early in life. In patients with large VSDs, there is an increased muscularity of the pulmonary vessels from early infancy, with intimal proliferation developing by the end of the first

year of life and fibrosis by the third year. Surgery should thus be offered by year 1 [7]. In a minority of cases, early obstructive intimal proliferation can develop, associated with a significant rise in PVR [10]. In patients with transposition of great arteries and a large VSD, the pulmonary vasculature does not remodel after birth, and intimal proliferation is seen from 2 months of age, which becomes significant after 5 months. By age 7–9 months, patients can be inoperable due to a high PVR [10, 26]. Similarly, intimal proliferation develops at an earlier stage and is more severe in patients with a complete atrioventricular septal defect (AVSD) compared to an isolated VSD, requiring repair very early in life [10]. Therefore, even in patients with large post-tricuspid defects, there is a large spectrum with regard to the timing of development of severe "irreversible" PAH, with some developing irreversible PVD within the first few months of life, while others reach teenage or adult life not having reached the stage of shunt reversal (Eisenmenger syndrome) [2]. Moreover, a small degree of reversibility may be maintained even in patients with long-standing Eisenmenger syndrome and predicts outcome [27].

1.4 Operability and Survival After Cardiac Repair

The short- and long-term outcome of repair of a left–right shunt depends heavily on the state of the pulmonary vascular bed at the time of repair. Patients with severe irreversible PVD should not undergo repair of the defect, as the risk of developing a pulmonary hypertensive crisis and right ventricular dysfunction perioperatively is high and can be fatal. Moreover, closure of a defect, which may act as a relief valve for a hypertensive RV, may lead to RV dilatation and dysfunction (heterometric adaptation; see below) resembling that of idiopathic PAH and adversely affect outcome.

In cases with less severe PVD, physicians are often faced with question of "operability" of the cardiac defect. Invasive haemodynamic assessment is essential for this purpose even though, to date, there is little evidence to guide clinical management [2, 6, 28]. Steele et al. reported the outcome at 4 years of 40 adult patients with an ASD and PVD (resistance greater than 7 WU × m^2) treated either medically or surgically. All patients who were not treated surgically had progression of their disease. Those who underwent surgical correction and had a preoperative PVR between 9 and 14 WU × m^2 showed no signs of disease progression and those between 7 and 9 WU × m^2 improved. No vasoreactivity test was performed prior to closure. The INOP test I was a multicentre study that gathered data on preoperative haemodynamics, including reversibility with oxygen and nitric oxide, in CHD patients with PAH (ratio of pulmonary-to-systemic resistance [Rp/Rs] ≥ 0.33) [29]. Data on a total of 124 patients (median age 28 months, range 1 month to 47 years) from ten institutions were collected. Of these, 74 patients underwent reparative surgery or transplantation. An Rp/Rs <0.42 with oxygen alone and <0.27 with oxygen plus nitric oxide were identified as optimal cut-off values for determining operability (reduced risk of death or right ventricular failure after surgery), but with a good but not perfect area under the curve of 0.86 as there were some patients with a "low" Rp/Rs who had a poor outcome. It is possible that "de-recruitment" of pulmonary

vessels, which had previously been recruited to accommodate the increased pulmonary blood flow, could explain the lower than expected drop in PVR after defect closure.

The 2015 PH guidelines introduced PVRi cut-offs for deciding operability based on expert consensus (Fig. 1.5), with a wide "grey area" in-between 4 and 8 WU × m^2 [1]. No clear recommendations were made on the interpretation of PVR obtained using vasodilators. It is clear that no single clinical parameter (or combination of parameters) is able to accurately predict the response of the pulmonary vasculature after repair, as operability is clearly not synonymous to reversibility observed in the catheter lab (or to histological changes seen on biopsy) [8, 9].

It is important to maintain a clear distinction between PAH and PVD in patients with large left–right shunts (systemic-to-pulmonary shunts) [2]. Indeed, PH (i.e. a rise in PAP) may occur as a result of a rise in PVR (reflecting PVD) or

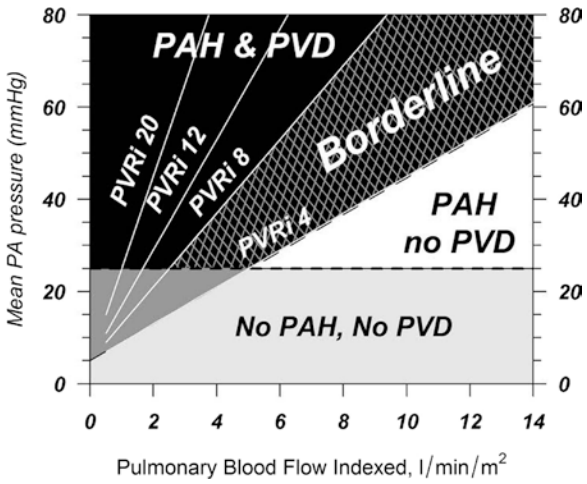

Fig. 1.5 The formula for pulmonary vascular resistance indexed (PVRi) is as follows: $\text{PVRi} = \frac{\text{Mean PA pressure} - \text{Mean LA pressure}}{\text{Pulmonary blood flow indexed}}$ where PA is pulmonary artery and LA is left atrium

Assuming a normal mean LA pressure of 5 mmHg, we plot the changes in mean PA pressure with increasing pulmonary blood flow, for different levels of PVR indexed (PVRi). This graph demonstrates the importance of accurately calculating PVRi during cardiac catheterization (i.e. pulmonary blood flow), as PA pressure alone is unable to reliably distinguish between patients with or without PVD in CHD. Patients with increased pulmonary blood flow due to a left–right shunt may have a raised PA pressure due to increased flow, with a normal PVR (white area to the right, *PAH no PVD*). In these cases, closure of a haemodynamically significant defect is advisable. According to international guidelines, closure of a defect should be considered when PVRi is below 4 but should be avoided if PVRi is above 8 (black area top left, *PAH & PVD*). Patients in the *"grey"* area (PVRi between 4 and 8, mesh pattern area labelled *Borderline*) should be assessed individually in expert *centres*. In patients with a Fontan-type circulation, rises in PVRi typically result in a drop in pulmonary blood flow. Therefore, there can be a rise in PVR with no rise in mean PA pressure (dark grey area bottom left). Accurate estimation of PVRi in these patients can be difficult, especially in the presence of multiple sources of pulmonary blood flow (e.g. from the Glenn anastomosis and total cavopulmonary connection (TCPC) conduit)

solely due to the increase in pulmonary blood flow in the absence of any PVD (Fig. 1.5). Accurate estimation of pulmonary blood flow (to be used as a denominator in the formula for calculating PVR) is important in making the decision between an operable defect, a defect that should remain open and act as a "RV" for the RV and a patient who may benefit from PAH therapies (see Chaps. 4 and 14).

1.5 Eisenmenger Syndrome: Viktor Eisenmenger and Paul Wood

Victor Eisenmenger's 1897 paper titled "congenital defects of the ventricular septum" provided a description of a typical example of a patient with Eisenmenger complex. This was a powerfully built 32-year-old man, with past history of moderate breathlessness since infancy and cyanosis which increased considerably on efforts. He led an active life until the age of 32 years when dyspnoea increased and peripheral oedema appeared leading to hospitalization a few months later. On admission, he was markedly cyanotic, clubbed (fingers and toes) with thickened distal joints and "polycythaemia". His venous pressure was raised and his liver was distended with extensive oedema; there was right heart enlargement and a thrill attributable to tricuspid regurgitation. A diastolic murmur, likely due to pulmonary regurgitation, later developed. He was treated with rest and digitalis, and despite some improvement, he later died following a large haemoptysis. On necropsy, there was a large perimembranous VSD, with a dilated RV and tricuspid annulus and an overriding aorta. "Atherosclerosis" of the pulmonary artery (PA), but not the aorta, was described, and haemorrhagic infarction of the left upper and right lower lung lobes was felt to be secondary to multiple thromboses.

Dr. Eisenmenger interpreted this situation as excessive left-to-right shunting through the VSD causing increased lung stiffness which hindered ventilation, while congestion hampered gas exchange. He, therefore, interpreted the cyanosis as a result of a low cardiac output (CO) and oxygen delivery rather than central, i.e. related to reversal of the shunt, even though he did state that a rise in pulmonary resistance could equilibrate pressures in the pulmonary and systemic circulation.

Later, in 1924, it was Abbott and Dawson who attributed the cyanosis to right–left shunting, and Baumgartner and Abbott described seven similar cases [30, 31]. They still attributed the systolic murmur to the VSD. Taussig in 1947 attributed the right–left shunting to the overriding aorta, even though she stated that the cause of the cyanosis remained unclear and pointed to alterations of the pulmonary vascular bed that may prevent oxygenation of the blood passing through the lungs [32].

Bing et al. in the same year demonstrated that Eisenmenger's patients have PH at systemic levels and bidirectional shunting [33]. This and later studies established the concept that in Eisenmenger syndrome, cyanosis is due to high PVR with bidirectional shunting.

Paul Wood was the one who systematically described Eisenmenger syndrome in two seminal papers in the British Medical Journal in 1958 [31, 34]. He pointed out that the distinct features of Eisenmenger syndrome do not depend on the anatomy of the underlying cardiac defect but on the behaviour of the pulmonary circulation. He defined Eisenmenger complex as PH at systemic level, due to a high PVR (above 800 dyn s cm^{-5} or 10 WU) with reversed or bidirectional shunt through a large VSD (1.5–3 cm across). He went on to point out that it matters very little where the shunt happens to be, as this physiological situation is similar when any large communication is complicated by systemic levels of PVR. He described 12 different anatomical conditions that may present with Eisenmenger complex (Table 1.3) and made a series of important observations. He pointed out that there were differences in age of onset and gender distribution between Eisenmenger patients with a pre (ASD)- or post-capillary (PDA or VSD) defect and suggested that there may be common physiology between Eisenmenger ASD and primary (idiopathic) PAH. He observed that Eisenmenger patients with a PDA tended to be less symptomatic and attributed this to the differential cyanosis, providing normal oxygen saturations to the head and neck. Well ahead of the discovery of peripheral chemoreceptors, he made a groundbreaking statement: "… breathlessness in Eisenmenger syndrome is due to a low arterial oxygen saturation in blood passing through the chemoreceptors of the head and neck"! He described the frequency of symptoms, including angina, syncope, haemoptysis and congestive heart failure. He highlighted that the frequency of haemoptysis was higher than in idiopathic pulmonary arterial hypertension (iPAH), was more common in adults and was the cause of death in 29% of fatalities. Paul Wood also provided detailed description of clinical, electrocardiogram (ECG) and CXR findings of Eisenmenger complex.

While numerous authors have since aided in expanding our knowledge of Eisenmenger syndrome, the contributions of Victor Eisenmenger, Paul Wood and Heath and Edwards are the cornerstone of current practice in PAH–CHD.

Table 1.3 Causes and frequency of Eisenmenger syndrome, as described by Paul Wood in 1958 [31]

Type of communication	Frequency (%) of Eisenmenger reaction (as reported by P. Wood)
Patent ductus arteriosus	16
Aortopulmonary septal defect (window)	60
(Persistent) truncus arteriosus	100
Transposition of the great vessels with a VSD	58
(Congenitally) corrected transposition with a VSD	100
Single ventricle physiology	100
Ventricular septal defect	16
Common atrioventricular canal or persistent ostium primum (atrioventricular septal defect, complete or partial)	43
Atrial septal defect	6
Hemianomalous (partially anomalous) pulmonary venous drainage	0
Total anomalous pulmonary venous drainage	17

1.6 The Effect of PAH on the Heart: RV Adaptation and Maladaptation and the Vicious Cycle of Heterometric Adaptation

Fundamental in the pathophysiology of PH is ventricular remodelling, an important component of most cardiovascular disorders. Ventricular remodelling is caused by cardiac load or injury, resulting in genome expression precipitating molecular, cellular and interstitial changes, which are clinically manifested as changes in size, shape and function of the heart [35]. Remodelling is influenced by the type and severity of haemodynamic load, neurohormonal activation and other factors. It can be adaptive or maladaptive.

In PH, mild increases in afterload lead to adaptive hypertrophy, with little or no dilatation of the RV (homeometric adaptation), allowing an increase in contractility and preservation of CO Fig. 1.6) [36]. As the afterload increases further or becomes chronic, the RV fails to increase its contractility accordingly and becomes uncoupled from the pulmonary circulation. Increased RV filling pressure and RV dilatation occurs (heterometric adaptation), with prolongation of RV contraction. RV dilatation stretches the tricuspid valve annulus and causes tricuspid regurgitation, causing further RV loading and affecting CO and filling pressures. Diastolic interaction between the RV and left ventricle (LV) affects LV preload, while increased RV wall tension and RV hypertrophy can promote myocardial ischaemia, especially with hypotension. The resultant increase in RA pressure and drop in CO negatively impact on the RV, precipitating a vicious cycle of events that lead to decompensated heart failure. Supraventricular arrhythmias caused by the severe dilatation of the RA can acutely reduce CO and lead to decompensated heart failure, hypotension and death quite rapidly in patients with severe PH.

Understanding these events is important for comprehending the management strategies for PH. PAH therapies are aimed at reducing PVR and RV afterload, hence allowing better coupling between the RV and the pulmonary circulation. RV contractility can be addressed in acutely unwell patients with the use of dobutamine or other inotropes. Noradrenaline can be used to combat hypotension and its detrimental effects on perfusion of the myocardium and other organs. Diuretics or fluids can be used to maintain RV filling pressure to an optimum on the Starling curve, usually around 10–12 mmHg: higher or lower filling pressures can cause further deterioration in RV output.

The relative stability of Eisenmenger patients who reach adulthood is attributed to optimal adaptation (largely homeometric) of the RV to the severely raised PVR. In fact, many adult Eisenmenger patients present with little or no RV dilatation, but significant RV hypertrophy and overall preserved contractility. This is mostly observed in patients with post-tricuspid shunts and has been attributed to preservation of the fetal RV phenotype or the optimal interaction between the RV and LV through a large ventricular communication [37, 38]. Eisenmenger patients with pre-tricuspid shunts (large ASDs) and even those with a large patent ductus often develop RV dilatation and dysfunction, demonstrating less optimal RV adaptation.

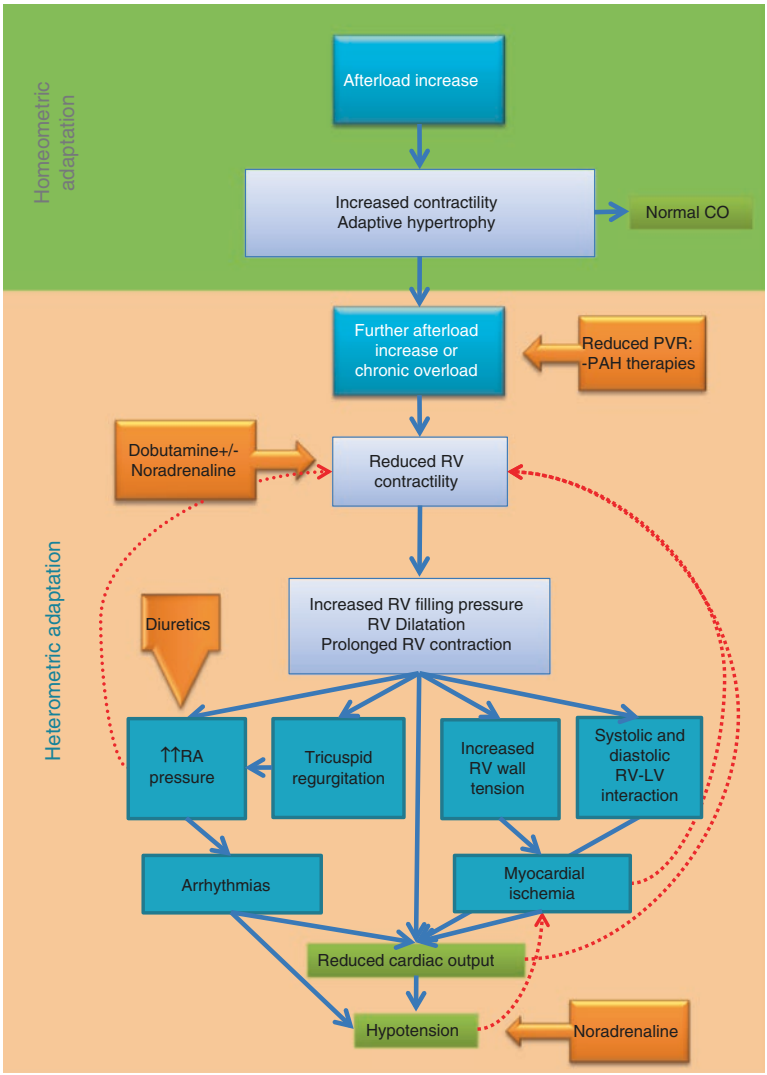

Fig. 1.6 Homeometric and heterometric adaptation of the right ventricle (RV) to pulmonary hypertension (PH) [36, 45]. Homeometric adaptation in PH consists in adaptive hypertrophy and an increase in contractility of the RV as a response to the rise in RV afterload, with little or no dilatation, hence preserving cardiac output. Prolonged excessive afterload to the RV may lead to failure of the homeometric adaptation. This results in an increase in RV filling pressures and volume (heterometric adaptation) and an attempt to maintain stroke volume through the Starling principle. There is uncoupling of the RV from the pulmonary circulation and prolongation of RV contraction. RV dilatation causes tricuspid regurgitation, while increased RV wall tension affects myocardial perfusion. All the above, together with a significant negative interaction between the RV and the left ventricle (LV), lead to a further increase in RV filling pressure and subsequent drop in cardiac output, precipitating a vicious cycle of events that lead to heart failure, hypotension and shock. Supraventricular arrhythmias caused by the severe dilatation of the RA can acutely precipitate cardiac output and lead to decompensated heart failure, hypotension and death quite rapidly in patients with severe PH. Reducing RV afterload, increasing RV contractility, avoiding hypotension and maintaining optimal RA/RV filling pressures (in *orange*) can be used to counteract this chain of events and aid homeometric adaptation

1.7 The Effect of PAH on the Large Pulmonary Arteries

PA dilatation is a common feature of PH and is used as a marker of disease. It is most commonly seen in patients with Eisenmenger syndrome and is often associated with in situ thrombosis, observed in up to a fifth of Eisenmenger patients [39, 40]. The morphology and mechanical characteristics of large PAs dictate not only the risk of major complications, such as PA dissection or rupture, but are also likely to have an impact on right ventricular function and the coupling between the RV and the pulmonary circulation: arterial stiffness of the proximal PAs is, indeed, a predictor of mortality in noncongenital PAH, while reduced proximal PA compliance has also been observed in patients with PAH–CHD and increased PA stiffness is a predictor of poor functional capacity [41–44]. An increased PA stiffness of the proximal PAs is thought to affect the pulsatile load of the RV, while stiff, conduit-like PAs promote further damage to distal PAs through increased flow pulsatility.

The dilatation of the larger PAs in patients with PAH–CHD appears to be related both to the high wall tension caused by the high pressure and also to intrinsic changes of the wall of the PAs. Prapa et al. showed fibrosis and atypical elastic patterns in proximal PAs of PAH–CHD patients, which are thought to affect vessel mechanical properties. These changes were more advanced in severely dilated PA vessels, with greater degrees of medial hypertrophy. An aortic phenotype of the media of PAs was observed, with rare cyst-like formations or medionecrosis, possibly explaining the low incidence of dissection of aneurysmal PAs in PAH–CHD. Histological changes were also present in the aorta of these patients, suggesting an inherent component of abnormalities of the great vessel wall.

While atherosclerosis is rare in the PAs of normal individuals, accelerated atherosclerosis has been noted in all types of PAH and was observed in over two thirds of PAH–CHD subjects in the study by Prapa et al. Intimal thickening was also very common at the level of the PA bifurcation, where abnormal blood flow and increased shear stress are expected. In situ thrombosis was present in 30%, most commonly in females, and was located in the PA branches where it was associated with aneurysmal dilatation and underlying coexisting confluent atheroma. In situ thrombosis is likely the result of the combination of local vascular injury (supported by the presence of atherosclerotic lesions), hypercoagulability and sluggish blood flow with red cell aggregation. All clots had similar characteristics of old organizing thrombus in multiple layers, supporting the fact that this is in situ thrombosis, even though distal embolization of fresh clot can occur. Patients with in situ thrombosis have more advanced disease with lower exercise capacity, ventricular function and higher natriuretic peptide levels [39].

Conclusions

Major advances have been made in the last 50 years in understanding PAH–CHD and its management. Great challenges remain in understanding the exact mechanisms behind the development of PVD in CHD and the different modalities of RV adaptation and coupling with the pulmonary circulation. Recent and future advances in genetic and proteomics will undoubtedly shed light onto this rare condition. However, careful clinical observation remains as invaluable.

References

1. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Noordegraaf AV, Beghetti M, Ghofrani A, Sanchez MAG, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M (2015) 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 46:903–975
2. Dimopoulos K, Wort SJ, Gatzoulis MA (2014) Pulmonary hypertension related to congenital heart disease: a call for action. Eur Heart J 35:691–700
3. Heath D, Edwards JE (1958) The pathology of hypertensive pulmonary vascular disease; a description of six grades of structural changes in the pulmonary arteries with special reference to congenital cardiac septal defects. Circulation 18:533–547
4. Heath D, Helmholz HF, Burchell HB, Dushane JW, Kirklin JW, Edwards JE (1958) Relation between structural change in the small pulmonary arteries and the immediate reversibility of pulmonary hypertension following closure of ventricular and atrial septal defects. Circulation 18:1167–1174
5. Rabinovitch M, Haworth SG, Castaneda AR, Nadas AS, Reid LM (1978) Lung biopsy in congenital heart disease: a morphometric approach to pulmonary vascular disease. Circulation 58:1107–1122
6. Dimopoulos K, Peset A, Gatzoulis MA (2008) Evaluating operability in adults with congenital heart disease and the role of pretreatment with targeted pulmonary arterial hypertension therapy. Int J Cardiol 129:163–171
7. Haworth SG (1987) Pulmonary vascular disease in ventricular septal defect: structural and functional correlations in lung biopsies from 85 patients, with outcome of intra-cardiac repair. J Pathol 152:157–168
8. Wagenvoort CA, Wagenvoort N, Draulans-Noë Y (1984) Reversibility of plexogenic pulmonary arteriopathy following banding of the pulmonary artery. J Thorac Cardiovasc Surg 87:876–886
9. Wagenvoort CA (1988) Morphological substrate for the reversibility and irreversibility of pulmonary hypertension. Eur Heart J 9(Suppl J):7–12
10. Haworth SG, Rabinovitch M (2009) Pulmonary circulation. In: Anderson R, Baker EJ, Redington A, Rigby ML, Penny D, Wernovsky G (eds) Paediatric cardiology: expert consult—online and print, 3rd edn. Churchill Livingstone, London
11. Morrell NW (2011) Pulmonary vascular remodeling and pathobiology of pulmonary hypertension. In: Peacock AJ, Naeije R, Rubin LJ (eds) Pulmonary circulation: diseases and their treatment, 3rd edn. CRC Press, London, pp 59–77
12. Rabinovitch M, Andrew M, Thom H, Trusler GA, Williams WG, Rowe RD, Olley PM (1987) Abnormal endothelial factor VIII associated with pulmonary hypertension and congenital heart defects. Circulation 76:1043–1052
13. Yoshibayashi M, Nishioka K, Nakao K, Saito Y, Matsumura M, Ueda T, Temma S, Shirakami G, Imura H, Mikawa H (1991) Plasma endothelin concentrations in patients with pulmonary hypertension associated with congenital heart defects. Evidence for increased production of endothelin in pulmonary circulation. Circulation 84:2280–2285
14. Fuse S, Kamiya T (1994) Plasma thromboxane B2 concentration in pulmonary hypertension associated with congenital heart disease. Circulation 90:2952–2955
15. Dorfmüller P (2011) Pathology of pulmonary vascular diseases. In: Peacock AJ, Naeije R, Rubin LJ (eds) Pulmonary circulation: diseases and their treatment, 3rd edn. CRC Press, London
16. Yaginuma G, Mohri H, Takahashi T (1990) Distribution of arterial lesions and collateral pathways in the pulmonary hypertension of congenital heart disease: a computer aided reconstruction study. Thorax 45:586–590
17. Cool CD, Stewart JS, Werahera P, Miller GJ, Williams RL, Voelkel NF, Tuder RM (1999) Three-dimensional reconstruction of pulmonary arteries in plexiform pulmonary hypertension using cell-specific markers. Evidence for a dynamic and heterogeneous process of pulmonary endothelial cell growth. Am J Pathol 155:411–419

18. Saldaña ME, Harley RA, Liebow AA, Carrington CB (1968) Experimental extreme pulmonary hypertension and vascular disease in relation to polycythemia. Am J Pathol 52:935–981
19. Lee SD, Shroyer KR, Markham NE, Cool CD, Voelkel NF, Tuder RM (1998) Monoclonal endothelial cell proliferation is present in primary but not secondary pulmonary hypertension. J Clin Invest 101:927–934
20. Daliento L, Rebellato L, Angelini A, Frescura C, Mazzotti E, Rotundo M, Thiene G (2002) Fatal outcome in Eisenmenger syndrome. Cardiovasc Pathol 11:221–228
21. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, del Nido P, Fasules JW, Graham TP Jr, Hijazi ZM, Hunt SA, King ME, Landzberg MJ, Miner PD, Radford MJ, Walsh EP, Webb GD, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Buller CE, Creager MA, Ettinger SM, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Page RL, Riegel B, Tarkington LG, Yancy CW, American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease); American Society of Echocardiography; Heart Rhythm Society; International Society for Adult Congenital Heart Disease; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons (2008) ACC/AHA 2008 guidelines for the management of adults with congenital heart disease. J Am Coll Cardiol 52:e143–e263
22. Machado RD, Southgate L, Eichstaedt CA, Aldred MA, Austin ED, Best DH, Chung WK, Benjamin N, Elliott CG, Eyries M, Fischer C, Gräf S, Hinderhofer K, Humbert M, Keiles SB, Loyd JE, Morrell NW, Newman JH, Soubrier F, Trembath RC, Viales RR, Grünig E (2015) Pulmonary arterial hypertension: a current perspective on established and emerging molecular genetic defects. Hum Mutat 36:1113–1127
23. D'Alto M, Romeo E, Argiento P, D'Andrea A, Sarubbi B, Correra A, Scognamiglio G, Papa S, Bossone E, Calabrò R, Vizza CD, Russo MG (2013) Therapy for pulmonary arterial hypertension due to congenital heart disease and Down's syndrome. Int J Cardiol 164:323–326
24. Chi T, Krovetz J (1975) The pulmonary vascular bed in children with Down syndrome. J Pediatr 86:533–538
25. Soudon P, Stijns M, Tremouroux-Wattiez M, Vliers A (1975) Precocity of pulmonary vascular obstruction of Down's syndrome. Eur J Cardiol 2:473–476
26. Hall SM, Haworth SG (1992) Onset and evolution of pulmonary vascular disease in young children: abnormal postnatal remodelling studied in lung biopsies. J Pathol 166:183–193
27. D'Alto M, Romeo E, Argiento P, Santoro G, Sarubbi B, Gaio G, Mélot C, Russo MG, Naeije R, Calabrò R (2010) Pulmonary vasoreactivity predicts long-term outcome in patients with Eisenmenger syndrome receiving bosentan therapy. Heart 96:1475–1479
28. Lanigan MJ, Chaney MA, Tissot C, Beghetti M, Dimopoulos K (2014) CASE 10—2014 Eisenmenger syndrome: close the hole? J Cardiothorac Vasc Anesth 28:1146–1153
29. Balzer DT, Kort HW, Day RW, Corneli HM, Kovalchin JP, Cannon BC, Kaine SF, Ivy DD, Webber SA, Rothman A, Ross RD, Aggarwal S, Takahashi M, Waldman JD (2002) Inhaled Nitric Oxide as a Preoperative Test (INOP Test I): the INOP Test Study Group. Circulation 106:I76–I81
30. Baumgartner E, Abbott M (1929) Interventricular septal defect with dextroposition of aorta and dilatation of the pulmonary artery ("Eisenmenger complex") terminating by cerebral abscess. J Med Sci 177:639–647
31. Wood P (1958) The Eisenmenger syndrome or pulmonary hypertension with reversed central shunt. I. Br Med J 2:701–709
32. Taussig HB, Blalock A (1947) Observations on the volume of the pulmonary circulation and its importance in the production of cyanosis and polycythemia. Am Heart J 33:413–419
33. Bing RJ, Vandam LD, Gray FD (1947) Physiological studies in congenital heart disease: results obtained in five cases of Eisenmenger's complex. Bull Johns Hopkins Hosp 80:323–347
34. Wood P (1958) The Eisenmenger syndrome or pulmonary hypertension with reversed central shunt. Br Med J 2:755–762
35. Cohn JN, Ferrari R, Sharpe N (2000) Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. J Am Coll Cardiol 35:569–582

36. Naeije R, Manes A (2014) The right ventricle in pulmonary arterial hypertension. Eur Respir Rev 23:476–487
37. Hopkins WE (2005) The remarkable right ventricle of patients with Eisenmenger syndrome. Coron Artery Dis 16:19–25
38. Moceri P, Kempny A, Liodakis E, Alonso Gonzales R, Germanakis I, Diller G-P, Swan L, Marino PS, Wort SJ, Babu-Narayan SV, Ferrari E, Gatzoulis MA, Li W, Dimopoulos K (2015) Physiological differences between various types of Eisenmenger syndrome and relation to outcome. Int J Cardiol 179:455–460
39. Broberg CS, Ujita M, Prasad S, Li W, Rubens M, Bax BE, Davidson SJ, Bouzas B, Gibbs JSR, Burman J, Gatzoulis MA (2007) Pulmonary arterial thrombosis in Eisenmenger syndrome is associated with biventricular dysfunction and decreased pulmonary flow velocity. J Am Coll Cardiol 50:634–642
40. Silversides CK, Granton JT, Konen E, Hart MA, Webb GD, Therrien J (2003) Pulmonary thrombosis in adults with Eisenmenger syndrome. J Am Coll Cardiol 42:1982–1987
41. Gan CT-J, Lankhaar J-W, Westerhof N, Marcus JT, Becker A, Twisk JWR, Boonstra A, Postmus PE, Vonk-Noordegraaf A (2007) Noninvasively assessed pulmonary artery stiffness predicts mortality in pulmonary arterial hypertension. Chest 132:1906–1912
42. Berger RMF, Cromme-Dijkhuis AH, Hop WCJ, Kruit MN, Hess J (2002) Pulmonary arterial wall distensibility assessed by intravascular ultrasound in children with congenital heart disease: an indicator for pulmonary vascular disease? Chest 122:549–557
43. Bogren HG, Klipstein RH, Mohiaddin RH, Firmin DN, Underwood SR, Rees RSO, Longmore DB (1989) Pulmonary artery distensibility and blood flow patterns: a magnetic resonance study of normal subjects and of patients with pulmonary arterial hypertension. Am Heart J 118:990–999
44. Kang K-W, Chang H-J, Kim Y-J, Choi B-W, Lee HS, Yang W-I, Shim C-Y, Ha J, Chung N (2011) Cardiac magnetic resonance imaging-derived pulmonary artery distensibility index correlates with pulmonary artery stiffness and predicts functional capacity in patients with pulmonary arterial hypertension. Circ J 75:2244–2251
45. Naeije R, Brimioulle S, Dewachter L (2014) Biomechanics of the right ventricle in health and disease (2013 Grover Conference series). Pulm Circ 4:395–406

Definition and Classification of Pulmonary Hypertension in Congenital Heart Disease

2

Gerhard-Paul Diller

2.1 Definition of Pulmonary Hypertension

Pulmonary hypertension (PH) is a haemodynamic and pathophysiological disorder that may involve multiple clinical conditions and can complicate various cardiovascular and respiratory diseases. PH is defined as an increase in mean pulmonary arterial pressure (mPAP) at rest ≥25 mmHg as assessed by right heart catheterization. The normal level of mPAP at rest is around 15 mmHg with the upper normal limit being reported at approximately 20 mmHg. The clinical significance of a mPAP between 21 and 24 mmHg remains currently unclear, but patients with a mPAP in this range should be carefully followed if they are at risk for developing PH. Haemodynamically, PH can be further classified as precapillary PH with pulmonary arterial wedge pressures (PAWP) ≤15 mmHg or post-capillary PH in case PAWP >15 mmHg [1].

Precapillary PH consists of four clinical groups according to the current guidelines: pulmonary arterial hypertension (PAH), PH due to lung disease, chronic thromboembolic PH and PH with unclear and/or multifactorial mechanisms. The term PAH (group 1) describes a group of PH patients characterized by PAWP ≤15 mmHg and pulmonary vascular resistance (PVR) >3 Wood units (WU) in the absence of other causes of precapillary PH such as PH due to lung diseases, chronic thromboembolic PH or other rare diseases. As mentioned previously, PAH can be associated with multiple clinical conditions including congenital heart disease (CHD).

On the other hand, post-capillary PH, defined as a mPAP ≥25 mmHg and PAWP >15 mmHg, includes two major clinical groups: PH due to left heart disease and PH

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with unclear and/or multifactorial mechanisms. PH due to left heart disease (group 2) represents the most common cause of PH, although severe PH is relatively uncommon in this group [2].

2.2 Classification of Pulmonary Hypertension

The classification of PH has evolved over the last few decades and continues to be updated at the regular World Symposia. As a consequence, the current classification represents the product of a series of modifications of the initial classification based largely on histological findings. Subsequent World Symposia in Evian (1998), Venice (2003), Dana Point (2008) and Nice (2013) have refined this classification with the focus shifting away from histology to clinical aspects of the disease [3]. The current classification groups various forms of PH based on similar pathophysiologic presentation and response to treatment. As such, it is much more than a system for defining PH, but also represents the very basis for an evidence-based treatment approach to the disease.

The current classification of PH classifies the disease based on pathological and pathophysiological findings into five groups (Table 2.1). This coarse grouping into major disease groups forms the framework for clinical studies and for determining the aetiology and most appropriate treatment strategy for patients presenting with PH and CHD. While most cases of congenital heart disease-pulmonary hypertension (CHD–PH) are due to PAH (group 1 of the classification), patients may also present with combinations of PH forms, or PH may be entirely caused by group 2 or 5 disease. These latter forms do not generally respond to specific PAH drug therapy. Nonetheless the classification represents only the starting point when assessing patients with CHD–PH. A further subclassification of the disease based on the location of the shunt, the direction of the shunt flow, dimensions of the defect, haemodynamic consequences and associated extra-cardiac anomalies has been proposed and serves to refine the disease. This subclassification is presented in Table 2.2. From a practical point of view, it should be highlighted that restrictive and nonrestrictive flow merely represents the gradient measured over the defect. Therefore, this aspect may be misleading and a restrictive defect may well be haemodynamically relevant in some patients. For clinical purposes, a simplified classification consisting of four groups of CHD–PH has proven to be sufficient in most circumstances. This classification divides CHD–PH into Eisenmenger syndrome, CHD–PH with relevant left-to-right shunt, PH without a haemodynamically relevant shunt and CHD–PH in patients with previously closed shunt lesions.

Table 2.3 provides an overview over this classification of CHD–PH. Eisenmenger syndrome represents the extreme end of the spectrum of PH in the setting of CHD. It is characterized by (supra)systemic pulmonary artery pressures, bidirectional or right-to-left shunt flow, cyanosis and associated stigmata and multisystem dysfunction.

Table 2.1 Classification of pulmonary hypertension according to the current recommendations published by the European Cardiac Society and the European Respiratory Society (from [1])

1.	*Pulmonary arterial hypertension (PAH)*			
	1.1	Idiopathic PAH		
	1.2	Hereditary PAH	1.2.1	BMPR2 mutation
			1.2.2	Other mutations
	1.3	Drug- and toxin-induced PAH		
	1.4	PAH associated with	1.4.1	Connective tissue disease
			1.4.2	HIV infections
			1.4.3	Portal hypertension
			1.4.4	Congenital heart disease
			1.4.5	Schistosomiasis
1′.	*Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis*			
	1′.1	Idiopathic		
	1′.2	Hereditary	1′.2.1	EIF2AK4 mutation
			1′.2.2	Other mutations
	1′.3	Drugs, radiation and toxin induced		
	1′.4	Associated with	1′.4.1	Connective tissue disease
			1′.4.2	HIV infections
1″.	*Persistent pulmonary hypertension of the newborn*			
2.	*Pulmonary hypertension due to left heart disease*			
	2.1	Left ventricular systolic dysfunction		
	2.2	Left ventricular diastolic dysfunction		
	2.3	Valvular disease		
	2.4	Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies		
	2.5	Congenital/acquired pulmonary vein stenosis		
3.	*Pulmonary hypertension due to lung diseases and/or hypoxia*			
	3.1	Chronic obstructive pulmonary disease		
	3.2	Interstitial lung disease		
	3.3	Other pulmonary diseases with mixed restrictive and obstructive pattern		
	3.4	Sleep-disordered breathing		
	3.5	Alveolar hypoventilation disorders		
	3.6	Chronic exposure to high altitude		
	3.7	Developmental lung diseases		
4.	*Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions*			
	4.1	Chronic thromboembolic pulmonary hypertension		
	4.2	Other pulmonary artery obstructions	4.2.1	Angiosarcoma
			4.2.2	Other intravascular tumours
			4.2.3	Arteritis
			4.2.4	Congenital pulmonary arteries stenoses
			4.2.5	Parasites

(continued)

Table 2.1 (continued)

5.	*Pulmonary hypertension with unclear and/or multifactorial mechanisms*	
	5.1	Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
	5.2	Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, neurofibromatosis
	5.3	Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
	5.4	Others: pulmonary tumoural thrombotic microangiopathy, osing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

Table 2.2 Clinical classification of congenital systemic-to-pulmonary shunts associated with pulmonary arterial hypertension in patients with congenital heart disease (adapted from [1])

Eisenmenger syndrome: Includes systemic-to-pulmonary shunts resulting from large defects and leading to a severe increase in PVR and a reversed (pulmonary-to-systemic) or bidirectional shunt; cyanosis, erythrocytosis and multiple organ involvement are present
PAH associated with systemic-to-pulmonary shunts: Includes moderate to large defects; PVR is mildly to moderately increased, systemic-to-pulmonary shunt is still prevalent and no cyanosis is present at rest. Depending on the prevailing haemodynamics/degree of pulmonary vascular disease, the defect may be still or correctable or may be non-correctable
PAH with small defects: Small defects (usually ventricular septal defects <1 cm and atrial septal defects <2 cm of effective diameter assessed by echocardiography); clinical picture is very similar to idiopathic PAH
PAH after corrective cardiac surgery: Congenital heart disease has been corrected, but PAH is still present immediately after surgery or recurs several months or years after surgery in the absence of significant postoperative residual lesions

Once Eisenmenger syndrome has developed, correction of the underlying heart defect is contraindicated. In contrast patients with PH and left-to-right shunt flow may be amenable to shunt repair depending on PVR and haemodynamics during exercise. A further subgroup is represented by patients with a small, haemodynamically insignificant shunt defect, presenting with significant PH. It is generally accepted that this could be, in fact, regarded as idiopathic PAH with coincidental CHD, as the congenital heart defect may aetiologically be a bystander but can prove to be a protecting factor in the course of the disease should severe PH ensue, by acting as a physiologic blow-off valve, thus unloading the right ventricle in case of suprasystemic right-sided pressures and a failing sub-pulmonary ventricle.

An important subgroup of CHD–PH patients is represented by those individuals presenting with PH despite correction of an underlying congenital shunt lesion. These can either be patients inappropriately undergoing surgical or interventional defect closure despite established pulmonary vascular disease (PVD) or, more frequently, patients with progressive PVD who develop PH after defect closure.

The different groups are represented in Fig. 2.1, which also illustrates that some of these entities represent different forms of a spectrum of disease. In addition to genetic predisposition, time is an important factor in this progressive disease.

It deserves emphasis that the classification of PH into specific groups is partly arbitrary, and many patients present with PH due to a combination of factors. For example,

Table 2.3 Classification of pulmonary hypertension in congenital heart disease depending on shunt dimensions, predominating shunt flow, associated anomalies and history of repair (from [3])

1.	*Type*					
	1.1.	Simple pre-tricuspid shunt lesions	1.1.1.	Atrial septal defect (ASD)	1.1.1.1.	Ostium secundum type
					1.1.1.2.	Sinus venosus type
					1.1.1.3.	Ostium primum type
			1.1.2.	Total or partial anomalous pulmonary venous drainage		
	1.2.	Simple post-tricuspid shunt lesions	1.2.1.	Ventricular septal defect (VSD)		
			1.2.2.	Patent arterial duct		
	1.3.	Combined shunt lesions				
	1.4.	Complex congenital heart disease	1.4.1.	Atrioventricular septal defect		
			1.4.2.	Truncus arteriosus		
			1.4.3.	Univentricular circulation with unobstructed pulmonary blood flow		
			1.4.4.	Transposition of the great arteries with VSD (without pulmonary stenosis) and/or patent arterial duct		
			1.4.5.	Other forms		
2.	*Dimension of the defect*					
	2.1.	Haemodynamic description	2.1.1.	Restrictive defect		
			2.1.2.	Nonrestrictive defect		
	2.2.	Anatomic description	2.2.1.	Small defect (ASD ≤ 2.0 cm und VSD ≤ 1.0 cm)		
			2.2.2.	Large defect (ASD > 2.0 cm und VSD > 1.0 cm)		
3.	*Shunt flow direction*					
	3.1.	Predominantly systemic-to-pulmonary flow				
	3.2.	Predominantly pulmonary-to-systemic flow				
	3.3.	Bidirectional flow				
4.	*Associated cardiac and extra-cardiac defects*					
5.	*Previous correction/defect closure*					
	5.1.	Uncorrected				
	5.2.	Palliated defect				
	5.3.	Closed/corrected defect				

a patient with repaired atrioventricular septal defect could well have PAH (*Class 1 PH*, due to late repair and/or predisposing factors such as Down syndrome) as well as post-capillary PH (*Class 2 PH*) due to left-sided atrioventricular valve disease after surgical repair. In addition, many CHD patients present with respiratory disease (*Class 3 PH*) and chronic thromboembolic PH (*Class 4 PH*), as well as segmental PH (*Class 5 PH*), potentially aggravating PH in this setting.

For practical clinical purposes, the classification system presented here appears sufficient in most circumstances. The classification system, however, is in constant flux, and clinicians should be aware that changes in nomenclature are not uncommon and can be confusing for colleagues not up to date with the most current classification. As a consequence, care should be taken when using the number system to describe

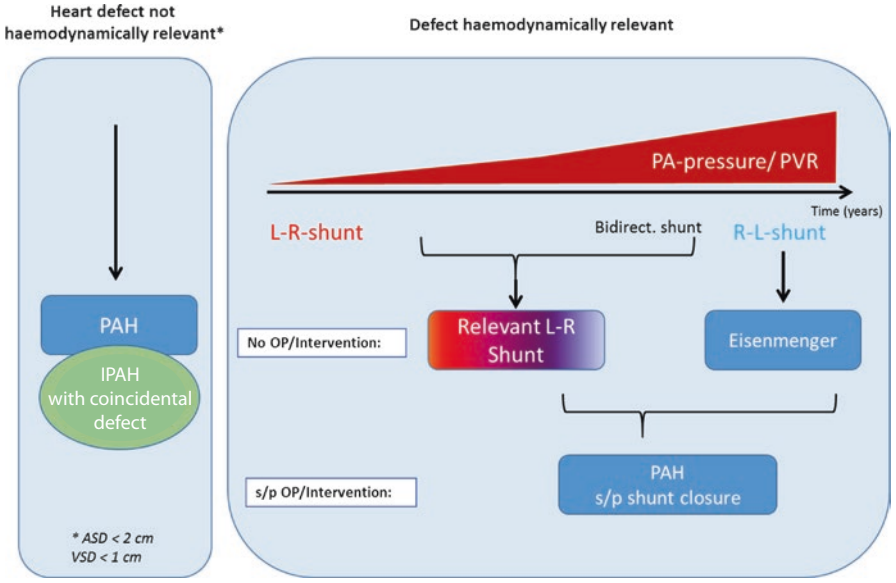

Fig. 2.1 Schematic representation of pulmonary arterial hypertension (PAH) in patient with congenital heart disease. PAH in patients with small, haemodynamically insignificant defects could be regarded as a form of idiopathic PAH (IPAH). Depending on repair status and time of disease, the figure illustrates that PAH associated with shunt lesions, postoperative PAH and Eisenmenger syndrome represents different forms of a disease spectrum modified by time and iatrogenic intervention

disease. In our experience, it is commonly more appropriate to describe the likely underlying causes of PH rather than using a numeric classification system (e.g. in medical correspondence). A more detailed classification system has been proposed by the Pulmonary Vascular Research Institute that may be useful for individual cases [4].

References

1. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M (2016) 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 37(1):67–119
2. Oudiz RJ (2007) Pulmonary hypertension associated with left-sided heart disease. Clin Chest Med 28(1):233–241
3. Simonneau G, Gatzoulis MA, Adatia I et al (2013) Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 62(25 Suppl):D34–D41
4. Cerro MJ, Abman S, Diaz G et al (2011) A consensus approach to the classification of pediatric pulmonary hypertensive vascular disease: report from the PVRI pediatric taskforce, Panama 2011. Pulm Circ 1:286–298

Eisenmenger Syndrome: Pathophysiology and Haematologic Effects

3

Craig S. Broberg

Abbreviations

ASD	atrial septal defect
AVSD	atrioventricular septal defect
BNP	b-type natriuretic peptide
ERA	endothelin receptor antagonist
ES	Eisenmenger syndrome
LA	left atrium
LV	left ventricle
MCV	mean corpuscular volume
PDA	patent ductus arteriosus
PA	pulmonary artery
PH	pulmonary hypertension
PVR	pulmonary vascular resistance
RA	right atrium
RV	right ventricle
SVR	systemic vascular resistance
VSD	ventricular septal defect
6MWD	6-minute walk distance

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3.1 Introduction

Eisenmenger syndrome (ES) is a unique form of pulmonary hypertension (PH) exhibiting several important pathophysiologic distinctions from other aetiologies. The eponym applies to those with three distinct features: a cardiac defect, increased pulmonary pressure and shunting of blood through the defect, leading to cyanosis. The combination of increased pulmonary vascular resistance (PVR) and a communication between the right and left sides of the heart allow for right-to-left shunting of desaturated venous blood to the systemic side.

ES sets itself apart in several distinct ways. Most important are issues related to cyanosis, such as the necessity of erythropoiesis and its effects on multiple organ systems. Distinctions between ES and other causes of PH also include factors related to the pulmonary arteries (PAs) and the right ventricle (RV). These nuances have significant implications for both treatment and prognosis. With chronic O_2 saturations well below normal, patients may be viewed as severely impaired with very poor prognosis. These are they for whom reparative surgery either was not or could not be offered in early life. Many such patients do not survive to adulthood. Therefore, adults with ES are remarkable survivors, and despite inherent limitations and fragilities, some go on to enjoy long, productive lives, often outliving all expectations for their survival despite significant inherent vulnerabilities.

3.2 Pathology

Patients born with an unrestricted communication between the two sides of the heart, including a communication between the great arteries, are at risk for developing, or maintaining, a high PVR. A ventricular defect provides two egresses for ventricular ejection (namely the semilunar valve or the septal defect), and blood flow will be greatest to the egress with the lowest resistance. In early life, as PVR falls, there will be a net left-to-right shunt through the defect, with over-circulation through the lungs. With time, endothelial injury and vascular remodelling within the pulmonary circulation occur in response to pressure loading [1, 2]. As a result, PVR rises and diminishes the drive to left-to-right shunt, eventually enabling bidirectional shunting through the same defect. This is the essence of the ES physiology. While specific criteria for determining a right-to-left shunt vary, ES has been defined as O_2 saturation <92% at rest or <87% with exercise [3].

Because the degree of bidirectional shunting is dependent on the relative resistance in the pulmonary and systemic circulation, O_2 saturation can be influenced by factors that change the resistance of either vascular bed. For example, a pulmonary vasodilator may lower PVR but may also lower systemic vascular resistance (SVR). Thus, the net effect on right-to-left shunt and O_2 saturation may not always be predictable.

Although the presence of PH is defined on the basis of PA pressure, high PA flow may increase the PA pressure but not the resistance. Hence PH in the setting of a shunt is not necessarily associated with increased PVR (see Fig. 1.5). Therefore, unlike other PH subtypes, elevated PVR is a necessary indicator of pulmonary pathology rather than just PA pressure. Providers should not rely on estimation of

the RV systolic pressure by echocardiography in making the diagnosis. For example, since pulmonary stenosis creates the necessary resistance to avoid exposure of the pulmonary vascular bed to high pressure and flow, its presence will protect against the Eisenmenger reaction in the setting of a large shunt, despite the triad of high RV systolic pressure right-to-left shunt and cyanosis. Pulmonary stenosis, including from previous surgical banding of the PA, creates an important distinction between ES and other forms of cyanotic congenital heart disease. As such it has been said that a cyanotic patient with a loud systolic murmur at the base likely does not have ES.

Unlike other congenital heart lesions defined anatomically, ES is a physiologic diagnosis. The process may result from many different types of shunts (Fig. 3.1) as first explained by Dr. Paul Wood [1]. Most commonly patients have an unrepaired ventricular septal defect (VSD) or a patent ductus arteriosus (PDA). Less commonly a large atrial septal defect (ASD) may be found. The same physiology may be present in patients with more rare diagnoses including atrioventricular septal defects (AVSD), single ventricles, uncorrected transposition of the great arteries or an aortopulmonary window (Fig. 3.1). The larger the size of the defect (and hence the lower the resistance to flow from the defect), the higher the likelihood of developing ES. There is significant variation between patients; the process may be present at birth (such as in persistent PH of the newborn) or develop over decades. Patients with a PDA are unique in that the right-to-left shunt delivers venous blood to the distal arch, and desaturation will only be manifested in the lower extremities.

Pulmonary vascular disease in ES is not necessarily the result of high flow alone, as is often believed. Many patients with large “pre-tricuspid” shunts, i.e. an ASD, may have high-volume left-to-right shunts and no increase in PVR. In contrast, those with a large “post-tricuspid” shunt at systemic level pressures, such as a VSD or PDA, will almost always develop increased PVR and reversed shunting over time with rare exceptions. ES patients with an ASD have been shown to be older, have higher circulating b-type natriuretic peptide (BNP) and have poorer exercise capacity relative to those with post-tricuspid shunts [4], possibly because increased PVR develops later in life or in response to other conditions. Despite these pathophysiologic distinctions, most series of ES will include those with an ASD, since these patients share many of the same clinical issues related to chronic right-to-left shunting and cyanosis [4–6], and they are generally considered part of the ES spectrum.

Another key feature that sets ES patients apart from other forms of PH is the structure and function of the RV. Normal individuals, including those that later develop PH, start life with a normal RV that thins and weakens in response to lower PVR over time; ES patients often have a pressure-loaded RV from birth. The morphology of the RV in utero, including its thicker free wall, is maintained, which in theory lends itself to a more favourable capacity for generating systemic level pressure throughout life. As will be discussed below, prognosis in ES is associated with ventricular function, as in other forms of PH, and therefore the preconditioned RV may be a reason why ES patients appear to have better survival than idiopathic PH.

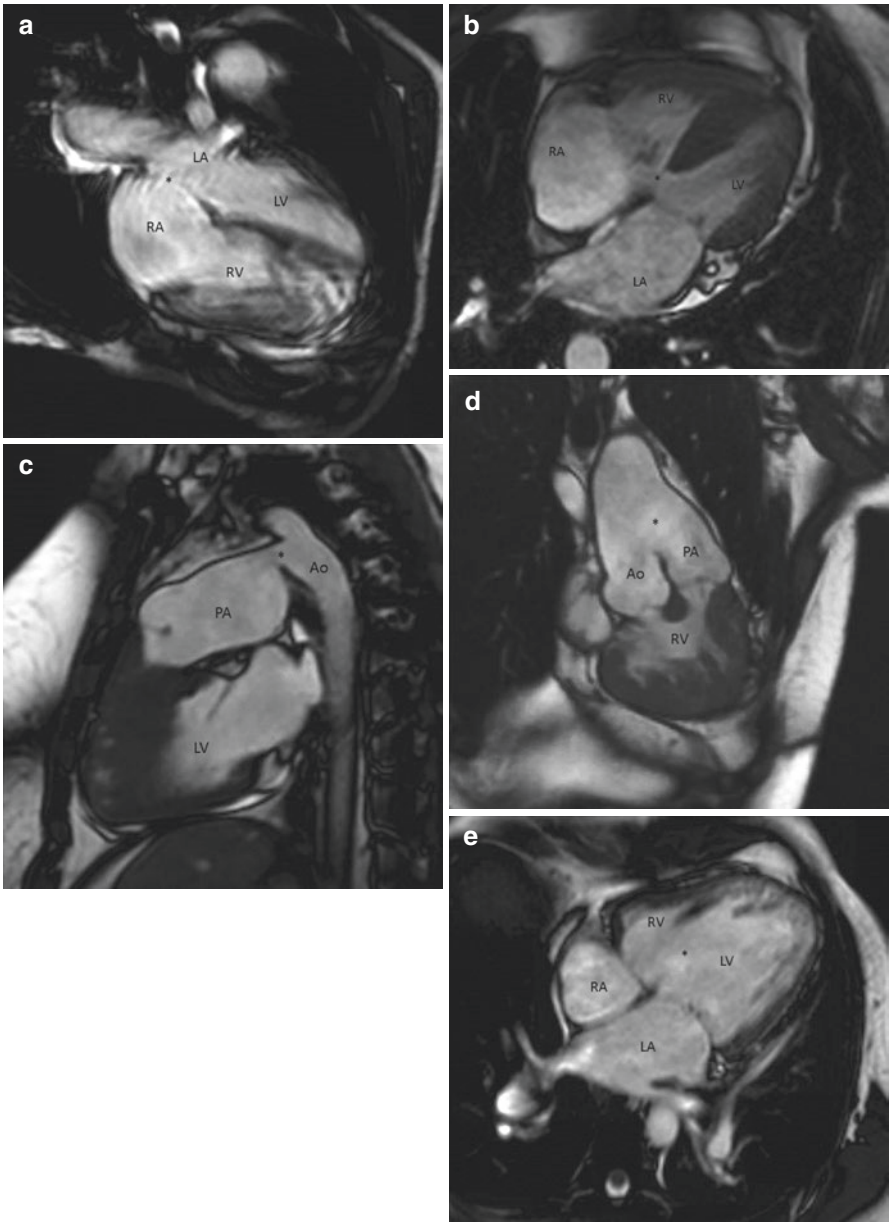

Fig. 3.1 Various examples of congenital heart defects associated with Eisenmenger physiology imaged with magnetic resonance. (**a**) Atrial septal defect. The RV is considerably larger than the LV. (**b**) Ventricular septal defect: the RV and LV are more similar in morphology and wall thickness. (**c**) Patent ductus arteriosus. (**d**) Aortopulmonary window. (**e**) Single ventricle (double inlet left ventricle). *RV* right ventricle, *LV* left ventricle, *RA* right atrium, *LA* left atrium, *PA* pulmonary artery, *Ao* aorta (*asterisk*) indicates the location of the defect in each case

3.3 Haematologic Considerations

3.3.1 Secondary Erythrocytosis

Secondary erythrocytosis, or an increase in red cell mass, is an expected and necessary adaptation in response to chronic hypoxaemia. Erythrocytosis includes both elevated haemoglobin and haematocrit, the former being the determinant of systemic O_2 delivery (the product of O_2-binding capacity, O_2 saturation and cardiac output). Erythrocytosis is distinct from polycythaemia since leucocyte and platelet counts are not similarly elevated. This distinction is important as leucocytes in particular may contribute to hyperviscosity (discussed below), and platelet counts in ES are often lower than normal.

The level of haemoglobin for an individual patient ought to be determined by the degree of tissue hypoxia reflected by the average O_2 saturation and be maintained at a level sufficient to achieve a normal systemic O_2 transport. Yet, in addition to being influenced by the degree of right-to-left shunt, peripheral O_2 saturation can also be affected by ventilation/perfusion mismatch, streaming effects or metabolic needs in response to activity and vary considerably in an individual patient through the course of a day. The range of O_2 saturation will be inversely proportional to heart rate, since both variables respond dynamically to metabolic need (Fig. 3.2). With

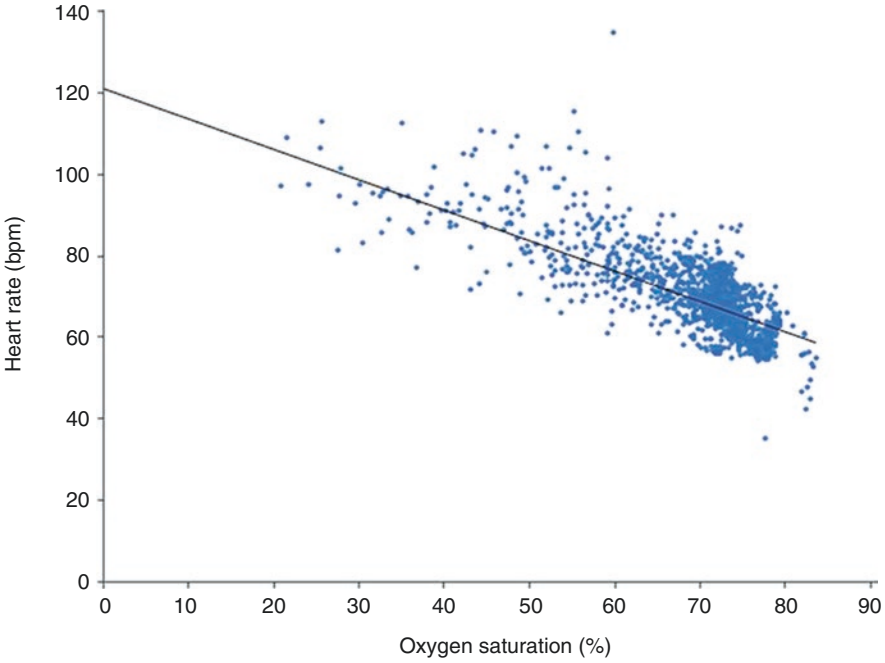

Fig. 3.2 Scatterplot of O_2 saturation and concurrent heart rate recorded over a 24-h period in a woman with an Eisenmenger VSD. There is a dynamic range of O_2 saturation that is inversely proportional to heart rate throughout the day, reflecting the fall in saturation and rise in heart rate with activity. The accuracy of percutaneous O_2 saturation monitors is much lower at low O_2 saturations

this range in mind, the haemoglobin level ought to reflect the overall burden of shunt in a given patient, similar to how haemoglobin A_{1C} indicates trends in blood glucose over time. However, many factors may disrupt the optimal haemoglobin/O_2 saturation relationship such that levels are lower than expected [7]. Other coping mechanisms include a shift in the P_{50} of the O_2 haemoglobin desaturation curve to promote tissue O_2 delivery [3, 8].

The effects of chronic cyanosis are evidenced across many organ systems [9]. These include abnormalities in myocardial blood flow [10, 11], retinal blood flow [12], uric acid handling [13] and kidney function [14, 15]. These vulnerabilities ought to be entertained in the context of any presenting new symptom or anticipated therapy.

3.3.2 Iron Deficiency

Iron deficiency is a common aetiology of an inadequate haemoglobin level [7]. It may be encountered in patients receiving excessive phlebotomy or those who have had significant bleeding events [3]. Because of a tendency towards macrocytosis in cyanotic patients, the mean corpuscular volume (MCV) is an inadequate screening test for iron deficiency, and a normal value does not indicate normal iron availability [16]. Instead, ferritin and transferrin saturation should be measured and followed. Despite theoretical concerns for decompensated erythropoiesis from excess iron, patients with evidence of iron deficiency should be offered iron supplementation until iron stores are replete [6, 17].

3.3.3 Hyperviscosity

While erythrocytosis should be viewed foremost as adaptive rather than maladaptive, there are potential drawbacks from excessive red cell production. Higher haematocrit raises blood viscosity, which may in theory compromise arteriolar blood flow and reduce O_2 delivery. Hence, there is a need for balance between adequate O_2 delivery and hyperviscosity.

There is much that is not understood about viscosity and its effects in ES. Measured viscosity in vitro correlates with haematocrit, yet symptoms and exertional capacity do not, and greater exercise capacity has been shown in those with higher haematocrit [3]. While there is an exponential rise in viscosity particularly at a haematocrit above 65%, viscosity varies considerably between different types of blood vessels and across different shear areas, adding to the complexities of understanding its impact on human blood flow. In fact SVR in hyperviscous conditions is determined by capillaries, not arterioles [18]. Some have argued in the past that haematocrit should be maintained below 65%, through phlebotomy if necessary, in order to avoid undesirable effects of viscosity. Yet there is little to substantiate such practice, and routine phlebotomy is neither necessary nor recommended.

Symptoms of hyperviscosity are nonspecific, and therefore alternative causes should be sought in a thorough clinical evaluation before phlebotomy is entertained as a therapeutic manoeuvre. A reasonable management strategy for a patient with

symptoms suspicious for hyperviscosity is to first offer hydration (oral or intravenous) and then remeasure the haematocrit. Phlebotomy should be reserved for rare situations where symptoms persist and the haematocrit remains elevated after fluid hydration, and only with further hydration thereafter using an equal volume of replacement saline.

Hyperviscosity may also affect coagulation properties, such as fibrinogen function [19]. Indeed, in the past, preoperative phlebotomy to improve coagulation has been recommended before elective surgery [20], as well as in response to haemoptysis [19]. Yet much more needs to be understood before such practices can be considered truly beneficial. Fundamentally, providers should recall that erythrocytosis is a necessary feature of the condition and, as such, the patient's own intrinsic erythropoietic mechanisms should be left undisturbed whenever possible.

3.3.4 Pulmonary Thrombosis and Haemoptysis

Both bleeding and thrombosis have been described with relatively high prevalence among ES. Specifically, PA thrombosis may be found in roughly 20% of patients [21, 22]. Epistaxis and haemoptysis are also not uncommon [1, 22–24]. Haemoptysis is a particular feature unique to ES and is often a cause of death, including in Dr. Eisenmenger's first index case [25]. There are several plausible mechanisms for haemoptysis, including microthrombi to the distal pulmonary vasculature, leading to infarction and arteriolar exposure to airways. Microthrombi may be due to venous emboli or fragments of chronic thrombosis in the large PAs [22]. The PAs are often dilated, either from volume loading secondary to left-to-right shunt in early life or from pressure loading as PVR rises. Atherosclerotic changes in the large-vessel walls, such as calcification, are not uncommon and are associated with PA thrombosis [26, 27]. Atherosclerotic changes, dilation and low velocity likely promote the formation of mural thrombi in situ, which in some cases may grow to be of considerable size [23]. Even in the absence of large-vessel thrombosis, peripheral lung perfusion abnormalities have been shown [27], which likely represent distal embolization of venous thrombi.

Unlike other PH cohorts, limited retrospective studies to date find no significant difference in vascular/bleeding events in ES with or without anticoagulation [27, 28], although these studies are small. Laboratory evidence of clotting factor derangements leading to both hypo- and hypercoagulability have been shown [29–31], though often these changes are subclinical.

Although anticoagulation is recommended in idiopathic PAH patients based on nonrandomized data [32], the same recommendation does not apply to ES. With evidence of both thrombosis and bleeding, there is a therapeutic paradox as to whether anticoagulation is beneficial [23]. Other factors to recall are that international normalized ratio (INR) measurement in a patient with increased haematocrit requires adjustment of the citrate volume in the collection vial before the blood is drawn, to account for the lower plasma volume. Experience with new oral anticoagulants has not been reported. Data are inadequate for making conclusive recommendations for either antiplatelet or anticoagulant therapy long term [33]. As such, most ES patients are not offered anticoagulation, unlike other PH subsets, unless there are secondary indications for doing so.

Treatment of haemoptysis is usually conservative. With quiet observation and use of cough suppressants and antibiotics (when there is any suspicion for bronchopneumonia), bleeding usually subsides with time. Blood products may be given to support the haematocrit to a level appropriate for their saturation [7] and correct any coagulation abnormalities if present. Bronchoscopy is not usually beneficial. Bronchial artery embolization has been pursued for refractory cases [34], though bronchial artery size does not correlate with thrombosis nor haemoptysis [26], and the practice should not be routinely utilized.

3.3.5 Non-haematologic Considerations

3.3.5.1 Cerebral Vascular Events

Cerebral vascular events are also somewhat unique to ES patients, but understandable in the setting of chronic right-to-left shunt and cyanosis. In a recent descriptive study using brain MRI, nearly half of the 72 patients' images showed evidence of a prior cerebral vascular injury, often in more than one territory [27]. Haematocrit, platelet count or iron levels were not different in affected individuals. These lesions could reflect either systemic embolization of thrombus or air (such as from an intravenous cannula) or ischaemia from inadequate tissue O_2 delivery. Causes of the latter could include suboptimal or supra-optimal haemoglobin, hypermetabolic states or poor systemic blood flow. Therefore, issues such as iron deficiency, epistaxis, haemoptysis, infection or systolic dysfunction may all be plausible triggers for cerebral events. Chronic right-to-left shunt also leaves patients vulnerable to cerebral abscess, a finding that is surprisingly common anecdotally in ES.

3.3.5.2 Pulmonary Mechanics and Gas Exchange

For most patients, supplemental O_2 will increase resting O_2 saturation by a few percentage points, reflecting some degree of pulmonary vasoreactivity despite the fact that cyanosis is driven by the intracardiac shunting. While supplemental O_2 may be helpful in acute situations or to provide relief of temporary symptoms such as headache, the majority of ES patients do not need continuous supplement of O_2. Some providers make the mistake of trying to restore normal saturation and overuse O_2 supplementation, a practice that is ineffective and unwarranted. Some patients may prefer to use supplemental O_2, though it may be counterproductive if it restricts their activity or leads to epistaxis.

Hypoxia drives hyperventilation and, thus, a tendency towards a resting respiratory alkalosis with a compensatory metabolic acidosis [35]. This is despite the coexisting shunt of circulating CO_2 from right to left, which in theory may compromise CO_2 clearance. Because of the natural tendency towards hyperventilation, conditions that may compromise ventilation should be avoided, such as excessive supplemental O_2, narcotics, pneumonia, etc.

3.3.6 Exercise Physiology

Not surprisingly, ES patients have the poorest maximal exercise capacity (measured by peak VO_2) of any congenital heart defect category [36]. All patients will be expected to show a drop in O_2 saturation during exercise, and there is typically a further drop in saturation for the first few minutes after rest. Baseline O_2 saturation is one of the strongest determinants of measured exertional capacity, but the range of O_2 saturation drop during exercise does not appear to be indicative of exercise performance or outcome.

Exercise is likely limited both by impaired systemic O_2 delivery and by compromised CO_2 clearance, as evidenced by the very high Ve/VCO_2 slopes demonstrated in ES [37]. Peak VO_2 however may not be the best differentiator of those with poorer exertional capacity [3, 38], possibly due to other factors that affect exercise capacity, including lung function, muscle strength or different patterns of intracardiac streaming. Submaximal exercise is also typically impaired and has been used as a differentiator of patients and/or as a more sensitive gauge of response to therapy than peak VO_2 [39].

3.3.6.1 Pulmonary Vasodilator Therapy

Unquestionably, ES patients benefit from pulmonary vasodilator therapy, particularly endothelin receptor antagonists (ERA) [40–42]. Favourable responses to each drug subclass have been described and are outlined [2], as summarized (Table 3.1). Most notably, the Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) study was the first randomized controlled trial in ES and a notable breakthrough in demonstrated treatment options for this group [42]. Since that time, several small nonrandomized studies have confirmed the findings. Published studies of disease targeting therapies in ES now involve a collective total of over 1000 patients (Table 3.1). They show consistently both initial and sustained improvement primarily in 6-minute walk distance (6MWD) [38], but also better functional class, lower PA pressure or PVR, lower BNP and even favourable changes in various metrics of RV function. Importantly, they do not show worsening of O_2 saturation, implying that the effects of potential SVR lowering, though present, are not detrimental. In fact some studies found improved resting O_2 saturation and haemoglobin [51, 52] in conjunction with the improved haemodynamics. The favourable effects appear independent of defect location [5] or complexity [48] and are also applicable in patients with trisomy 21 (Down syndrome) [58]. There is also gradually mounting evidence that combination therapy with more than one drug class is beneficial [56], consistent with the understanding that several pathways are involved in pulmonary vasodilatation, as discussed elsewhere in this volume (see Chap. 16).

In addition to improvements in submaximal exertional capacity and pulmonary haemodynamics [42], including sustained responses over time [46, 57], observational studies suggest that there is a survival advantage from pulmonary vasodilators [49]. Therefore, the collective literature strongly supports a policy of offering ES patients advanced therapies universally, including combination therapy when prudent or when indicated by progressive symptoms.

Table 3.1 Published studies of pulmonary vasoactive medications in Eisenmenger syndrome

First author	Year	Therapy	N	Follow-up	Improved variables	Comments
Galie[a] [42]	2006	Bosentan	54	4 months	6MWD, PVR	No change in O_2 saturation
Diller [43]	2007	Bosentan	15	2.3 years	6MWD and WHO class	Improvements persistent over time
van Loon [44]	2007	Bosentan	30[b]	2.7 years	6MWD	Improvement in children did not persist as long as adults
D'Alto [45]	2007	Bosentan	22	1 year	6MWD, PVR, PBF, SVR, SBF, O_2 saturation	
Gatzoulis [46]	2008	Bosentan	37	6 months	6MWD	Original placebo patients also improved, no change in O_2 saturation
Mehta [47]	2008	ERA	24	1.5 years	6MWD, PA pressure	
Diaz-Caraballo [48]	2009	Bosentan	10	2 years	6MWT and NYHA class	All with complex congenital defects
Berger [5]	2010	Bosentan	37	3.5 months	6MWD in both VSD and ASD	Drug effects independent of shunt position
Dimopoulos [49]	2010	All	229	4 years	Mortality	The majority of treated patients were on bosentan
Iversen[a] [41]	2010	Sildenafil + bosentan	21	9 months	6MWD, PBF and PVR	Sildenafil vs. placebo 3-month crossover, no further improvement
Garg [50]	2011	Sildenafil	22	6 months	6MWD, PA pressure, PVR, O_2 saturation	
Zhang [51]	2011	Sildenafil	84	12 months	6MWD, O_2 saturation, PA pressure and PVR	
Zuckerman [52]	2011	Ambrisentan	17	2.5 years	6MWD, exercise O_2 saturation, WHO class, haemoglobin	
Mukhopadhyay[a] [53]	2011	Tadalafil	28	6 weeks	6MWD, PVR, WHO class, pulmonary blood flow	

Table 3.1 (continued)

First author	Year	Therapy	N	Follow-up	Improved variables	Comments
Tay [54]	2011	Sildenafil	12	3 months	6MWD, NYHA class and CAMPHOR survey score	
Williams [39]	2012	Bosentan	24	3.3 years	6MWD (both in simple and complex)	No change in VO_2, O_2 saturation or BNP
Kaya [55]	2012	Bosentan	23	2 years	6MWD, WHO class, PA pressure by echo and echo function parameters	
D'Alto [56]	2012	Sildenafil + bosentan	32	6 months	6MWD, WHO class, PVR, BNP	
Diller [57]	2013	All	79	3.3 years	6MWD persistently, O_2 saturation	Two deaths during follow-up
Crepaz [58]	2013	Bosentan	7	4 weeks	6MWD, pulmonary acceleration time by echo	Down syndrome
D'Alto [59]	2013	Bosentan	74	12 months	Exercise and haemodynamics	Down syndrome compared to non-Down, both improved
Sun [60]	2013	Sildenafil	121	3.5 months	6MWD, haemoglobin, haemodynamics	15 patient deaths after 3 years. Sildenafil was independently associated with survival
Vis [61]	2013	Bosentan	57[b]	3.5 years	6MWD and stroke volume in those without Down syndrome	13 deaths during follow-up
Abd El Rahman[62]	2014	Bosentan	40	24 weeks	RV function by echocardiography, NT-proBNP	Changes were small. No change in estimated Qp/Qs

6MWD 6-min walk distance, *PA* pulmonary artery, *BNP* b-type natriuretic peptide, *PVR* pulmonary vascular resistance, *ERA* endothelin receptor antagonist, *WHO* World Health Organization, *NYHA* New York Heart Association

[a]Denotes a randomized controlled trial

[b]Denotes not all study participants were ES

3.3.7 Prognosis

Adults with ES are survivors of congenital defects that traditionally carry a very high mortality rate in childhood. Accurate prognostication in ES is difficult, in part because patients have already outlived previous expectations. Many recall being told they would not live to see their 18th birthday, yet anecdotally may continue to survive late into adult life, including some with survival into their sixth, seventh or even eighth decade. Hence, predicting survival in those who have already beaten the odds is somewhat misleading.

Cross-sectional cohort studies include a broad range of survivors, at various ages, from which a steady attrition can be demonstrated. Most published series are not true longitudinal studies and may include a survivorship (immortal time) bias [63]. ES patients die of many causes, including heart failure [64], haemoptysis [24, 25], sudden cardiac death [65] or even malignancy.

Recurring themes in published series are that prognosis worsens as pulmonary blood flow worsens, as evidenced by a lower O_2 saturation [38]. This is coupled with worse prognosis in the setting of ventricular dysfunction [66] or RA pressure [67], including as demonstrated through indirect markers such as BNP [4, 68]. Chronic load and hypoxia likely contribute to gradual fibrotic changes in the ventricle [69] and, eventually, deterioration of myocardial function. This also includes a predilection for arrhythmia [24, 65, 70]. As stated above, persistent RV loading may contribute to a more favourable prognosis in ES relative to those with other PH subtypes [71]. However, survival of both ES and non-ES PH is probably improved in the era of pulmonary vasodilators [49]. This survival advantage of ES compared to other PH still holds in some series [72], though not all [73].

Conclusions

The unique characteristics of ES set it apart from other forms of PH. Despite inherent vulnerabilities and risk, adaptations to chronic cyanosis allow some patients to have surprising longevity. The nuanced management of ES should be recognized by providers caring for these exceptional patients and their care preferably provided at or in conjunction with tertiary care centres.

References

1. Wood P (1958) The Eisenmenger syndrome or pulmonary hypertension with reversed central shunt. Br Med J 2(701–709):755–762
2. Beghetti M, Galie N (2009) Eisenmenger syndrome a clinical perspective in a new therapeutic era of pulmonary arterial hypertension. J Am Coll Cardiol 53:733–740
3. Broberg CS, Bax BE, Okonko DO, Rampling MW, Bayne S, Harries C, Davidson SJ, Uebing A, Khan AA, Thein S, Gibbs JS, Burman J, Gatzoulis MA (2006) Blood viscosity and its relation to iron deficiency, symptoms, and exercise capacity in adults with cyanotic congenital heart disease. J Am Coll Cardiol 48:356–365
4. Moceri P, Kempny A, Liodakis E, Alonso Gonzales R, Germanakis I, Diller GP, Swan L, Marino PS, Wort SJ, Babu-Narayan SV, Ferrari E, Gatzoulis MA, Li W, Dimopoulos K (2015)

Physiological differences between various types of Eisenmenger syndrome and relation to outcome. Int J Cardiol 179:455–460
5. Berger RM, Beghetti M, Galie N, Gatzoulis MA, Granton J, Lauer A, Chiossi E, Landzberg M (2010) Atrial septal defects versus ventricular septal defects in breathe-5, a placebo-controlled study of pulmonary arterial hypertension related to Eisenmenger's syndrome: a subgroup analysis. Int J Cardiol 144:373–378
6. Gatzoulis MA, Beghetti M, Landzberg MJ, Galie N (2014) Pulmonary arterial hypertension associated with congenital heart disease: recent advances and future directions. Int J Cardiol 177:340–347
7. Broberg CS, Jayaweera AR, Diller GP, Prasad SK, Thein SL, Bax BE, Burman J, Gatzoulis MA (2011) Seeking optimal relation between oxygen saturation and hemoglobin concentration in adults with cyanosis from congenital heart disease. Am J Cardiol 107:595–599
8. Harinck E, Hutter PA, Hoorntje TM, Simons M, Benatar AA, Fischer JC, de Bruijn D, Meijboom EJ (1996) Air travel and adults with cyanotic congenital heart disease. Circulation 93:272–276
9. Opotowsky AR (2015) Clinical evaluation and management of pulmonary hypertension in the adult with congenital heart disease. Circulation 131:200–210
10. Dedkov EI, Perloff JK, Tomanek RJ, Fishbein MC, Gutterman DD (2006) The coronary microcirculation in cyanotic congenital heart disease. Circulation 114:196–200
11. Warnes CA, Liberthson R, Danielson GK, Dore A, Harris L, Hoffman JI, Somerville J, Williams RG, Webb GD (2001) Task force 1: the changing profile of congenital heart disease in adult life. J Am Coll Cardiol 37:1170–1175
12. Tsui I, Shamsa K, Perloff JK, Lee E, Wirthlin RS, Schwartz SD (2009) Retinal vascular patterns in adults with cyanotic congenital heart disease. Semin Ophthalmol 24:262–265
13. Oya H, Nagaya N, Satoh T, Sakamaki F, Kyotani S, Fujita M, Nakanishi N, Miyatake K (2000) Haemodynamic correlates and prognostic significance of serum uric acid in adult patients with Eisenmenger syndrome. Heart 84:53–58
14. Wykretowicz A, Trojnarska O, Guzik P, Katarzyska A (2007) Arterial stiffness in adult patients with cyanotic congenital heart disease. Congenit Heart Dis 2:134–138
15. Diller GP, Alonso-Gonzalez R, Kempny A, Dimopoulos K, Inuzuka R, Giannakoulas G, Castle L, Lammers AE, Hooper J, Uebing A, Swan L, Gatzoulis M, Wort SJ (2012) B-type natriuretic peptide concentrations in contemporary Eisenmenger syndrome patients: predictive value and response to disease targeting therapy. Heart 98:736–742
16. Kaemmerer H, Fratz S, Braun SL, Koelling K, Eicken A, Brodherr-Heberlein S, Pietrzik K, Hess J (2004) Erythrocyte indexes, iron metabolism, and hyperhomocysteinemia in adults with cyanotic congenital cardiac disease. Am J Cardiol 94:825–828
17. Tay EL, Peset A, Papaphylactou M, Inuzuka R, Alonso-Gonzalez R, Giannakoulas G, Tzifa A, Goletto S, Broberg C, Dimopoulos K, Gatzoulis MA (2011) Replacement therapy for iron deficiency improves exercise capacity and quality of life in patients with cyanotic congenital heart disease and/or the Eisenmenger syndrome. Int J Cardiol 151(3):307–312
18. Rim SJ, Leong-Poi H, Lindner JR, Wei K, Fisher NG, Kaul S (2001) Decrease in coronary blood flow reserve during hyperlipidemia is secondary to an increase in blood viscosity. Circulation 104:2704–2709
19. Jensen AS, Johansson PI, Idorn L, Sorensen KE, Thilen U, Nagy E, Furenas E, Sondergaard L (2013) The haematocrit—an important factor causing impaired haemostasis in patients with cyanotic congenital heart disease. Int J Cardiol 167:1317–1321
20. Roos-Hesselink JW, Meijboom FJ, Spitaels SE (1999) Eisenmenger syndrome in adults. Ned Tijdschr Geneeskd 143:501–505
21. Silversides CK, Granton JT, Konen E, Hart MA, Webb GD, Therrien J (2003) Pulmonary thrombosis in adults with Eisenmenger syndrome. J Am Coll Cardiol 42:1982–1987
22. Broberg C, Ujita M, Bouzas B, Rubens M, Gibbs S, Prasad SK, Gatzoulis MA (2007) Pulmonary artery thrombosis in Eisenmenger syndrome is associated with ventricular dysfunction, neurohormonal activation, and poorer exercise capacity. Circulation 110:497
23. Broberg C, Ujita M, Babu-Narayan S, Rubens M, Prasad SK, Gibbs JS, Gatzoulis MA (2004) Massive pulmonary artery thrombosis with haemoptysis in adults with Eisenmenger's syndrome: a clinical dilemma. Heart 90:e63

24. Daliento L, Somerville J, Presbitero P, Menti L, Brach-Prever S, Rizzoli G, Stone S (1998) Eisenmenger syndrome. Factors relating to deterioration and death. Eur Heart J 19:1845–1855
25. Eisenmenger V (1897) Die angeborenen defekte der kammerscheidwand des herzens. Z Klin Med 32:1–28
26. Broberg CS, Ujita M, Prasad S, Li W, Rubens M, Bax BE, Davidson SJ, Bouzas B, Gibbs JS, Burman J, Gatzoulis MA (2007) Pulmonary arterial thrombosis in Eisenmenger syndrome is associated with biventricular dysfunction and decreased pulmonary flow velocity. J Am Coll Cardiol 50:634–642
27. Jensen AS, Idorn L, Thomsen C, von der Recke P, Mortensen J, Sorensen KE, Thilen U, Nagy E, Kofoed KF, Ostrowski SR, Sondergaard L (2015) Prevalence of cerebral and pulmonary thrombosis in patients with cyanotic congenital heart disease. Heart 101(19):1540–1546
28. Sandoval J, Santos LE, Cordova J, Pulido T, Gutierrez G, Bautista E, Martinez Guerra ML, Pena H, Broberg CS (2012) Does anticoagulation in Eisenmenger syndrome impact long-term survival? Congenit Heart Dis 7:268–276
29. Broberg CS, Uebing A, Cuomo L, Thein SL, Papadopoulos MG, Gatzoulis MA (2007) Adult patients with Eisenmenger syndrome report flying safely on commercial airlines. Heart 93:1599–1603
30. Jensen AS, Iversen K, Vejlstrup NG, Hansen PB, Sondergaard L (2009) Eisenmenger syndrome. Ugeskr Laeger 171:1270–1275
31. Ekert H, Gilchrist GS, Stanton R, Hammond D (1970) Hemostasis in cyanotic congenital heart disease. J Pediatr 76:221–230
32. Archer S, Rich S (2000) Primary pulmonary hypertension: a vascular biology and translational research "work in progress". Circulation 102:2781–2791
33. Jensen AS, Johansson PI, Bochsen L, Idorn L, Sorensen KE, Thilen U, Nagy E, Furenas E, Sondergaard L (2013) Response letter to: "Hypocoagulable" thromboelastography profiles in patients with cyanotic congenital heart disease: facts or technical artifacts? Int J Cardiol 168:4426
34. Yoon W, Kim JK, Kim YH, Chung TW, Kang HK (2002) Bronchial and nonbronchial systemic artery embolization for life-threatening hemoptysis: a comprehensive review. Radiographics 22:1395–1409
35. Broberg CS, Van Woerkom RC, Swallow E, Dimopoulos K, Diller GP, Allada G, Gatzoulis MA (2014) Lung function and gas exchange in Eisenmenger syndrome and their impact on exercise capacity and survival. Int J Cardiol 171:73–77
36. Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, Johansson B, Bouzas B, Mullen MJ, Poole-Wilson PA, Francis DP, Gatzoulis MA (2005) Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. Circulation 112:828–835
37. Dimopoulos K, Okonko DO, Diller GP, Broberg CS, Salukhe TV, Babu-Narayan SV, Li W, Uebing A, Bayne S, Wensel R, Piepoli MF, Poole-Wilson PA, Francis DP, Gatzoulis MA (2006) Abnormal ventilatory response to exercise in adults with congenital heart disease relates to cyanosis and predicts survival. Circulation 113:2796–2802
38. Kempny A, Dimopoulos K, Alonso-Gonzalez R, Alvarez-Barredo M, Tutarel O, Uebing A, Piatek P, Marino P, Swan L, Diller GP, Wort SJ, Gatzoulis MA (2013) Six-minute walk test distance and resting oxygen saturations but not functional class predict outcome in adult patients with Eisenmenger syndrome. Int J Cardiol 168:4784–4789
39. Williams R, Houser L, Miner P, Aboulhosn J (2012) Efficacy and safety of bosentan in adults with simple and complex Eisenmenger's syndrome. Congenit Heart Dis 7:12–15
40. Duffels MG, Vis JC, van Loon RL, Nieuwkerk PT, van Dijk AP, Hoendermis ES, de Bruin-Bon RH, Bouma BJ, Bresser P, Berger RM, Mulder BJ (2009) Effect of bosentan on exercise capacity and quality of life in adults with pulmonary arterial hypertension associated with congenital heart disease with and without down's syndrome. Am J Cardiol 103:1309–1315
41. Iversen K, Jensen AS, Jensen TV, Vejlstrup NG, Sondergaard L (2010) Combination therapy with bosentan and sildenafil in Eisenmenger syndrome: a randomized, placebo-controlled, double-blinded trial. Eur Heart J 31:1124–1131

42. Galie N, Beghetti M, Gatzoulis MA, Granton J, Berger RM, Lauer A, Chiossi E, Landzberg M (2006) Bosentan Randomized Trial of Endothelin Antagonist Therapy I. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. Circulation 114:48–54
43. Diller GP, Dimopoulos K, Kaya MG, Harries C, Uebing A, Li W, Koltsida E, Gibbs JS, Gatzoulis MA (2007) Long-term safety, tolerability and efficacy of bosentan in adults with pulmonary arterial hypertension associated with congenital heart disease. Heart 93:974–976
44. van Loon RL, Hoendermis ES, Duffels MG, Vonk-Noordegraaf A, Mulder BJ, Hillege HL, Berger RM (2007) Long-term effect of bosentan in adults versus children with pulmonary arterial hypertension associated with systemic-to-pulmonary shunt: does the beneficial effect persist? Am Heart J 154:776–782
45. D'Alto M, Vizza CD, Romeo E, Badagliacca R, Santoro G, Poscia R, Sarubbi B, Mancone M, Argiento P, Ferrante F, Russo MG, Fedele F, Calabro R (2007) Long term effects of bosentan treatment in adult patients with pulmonary arterial hypertension related to congenital heart disease (Eisenmenger physiology): safety, tolerability, clinical, and haemodynamic effect. Heart 93:621–625
46. Gatzoulis MA, Beghetti M, Galiè N, Granton J, Berger RM, Lauer A, Chiossi E, Landzberg M, BREATHE-5 Investigators (2008) Longer-term bosentan therapy improves functional capacity in Eisenmenger syndrome: results of the breathe-5 open-label extension study. Int J Cardiol 127:27–32
47. Mehta PK, Simpson L, Lee EK, Lyle TA, McConnell ME, Book WM (2008) Endothelin receptor antagonists improve exercise tolerance and oxygen saturations in patients with Eisenmenger syndrome and congenital heart defects. Tex Heart Inst J 35:256–261
48. Diaz-Caraballo E, Gonzalez-Garcia AE, Renones M, Sanchez-Recalde A, Garcia-Rio F, Oliver-Ruiz JM (2009) Long-term bosentan treatment of complex congenital heart disease and Eisenmenger's syndrome. Rev Esp Cardiol 62:1046–1049
49. Dimopoulos K, Inuzuka R, Goletto S, Giannakoulas G, Swan L, Wort SJ, Gatzoulis MA (2010) Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension. Circulation 121:20–25
50. Garg N, Tripathy N, Sinha N (2011) Comparative efficacy of sildenafil in Eisenmenger's syndrome secondary to atrial septal defect versus ventricular septal defect: a cardiac catheterisation follow-up study. Cardiol Young 21:631–638
51. Zhang ZN, Jiang X, Zhang R, Li XL, Wu BX, Zhao QH, Wang Y, Dai LZ, Pan L, Gomberg-Maitland M, Jing ZC (2011) Oral sildenafil treatment for Eisenmenger syndrome: a prospective, open-label, multicentre study. Heart 97:1876–1881
52. Zuckerman WA, Leaderer D, Rowan CA, Mituniewicz JD, Rosenzweig EB (2011) Ambrisentan for pulmonary arterial hypertension due to congenital heart disease. Am J Cardiol 107:1381–1385
53. Mukhopadhyay S, Nathani S, Yusuf J, Shrimal D, Tyagi S (2011) Clinical efficacy of phosphodiesterase-5 inhibitor tadalafil in Eisenmenger syndrome—a randomized, placebo-controlled, double-blind crossover study. Congenit Heart Dis 6:424–431
54. Tay EL, Papaphylactou M, Diller GP, Alonso-Gonzalez R, Inuzuka R, Giannakoulas G, Harries C, Wort SJ, Swan L, Dimopoulos K, Gatzoulis MA (2011) Quality of life and functional capacity can be improved in patients with Eisenmenger syndrome with oral sildenafil therapy. Int J Cardiol 149:372–376
55. Kaya MG, Lam YY, Erer B, Ayhan S, Vatankulu MA, Nurkalem Z, Meric M, Eren M, Eryol NK (2012) Long-term effect of bosentan therapy on cardiac function and symptomatic benefits in adult patients with Eisenmenger syndrome. J Card Fail 18:379–384
56. D'Alto M, Romeo E, Argiento P, Sarubbi B, Santoro G, Grimaldi N, Correra A, Scognamiglio G, Russo MG, Calabro R (2012) Bosentan-sildenafil association in patients with congenital heart disease-related pulmonary arterial hypertension and Eisenmenger physiology. Int J Cardiol 155:378–382
57. Diller GP, Alonso-Gonzalez R, Dimopoulos K, Alvarez-Barredo M, Koo C, Kempny A, Harries C, Parfitt L, Uebing AS, Swan L, Marino PS, Wort SJ, Gatzoulis MA (2013) Disease targeting therapies in patients with Eisenmenger syndrome: response to treatment and long-term efficiency. Int J Cardiol 167:840–847

58. Crepaz R, Romeo C, Montanaro D, De Santis S (2013) Long-term results of treatment with bosentan in adult Eisenmenger's syndrome patients with down's syndrome related to congenital heart disease. BMC Cardiovasc Disord 13:74
59. D'Alto M, Romeo E, Argiento P, D'Andrea A, Sarubbi B, Correra A, Scognamiglio G, Papa S, Bossone E, Calabro R, Vizza CD, Russo MG (2013) Therapy for pulmonary arterial hypertension due to congenital heart disease and down's syndrome. Int J Cardiol 164:323–326
60. Sun YJ, Yang T, Zeng WJ, Gu Q, Ni XH, Zhao ZH, Liu ZH, Xiong CM, He JG (2013) Impact of sildenafil on survival of patients with Eisenmenger syndrome. J Clin Pharmacol 53:611–618
61. Vis JC, Duffels MG, Mulder P, de Bruin-Bon RH, Bouma BJ, Berger RM, Hoendermis ES, van Dijk AP, Mulder BJ (2013) Prolonged beneficial effect of bosentan treatment and 4-year survival rates in adult patients with pulmonary arterial hypertension associated with congenital heart disease. Int J Cardiol 164:64–69
62. Abd El Rahman MY, Rentzsch A, Scherber P, Mebus S, Miera O, Balling G, Bottler P, Dubowy KO, Farahwaschy B, Hager A, Kreuder J, Peters B, Berger F, Schulze-Neick I, Abdul-Khaliq H (2014) Effect of bosentan therapy on ventricular and atrial function in adults with Eisenmenger syndrome. A prospective, multicenter study using conventional and Speckle tracking echocardiography. Clin Res Cardiol 103:701–710
63. Diller GP, Kempny A, Inuzuka R, Radke R, Wort SJ, Baumgartner H, Gatzoulis MA, Dimopoulos K (2014) Survival prospects of treatment naive patients with Eisenmenger: a systematic review of the literature and report of own experience. Heart 100:1366–1372
64. Saha A, Balakrishnan KG, Jaiswal PK, Venkitachalam CG, Tharakan J, Titus T, Kutty R (1994) Prognosis for patients with Eisenmenger syndrome of various aetiology. Int J Cardiol 45:199–207
65. Koyak Z, Harris L, de Groot JR, Silversides CK, Oechslin EN, Bouma BJ, Budts W, Zwinderman AH, Van Gelder IC, Mulder BJ (2012) Sudden cardiac death in adult congenital heart disease. Circulation 126:1944–1954
66. Moceri P, Dimopoulos K, Liodakis E, Germanakis I, Kempny A, Diller GP, Swan L, Wort SJ, Marino PS, Gatzoulis MA, Li W (2012) Echocardiographic predictors of outcome in Eisenmenger syndrome. Circulation 126:1461–1468
67. Oya H, Nagaya N, Uematsu M, Satoh T, Sakamaki F, Kyotani S, Sato N, Nakanishi N, Miyatake K (2002) Poor prognosis and related factors in adults with Eisenmenger syndrome. Am Heart J 143:739–744
68. Reardon LC, Williams RJ, Houser LS, Miner PD, Child JS, Aboulhosn JA (2012) Usefulness of serum brain natriuretic peptide to predict adverse events in patients with the Eisenmenger syndrome. Am J Cardiol 110:1523–1526
69. Broberg CS, Prasad SK, Carr C, Babu-Narayan SV, Dimopoulos K, Gatzoulis MA (2014) Myocardial fibrosis in Eisenmenger syndrome: a descriptive cohort study exploring associations of late gadolinium enhancement with clinical status and survival. J Cardiovasc Magn Reson 16:32
70. Cantor WJ, Harrison DA, Moussadji JS, Connelly MS, Webb GD, Liu P, McLaughlin PR, Siu SC (1999) Determinants of survival and length of survival in adults with Eisenmenger syndrome. Am J Cardiol 84:677–681
71. Hopkins WE, Ochoa LL, Richardson GW, Trulock EP (1996) Comparison of the hemodynamics and survival of adults with severe primary pulmonary hypertension or Eisenmenger syndrome. J Heart Lung Transplant 15:100–105
72. Manes A, Palazzini M, Leci E, Bacchi Reggiani ML, Branzi A, Galie N (2014) Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: a comparison between clinical subgroups. Eur Heart J 35:716–724
73. Bonello B, Renard S, Mancini J, Hubert S, Habib G, Fraisse A (2014) Life span of patients with Eisenmenger syndrome is not superior to that of patients with other causes of pulmonary hypertension. Cardiovasc Diagn Ther 4:341–349

PAH in Patients with Prevalent Systemic–Pulmonary Shunts and PAH in Patients with Small Cardiac Defects

4

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Abbreviations

APVR	anomalous pulmonary venous return
CHD	congenital heart disease
ES	Eisenmenger syndrome
PAH–CHD	pulmonary arterial hypertension related to congenital heart disease
PAP	pulmonary artery pressure
PH	pulmonary hypertension
PVD	pulmonary vascular disease
PVR	pulmonary vascular resistance
PVRi	pulmonary vascular resistance indexed
RCT	randomized controlled trial
RV	right ventricle
SPs	systemic-to-pulmonary shunts
SVR	systemic vascular resistance
VSD	ventricular septal defect
WHO	World Health Organization

4.1 Introduction

Pulmonary arterial hypertension (PAH) is a severe and well-known complication of congenital heart disease (CHD), specifically of CHD with systemic-to-pulmonary shunts (SPs). Large SPs expose the pulmonary vasculature to increased blood flow and, in post-tricuspid SPs, also to increased pressure [1, 2]: the persistent pulmonary volume

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and pressure overload induces endothelial dysfunction and vascular remodelling, leading to obstructive structural changes of the distal pulmonary arteries with progressive increase of pulmonary vascular resistance (PVR); when PVR approaches or exceeds systemic vascular resistance (SVR), the shunt becomes reversed (pulmonary-to-systemic) or bidirectional and the patient develops Eisenmenger syndrome (ES) [3].

A large proportion of patients with relevant SPs develops pulmonary vascular disease (PVD) and PAH, which can become irreversible if not treated early. ES represents the most advanced form of PAH associated with CHD (PAH–CHD), characterized by irreversible PVD. It has to be emphasized that, despite being a life-threatening complication with an adverse impact on quality of life and survival prospects [3–6], PAH–CHD also represents a preventable form of PAH: in the recent decades, advances in diagnostic procedures and cardiac surgery have resulted in the prevention of PAH in most children with CHD and SPs in Western countries; this is, unfortunately, not yet the case in developing countries. A wide spectrum of CHDs may be associated with PAH. Indeed, PAH–CHD is a heterogeneous group of clinical conditions, ranging from systolic pulmonary hypertension (PH) in patients with significant left-right shunting and massive pulmonary blood flow, to a variety of phenotypes characterized by different extent of PVR increase [7–9]. Moreover, a significant proportion of CHD patients who are repaired successfully and survive into adulthood may develop PAH [8, 10]. This remarkable heterogeneity has prevented the evidence-based identification of the "appropriate therapeutic approach" in most patients, and, thus, treatment algorithms remain a challenge in this field.

4.2 Classification of PAH Associated with Systemic-to-Pulmonary Shunts

In the clinical classification of PH [2] (Table 4.1), patients with congenital SPs were included among the associated forms of PAH (group 1 of the clinical classification of PH): in fact, apart from the presence of CHD and its pathophysiological consequences, the histopathological changes of PAH–CHD are identical to those observed in all other PAH conditions.

Because of the extreme clinical heterogeneity of PAH–CHD [9], a clinical subclassification was proposed at the 4th World Symposium on PH in 2009 [11]; it was updated in 2013 [12] and recently adopted by the 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines for the diagnosis and treatment of PH [2] (Table 4.2). In this classification, PAH–CHD was grouped on the basis of its clinical presentation and pathophysiology into four broad

Table 4.1 Comprehensive clinical classification of pulmonary hypertension [2]

1. *Pulmonary arterial hypertension*
1.1. Idiopathic
1.2. Heritable
1.2.1. BMPR2 mutation
1.2.2. Other mutations

Table 4.1 (continued)

1.3. Drugs and toxins induced
1.4. Associated with:
1.4.1. Connective tissue disease
1.4.2. HIV infection
1.4.3. Portal hypertension
1.4.4. Congenital heart disease
1.4.5. Schistosomiasis
1′. *Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis*
1′.1. Idiopathic
1′.2. Heritable
1′.2.1. EIF2AK4 mutation
1′.2.2. Other mutations
1′.3. Drugs, toxins and radiation induced
1′.4. Associated with:
1′.4.1. Connective tissue disease
1′.4.2. HIV infection
1″. *Persistent pulmonary hypertension of the newborn*
2. *Pulmonary hypertension due to left heart disease*
2.1. Left ventricular systolic dysfunction
2.2. Left ventricular diastolic dysfunction
2.3. Valvular disease
2.4. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
2.5. Congenital/acquired pulmonary veins stenosis
3. *Pulmonary hypertension due to lung diseases and/or hypoxia*
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4. Sleep-disordered breathing
3.5. Alveolar hypoventilation disorders
3.6. Chronic exposure to high altitude
3.7. Developmental lung diseases
4. *Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions*
4.1. Chronic thromboembolic pulmonary hypertension
4.2. Other pulmonary artery obstructions
4.2.1. Angiosarcoma
4.2.2. Other intravascular tumours
4.2.3. Arteritis
4.2.4. Congenital pulmonary arteries stenoses
4.2.5. Parasites (hydatidosis)
5. *Pulmonary hypertension with unclear and/or multifactorial mechanisms*
5.1. Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
5.2. Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, neurofibromatosis
5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4. Others: pulmonary tumoral thrombothic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

BMPR2 bone morphogenetic protein receptor, type 2, *EIF2AK4* eukaryotic translation initiation factor 2 alpha kinase 4, *HIV* human immunodeficiency virus

Table 4.2 Clinical classification of pulmonary arterial hypertension associated with congenital heart disease [2]

1.	*Eisenmenger syndrome*
	Includes all large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of PVR and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis and multiple organ involvement are usually present
2.	*PAH associated with prevalent systemic-to-pulmonary shunts*
	• Correctable[a]
	• Non-correctable
	Includes moderate-to-large defects; PVR is mildly to moderately increased, systemic-to-pulmonary shunting is still prevalent, whereas cyanosis at rest is not a feature
3.	*PAH with small/coincidental defects*[b]
	Marked elevation in PVR in the presence of small cardiac defects (usually ventricular septal defects <1 cm and atrial septal defects <2 cm of effective diameter assessed by echo), which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. Closing the defects is contraindicated
4.	*PAH after defect correction*
	Congenital heart disease is repaired, but PAH either persists immediately after correction or recurs/develops months or years after correction in the absence of significant postoperative haemodynamic lesions

PAH pulmonary arterial hypertension, *PVR* pulmonary vascular resistance
[a]With surgery or intravascular percutaneous procedure
[b]The size applies to adult patients. However, also in adults the simple diameter may be not sufficient for defining the haemodynamic relevance of the defect and also the pressure gradient, the shunt size and direction and the pulmonary-to-systemic flow ratio should be considered

phenotypes: ES (group 1), PAH associated with still prevalent SPs (group 2), PAH with small, coincidental CHD (group 3) and postoperative PAH (group 4).

This classification clearly does not embrace all forms of PH and PAH associated with CHD. Nevertheless, it has the advantage of being clinical and simple, thus, widely applicable, allowing easy categorization of the vast majority of patients with PAH–CHD according to practical information. The clinical classification of PAH–CHD patients may also help to collect more uniform and consistent data among different centres, thus, facilitating standardization of treatment and multicentre collaborations, overcoming limitations of sample size. In particular, it may favour the planning of randomized controlled clinical trials (RCTs), which would be very useful in defining the real potential of emerging therapies targeting PVD in this peculiar PAH population and, especially specific subgroups.

Each of the four PAH–CHD subgroups has distinct pathophysiological features and may, thus, differ in their management and overall outcome. Much of the recent progress in PAH–CHD has focused on the extreme end of the disease spectrum, namely, on ES patients (group 1): the demographic, clinical, haemodynamic and prognostic characteristics of ES patients have been extensively described [3, 5, 13], and a specific RCT documented the favourable effects of the dual endothelin-1 receptor antagonist bosentan in this specific PAH–CHD subgroup [14]. Patients with postoperative PAH without residual shunts (group 4) were included in most of the pivotal RCTs performed to assess the effects of targeted therapies in PAH, and subgroup

analysis has shown consistent therapeutic effects regardless of PAH aetiology. Unfortunately, little information is available on the characteristics of patients with PAH associated with persistent SPs (group 2) and PAH associated with small cardiac defects (group 3).

This chapter focuses on the clinical peculiarities of these two PAH–CHD subgroups.

4.3 PAH in Patients with Prevalent Systemic–Pulmonary Shunts and PAH in Patients with Small Cardiac Defects

PAH–CHD with prevalent SPs (group 2) and PAH–CHD with small cardiac defects (group 3) represent two intermediate clinical groups, included between the extreme ends of the *classical ES* (patients with reversed or bidirectional shunting through a large cardiac defect, which is considered inoperable) and the *postoperative PAH–CHD* (patients who maintain or develop PAH early or late after repair of a cardiac defect in the absence of significant residual lesions).

An underlying genetic predisposition and/or constitutional susceptibility towards developing PAH has been hypothesized in both groups 2 and 3 of the PAH–CHD spectrum. In fact, only a minority of patients with small cardiac defects (group 3) or with pre-tricuspid SPs (group 2) are expected to develop PAH and PVD, suggesting that there are additional factors influencing the development of PVD besides the presence of the cardiac defect and its pathophysiological consequences (see also Chaps. 1.3 and 1.4, and Fig. 1.5). Even in large post-tricuspid SPs (group 2), in which "flooding" of the lungs with combined volume and pressure overload is sufficient to explain the development of PVD, further underlying factors may interfere with the clinical course of the disease: in fact, some of these patients maintain a prevalent left-right shunt until their teens and beyond, while others develop an Eisenmenger phenotype earlier than expected during infancy. Furthermore, patients with Down syndrome are generally prone to develop PVD earlier in infancy compared with their non-Down counterparts [16]. Despite the clear clinical evidence of a different response of the pulmonary vascular bed to similar haemodynamic stimuli, the specific genetic or constitutional traits implicated in the predisposition to PVD and PAH are still unknown. In particular, mutations in genes causing heritable PAH are exceptionally found in patients with PAH–CHD [15–17], thus, excluding this potential linkage.

From the epidemiological standpoint, patients belonging to group 2 and group 3 represent a small percentage of the total PAH–CHD population: in different series, their prevalence is significantly lower as compared to that of ES and postoperative PAH patients [9, 18]. As a consequence, little data is available on the characteristics of these PAH–CHD subgroups, and the treatment strategy currently adopted is neither standardized nor evidence-based. Despite the lack of formal evidence of efficacy, PAH-specific treatments are currently utilized in PAH patients with small cardiac defects (as their disease course can be more aggressive than ES and bears similarities to idiopathic PAH) and in patients with prevalent SPs and a raised PVR,

for whom surgery is contraindicated (with the aim to avoid or limit further progression of the PVD).

Herein, we discuss separately the clinical and management peculiarities of these two specific subgroups of PAH–CHD patients.

4.4 PAH Associated with Prevalent Systemic–Pulmonary Shunts

PAH associated with persistent SPs includes patients with sizeable defects and mild-to-moderate PAH who shunt predominantly left-to-right and are not cyanosed at rest (i.e. patients who have not developed reversal of shunting). Pre-tricuspid shunts are the most frequent defects in this group [9]. Reversal of the shunt (pulmonary-to-systemic) may occur over time as a result of a gradual increase in right atrial pressure due to right ventricular failure secondary to chronic volume overload, severe tricuspid regurgitation directing blood through the defect or due to progression of the pulmonary vascular changes with elevation of PVR. Indeed, shunt reversal is often considered a marker of irreversible PVD and a formal contraindication to CHD correction.

4.4.1 Prognostic Relevance of the Appropriate Identification of Correctable versus Non-correctable CHD

PAH associated with prevalent SPs are an intermediate condition between SPs with normal PVR and ES, the more advanced form of PVD. In fact, patients with moderate-to-large defects can have PH without having advanced PVD in terms of permanent and extensive changes in their pulmonary vascular bed [19, 20]. Indeed, in many patients with a high pulmonary blood flow, mean pulmonary artery pressure may be raised while maintaining a normal PVR; in these patients the defect is correctable (see Fig. 1.5, Chap. 1). The possibility to close a defect is undoubtedly a crucial issue with considerable clinical and prognostic relevance. Timely correction of CHD improves long-term prognosis by preventing the progression to permanent irreversible pulmonary vascular obstructive lesions, as observed in ES. In addition, recent advances in surgical and percutaneous treatment of CHD allow the repair of even complex defects, with reduced perioperative morbidity and mortality. Despite these favourable considerations, it should be emphasized that in some patients, an underlying predisposition to develop PAH may be triggered by the presence of a SPs and PAH may develop later on in life, even after timely repair of a defect in the absence of a significant residual shunt [21]. This means that in patients with high genetic or constitutional susceptibility towards developing PAH, the progression towards PAH and PVD may not be altered by early surgical or percutaneous interventions. In these patients, successful defect closure and a good short-term outcome are not necessarily predictive of a satisfactory long-term result. An unfavourable long-term outcome is more frequently expected when defect repair is performed in

patients who have already developed "significant" PVD. Pulmonary vascular lesions and right ventricular dysfunction often progress in the weeks, months or years after defect closure, and patients with post-repair PAH have a worse long-term prognosis compared to ES patients [9], despite the presence of more severe PAH in the latter. In fact, in ES, the defect is thought to act as a "relief valve" for the right ventricle (RV) and may help maintain systemic output at the expense of cyanosis.

In the recently updated clinical classification of PAH–CHD [2] (Table 4.2), the subgroup "PAH associated with prevalent SPs" includes two specific categories of patients according to operability status:

1. Patients with correctable CHD (with surgery or intravascular percutaneous procedure)
2. Patients with non-correctable CHD

Deciding which patient may be suitable for and will benefit from surgical or percutaneous closure requires significant expertise, and in some patients the crucial question "can the shunt be closed?" often remains essentially unanswered.

In everyday clinical practice, the question of operability typically arises in older children and adults with large post-tricuspid SPs [ventricular septal defects (VSD) or patent ductus arteriosus (PDA)] and in selected patients (mostly adults) with shunts at atrial level (pre-tricuspid) who present with raised PVR. In patients with *post-tricuspid SPs*, the repair of the defect leads to normalization of pulmonary pressure when performed early enough, before the development of PVD: most patients with large post-tricuspid SPs develop pulmonary vascular lesions within their first 1–2 years of life, hence the urgency to establish this diagnosis and intervene very early. In *pre-tricuspid SPs*, the response of the pulmonary vasculature to persistent high pulmonary blood flow may not be uniform and may not occur in a predictable fashion. This results in difficulties when making decisions regarding the operability of these defects, particularly in patients who present beyond childhood with a raised PVR. Advances in paediatric cardiology and the rapid evolution of paediatric cardiac surgery and interventional cardiology in the last five decades have led to an improvement in early identification and treatment of these SPs, therefore preventing the development of PVD in most cases. However, in some individuals, mostly in developing countries, both post- and pre-tricuspid SPs may pass undetected until childhood or even adulthood and are diagnosed late when PVD has already developed.

Even through progress in surgical and interventional techniques has meant that most CHD can, nowadays, be easily repaired with low procedural risks, this should not be the only indication for surgery. In fact, an approach based on the assumption that closing the defect will improve symptoms and prognosis regardless of age and preoperative haemodynamics is definitely questionable, and serious concerns are raised by evidence of an unfavourable outcome after CHD correction in many case reports and case series [9, 22–24]. Data from a case series of 38 patients showed that one-fifth of patients had a poor short-term outcome following surgical closure of their VSD in the presence of elevated preoperative PVR: five patients died

Table 4.3 Demographic clinical, pathological, functional and haemodynamic characteristics of 192 patients with pulmonary arterial hypertension associated with congenital heart disease, according to clinical subgroups [9]

Characteristic	Eisenmenger syndrome	PAH with systemic-to-pulmonary shunt	PAH with small defects	PAH after defect correction	*P*-value
Patients, *n* (%)	90 (47)	48 (25)	10 (5)	44 (23)	N/A
Age, years	41 ± 16	47 ± 18	25 ± 21	36 ± 17	0.0002
Female sex, *n* (%)	56 (63)	34 (71)	6 (60)	20 (45)	0.08
PAH diagnosis to referral[a], *n* (%)					
≥0 to <1 year	29 (33)	29 (60)	6 (60)	26 (59)	<0.001
≥1 to <5 year	2 (2)	4 (8)	1 (10)	8 (19)	
≥5 year	59 (65)	15 (31)	3 (30)	10 (22)	
Type of the defect, *n* (%)					
Atrial septal defect	10 (11)	22 (46)	4 (40)	12 (27)	0.0001
Ventricular septal defect	36 (40)	10 (21)	5 (50)	18 (41)	0.106
Patent ductus arteriosus	15 (17)	0	0	3 (7)	0.009
Partial APVR-isolated	0	3 (6)	0	0	0.035
Partial APVR + atrial septal defect	3 (3)	10 (21)	0	3 (7)	0.004
Other combined[b]	11 (12)	2 (4)	1 (10)	2 (5)	0.393
Complex[c]	15 (17)	1 (2)	0	6 (13)	0.058
6-min walk distance (m)	367 ± 108	420 ± 128	406 ± 130	415 ± 136	0.0661
Borg dyspnoea score	5 ± 3	4 ± 3	4 ± 2	5 ± 3	0.0961
WHO functional class, *n* (%)					
Class I	5 (5)	4 (8)	0	2 (5)	0.641
Class II	23 (26)	20 (42)	4 (40)	16 (36)	
Class III	61 (68)	24 (50)	6 (60)	26 (59)	
Class IV	1 (1)	0	0	0	
Mean right atrial pressure	7 ± 4	7 ± 3	5 ± 2	10 ± 6	<0.0001
Mean pulmonary artery pressure (mmHg)	80 ± 20	52 ± 19	67 ± 34	64 ± 18	<0.0001

Table 4.3 (continued)

Characteristic	Eisenmenger syndrome	PAH with systemic-to-pulmonary shunt	PAH with small defects	PAH after defect correction	*P*-value
Pulmonary vascular resistance (dyn/s/cm^5)	1904 ± 940	721 ± 743	1078 ± 650	1182 ± 693	<0.0001
Systemic cardiac index (L/min/m^2)	2.5 ± 1.3	2.2 ± 0.7	2.3 ± 0.9	2.6 + 1.0	0.3594

All data are presented as means ± SD unless otherwise stated
PAH pulmonary arterial hypertension, *APVR* anomalous pulmonary venous return, *WHO* World Health Organization, *N/A* not applicable
[a]Time from the first right heart catheterization diagnostic for pulmonary arterial hypertension to referral to a PAH centre
[b]Any combination of defects other than APVR with atrial septal defect
[c]Atrioventricular septal defects or univentricular pathophysiology

immediately after surgery, one died 6 months later, and two were reported to have persistent severe PAH [23]. Longer-term data from this cohort are lacking, but there is legitimate concern that patients with established PVD have a prognosis that is unlikely to be favourably influenced by surgical intervention. More recently, the clinical characteristics and comparative survival data of a large cohort of PAH–CHD patients classified according to the four clinical subgroups were analysed (Table 4.3) [9]. This study clearly showed that patients with PAH after cardiac defect correction have a far worse outcome than any other type of PAH–CHD. In particular, patients with ES (group 1) had the best survival rate, similar to patients with PAH associated with SPs (group 2) and significantly better compared to postoperative PAH patients (group 3). In the latter, PAH was detected after a median of 16.9 years from cardiac defect correction, and the reasons for the initiation and progression of PAH include a delayed correction of the defect, that may have occurred when the PVD had already developed. In fact, this group was characterized by a predominance of post-tricuspid shunts (72.7%), and median age at correction was 11.0 years. The reasons for the worse prognosis of postoperative PAH patients compared with ES patients are unclear, but may include the lack of a "relief valve" for the RV when PVR is elevated: in fact, closure of the defect prevents both the decompression of the RV and the maintenance of systemic cardiac output through right–left shunting. Another possible reason for the worse prognosis observed in this group is the impaired adaptation of the RV to an increasing afterload, when PVD develops after the first months/years of life. This last hypothesis is supported by the presence of a higher right atrial

pressure (preload) despite a lower PVR (afterload) in patients with corrected defects compared with ES patients in this study (Table 4.3). It is noteworthy that the survival curve of patients with postoperative PAH starts to diverge from that of ES patients at approximately 2–5 years after the first diagnosis of PAH, but the largest difference between the two curves is observed after 10–12 years. Data on PAH–CHD from the *Registry to Evaluate Early And Long-term Pulmonary Arterial Hypertension Disease Management* (REVEAL) showed no survival difference between paediatric PAH patients with unrepaired and repaired defects during the first few years after correction (2-year survival estimated as 86 + 7% vs. 85 + 5%) [25]. However, in the British PAH paediatric registry, longer-term follow-up data (up to 5 years) were collected, and a worse survival was reported in children with repaired defects compared to ES patients [22], thus, confirming the limited prognostic relevance of any favourable short-term results of corrective intervention. These findings should be considered when planning medical or interventional treatment strategies in PAH–CHD patients. In a recent study on PAH–CHD, retrospectively assessing the preoperative haemodynamic profile of patients who developed PAH late after shunt closure, high baseline values of PVR (≥5 WU), pulmonary vascular resistance indexed (PVRi) (≥6 WU × m^2) and PVR/SVR (≥0.33) were common findings, supporting the need for a cautious approach in subjects with PVD [26]. In conclusion, in patients with PAH and moderate-to-large defects who are still shunting left to right at rest, the correction of the cardiac defect may not necessarily have favourable effects in terms of long-term mortality and morbidity. In particular, there is legitimate concern that patients with advanced PVD may have a prognosis that is unlikely to be favourably influenced by surgery or intervention. The appropriate identification of correctable CHD, namely, of patients likely to have a clear and long-standing benefit from CHD correction, requires significant expertise, and current PH guidelines recommend the individual evaluation of these patients in tertiary centres.

4.4.2 Assessment of Operability

The operability of CHD with SPs depends on the severity of the PVD induced by the increased pulmonary blood flow and pulmonary arterial pressure: the presence of vascular changes results in a high operative risk and a poor long-term outcome. On the other hand, if surgery is felt to be contraindicated and the SPs persists, pulmonary vascular changes may progress further. These potential outcomes and the benefit-to-risk ratio should be considered when deciding whether to perform corrective surgery (see also Chap. 1.4).

At present, the biggest problem in the assessment of operability remains the lack of evidence-based pathological, clinical or haemodynamic criteria to determine whether patients have developed significant, irreversible pulmonary vascular changes and are, thus, at a high risk of poor postoperative long-term outcome. In fact, data on the operability of patients with PVD secondary to large SPs is limited to retrospective cohorts and case studies. In the absence of solid evidence, such patients are currently

Table 4.4 Recommendations for correction of congenital heart disease with prevalent systemic-to-pulmonary shunts [2]

Recommendations					
PVRi (WU × m^2)	PVR (WU)	Correctable[d]	Class[a]	Level[b]	Ref.[c]
<4	<2.3	Yes	IIa	C	[28]
>8	>4.6	No	IIa	C	[28]
4–8	2.3–4.6	Individual patient evaluation in tertiary centres	IIa	C	[28]

PVR pulmonary vascular resistance, *PVRi* pulmonary vascular resistance indexed, *WU* Wood units
[a]Class of recommendation
[b]Level of evidence
[c]Reference(s) supporting recommendations
[d]With surgery or intravascular percutaneous procedure

managed on a case-by-case basis. Commonly, the two main factors considered in the decision-making with regard to operability in patients with prevalent SPs are age at repair and preoperative haemodynamics [27]. In general, corrective interventions are unlikely to convey long-term benefits when the shunt is discovered late in life (particularly in post-tricuspid SPs) and if patients already have "elevated" PVR (i.e. intervention is unlikely to reverse the established PVD). Even more importantly, the decision to correct the defect should certainly not be based on procedural feasibility alone, on the ability to reduce or abolish a small left-to-right shunt, or mildly improve systemic oxygen saturations. Nevertheless, these important rules remain "broad suggestions" and represent only a generic help in the decision-making for the specific patient with prevalent SPs. In fact, neither age limits nor evidence-based cut-off values for PVR are able to predict with certainty the long-term outcome after defect closure, and both surgical and catheter therapy may have late detrimental effects even after an immediate "technical" success. Therefore, there are still uncertainties regarding the precise operative indications for SPs with PAH, and the appropriate therapeutic approach for most patients remains controversial.

Future research should aim to provide more insight into patients who are at highest risk of developing postoperative PAH, in order to be able to offer tailored care to patients born with SPs. Recently, an attempt to fill this gap was proposed at the 5th World Symposium on PH in 2013 [12], and has been adopted by the 2015 ESC/ERS guidelines for the diagnosis and treatment of PH [2]: according to these recommendations, which are based on available literature data [28–30], the appropriate therapeutic approach for these patients should be based mainly on baseline PVR, and specific criteria for shunt closure have been provided (Table 4.4 and Fig. 1.5). These criteria support defect repair only in patients with no PVD, in whom a clear and long-standing benefit from the intervention is predicted: indeed, no PVD is expected in patients with normal or near normal PVR values (<2.3 WU or <4 WU × m^2). On the other hand, PVD is likely to be present when PVR is above 2.3 WU, and patients should be deemed inoperable when PVR is greater than 4.6 WU (or 8 WU × m^2), a value that is likely to be associated with an advanced and

irreversible form of PVD. A grey area of uncertainty remains when PVR is between 2.3 and 4.6 WU (4–8 WU × m^2): as previously discussed, data available in literature are controversial, and there is no clear evidence for a long-term prognostic benefit of intervention in these patients, as closure of the defect can adversely affect the natural history of a disease that would otherwise allow a better survival if left untreated.

In patients with a PVR between 2.3 and 4.6 WU, additional parameters are commonly utilized in the decision-making regarding operability [31], and the characteristics generally considered indicative of a favourable outcome after surgical/interventional closure of a SPs are the following: pre-tricuspid shunt and simple lesions, younger age (<5 years), PVR/SVR ratio <0.5 and pulmonary flow/systemic flow (Qp/Qs) ratio >1.5. Vasoreactivity testing using 100% oxygen or pulmonary vasodilators such as nitric oxide has been utilized to preoperatively assess the degree of "reversibility" of the PVD [32]. However, its role in predicting mid- to long-term postoperative outcomes in patients with SPs and PAH is uncertain and controversial [20]. To date, no prospective data are available on the usefulness of acute balloon defect closure testing or lung biopsy for assessing operability, and the overall reliability of these preoperative evaluations is definitely poor. In addition, surgical lung biopsy is associated with a significant procedural risk.

4.4.3 Treat-and-Repair Approach

The "treat-and-repair approach" represents a combined therapeutic strategy for patients with PAH–CHD and increased PVR (namely, for patients belonging to the "PVR grey zone") meant to reduce PVR with medical treatments, in order to reach criteria for operability: the patient is treated with PAH-approved drugs, and the defect is repaired if PVR drops to "acceptable levels" [33]. Using this approach, it would, in theory, be possible to considerably expand the operative indications in these patients. However, a significant limitation of this strategy is the possibility that the reduction in PVR obtained with PAH therapy is not due to a regression of PVD, but simply linked to the temporary effects of pulmonary vasodilatation and/or the increase in pulmonary blood flow. If this is the case, closure of the defect may convert the disease to a more severe form of PAH, preventing the possibility of shunt reversal and the benefits of having an open defect in a patient with PVD. This is particularly important considering that patients with PAH and SPs can have a good prognosis with PAH-specific therapy if their defect is left untreated [9].

For these reasons, a "treat-and-repair approach" should not be adopted based on procedural feasibility and perioperative survival prospects, but must be judged on its long-term results. Currently, despite favourable case reports (mainly in patients with atrial septal defects), the "treat-and-repair approach" lacks support from any prognostic data [33], and, in view of the potentially detrimental effect of defect closure on RV function, treat-and-repair cannot be recommended.

In view of the lack of management guidelines regarding operability in "borderline" patients with SPs and PAH, it is recommended that defect closure should be approached with caution in patients with evidence of PVD, and considerable

expertise and experience are crucial to gauge the risk of developing irreversible PAH after surgery. Thus, a very careful and comprehensive assessment is required and individual patient evaluation in tertiary centres is recommended (see also Chapter 17).

4.5 PAH Associated with Small Cardiac Defects

Patients included in this group (*group 3*) are characterized by severe PAH associated with small, restrictive septal defects (usually VSD <1 cm and/or ASD <2 cm of effective diameter assessed by echocardiography). These defects have been defined as "coincidental" in order to underline the clinical similarities of patients included in this group with those affected by idiopathic PAH. In fact, the influence of the septal defect in the induction and progression of PAH is unclear, and a definite pathogenetic correlation between the small defect and PAH cannot be established: the defect itself is not thought to be responsible for the development of PAH, since the shunt is too small to produce significant pulmonary blood flow and the subsequent detrimental effects on pulmonary vasculature. Therefore, the diagnosis of idiopathic PAH with a concomitant CHD has been proposed, even though this is a statistically exceptional association. Additional hypotheses have been formulated to explain this specific form of PAH–CHD, including the influence of an underlying genetic factor, namely, the presence of mutations in genes causing heritable PAH in patients with a small shunt favouring the induction of PVD; however, mutations in PAH genes are uncommon in PAH–CHD patients [34]. Additional genetic traits or constitutional factors that may accelerate the evolution of PVD in patients with small septal defects have been hypothesized; however, these remain as yet unidentified.

4.5.1 Epidemiology

In different series, patients with PAH and coincidental CHD represent the smallest subgroup of the overall PAH–CHD population: they only account for 5% in a recent analysis of a large cohort of PAH–CHD patients classified according to the four clinical subgroups [9] and 4% in a cross-sectional study performed to assess the prevalence of PAH in adult CHD using the population-based Dutch CONgenital CORvitia (CONCOR) registry [9]. Due to the low number of patients, few data are available on the demographic, clinical, haemodynamic and prognostic characteristics and the management of this PAH–CHD subgroup.

4.5.2 Clinical Picture

The clinical and prognostic profiles of patients with PAH associated with small defects have been examined in a study on a large cohort of PAH–CHD patients aimed at analysing and comparing the characteristics of the four clinical subgroups

[9]. Except for the presence of a septal defect, the clinical picture of these patients is very similar to that of idiopathic PAH. As compared to patients belonging to the other PAH–CHD subgroups, they were the youngest and their haemodynamic profile was characterized by the lowest mean right atrial pressure, as right-to-left shunting through the septal communication allows RV decompression. From a prognostic standpoint, the long-term survival of patients with PAH–CHD associated with small defects was worse when compared to that of patients with ES and those with SPs: indeed, the 15-year survival was 87% in ES patients, 86% in patients with SPs and 66% in patients with PAH associated with small defects. Nevertheless, the 15-year survival of the small defects group was far better when compared to that of idiopathic PAH patients (38%). The reason why patients with PAH–CHD associated with small defects have an intermediate survival between patients with idiopathic PAH and patients with PAH and larger uncorrected defects is unclear. Possible explanations include the favourable prognostic influence of small septal defects, which may allow pulmonary-to-systemic shunting in the advanced stages of the disease allowing partial relief of the overload on the RV and limiting the progressive reduction in systemic cardiac output. This mechanism, which may explain the better survival compared with idiopathic PAH patients, may not be sufficient to obtain the more favourable prognosis of patients with larger defects.

4.5.3 Therapy

Despite the lack of formal evidence of efficacy, patients with PAH associated with small septal defects are usually treated with PAH-specific therapy because their disease bears similarities to idiopathic PAH, and can be more aggressive than ES [9]. In most experienced centres, the therapeutic approach adopted in these patients is identical to that used in idiopathic PAH.

There is, clearly, no indication for cardiac surgery or catheter defect closure in patients with PAH associated with small septal defects [2].

References

1. Adatia I, Kothari SS, Feinstein JA (2010) Pulmonary hypertension associated with congenital heart disease: pulmonary vascular disease: the global perspective. Chest 137(6 Suppl):52S–61S
2. Galie N, Humbert M, Vachiery JL, Gibbs JS, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez-Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci-Cerinic M, McDonagh T, Pierard L, Trindade PT, Zompatori M, Hoeper M (2016) 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 37(1):67–119
3. Beghetti M, Galiè N (2009) Eisenmenger syndrome: a clinical perspective in a new therapeutic era of pulmonary arterial hypertension. J Am Coll Cardiol 53(9):733–740
4. Diller GP, Gatzoulis MA (2007) Pulmonary vascular disease in adults with congenital heart disease. Circulation 115(8):1039–1050
5. Daliento L, Somerville J, Presbitero P, Menti L, Brach-Prever S, Rizzoli G, Stone S (1998) Eisenmenger syndrome. Factors relating to deterioration and death. Eur Heart J 19(12):1845–1855

6. Hopkins WE, Ochoa LL, Richardson GW, Trulock EP (1996) Comparison of the hemodynamics and survival of adults with severe primary pulmonary hypertension or Eisenmenger syndrome. J Heart Lung Transplant 15(1 Pt 1):100–105
7. Galiè N, Manes A, Palazzini M, Negro L, Marinelli A, Gambetti S, Mariucci E, Donti A, Branzi A, Picchio FM (2008) Management of pulmonary arterial hypertension associated with congenital systemic-to-pulmonary shunts and Eisenmenger's syndrome. Drugs 68:1049–1066
8. Brickner ME, Hillis LD, Lange RA (2000) Congenital heart disease in adults. Second of two parts [published erratum appears in N Engl J med 2000 mar 30;342(13):988]. N Engl J Med 342(5):334–342
9. Manes A, Palazzini M, Leci E, Bacchi Reggiani ML, Branzi A, Galie N (2014) Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: a comparison between clinical subgroups. Eur Heart J 35(11):716–724
10. Engelfriet PM, Duffels MGJ, Moller T, Boersma E, Tijssen JGP, Thaulow E, Gatzoulis MA, Mulder BJM (2007) Pulmonary arterial hypertension in adults born with a heart septal defect: the euro heart survey on adult congenital heart disease. Heart 93(6):682–687
11. Simonneau G, Robbins I, Beghetti M, Channick RN, Delcroix M, Denton CP, Elliott CG, Gaine S, Gladwin MT, Jing ZC, Krowka MJ, Langleben D, Nakanishi N, Souza R (2009) Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 54:S43–S54
12. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, Gomez Sanchez MA, Krishna Kumar R, Landzberg M, Machado RF, Olschewski H, Robbins IM, Souza R (2013) Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 62:D34–D41
13. Dimopoulos K, Inuzuka R, Goletto S, Giannakoulas G, Swan L, Wort SJ, Gatzoulis MA (2010) Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension. Circulation 121(1):20–25
14. Galie N, Beghetti M, Gatzoulis MA, Granton J, Berger RMF, Lauer A, Chiossi E, Landzberg M, Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) Investigators (2006) Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. Circulation 114(1):48–54
15. Sztrymf B, Coulet F, Girerd B, Yaici A, Jais X, Sitbon O, Montani D, Souza R, Simonneau G, Soubrier F, Humbert M (2008) Clinical outcomes of pulmonary arterial hypertension in carriers of BMPR2 mutation. Am J Respir Crit Care Med 177(12):1377–1383
16. Therrien J, Rambihar S, Newman B, Siminowitch K, Langleben D, Webb G, Granton J (2006) Eisenmenger syndrome and atrial septal defect: nature or nurture? Can J Cardiol 22:1133–1136
17. Newman JH, Trembath RC, Morse JA, Grunig E, Loyd JE, Adnot S, Coccolo F, Ventura C, Phillips III (2004) Genetic basis of pulmonary arterial hypertension: Current understanding and future directions. J Am Coll Cardiol 43(12 Suppl S):33S–39S
18. van Riel ACMJ, Schuuring MJ, van Hessen ID, Zwinderman AH, Cozijnsen L, Reichert CLA, Hoorntje JCA, Wagenaar LJ, Post MC, van Dijk APJ, Hoendermis ES, Mulder BJM, Bouma BJ (2014) Contemporary prevalence of pulmonary arterial hypertension in adult congenital heart disease following the updated clinical classification. Int J Cardiol 174(2):299–305
19. Gatzoulis MA, Alonso-Gonzalez R, Beghetti M (2009) Pulmonary arterial hypertension in paediatric and adult patients with congenital heart disease. Eur Respir Rev 18(113):154–161
20. Viswanathan S, Kumar RK (2008) Assessment of operability of congenital cardiac shunts with increased pulmonary vascular resistance. Catheter Cardiovasc Interv 71(5):665–670
21. Baumgartner H, Bonhoeffer P, de Groot N, de Haan F, Deanfield J, Galiè N, Gatzoulis M, Gohlke-Baerwolf C, Kaemmerer H, Kilner P, Meijboom F, Mulder B, Oechslin E, Oliver JM, Serraf A, Szatmari A, Thaulow E, Vouhe P, Walma E, Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology (ESC), Association for European Paediatric Cardiology (AEPC); ESC Committee for Practice Guidelines (CPG) (2010) ESC guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J 31:2915–2957
22. Haworth SG, Hislop AA (2009) Treatment and survival in children with pulmonary arterial hypertension: the UK pulmonary hypertension Service for Children 2001–2006. Heart 95(4):312–317

23. Kannan BR, Sivasankaran S, Tharakan JA, Titus T, Ajith Kumar VK, Francis B, Krishnamoorthy KM, Harikrishnan S, Padmakumar RNK (2003) Long-term outcome of patients operated for large ventricular septal defects with increased pulmonary vascular resistance. Indian Heart J 55(2):161–166
24. Gatzoulis MA (2011) The management of Eisenmenger syndrome in the modern treatment era: a case report. Eur Respir Rev 20(122):293–296
25. Barst RJ, McGoon MD, Elliott CG, Foreman AJ, Miller DP, Ivy DD (2012) Survival in childhood pulmonary arterial hypertension: insights from the registry to evaluate early and long-term PAH disease management. Circulation 125(1):113–122
26. D'Alto M, Romeo E, Argiento P, Correra A, Santoro G, Gaio G, Sarubbi B, Calabrò R, Russo MG (2013) Hemodynamics of patients developing pulmonary arterial hypertension after shunt closure. Int J Cardiol 168(4):3797–3801
27. Bando K, Turrentine MW, Sharp TG, Sekine Y, Aufiero TX, Sun K, Sekine E, Brown JW (1996) Pulmonary hypertension after operations for congenital heart disease: analysis of risk factors and management. J Thorac Cardiovasc Surg 112(6):1600–1609
28. Moller JH, Patton C, Varco RL, Lillehei CW (1991) Late results (30 to 35 years) after operative closure of isolated ventricular septal defect from 1954 to 1960. Am J Cardiol 68(15):1491–1497
29. van Albada ME, Berger RM (2008) Pulmonary arterial hypertension in congenital cardiac disease—the need for refinement of the Evian-Venice classification. Cardiol Young 18(1):10–17
30. Schulze-Neick I, Beghetti M (2008) Classifying pulmonary hypertension in the setting of the congenitally malformed heart—cleaning up a dog's dinner. Cardiol Young 18(1):22–25
31. Lopes AA, Leary PW (2009) Measurement, interpretation and use of hemodynamic parameters. Cardiol Young 19(S1):8–12
32. Balzer DT, Kort HW, Day RW, Corneli HM, Kovalchin JP, Cannon BC, Kaine SF, Ivy DD, Webber SA, Rothman A, Ross RD, Aggarwal S, Takahashi M, Waldman JD (2002) Inhaled nitric oxide as a preoperative test (INOP test I): the INOP test study group. Circulation 106(12 Suppl 1):I76–I81
33. Dimopoulos K, Peset A, Gatzoulis MA (2008) Evaluating operability in adults with congenital heart disease and the role of pretreatment with targeted pulmonary arterial hypertension therapy. Int J Cardiol 129(2):163–171
34. Roberts KE, McElroy JJ, Wong WP, Yen E, Widlitz A, Barst RJ, Knowles JA (2004) BMPR2 mutations in pulmonary arterial hypertension with congenital heart disease. Eur Respir J 24(3):371–374

Pulmonary Arterial Hypertension in Patients with Previous Reparative Surgery

5

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Abbreviations

ASD	Atrial septal defect
AVSD	Atrioventricular septal defect
BMPR-2	Bone morphogenetic protein receptor type 2
CHD	Congenital heart disease
CTD	Connective tissue disease
ERA	Endothelin receptor antagonist
ES	Eisenmenger syndrome
FC	Functional class
iPAH	Idiopathic pulmonary arterial hypertension
LHD	Left heart disease
mPAP	Mean pulmonary artery pressure
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
PAH	Pulmonary arterial hypertension
PAH–CHD	Pulmonary arterial hypertension in congenital heart disease
PDE5	Phosphodiesterase 5
PGs	Prostaglandins
PVR	Pulmonary vascular resistance
PVRI	Pulmonary vascular resistance indexed
RCT	Randomized control trials
RV	Right ventricle

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TGA	Transposition of great arteries
VSD	Ventricular septal defect
WHO	World Health Organization
6MWT	6-min walk test

5.1 Introduction

Pulmonary arterial hypertension (PAH) is a frequently diagnosed complication in patients with congenital heart disease (CHD). The majority of the cases involve patients with nonrestrictive congenital cardiac shunts with unprotected pulmonary blood flow [1]. Exposure of the pulmonary vasculature to increased blood flow and pressure results in vascular remodelling and eventually established pulmonary vascular disease. Despite advances in the understanding of the pulmonary vascular disease, advances in surgical repair of CHD and the development of drug therapies, PAH still occurs after successful corrective surgery in patients with CHD and results in significant morbidity and mortality [2–4].

5.2 Classification and Epidemiology

The recent update of the clinical classification of Pulmonary arterial hypertension in congenital heart disease (PAH–CHD) has taken into account several factors, such as type and size of defects, haemodynamic parameters and repair status and divides the patients into four phenotypes: Eisenmenger syndrome (ES), PAH associated with systemic-to-pulmonary shunts, PAH associated with small defects and persistent/recurrent PAH after defect correction [5].

The estimated prevalence of CHD is approximately 6–10/1000 live births [6, 7], and 4–28% of those patients are expected to develop PAH [8–11]. Limited information is available about the incidence of PAH late after cardiac defect correction. In the Euro Heart Survey, the prevalence of postoperative PAH in adults with previously corrected atrial septal defect (ASD) or ventricular septal defect (VSD) was 12% and 13%, respectively [12]. In the Spanish REHAP registry [13] of adults with PAH–CHD, 23.8% had corrective cardiac surgery. In the paediatric population, postoperative PAH accounted for 15% of PAH–CHD in a large retrospective study from the Netherlands [14], 35% of PAH–CHD in the multicentre TOPP registry [15] and 45% in early data from the UK registry [16].

5.3 Mechanisms for the Development of Late Postoperative PAH

The primary mechanism for the development of pulmonary vascular disease in the setting of CHD is thought to be the result of increased pulmonary blood flow and pressure triggering vascular remodelling. Abnormal vessel shear stress results in endothelial dysfunction and damage, smooth muscle hypertrophy and proliferation

and altered expression of vasoactive mediators in favour of vasoconstriction [17]. Furthermore, endothelial damage may result in adherence and activation of platelets and leukocytes favouring inflammation and thrombosis as well as activation of coagulation pathways.

The shear stress-mediated remodelling hypothesis is supported by the widespread observation that lesions which result in high flow and pressure (e.g. complete AVSD, truncus arteriosus) result in pulmonary vascular disease sooner and more reliably than lesions expected to result in less shear stress. In addition, both haemodynamic and histological [17–19] disease severity have been shown to correlate with age and lesion type.

Changes to the pulmonary vasculature are likely to be reversible if the corrective surgery takes place early in life, and if it occurs within few months of age, the pulmonary vascular resistance (PVR) is frequently normal within 1 year [18]. On the other hand, if surgery is delayed until later in childhood (after 2 years of age), normal PVR levels may never be achieved, and on the contrary the repair of an intracardiac shunt in the presence of PAH may even accelerate disease progression [20]. This suggests that there may be a "point of no return" where changes of the pulmonary bed have progressed beyond a stage of full or partial reversibility despite the correction of the associated defect [10].

Such observations suggest that the greatest risk factor for the development of PAH in CHD may be considered to be the cumulative burden of shear stress (i.e. size and location of shunt lesion as well as duration of exposure) experienced by the vasculature.

While flow-mediated vascular remodelling is undoubtedly a major factor in the development of PAH–CHD, there remains variability in disease expression, and the situation is unlikely to be so deterministic.

5.3.1 Maladaptation/Developmental Factors

In paediatric cohorts, CHD patients who are diagnosed with PAH within weeks of birth are well recognized. This is too soon to be mediated by shear stress and suggests other factors such as disturbed postnatal adaptation of the pulmonary vascular bed [14] or abnormal fetal blood flow, for example, with restrictive ductus venosus or atrial communications. Additionally the Dutch registry has described a subgroup of infants with post-tricuspid shunt who showed accelerated development of PAH in the weeks to months after birth. All the patients had syndromal abnormalities, including Down syndrome, which is associated with higher susceptibility for PAH [14].

That PAH is observed in CHD patients despite early repair of CHD or in CHD with small defects at a much higher rate than would be expected by chance also suggests shared genetic or developmental processes are at play.

5.3.2 PAH Late After Repair

Late occurrence after surgery of PAH has been described in patients, many of whom did not have clinically evident pulmonary hypertension for years after surgery [18, 20]. In an adult cohort of PAH–CHD patients reported by Manes et al., the median time from surgical repair to diagnosis of PAH was 16.9 years. The mechanism of such "late onset"

PAH is unclear, and it has been suggested that there might be an underlying predisposition which is triggered by the presence of a shunt and may manifest years after closure of the defect. The influence of residual defects after correction on the development of PAH is also unclear. The presence of residual shunts alone did not appear sufficient to justify the development of late PAH, as the residual defects were present in no more than 20% of the patients in this group, and the majority were small in size [20].

5.4 Genetic Factors

In a small study of adults and children with heterogeneous forms of PAH–CHD, a small percentage (approximately 6%) of patients with PAH–CHD were found to have missense mutations in bone morphogenetic protein receptor type 2 (BMPR-2), but this was considerably lower than that observed in patients with idiopathic or familial PAH (~50%) [21]. The relevance of BMPR-2 mutations in PAH–CHD remains uncertain. Genetic syndromes associated with pulmonary hypertension and which can be associated with PAH–CHD include DiGeorge syndrome, vertebral defects, anal atresia, cardiac defects, tracheo-oesophageal fistula, renal anomalies, and limb abnormalities (VACTERL) syndrome, CHARGE syndrome, Scimitar syndrome [22], Noonan syndrome [23], chromosome 1p36 deletion [24] and chromosomal anomalies associated with congenital diaphragmatic hernia [25].

The age of presentation for paediatric patients is between 4.8 and 7.5 years and 27 and 38 years for adults, and it is earlier than patients with ES or shunt-associated PAH. In some cohorts the median age at the time of surgery was as late as 11.0 years of age, and the PAH was diagnosed after a median of approximately 17 years from surgery. The mean pulmonary artery pressure (mPAP) values ranged between 45 and 67 mmHg and pulmonary vascular resistance indexed (PVRI) from 11.8 to 15 Wood units (WU) m^2. Otherwise the clinical characteristics and haemodynamics of these patients are broadly similar to iPAH (Table 5.1).

Table 5.1 The population of the post-op CHD patients and their baseline characteristics included in major published registries are summarized

Cohorts	PAH–CHD (n)	Post-op PAH-CHD	Age range (years)	Treatment	Comments
Howarth et al. [16]	104	47 (45%)	0.2–19.5	PD-5, ERA, PGs	5-year survival 59.6%
Barst et al. (REVEAL) [26]	77	29(38%)	Mean 5	PD-5, ERA, PGs	5-year survival 71%
Van Loon et al. [14]	111	17(15%)	0.3–4.6	Not known	Incidence and prevalence for paediatric PAH–CHD are higher than in adults; 5-year survival 47%
Manes et al. [20]	192	44(23%)	19–53	PDE-5i, ERA, PGs	5-year survival 83%, 20-year survival 36%
Engelfriet et al. [12]	1877	652(35%)	21–50	Not known	5-year survival 93.9%
Alonso-Gonzalez et al. (REHAP) [13]	240	57(24%)	13.6–51.8	Not known	Worse survival than Eisenmenger syndrome

5.5 Treatment

Patients with postoperative PAH–CHD are absent or underrepresented in the large randomized control trials of pharmacological therapy for group 1 PAH. Studies aimed at PAH–CHD have focused on ES. Hence, treatment strategies for postoperative PAH–CHD are still largely based on expert opinion and extrapolation [27]. In the reviewed cohorts, patients with late postoperative PAH–CHD were treated using the same rationale and European Society of Cardiology (ESC) algorithm used for patients with iPAH [14, 16, 20]. Until such time as more specific studies can be performed, this approach seems reasonable and is supported by phenotypic and histological similarities between diseases in group 1. Recently, a post hoc analysis of the PATENT studies using Riociguat demonstrated improvement in a range of clinical outcomes including 6-min walk test (6MWT), PVR, the World Health Organization functional class (WHO FC) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) in a small subgroup of patients with persistent/recurrent PAH following complete repair of CHD. This improvement was sustained throughout the 2-year follow-up period [27]. In addition, two recent studies with a combined morbidity/mortality endpoint have included patients with simple, corrected defects and PAH and suggested that Macitentan (an endothelin receptor antagonist (ERA)) and Selexipag (an oral prostacyclin-receptor antagonist) may be beneficial in this setting [28, 29].

The inherent heterogeneity of underlying cardiac defect and residual defects make application of treatment guidelines more challenging in practice. However, given the general lack of intracardiac right-to-left shunts, intravenous prostanoid therapy may be considered a more viable option than in patients with ES where the risk of paradoxical embolism may restrict its use.

Lung and heart–lung transplantation remains an option in severe cases not responsive to medical treatment; however, the effect of previous cardiothoracic surgery on the chest wall and pleura, residual cardiac defects and possible human leukocyte antigen (HLA) sensitization mean that this may not be a viable option for many patients [30].

5.6 Natural Course: Outcome

There is a paucity of data on the outcome of patients with postoperative PH, with most data derived from retrospective cohorts with concomitant biases. The majority of paediatric cohorts suggest that such patients have more rapid disease progression and worse outcome than patients with ES, but similar to patients with iPAH [16, 20, 31]. Adult cohorts suggest that survival is better than in those with idiopathic pulmonary arterial hypertension (PAH); however, it is the lowest among all patients with PAH–CHD. The notable exception is the Euro Heart Survey for adults with CHD in which patients with postoperative PAH–CHD showed a better survival compared to ES. However, postoperative PH was defined by echo criteria in this study, possibly biasing the population towards milder disease [12]. The survival disadvantage cannot be attributed to a different treatment strategy, as patients with PAH and small or corrected defects are more likely to be treated with approved PAH-specific drugs compared with the other two groups.

Data from the UK paediatric cohort suggests survival rates are lower when PAH is detected early after the corrective surgery. The mean predicted survival in this case drops to 3.5 years if PAH is left untreated, but only rises to 4.1 years after PAH treatment [16]. Survival rates are significantly poorer in patients with complex underlying cardiac defects and those with Down syndrome [32].

The reasons for the worse prognosis of postoperative PAH patients when compared to ES are unclear. One likely factor is that, as PVR increases, a patent shunt, as in unoperated CHD, permits right-to-left shunting. For post-tricuspid shunts, the right ventricle (RV) has access to both pulmonary and systemic vascular beds in parallel and, as such, experiences a lower afterload for any given degree of vascular disease, while maintaining cardiac output at the expense of cyanosis. The absence of a shunt, as in postoperative PAH-CHD, has the potential to expose the RV to higher afterload at rest and particularly during exercise. This effect has been demonstrated in reverse with the creation of a post-tricuspid shunt, the Potts shunt, as a treatment for iPAH [33].

The RV of patients with ES may also be better adapted to cope with an increased afterload due to the maintenance of a fetal phenotype of RV hypertrophy. This may be absent in patients who have had a period of low RV pressure following CHD repair and later face increased pulmonary vascular resistance.

Additional factors specific to patients who have undergone repair of CHD may further prejudice outcomes in these patients. Residual small shunt defects may influence the development of PAH and RV adaptation [20]. Valve dysfunction is frequently seen in patients with previous cardiac surgery and PAH, particularly tricuspid regurgitation. While often well tolerated in patients without PAH, tricuspid regurgitation is likely to be exacerbated by the abnormal loading conditions experienced in pulmonary hypertension (PH), and this in turn adds to inefficiency of the cardiac pump. Ventricular surgery, especially previous right ventricular incision and scarring, can also contribute to the progression of RV dysfunction in these patients.

Rhythm disturbances (right bundle branch block, complete heart block, atrial tachyarrhythmias) are an increasing clinical problem in postoperative PAH–CHD patients both as a surgical complication (conduction system injury, myocardial scar) and as a PH consequence (atrial dilatation). Rhythm disturbances can lead to right ventricular dysfunction and increase the risk of sudden death [34, 35]. In addition right bundle branch block, a common occurrence following intracardiac repair, may exacerbate the already adverse right-left ventricular interaction, further reducing pump efficiency [36].

Conclusion

Patients with postoperative PAH are a diverse group, with likely varying aetiology. Outcome is worse than other forms of PAH–CHD despite treatment with targeted therapies. The majority represent potentially avoidable morbidity, either through timely diagnosis and repair of CHD, or through expert assessment and avoidance of surgery once pulmonary vascular disease is established.

References

1. Wood P (1958) The Eisenmenger syndrome or pulmonary hypertension with reversed central shunt. I. Br Med J 2(5098):701–709
2. Lowe BS, Therrien J, Ionescu-Ittu R, Pilote L, Martucci G, Marelli AJ (2011) Diagnosis of pulmonary hypertension in the congenital heart disease adult population impact on outcomes. J Am Coll Cardiol 58(5):538–546
3. Diller GP, Gatzoulis MA (2007) Pulmonary vascular disease in adults with congenital heart disease. Circulation 115(8):1039–1050
4. Sanatani S, Wilson G, Smith CR, Hamilton RM, Williams WG, Adatia I (2006) Sudden unexpected death in children with heart disease. Congenit Heart Dis 1(3):89–97
5. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A et al (2013) Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 62(25 Suppl):D34–D41
6. Marelli AJ, Mackie AS, Ionescu-Ittu R, Rahme E, Pilote L (2007) Congenital heart disease in the general population: changing prevalence and age distribution. Circulation 115(2):163–172
7. Adatia I, Kothari SS, Feinstein JA (2010) Pulmonary hypertension associated with congenital heart disease: pulmonary vascular disease: the global perspective. Chest 137(6 Suppl):52S–61S
8. Duffels MG, Engelfriet PM, Berger RM, van Loon RL, Hoendermis E, Vriend JW et al (2007) Pulmonary arterial hypertension in congenital heart disease: an epidemiologic perspective from a Dutch registry. Int J Cardiol 120(2):198–204
9. Mulder BJ (2010) Changing demographics of pulmonary arterial hypertension in congenital heart disease. Eur Respir Rev 19(118):308–313
10. D'Alto M, Mahadevan VS (2012) Pulmonary arterial hypertension associated with congenital heart disease. Eur Respir Rev 21(126):328–337
11. Gatzoulis MA, Alonso-Gonzalez R, Beghetti M (2009) Pulmonary arterial hypertension in paediatric and adult patients with congenital heart disease. Eur Respir Rev 18(113):154–161
12. Engelfriet PM, Duffels MG, Moller T, Boersma E, Tijssen JG, Thaulow E et al (2007) Pulmonary arterial hypertension in adults born with a heart septal defect: the euro heart survey on adult congenital heart disease. Heart 93(6):682–687
13. Alonso-Gonzalez R, Lopez-Guarch CJ, Subirana-Domenech MT, Ruiz JM, Gonzalez IO, Cubero JS et al (2015) Pulmonary hypertension and congenital heart disease: an insight from the REHAP National Registry. Int J Cardiol 184:717–723
14. van Loon RL, Roofthooft MT, Hillege HL, ten Harkel AD, van Osch-Gevers M, Delhaas T et al (2011) Pediatric pulmonary hypertension in the Netherlands: epidemiology and characterization during the period 1991 to 2005. Circulation 124(16):1755–1764
15. Berger RM, Beghetti M, Humpl T, Raskob GE, Ivy DD, Jing ZC et al (2012) Clinical features of paediatric pulmonary hypertension: a registry study. Lancet 379(9815):537–546
16. Haworth SG, Hislop AA (2009) Treatment and survival in children with pulmonary arterial hypertension: the UK pulmonary hypertension Service for Children 2001-2006. Heart 95(4):312–317
17. Rabinovitch M (1999) Pulmonary hypertension: pathophysiology as a basis for clinical decision making. J Heart Lung Transplant 18(11):1041–1053
18. Haworth SG (2002) Pulmonary hypertension in the young. Heart 88(6):658–664
19. Haworth SG (1984) Pulmonary vascular disease in different types of congenital heart disease. Implications for interpretation of lung biopsy findings in early childhood. Br Heart J 52(5):557–571
20. Manes A, Palazzini M, Leci E, Bacchi Reggiani ML, Branzi A, Galie N (2013) Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: a comparison between clinical subgroups. Eur Heart J 35(11):716–724
21. Roberts KE, McElroy JJ, Wong WP, Yen E, Widlitz A, Barst RJ et al (2004) BMPR2 mutations in pulmonary arterial hypertension with congenital heart disease. Eur Respir J 24(3):371–374

22. Vida VL, Padalino MA, Boccuzzo G, Tarja E, Berggren H, Carrel T et al (2010) Scimitar syndrome: a European Congenital Heart Surgeons Association (ECHSA) multicentric study. Circulation. 122(12):1159–1166
23. Tinker A, Uren N, Schofield J (1989) Severe pulmonary hypertension in Ullrich-Noonan syndrome. Br Heart J 62(1):74–77
24. Slavotinek A (2003) Chromosome 1p36 deletions. Orphanet encyclopedia [Internet]
25. Soubrier F, Chung WK, Machado R, Grunig E, Aldred M, Geraci M et al (2013) Genetics and genomics of pulmonary arterial hypertension. J Am Coll Cardiol 62(25 Suppl):D13–D21
26. Barst RJ, McGoon MD, Elliott CG, Foreman AJ, Miller DP, Ivy DD et al (2012) Survival in childhood pulmonary arterial hypertension: insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management. Circulation 125(1):113–122
27. Rosenkranz S, Ghofrani HA, Beghetti M, Ivy D, Frey R, Fritsch A et al (2015) Riociguat for pulmonary arterial hypertension associated with congenital heart disease. Heart 101(22):1792–1799
28. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galie N, Ghofrani HA et al (2013) Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med 369(9):809–818
29. Sitbon O, Channick R, Chin KM, Frey A, Gaine S, Galie N et al (2015) Selexipag for the treatment of pulmonary arterial hypertension. N Engl J Med 373(26):2522–2533
30. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A et al (2016) 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 37(1):67–119
31. Dimopoulos K, Giannakoulas G, Wort SJ, Gatzoulis MA (2008) Pulmonary arterial hypertension in adults with congenital heart disease: distinct differences from other causes of pulmonary arterial hypertension and management implications. Curr Opin Cardiol 23(6):545–554
32. Daliento L, Somerville J, Presbitero P, Menti L, Brach-Prever S, Rizzoli G et al (1998) Eisenmenger syndrome. Factors relating to deterioration and death. Eur Heart J 19(12):1845–1855
33. Baruteau AE, Belli E, Boudjemline Y, Laux D, Levy M, Simonneau G et al (2015) Palliative Potts shunt for the treatment of children with drug-refractory pulmonary arterial hypertension: updated data from the first 24 patients. Eur J Cardiothorac Surg 47(3):e105–e110
34. Perloff JK, Warnes CA (2001) Challenges posed by adults with repaired congenital heart disease. Circulation 103(21):2637–2643
35. Rajdev A, Garan H, Biviano A (2012) Arrhythmias in pulmonary arterial hypertension. Prog Cardiovasc Dis 55(2):180–186
36. Handoko ML, Lamberts RR, Redout EM, de Man FS, Boer C, Simonides WS et al (2009) Right ventricular pacing improves right heart function in experimental pulmonary arterial hypertension: a study in the isolated heart. Am J Physiol Heart Circ Physiol 297(5):H1752–H1759

Segmental Pulmonary Hypertension

6

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Abbreviations

CHD	congenital heart disease
CT	computed tomography
CXR	chest X-ray
IVC	inferior vena cava
LA	left atrium
LPA	left pulmonary artery
MAPCA	major aortopulmonary collateral artery
MPA	main pulmonary artery
PA	pulmonary artery
PAH	pulmonary arterial hypertension
PAH–CHD	pulmonary arterial hypertension related to congenital heart disease
PAP	pulmonary artery pressure
PDA	patent ductus arteriosus

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PH	pulmonary hypertension
PS	pulmonary stenosis
PVD	pulmonary vascular disease
RA	right atrium
RPA	right pulmonary artery
RV	right ventricle
TOF	tetralogy of Fallot
TPG	transpulmonary gradient
VSD	ventricular septal defect

6.1 Introduction

Pulmonary hypertension (PH) is defined by the latest European guidelines as a pathophysiological disorder characterized by increased mean pressure into the pulmonary vascular system [1]. Since 1998, many classifications have been proposed for PH to identify common aspects in a multitude of aetiologies and define subgroups that share similar pathological and haemodynamic characteristics, hence guiding management. The latest PH classification agreed during the recent World PH Symposium in 2013 in Nice created a mutual classification for paediatric and adult patients. In this classification, a new entity was introduced, called "segmental PH", and was included in group 5 (unclear of multifactorial mechanisms) [1, 2].

6.2 Segmental Pulmonary Hypertension: Definition and Classification

Segmental PH was described in the recent guidelines as PH "observed in discrete lung areas perfused by aortopulmonary (AP) collaterals in congenital heart diseases such as pulmonary or tricuspid atresia". The definition of segmental PH differed somewhat in the published proceeding of the Nice World Symposium [2]: "PH in one or more lobes of one or both lungs". Previous authors have used a wider and perhaps more comprehensive definition of segmental PH [3]: PH that does not follow a homogeneous distribution, with some pulmonary areas being exposed to higher pressures than others. Indeed, the term "segmental" refers to any portion of the lung affected (one or more segments, lobes or even an entire lung), with at least one non-hypertensive segment.

Pulmonary arterial hypertension (PAH) in congenital heart disease (CHD) is typically caused by long-standing volume and/or pressure overload of the pulmonary circulation. The prolonged shear stress on the pulmonary endothelium results in cell hypertrophy and proliferation, leading to progressive narrowing of pulmonary vessels and a rise in pulmonary vascular resistance. The two predominant changes leading to pulmonary vascular disease (PVD) are hypertrophy and fibrosis of the pulmonary arterial structure, with loss of intrinsic elasticity (due to rupture of the internal elastic lamina and the formation of plexiform lesion) and consequently increased stiffness and narrowing of the lumen (Fig. 6.1; see also Chap. 1).

While the pathophysiology of segmental PH is not well studied, the underlying histological changes of segmental PH in CHD are not expected to differ substantially from most types of pulmonary arterial hypertension related to congenital heart disease (PAH–CHD) (or other forms of PAH). However, there are substantial differences in terms of cardiovascular anatomy and the impact of segmental PH on pulmonary perfusion and the heart, all of which influence management and the potential response to specific PAH therapies.

There are various congenital or acquired conditions that can lead to segmental PH. Congenital lesions that may predispose to segmental PH include pulmonary atresia, hemitruncus arteriosus, absence/atresia of a single pulmonary artery (PA) and anomalous PA from the aorta feeding a segment of the lung (Fig. 6.2). Moreover, any large post-tricuspid cardiac defect (ventricular septal defect [VSD], atrioventricular septal defect [AVSD], patent ductus arteriosus [PDA], AP window and truncus arteriosus) can result in segmental PH in the presence of peripheral pulmonary stenosis (PS) protecting certain (but not all) segments of the lung from the development of PVD.

In this chapter, a brief description of major conditions in which segmental PH may be encountered will be provided, but focus will be placed on pulmonary atresia.

6.2.1 Pulmonary Atresia

This entity may coexist with numerous conditions, and agreement on its anatomic and clinical classification remains elusive [4, 5]. The presence of a VSD defines the natural history and surgical management. Patients with pulmonary atresia and a VSD may be considered as the extreme end of the spectrum of tetralogy of Fallot (TOF), with overriding of the aorta and the typical antero-cephalad deviation of the

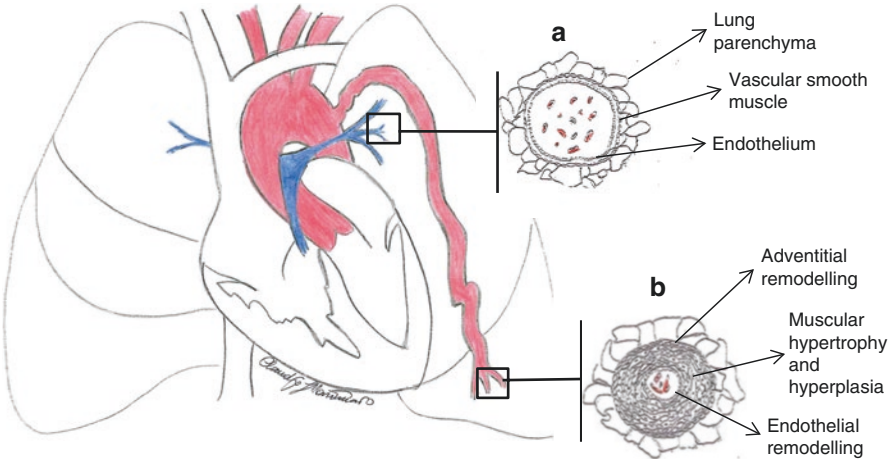

Fig. 6.1 Pulmonary vascular disease in complex pulmonary atresia. While the pulmonary vasculature of hypoperfused and normally perfused areas is expected to be normal (**a**), in areas supplied by large collateral arteries from the aorta, pulmonary vascular disease similar to PAH is expected (**b**)

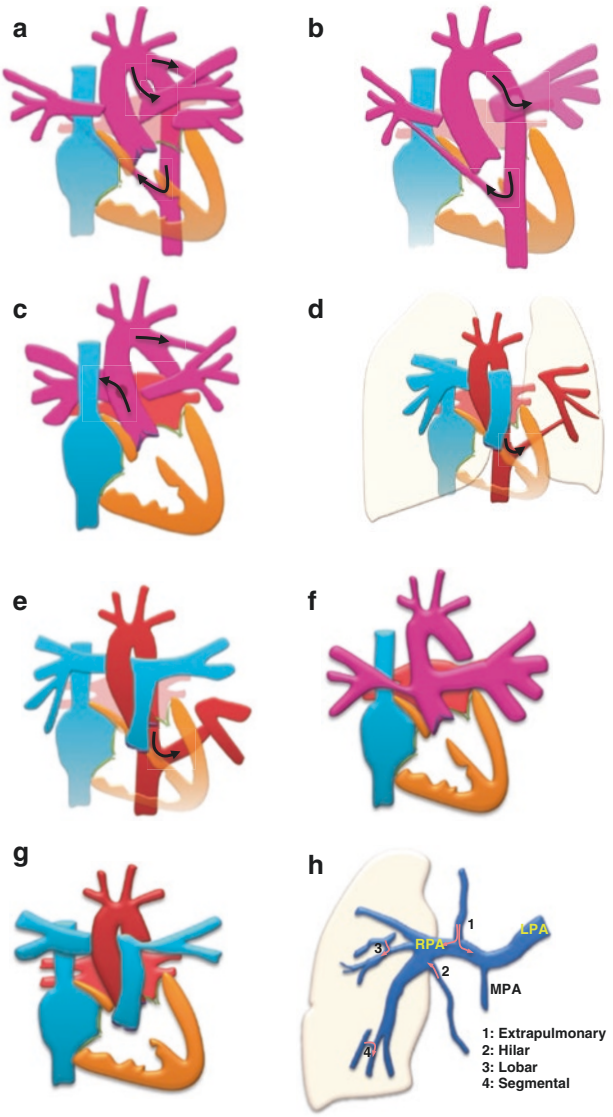

Fig. 6.2 Examples of segmental pulmonary hypertension. In (**a**), complex pulmonary atresia, with non-confluent pulmonary arteries supplied by a patent ductus arteriosus and major aortopulmonary collateral arteries (MAPCAs) from the descending aorta (*arrows*). In (**b**), the left pulmonary artery is supplied by a Potts shunt and the right by a MAPCA from the descending aorta. In (**c**), the right pulmonary artery is supplied by a Waterston shunt. In (**d**), disconnected left pulmonary artery, supplied by a MAPCA from the descending aorta. Potts and Waterston shunts are difficult to size and are likely to cause pressure and volume overload of the lung segments supplied, over time causing pulmonary hypertension. In (**e**), a single segment of the left pulmonary artery (lower segment) is disconnected and supplied by a large MAPCA. In this situation, only the left lower lung lobe will be hypertensive. In (**f**), common arterial trunk, with stenosis of the origin of the right pulmonary artery. In this case, only the left lung will be hypertensive. In (**g**), large ventricular septal defect and stenosis of the origin of the left pulmonary artery. In this situation, the VSD is likely to cause pulmonary hypertension in the right but not the left lung. In (**h**), the various types of collateral arteries

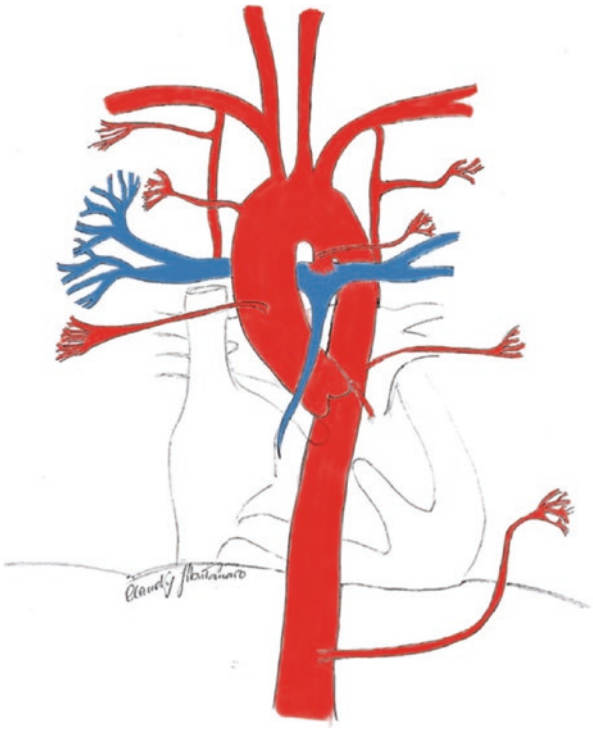

Fig. 6.3 Examples of collateral arteries in pulmonary atresia. Collaterals can derive for the aorta (typically the descending aorta), subclavian arteries, patent ductus arteriosus or coronaries

outlet septum. Pulmonary atresia may also be associated with an intact ventricular spectrum or more complex anatomy (e.g. transposition of great arteries, tricuspid atresia, etc.).

Within pulmonary atresia, there exists significant variability with regard to PA anatomy [6]. The PAs may be confluent and of adequate size, allowing repair by implantation of a right ventricle (RV) to PA conduit. When the PAs are small, implantation of a Blalock–Taussig or a central shunt may be required to promote growth and allow subsequent conduit repair. However, PAs are often small and may or may not be confluent, and may be supplied by arterial ducts or systemic-to-pulmonary collateral arteries, called major aortopulmonary collateral arteries (MAPCAs). In most severe cases, the entire intrapericardial pulmonary arterial tree may be absent and blood supply to the lungs is maintained exclusively by systemic-to-pulmonary collateral arteries (Fig. 6.3) [7]. MAPCAs may also develop in patients born with very severe right ventricular outflow tract obstruction [8].

Many but not all patients with pulmonary atresia may be amenable to repair, depending on the presence and size of the central pulmonary arteries or MAPCAs. "Unifocalization" involves a staged approach of reconstruction of the left and right PAs, with arterial shunting (typically Blalock–Taussig shunts). Eventually, the reconstructed PAs are connected and anastomosed to the RV by a conduit, with closure of the VSD in most cases.

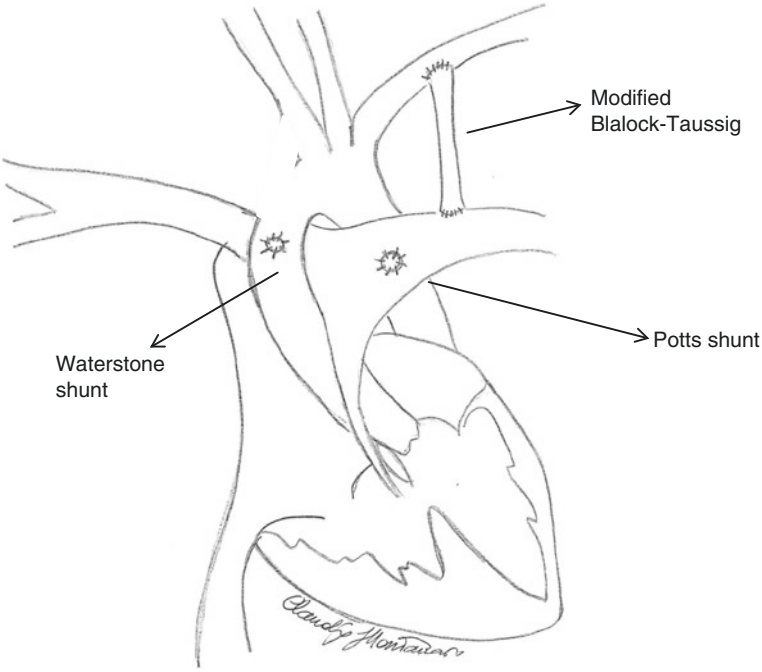

Fig. 6.4 The two types of central shunts: Waterston (between the ascending aorta and main or right pulmonary artery) and Potts (between the descending aorta and left pulmonary artery). These types of shunts have now been abandoned for the more easily sizeable modified Blalock–Taussig shunt (Gore-Tex tube from the left or right subclavian artery and the corresponding pulmonary artery). Older patients palliated with a Waterston or Potts shunt are likely to have developed pulmonary vascular disease in the pulmonary artery supplied by the shunt itself: when the pulmonary arteries are disconnected, or there are peripheral pulmonary stenoses, this will be segmental pulmonary hypertension

Not all patients are candidates for unifocalization and only relatively recently has outcome from this procedure improved [9–11]. Therefore, there exists a substantial population of patients with pulmonary atresia who have either undergone no surgery or have only received a palliative intervention or partial unifocalization. In these patients, PH may be present due to large collaterals or palliative shunts, especially Waterston or Potts shunts, which are difficult to size and may cause excessive flow to the lungs (Fig. 6.4). Moreover, there are patients in whom unifocalization has been achieved and an RV–PA conduit implanted, but the VSD was left open as a "relief valve" for the RV due to established high PA pressures resulting from peripheral pulmonary stenoses or PVD.

6.2.2 PH in Repaired Pulmonary Atresia

Right ventricular hypertension can often persist after total repair and may be due to PVD. Peripheral PS and segmental pulmonary hypertension are likely to divert

significant amounts of pulmonary blood flow, through "healthier" lung segments, which may result in increased shear stress and the development of PVD. Moreover, diastolic and systolic RV dysfunction is not uncommon due to long-standing cyanosis and hypertension, repeat surgery and the placement of the RV conduit. The decreased myocardial reserve is likely to affect long-term adaptation to RV hypertension and response to therapies, as it may behave different to the RV of patients with idiopathic PAH (iPAH) or even large VSDs. This may be aggravated by the closure of the VSD, which could otherwise act as a "relief valve" for the RV. Within PAH–CHD, patients with previously repaired defects are known to have a worse prognosis in adult life compared to patients in whom a defect remains patent. This may also apply to patients with repaired pulmonary atresia.

6.2.3 Unilateral Absence of Pulmonary Artery

Unilateral absence of PA is a very rare congenital cardiovascular defect. While no antegrade flow from the main to the "absent" PA is present, a hilar PA is often present, especially if supplied by a PDA of large collaterals. For this reason, the terms "proximal interruption of a PA", "non-confluent pulmonary arteries" or "ductal origin of the distal PA" have also been used [12].

Its prevalence, when isolated, is estimated at 1 in 200,000 to 1 in 300,000 adults [12–15]. However, 80% of reported cases involving the left PA were associated with other CHD, such as TOF and pulmonary atresia or truncus arteriosus [12, 14]. A review of the literature in 2011 found 352 cases of unilateral absence of PA, two thirds of which ($n = 237$) were associated with other congenital heart defects [16]. When a PDA is absent, collaterals to the affected lung may arise from bronchial, intercostal, subdiaphragmatic, subclavian or coronary arteries [17]. These connections may persist in the form of MAPCAs.

In the majority of cases with isolated unilateral absence of PA, there are no or minor symptoms, and individuals may reach adulthood undiagnosed. Some do complain of exercise intolerance and present with haemoptysis (in 19–44%) or recurrent chest infections, likely due to alveolar hypocapnia and bronchoconstriction, as well as poor delivery of inflammatory cells [12].

PH is present in 44% of cases and affects outcome, together with coexistent CHD [14]. Treatment depends on symptoms and anatomy, including the presence of AP collaterals, associated cardiovascular anomalies and PH [13, 18]. PH may occur due to increased flow to the "healthy" lung, which receives the entire cardiac output, and result in shear stress to the pulmonary vascular endothelium and vasoconstriction, which may cause vascular remodelling and a rise in pulmonary vascular resistance [18]. Animal models after ligation of the left PA and ductus arteriosus (14 newborn pigs) showed persistent muscular small pulmonary arteries after birth and an elevated PA pressure and RV hypertrophy [19, 20].

The management of isolated absence of PA should be based on symptoms, PA anatomy, associated cardiovascular anomalies and AP collaterals as well as the

presence of PH. No treatment is required in asymptomatic adult patients without evidence of cardiovascular overload. Patients with recurrent haemoptysis may benefit from embolization of collaterals or, in severe refractory cases, pneumonectomy [21–23].

In infants, repair may be possible through early or staged repair (starting with a shunt to the disconnected PA) to promote growth of the pulmonary arteries and lung. This may also reduce the prevalence of PH. In older patients, intrapulmonary arteries are usually severely hypoplastic or obstructed, and repair is not possible. In patients with PH, the use of PAH-specific therapies has been reported [12, 14, 24].

6.2.4 Hemitruncus Arteriosus

This is defined as abnormal origin of a single PA from the ascending aorta, with normal origin of the other PA from the RV [5–7]. As the heart has separate ventriculo-arterial junctions with separate aortic and pulmonary arterial valves, hemitruncus is felt to be a separate entity to common arterial trunk. Most commonly, it is the right PA which arises from the posterior aspect of the ascending aorta, near to the aortic valve. When the left PA originates for the aorta, there is usually a right aortic arch. The lung supplied by the PA originating from the aorta is pressure and volume overloaded. Over time, PVD develops, and mortality in the first year of life is high (up to 70%) unless timely repair is undertaken [8]. A small proportion of unrepaired patients do survive to adulthood and beyond, with unilateral (segmental) PH.

6.2.5 Truncus Arteriosus with Stenosis of a Single Pulmonary Artery

Truncus arteriosus or common arterial trunk is defined by the presence of an arterial trunk arising from the ventricular mass through a common ventriculo-arterial junction, giving rise to both systemic and pulmonary circulations. The pulmonary arteries originate from the arterial trunk in various patterns, classified into four types, according to Collett and Edwards (Fig. 6.5): [25]

- Type I: single pulmonary trunk from the left lateral aspect of the common arterial trunk, branching into left and right PA.
- Type II: separate origin of the PAs, but in proximity to each other, at the postero-lateral aspect of the common arterial trunk.
- Type III: the pulmonary arteries originate independent from each other from the left to the right lateral aspect of the common trunk.

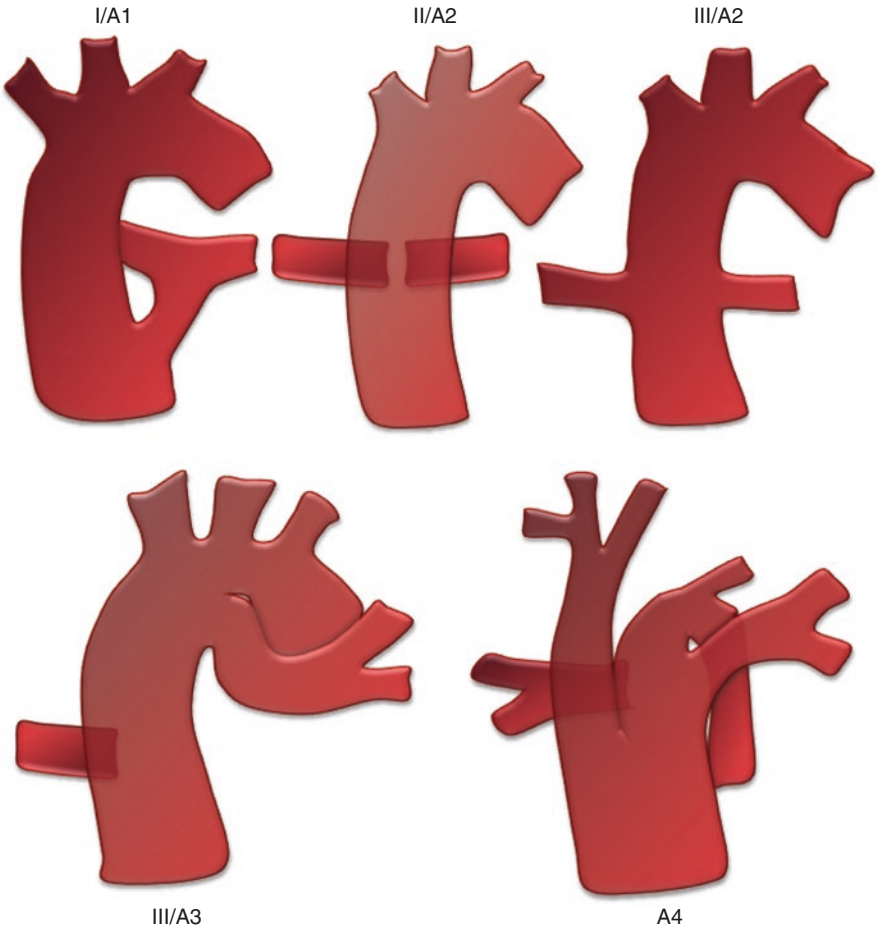

Fig. 6.5 Common arterial trunk: anatomic classification according to Collett and Edwards/Vann Praagh

There was a fourth type in this classification, with neither of the PAs originating from the common trunk, now classified as pulmonary atresia rather than truncus arteriosus. Van Praagh has proposed a separate classification (Types A1–A4, Fig. 6.5).

Stenosis of the origin of one or both PAs is present in up to one half of patients and, depending on its severity, may in a minority of patients protect one or both PAs from the development of PVD [26]. In the past, banding of the PAs was attempted prior to repair, while nowadays complete repair is the treatment of choice. Banding of the confluence of the PAs or of separate PA origins was not always effective, with stenosis of one of the PAs and the development of PH in one of two lungs. In other cases, certain pulmonary branches may be hypoplastic [27].

6.2.6 Large Post-tricuspid Defects with Peripheral Pulmonary Stenosis

Patients with large VSD, AVSD, PDA or AP window are expected to develop PVD unless they are repaired in a timely fashion or receive effective PA banding. Segmental PH may occur when the above defects are associated with peripheral PS (one or more), which, if severe enough, is able to protect the corresponding pulmonary vascular bed from the development of PVD. Moreover, a PA band may slip (dislocate) towards the bifurcation, causing stenosis of one of the two PAs, leaving the contralateral lung unprotected.

6.2.7 Waterston and Potts Shunts to a Single Lung

Systemic-to-pulmonary artery shunts are surgical procedures aimed at improving pulmonary blood flow and oxygenation and allowing the growth of the PAs in preparation of total repair of cyanotic congenital heart defects. Nowadays, this is most commonly achieved by means of a modified Blalock–Taussig shunt, (Fig. 6.4), using an appropriately sized interposition polytetrafluoroethylene (PTFE) graft between the subclavian artery and the PA, hence not sacrificing the subclavian artery (as was the case with the "classical B–T shunt"). Older types of shunts, such as the Waterston (ascending aorta and right pulmonary artery (RPA)) or the Potts shunt (descending aorta and left PA), have been abandoned, as they are difficult to size, and the risk of developing PH was high. When these shunts connect the aorta to a single PA (disconnected pulmonary arteries) or when peripheral PS is present or occurs as a result of the shunt, then segmental PH may develop (Fig. 6.2).

6.2.8 Scimitar Syndrome

Scimitar syndrome (i.e. right pulmonary vein to inferior vena cava) can be associated with abnormal arterial supply to the right lung (abnormal size and branching of the RPA and systemic arterial supply to part of the right lung) and at times PH (Fig. 6.6) [28]. A dilated capillary bed has been described in areas of the lung perfused not by the RPA but by systemic arteries. The development of PVD in the absence of a post-tricuspid defect may be due to large volumes of systemic arterial flow to the hypoplastic right lung. However, in histology in infants with scimitar syndrome who developed PH, arterial medial thickness was increased in both lungs, despite this being a pathology that affects the right lung only [29]. Guidelines on paediatric PH by the American Heart Association and American Thoracic Society use scimitar syndrome as an example of multifactorial PH, associated with venous obstruction, the sequelae of high flow from AP collaterals or anomalous pulmonary venous connection and/or lung hypoplasia [30, 31].

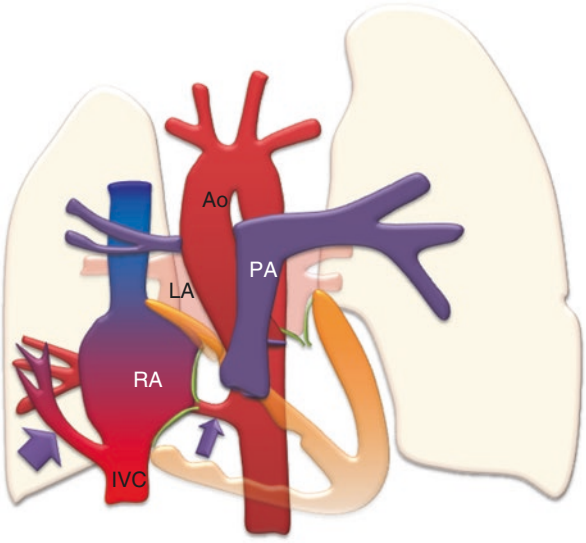

Fig. 6.6 Example of scimitar syndrome. The right pulmonary artery is hypoplastic. The mid-lower segments of the right lung are supplied by a collateral artery from the descending aorta (*thin arrow*). Pulmonary venous return from this portion of the lung occurs through a scimitar vein (*wide arrow*) to the inferior vena cava (often with stenosis at this level). The right lung is hypoplastic. *RA* right atrium, *IVC* inferior vena cava, *PA* pulmonary artery, *Ao* aorta, *LA* left atrium

Whether scimitar syndrome can be considered as part of the spectrum of segmental PH remains to be established.

6.2.9 Pulmonary Vein Stenosis

Stenosis of one or more pulmonary veins can cause an increase in pulmonary pressures through a rise in post-capillary pressure in the affected segment. In the presence of confluent pulmonary arteries, the rise in PA pressure will be detectable in the entire pulmonary arterial tree, despite being generated by increased resistance in part of the lung. The measurement of pulmonary wedge pressures in various lung segments will identify the region affected. Pulmonary vein stenosis can be congenital or acquired [32]. The latter is usually a result of previous surgery (e.g. atrial switch procedure for transposition of great arteries or repair of anomalous pulmonary venous return) or interventional procedures (e.g. ablation of atrial fibrillation), radiotherapy or extrinsic compression by enlarged cardiac chambers (e.g. a large right atrium (RA) in Fontan patients) or other masses.

While pulmonary vein stenosis is classified within group 2 of the PH classification, it is PH caused by disease of a single segment of the lung. If pulmonary arteries are confluent, the result will be a rise in PA pressures in the entire lung (Fig. 6.7).

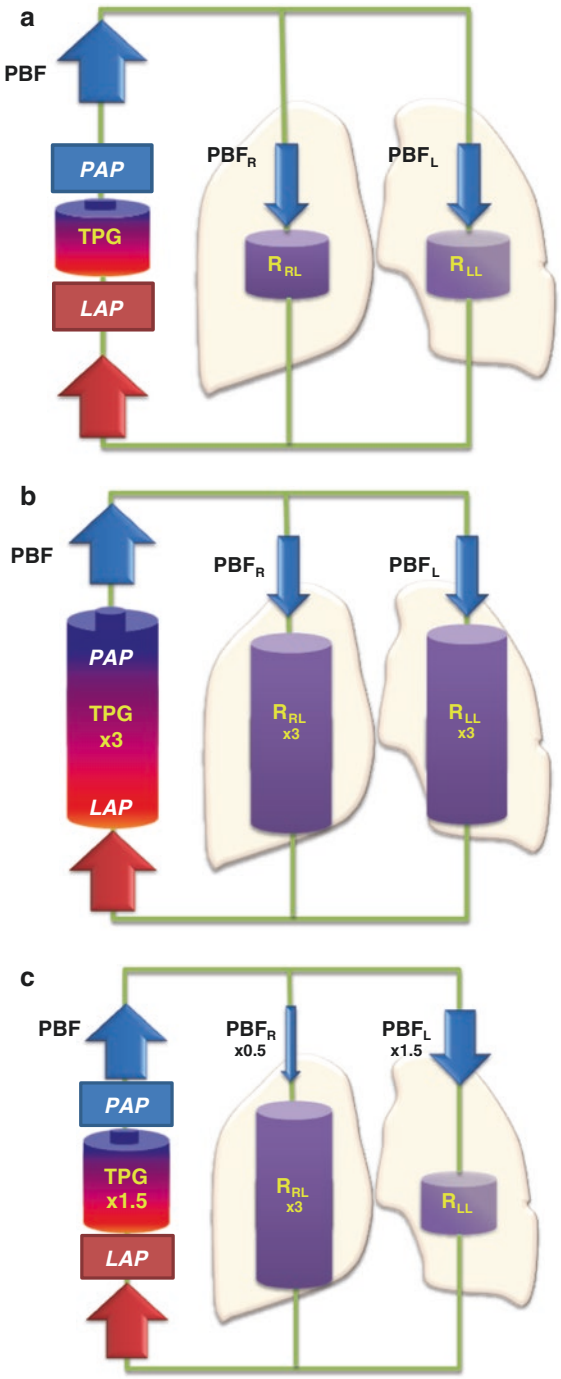

Fig. 6.7 Analogy of the pulmonary circulation to a simple electrical circuit. Each lung is represented by a resistance (R_{RL} and R_{LL} for the right and left lung, respectively), while a battery represents the transpulmonary gradient (TPG), i.e. the pressure gradient between the mean PA pressure and mean left atrial pressure. The electrical current equates to the pulmonary blood flow (PBF), divided into right (PBF_R) and left lung blood flow (PBF_L). In (**a**), both lungs have a normal resistance, and a normal TPG (low voltage battery) is sufficient to maintain a normal PBF. When the resistance in both lungs increases by three times (**b**), the TPG (voltage) has to increase threefold in order to preserve the PBF (current). If the resistance increases threefold in a single lung (**c**), the TPG has to be increased by 50% to maintain the total PBF. In this case, the PBF to the diseased lung will be 50% of normal, while that to the "healthy lung" is increased by 50%. The lung with normal resistance will also be hypertensive, and the shear stress may over time cause an increase in resistance in this lung as well. While this is an extremely simplified model of a theoretical state, it demonstrates that any condition that affects the vasculature of a single lung segment is likely to have a repercussion on the rest of the lung. This phenomenon is well described in chronic thromboembolic pulmonary hypertension, in which unobstructed segments develop pulmonary vascular disease [33]

6.3 Pulmonary Atresia in Tetralogy of Fallot

In the following sections of this chapter, we will focus on pulmonary atresia in TOF, which is one of the most common types of pulmonary atresia and the most common types of segmental PH.

The anatomy of the intrapericardial pulmonary arteries varies significantly between individuals with pulmonary atresia within the spectrum of TOF. In cases with an imperforate pulmonary valve, the pulmonary trunk is usually present and patent, but may supply only one PA, while the other PA may be disconnected or absent. In other cases, the pulmonary trunk can be atretic, presenting as a fibrous strand from the ventricular outflow tract to the PAs. When the right and left pulmonary arteries are present, they are usually confluent and tethered by the pulmonary trunk to the ventricle, resulting in the "seagull sign" on angiography. When the PAs are not confluent, one is typically connected to the remnant of the pulmonary trunk. The PAs can be supplied by PDAs or MAPCAs. In the most extreme cases, there are no intrapericardial PAs, and supply to the lungs is provided exclusively by MAPCAs (Fig. 6.3).

Blood supply to the PAs can, thus, be uni- or multifocal, depending on whether the lung is supplied by one or more sources. Unifocal supply requires unobstructed and confluent intrapericardial pulmonary arteries supplying both lungs, typically via a PDA, rarely by a single MAPCA, an AP window or a fistula from the coronary arteries. With multifocal pulmonary arterial supply, multiple MAPCAs feed the lungs, usually when a large PDA is absent. Confluent intrapericardial pulmonary arteries may exist but are usually not connected to all segments of both lungs, while the remaining lung parenchyma is supplied directly by MAPCAs to segments, or groups of segments, which may communicate with the confluent PAs. With non-confluent PAs, various parts of the lung can be supplied by a combination of MAPCAs, a PDA and AP window or, in the absence of these, by "acquired" collateral arteries through bronchial, intercostal or coronary arteries (Fig. 6.2 and. 6.3).

The above could be categorized in three patterns of PA supply:

1. Confluent PAs supplied by a large PDA.
2. Confluent PAs coexisting with MAPCAS: In this case, MAPCAs provide flow to the PAs through a variety of collaterals. Moreover, segments of the lung can be supplied directly by MAPCAs.
3. Absence of intrapericardial PAs: Blood flow supplied by MAPCAs only.

MAPCAs can either connect a systemic artery to the origin of the intrapulmonary arteries near the hilum or they can extend and branch along the bronchial tree. They are typically two to six, and they usually arise from the anterior wall of the aorta opposite the origin of the intercostal arteries but can also originate from the brachiocephalic or coronary arteries.

Large MAPCAs, with no stenotic segments, like large PDAs, cause pressure and volume overload in the segment of lung perfused; the shear stress to the arterioles

leads to the development of PVD, a situation not dissimilar to that observed in large post-tricuspid defects (Fig. 6.1), but, in this case, it only affects segments of the lung perfused by the large collaterals. The presence of MAPCAs is, of course, not synonymous to PH. MAPCAs are essential in maintaining adequate pulmonary blood flow in pulmonary atresia. A balance between adequate blood supply to most areas of the lung, and absence of PVD, is desirable and can help achieve acceptable oxygenation, reflected by peripheral systemic oxygen saturations.

6.4 The Assessment of Patients with Complex Pulmonary Atresia

Most patients with pulmonary atresia are cyanosed at birth, with obligatory mixing of oxygenated and deoxygenated blood within the aorta [6]. Cyanosis is worse when the collateral circulation is inadequate. In infants with excessive pulmonary flow, the praecordium is active. The first heart sound is normal, but the second heart sound is single and loud due to the vicinity of the aorta to the chest wall. An aortic ejection click can be heard due to the dilatation of the aortic root. Most characteristic are the continuous murmurs relating to the PDA or MAPCAs. Most importantly, if pulmonary vascular resistance increases distal to a large MAPCA, the continuous murmur will become systolic and will be ever less prominent as PVD progresses. Aortic regurgitation is not uncommon, but the murmur may be masked by the murmurs relating to the collaterals. In older patients, aortic stenosis may also develop. Electrocardiography reflects the right ventricular hypertrophy and right atrial dilatation.

Echocardiography is essential in the screening for segmental PH but is not sufficient for firmly establishing the diagnosis. By definition, neither estimates of right ventricular pressure (e.g. using the tricuspid regurgitation Doppler) nor any property of the RV (e.g. size or function) is a reflection of the state of the pulmonary circulation. Doppler can be used to interrogate flow through MAPCAs, a PDA or surgical shunts, providing rough estimates of the gradient between the aorta and the PAs, which is expected to be high in the absence of PH in the segment of the lung fed by the shunt.

Other noninvasive investigations can provide valuable information in the assessment of patients with pulmonary atresia. A plain chest x-ray (CXR) can provide information on the size of the pulmonary arteries, which are often dilated when hypertensive. Cardiac magnetic resonance provides valuable information of cardiovascular anatomy, including the morphology and size of central PAs, the presence and function of larger collateral arteries and shunts as well as the ventricular function, aortic dimensions and the function of the aortic valve, which is often regurgitant.

With recent advances in computed tomography (CT) imaging, this modality is now frequently used for obtaining anatomic information on the aorta and pulmonary arteries. Moreover, CT provides detailed information on shunts and MAPCAs and the presence of stenoses of occluded shunts and can facilitate repair in younger patients, also through 3D printing. Identification of large MAPCAs or a large PDA

invariably implies that the area of the lung perfused by these is hypertensive in adult patients. This is also supported by the presence of dilated pulmonary arteries or MAPCAs, often with evidence of intracavitary thrombosis.

Cardiac catheterization remains the gold standard for assessing all patients suspected to have PH, and this holds true also for segmental PH. Performing a full haemodynamic study in patients with complex pulmonary atresia requires pump injections into the aorta for the identification of MAPCAs and other shunts, followed by careful selective angiography and haemodynamic assessment of each vessel. This is a long and laborious process, often requiring large amounts of contrast medium. It is not without risks as collateral vessels need to be deeply intubated to assess pressures in the respective pulmonary segments and gradients along the collaterals. Damage to important collateral vessels and shunts can have devastating effects, and cardiac catheterization is currently undertaken only when important information is required for planning surgery or investigation for causes of symptomatic deterioration. In fact, the aims of cardiac catheterization in pulmonary atresia are to delineate the origin and distribution of blood flow to various lung segments, to assess the anatomy of the central pulmonary arteries (when present) and their relation of MAPCAs and to identify stenosis within the collateral vessels or shunts or at the level of the PAs. Cardiac catheterization in this setting is also limited by the inability to accurately assess pulmonary vascular resistance, especially in the presence of multifocal blood supply, with hyperperfused and hypoperfused segments of lungs immediately adjacent to each other. When blood supply is strictly unifocal (e.g. single large PDA or MAPCA), the central intrapericardial pulmonary arteries should be entered, whenever possible, to estimate pulmonary vascular resistance.

While the catheters introduced in the venous system can reach the aorta through the VSD, it is easier to identify and selectively assess MAPCAs and shunts through a retrograde arterial route. When attempting to intubate MAPCAs from the descending aorta, intercostal arteries (which may be enlarged when providing collateral circulation to the lung) may be entered. In this case, the catheter follows a posterior course from the aorta towards the paravertebral gutter; in contrast, MAPCAs follow an anterior course towards the hilum.

6.5 Surgical, Interventional and Medical Management

In all children born with complex pulmonary atresia with a VSD, the aim is to repair the defect abolishing cyanosis. In most cases, biventricular repair can be achieved through a Rastelli procedure in case of confluent PAs or after unifocalization, while in a minority of cases, only a Fontan-type palliation and other palliative procedures are undertaken (or no repair at all is possible) [34–36]. Palliative procedures in children are aimed at increasing pulmonary blood flow and peripheral oxygenation, allowing children to grow, before undertaking more complex surgery. Unifocalization of all the collaterals into a single pulmonary vascular tree, which can then be connected to the RV, is the ultimate aim (Fig. 6.8), unless there is clear evidence of established PVD. In unrepaired adult patients, placement of palliative shunts or

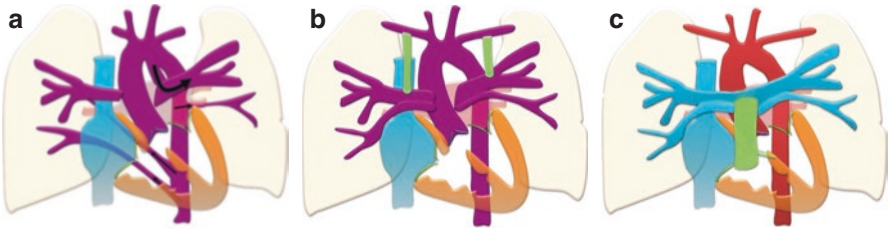

Fig. 6.8 Complex pulmonary atresia repair through unifocalization. Simplified schematic representation of the unifocalization process or repair of complex pulmonary atresia. In (s) pulmonary atresia with MAPCAs feeding the right lung and the midzone of the left lung, with a large PDA feeding the left mid-upper lung (*arrows*). Unifocalization is typically performed in stages (one lung at a time) and uses the MAPCAs to reconstruct the PA in each lung, attaching this to a Blalock–Taussig (B–T) shunt (b, B–T shunts in *green*). Thereafter, anastomosis of the PAs to an RV–PA conduit completes the procedure, with or without VSD closure. Unfortunately, peripheral pulmonary stenoses, persistent pulmonary vascular disease in pulmonary segments previously supplied by large collaterals and MAPCAs persisting or developing after repair are not uncommon. All of the above result in further overload of the RV, which may already be impaired as a result of the previously pressure overload and severe hypertrophy, cyanosis and repeat major surgery with implantation of a conduit

dilatation of existing but stenosed MAPCAs can be undertaken in symptomatic patients to improve pulmonary flow and systemic oxygen saturations.

Current medication for PAH (so-called specific or advanced therapies) acts directly or indirectly on smooth vascular musculature relaxation and proliferation by stimulation or inhibition of different pathways. The use of these medications is already approved in PAH and Eisenmenger physiology. There are only few studies in the literature that describe the effects of advanced therapies in segmental PH. A multicentre study by Schuuring et al. on seven patients with diagnosis of segmental PH due to pulmonary atresia treated with the endothelin receptor antagonist bosentan demonstrated a significant improvement in functional class and exercise tolerance, as 6-min walk test distance improved by 62 m [3].

Another observational study by Lim et al. on five adult patients with complex pulmonary atresia (or severe PS) and MAPCAs treated with the phosphodiesterase-type 5 inhibitor sildenafil showed good tolerance to the drug in four of five cases with good clinical response to treatment [37]. The five cases are briefly presented below to illustrate the potential effects and complications of treatment: Patient number 1 had undergone unifocalization and RV–PA conduit with partial closure of the VSD. She had stenotic PAs on the right treated with balloon dilatations. The left PA was still supplied by the large left Blalock–Taussig shunt and was hypertensive even after test occlusion of the shunt. The shunt was occluded and sildenafil was started, with unclear effects, as the patient deteriorated and died 2 years later. Patient number 2 was a 47-year-old man with hypoplastic PAs and had a previous Brock procedure (to relieve of RV outflow tract stenosis) and subsequent PA balloon angioplasty. He had hypoplastic PAs and MAPCAs and the PA pressure was two thirds of systemic. He started on sildenafil with a reported "striking" improvement in effort tolerance and oxygen saturations. Unfortunately, he died 7 months later with pneumonia complicated by haemoptysis and multi-organ failure. Patient 3 was an 18-year-old

patient with pulmonary atresia who had undergone unifocalization without closure of the VSD due to established PH in childhood. She was severely limited, and significant vasoreactivity was observed with acute nitric oxide testing on cardiac catheterization. Sildenafil was started but was not tolerated, and she was put on nifedipine, with some improvement in exercise capacity but not oxygen saturations. Patient 4 was a 17-year-old born with pulmonary atresia and hypoplastic confluent PAs. She had undergone repair (unifocalization) with VSD closure and embolization of persistent MAPCAs thereafter. PH was present during cardiac catheterization, and she was treated with sildenafil with a "remarkable" improvement in symptoms but no significant changes in haemodynamics. The last case was a 28-year-old with Di George syndrome and pulmonary atresia who received a Waterston (ascending aorta to PA) shunt and subsequent RV–PA conduit without VSD closure. He had near-systemic PA pressures and a severely hypoplastic right PA. There was some vasoreactivity with nitric oxide. Her symptoms improved significantly on sildenafil, as did oxygen saturations.

Yamamura et al. presented two children with segmental PH after pulmonary atresia treated with bosentan [38]. In both cases, there was an improvement in symptoms, haemodynamics and brain natriuretic peptide levels. Yasujara and Yamagishi presented three cases which could, possibly, have had segmental PH [8]. There was one paediatric case who developed PH after repair of pulmonary atresia (with unifocalization). PA pressure improved through percutaneous treatment of a peripheral PS and administration of phosphodiesterase-type 5 inhibitor and an endothelin receptor antagonist. Another case of an adult with unrepaired TOF with severe PS, hypoplastic PA tree and MAPCAs was found to have raised (peripheral) PA pressures and was treated with an endothelin receptor antagonist. There was alleviation of his symptoms of exercise intolerance and an improvement in his quality of life. The third case described was an adult with TOF and a hypoplastic left PA repaired at the age of 5 years. At age 27 years, his left PA was found to be occluded, and there were raised PA pressures on the right PA. Treatment with an endothelin receptor antagonist lead to a deterioration of his oxygen saturations, which the authors attributed to ventilation/perfusion mismatch or volume overload.

Overall, the effect of PAH therapy in patients with segmental PH is still debated. There are some promising data, but not all patients benefit and some may even become intolerant to such therapies. Segmental disease, by definition, does not involve the entire pulmonary vasculature, while the effects of medical treatment are on the entire lung and may cause ventilation/perfusion mismatch in hypoventilated segments. An increase in pulmonary blood flow may also theoretically overload the left ventricle, and care is recommended when considering specific PAH therapies in patients with established left ventricular dysfunction and/or aortic stenosis or regurgitation. Limitations in the assessment of pulmonary vascular resistance in patients with multiple sources of pulmonary blood flow and/or peripheral pulmonary stenoses also make the identification of patients who have developed significant PVD and could, thus, benefit the most for PAH therapies, quite difficult.

6.6 Which Group Does Segmental Pulmonary Hypertension Belong to?

Segmental PH is likely to share histological features with PAH (group 1), with the exception of cases caused by pulmonary vein stenosis. It is, indeed, difficult to imagine why the arteriolar changes in the portion of the lung supplied by a large MAPCA or PDA in the case of complex pulmonary atresia should differ to the changes caused to the entire lung by an isolated large PDA or AP window. Intimal proliferation but also impaired lung development has been described in hypertensive lung segments of young patients with pulmonary atresia, although most of the available data is in infants, when hypoxia due to lung hypoperfusion is a greater concern [39, 40]. Patients with pulmonary atresia surviving to adulthood are most likely to have been born with large collaterals, ensuring adequate flow to the lungs, but with the risk of developing PH.

The features of medial hypertrophy and intimal proliferation in pulmonary hypertensive areas in pulmonary atresia resemble the changes seen in PAH (see Chap. 1). However, the conditions grouped under PAH share not only histological but also clinical features and a similar response to therapy. In this chapter, we have described the wide range of conditions that could be grouped under the term of segmental PH, which differ significantly from PAH in terms of pathophysiology and the interaction between the heart and lungs. Moreover, there is still little evidence on the management of segmental PH, and extrapolation from PAH studies requires caution. While segmental PH does not appear to strictly fulfil the criteria for entering group 1 (PAH), it is clear that high levels of expertise are required for managing these patients and identifying potential therapeutic targets.

Conclusion

Segmental PH develops in patients when different portions of the lung are perfused differently in terms of origin of the flow (antegrade vs. collateral circulation or shunts) or due to the presence of obstructions in the pulmonary tree that “shield” some segments but not the entire lung. It can be congenital or acquired/iatrogenic. The prevalence of segmental PH is unknown, and the diagnosis requires in-depth understanding of the anatomy and heavily relies on invasive data. While the presence of large AP collateral vessels is not synonymous with segmental PH, it is likely to be the case when no significant gradient is present on echocardiography, and the flow through the collateral is systolic rather than continuous. The efficacy of PAH-specific therapies in segmental PH remains to be established, and, for this purpose, multicentre studies are warranted.

References

1. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M, Aboyans V, Vaz Carneiro A, Achenbach S, Agewall S, Allanore Y, Asteggiano R, Paolo Badano L, Albert Barberà J, Bouvaist H, Bueno H, Byrne RA, Carerj S, Castro G, Erol Ç, Falk V, Funck-Brentano C, Gorenflo M, Granton J, Iung B, Kiely DG, Kirchhof P, Kjellstrom B, Landmesser U, Lekakis J, Lionis C, Lip GYH, Orfanos SE, Park MH, Piepoli MF, Ponikowski P, Revel M-P, Rigau D, Rosenkranz S, Völler H, Luis ZJ (2016) 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 37:67–119
2. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, Gomez Sanchez MA, Krishna Kumar R, Landzberg M, Machado RF, Olschewski H, Robbins IM, Souza R (2013) Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 62:D34–D41
3. Schuuring MJ, Bouma BJ, Cordina R, Gatzoulis MA, Budts W, Mullen MP, Vis JC, Celermajer D, Mulder BJM (2013) Treatment of segmental pulmonary artery hypertension in adults with congenital heart disease. Int J Cardiol 164:106–110
4. Tchervenkov CI, Roy N (2000) Congenital Heart Surgery Nomenclature and Database Project: pulmonary atresia—ventricular septal defect. Ann Thorac Surg 69:S97–105
5. Barbero-Marcial M (2001) Classification of pulmonary atresia with ventricular septal defect. Ann Thorac Surg 72:316–317
6. Baker E, Anderson R (2009) Tetralogy of Fallot with pulmonary atresia. In: Anderson R, Baker EJ, Redington A, Rigby ML, Penny D, Wernovsky G (eds) Paediatric cardiology: expert consult—online and print, 3rd edn. Churchill Livingstone, London
7. Anderson R, Baker EJ, Redington A, Rigby ML, Penny D, Wernovsky G (eds) (2009) Paediatric cardiology: expert consult—online and print, 3rd edn. Churchill Livingstone, London
8. Yasuhara J, Yamagishi H (2015) Pulmonary arterial hypertension associated with tetralogy of Fallot. Int Heart J 56(Suppl):S17–S21
9. Ashburn DA, Blackstone EH, Wells WJ, Jonas RA, Pigula FA, Manning PB, Lofland GK, Williams WG, BW MC, Congenital Heart Surgeons Study members (2004) Determinants of mortality and type of repair in neonates with pulmonary atresia and intact ventricular septum. J Thorac Cardiovasc Surg 127:1000–1007
10. Lightfoot NE, Coles JG, Dasmahapatra HK, Williams WG, Chin K, Trusler GA, Freedom RM (1989) Analysis of survival in patients with pulmonary atresia and intact ventricular septum treated surgically. Int J Cardiol 24:159–164
11. Hoashi T, Kagisaki K, Kitano M, Kurosaki K, Shiraishi I, Yagihara T, Ichikawa H (2012) Late clinical features of patients with pulmonary atresia or critical pulmonary stenosis with intact ventricular septum after biventricular repair. Ann Thorac Surg 94:833–841. discussion 841
12. Kruzliak P, Syamasundar RP, Novak M, Pechanova O, Kovacova G (2013) Unilateral absence of pulmonary artery: pathophysiology, symptoms, diagnosis and current treatment. Arch Cardiovasc Dis 106:448–454
13. Welch K, Hanley F, Johnston T, Cailes C, Shah MJ (2005) Isolated unilateral absence of right proximal pulmonary artery: surgical repair and follow-up. Ann Thorac Surg 79:1399–1402

14. Jan Ten Harkel AD, Blom NA, Ottenkamp J (2002) Isolated unilateral absence of a pulmonary artery: a case report and review of the literature. Chest 122:1471–1477
15. Bouros D, Pare P, Panagou P, Tsintiris K, Siafakas N (1995) The varied manifestation of pulmonary artery agenesis in adulthood. Chest 108:670–676
16. Bockeria LA, Makhachev OA, Khiriev TK, Abramyan MA (2011) Congenital isolated unilateral absence of pulmonary artery and variants of collateral blood supply of the ipsilateral lung. Interact Cardiovasc Thorac Surg 12:509–510
17. Gupta K, Livesay JJ, Lufschanowski R (2001) Absent right pulmonary artery with coronary collaterals supplying the affected lung. Circulation 104:E12–E13
18. Pool PE, Vogel JHK, Blount SG (1962) Congenital unilateral absence of a pulmonary artery. Am J Cardiol 10:706–732
19. Haworth SG, De L, Macartney FJ (1981) Hypoperfusion and hyperperfusion in the immature lung. Pulmonary arterial development following ligation of the left pulmonary artery in the newborn pig. J Thorac Cardiovasc Surg 82:281–292
20. Haworth SG, McKenzie SA, Fitzpatrick ML (1981) Alveolar development after ligation of left pulmonary artery in newborn pig: clinical relevance to unilateral pulmonary artery. Thorax 36:938–943
21. Bekoe S, Pellegrini RV, DiMarco RF, Grant KJ, Woelfel GF (1993) Pneumonectomy for unremitting hemoptysis in unilateral absence of pulmonary artery. Ann Thorac Surg 55:1553–1554
22. Brinson GM, Noone PG, Mauro MA, Knowles MR, Yankaskas JR, Sandhu JS, Jaques PF (1998) Bronchial artery embolization for the treatment of hemoptysis in patients with cystic fibrosis. Am J Respir Crit Care Med 157:1951–1958
23. Taguchi T, Ikeda K, Kume K, Nagasaki A, Goto S, Matsuo S, Hasuo K, Tamura S (1987) Isolated unilateral absence of left pulmonary artery with peribronchial arteriovenous malformation showing recurrent hemoptysis. Pediatr Radiol 17:316–318
24. Shostak E, Sarwar A (2009) A 50-year-old woman with dyspnea, lower extremity edema, and volume loss of the right hemithorax. Chest 136:628–632
25. Collett RW, Edwards JE (1949) Persistent truncus arteriosus; a classification according to anatomic types. Surg Clin North Am 29:1245–1270
26. Calder L, Van Praagh R, Van Praagh S, Sears WP, Corwin R, Levy A, Keith JD, Paul MH (1976) Truncus arteriosus communis. Clinical, angiocardiographic, and pathologic findings in 100 patients. Am Heart J 92:23–38
27. Van Praagh R, Van Praagh S (1965) The anatomy of common aorticopulmonary trunk (truncus arteriosus communis) and its embryologic implications. Am J Cardiol 16:406–425
28. Honey M (1977) Anomalous pulmonary venous drainage of right lung to inferior vena cava ("scimitar syndrome"): clinical spectrum in older patients and role of surgery. Q J Med 46:463–483
29. Haworth SG, Sauer U, Bühlmeyer K (1983) Pulmonary hypertension in scimitar syndrome in infancy. Br Heart J 50:182–189
30. Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, Hanna BD, Rosenzweig EB, Raj JU, Cornfield D, Stenmark KR, Steinhorn R, Thébaud B, Fineman JR, Kuehne T, Feinstein JA, Friedberg MK, Earing M, Barst RJ, Keller RL, Kinsella JP, Mullen M, Deterding R, Kulik T, Mallory G, Humpl T, Wessel DL (2015) Pediatric pulmonary hypertension guidelines from the American Heart Association and American Thoracic Society. Circulation 132:2037–2099
31. Vida VL, Padalino MA, Boccuzzo G, Tarja E, Berggren H, Carrel T, Çiçek S, Crupi G, Carlo DD, Donato RD, Fragata J, Hazekamp M, Hraska V, Maruszewski B, Metras D, Pozzi M, Pretre R, Rubay J, Sairanen H, Sarris G, Schreiber C, Meyns B, Tlaskal T, Urban A, Thiene G, Stellin G (2010) Scimitar syndrome a European Congenital Heart Surgeons Association (ECHSA) multicentric study. Circulation 122:1159–1166
32. Latson LA, Prieto LR (2007) Congenital and acquired pulmonary vein stenosis. Circulation 115:103–108
33. Lang IM, Madani M (2014) Update on chronic thromboembolic pulmonary hypertension. Circulation 130:508–518

34. Rastelli GC, Ongley PA, Davis GD, Kirklin JW (1965) Surgical repair for pulmonary valve atresia with coronary-pulmonary artery fistula: report of case. Mayo Clin Proc 40:521–527
35. Alfieri O, Blackstone EH, Kirklin JW, Pacifico AD, Bargeron LM (1978) Surgical treatment of tetralogy of Fallot with pulmonary atresia. J Thorac Cardiovasc Surg 76:321–335
36. Yagihara T, Yamamoto F, Nishigaki K, Matsuki O, Uemura H, Isizaka T, Takahashi O, Kamiya T, Kawashima Y (1996) Unifocalization for pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries. J Thorac Cardiovasc Surg 112:392–402
37. Lim ZS, Vettukattill JJ, Salmon AP, Veldtman GR (2008) Sildenafil therapy in complex pulmonary atresia with pulmonary arterial hypertension. Int J Cardiol 129:339–343
38. Yamamura K, Nagata H, Ikeda K, Ihara K, Hara T (2012) Efficacy of bosentan therapy for segmental pulmonary artery hypertension due to major aortopulmonary collateral arteries in children. Int J Cardiol 161:e1–e3
39. Thiene G, Frescura C, Bini RM, Valente M, Gallucci V. Histology of pulmonary arterial supply in pulmonary atresia with ventricular septal defect. Circulation 1979;60:1066–1074
40. Haworth SG, Reid L. Quantitative structural study of pulmonary circulation in the newborn with pulmonary atresia. Thorax 1977;32:129–133

Pulmonary Vascular Disease in Patients with Fontan-Type Circulation

7

Lars Idorn and Lars Søndergaard

Abbreviations

ACE	angiotensin converting enzyme
BDG	bidirectional Glenn
BSA	body surface area
CHD	congenital heart disease
HTx	heart transplantation
ICD	implantable cardioverter defibrillator
IVIG	intravenous immunoglobulin
IVC	inferior vena cava
MCT	medium-chained triglyceride
MPA	main pulmonary artery
MRI	magnetic resonance imaging
PA	pulmonary artery
PVR	pulmonary vascular resistance
RA	right atrium
SVC	superior vena cava
TCPC	total cavopulmonary connection
UVH	univentricular heart

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Functional univentricular heart (UVH) is a complex (congenital heart disease (CHD)) with an incidence of 3–5 per 100 children with CHD [1, 2]. The natural prognosis of UVH is poor with a reported survival rate of less than 50% at 1 year and 10% at 10 years [3]. UVH is a heterogeneous patient group defined as one ventricle being incapable of supporting either the systemic or the pulmonary circulation and/or biventricular repair is impossible [4]. Examples of UVH are double inlet left ventricle, tricuspid or mitral atresia, pulmonary atresia with intact ventricular septum, hypoplastic left heart syndrome and unbalanced atrioventricular septal defect. An example when biventricular repair is impossible despite there being two well-developed ventricles is a large ventricular septal defect with straddling atrioventricular valve.

The Fontan operation represents the final stage in the strategy of choice for management of these patients. Despite improved prognosis after the introduction of the Fontan procedure, as originally described by Fontan and Baudet in 1971 [5], mortality in children born with UVH remains high, with 5-year survival from 38 to 75% depending on the diagnostic category of UVH [6]. This high mortality reflects the fact that many children born with UVH will die without completion of a Fontan-type circulation. On the other hand, survival in UVH children completing the Fontan procedure is relatively good with a 10-year postoperative survival rate above 90% [7]. An increasing number of Fontan patients are entering adulthood; it is clear that this procedure, despite modifications since the initial Fontan procedure, remains palliative. Patients are prone to developing arrhythmias, exercise intolerance, thromboembolic events, heart failure, protein-losing enteropathy, liver problems and other severe Fontan-related complications [8]. The aetiology of many of the complications is incompletely understood and treatment remains a challenge (Table 7.1).

With the current surgical techniques, the prospects for significant improvement of long-term complications seem limited. The main cause of the prognosis problem is that the Fontan operation fails to achieve the normal physiology observed in a two-ventricle circulation as a result of the lack of a sub-pulmonary ventricle pumping blood through the pulmonary circulation.

This chapter aims to give an overview of the Fontan procedure and its physiology, focusing on the pulmonary circulation.

7.1 Classic Fontan Procedure and Modifications

In the UVH circulation, the pulmonary and systemic circulations are placed in parallel, whereas after Fontan completion the two circulations are separated and placed in series excluding the functional ventricle from the pulmonary circulation. Hence, blood ejected from the single ventricle into the aorta, flows through both the systemic and pulmonary circulation without any further myocardial propulsive contribution, until it once again reaches the ventricle. Consequently, non-pulsatile or severely attenuated pulsatile blood flow enters the lungs due to the absence of a sub-pulmonary ventricle.

Table 7.1 Long-term complications following Fontan surgery

Complication	Potential aetiology	Potential treatment
Arrhythmias Brady- and tachyarrhythmias	– Atrial dilatation	– Electrical cardioversion
	– Atrial fibrosis	– Class IC or class III agents
	– Suture lines	– Radiofrequency ablation
		– Haemodynamic evaluation and potential surgical corrections
		– Pacemaker/ implantable cardioverter defibrillator ICD
Thromboembolic events	– Incompletely understood, most likely multifactorial involving hypercoagulability, abnormal haemodynamics and endothelial injury/dysfunction	No consensus. Anticoagulation is indicated in the presence of atrial thrombus, atrial arrhythmias or thromboembolic events. Antiplatelet therapy
Exercise intolerance	– Reduced preload	Improvement may be achieved from pulmonary vasodilators
	– Ventricular impairment	
	– Chronotropic incompetence	
	– Reduced pulmonary diffusing capacity	
	– Pulmonary vascular disease	
Impaired ventricular function	– Overloaded and dilated ventricle in the neonatal period	Conventional heart failure therapy has limited effect in most patients
	– Underfilled and preload-deprived ventricle after Fontan completion	
Hypoxemia	– Veno-venous collateralization	Surgical or transcatheter correction
	– Pulmonary arteriovenous malformations	
	– Progressive ventricular impairment with or without AV valve regurgitation	
	– Fenestration, baffle leak or residual interatrial communication (classic Fontan)	
	– Pulmonary vein compression by giant right atrium or aorta	
Reduced pulmonary diffusing capacity	– No sub-pulmonary ventricle	No available data
	– Pulmonary vascular disease	

(continued)

Table 7.1 (continued)

Complication	Potential aetiology	Potential treatment
Hepatic dysfunction	– Chronic liver congestion due to increased central venous pressure and reduced hepatic circulation due to low cardiac output	No available data
Protein-losing enteropathy	– Decreased cardiac output	– Diet: medium-chained triglyceride MCT diet
	– Increased systemic venous pressure	– Medical: angiotensin converting enzyme ACE inhibitors, steroids, unfractionated heparin, diuretics, transfusion with albumin, intravenous immunoglobulin IVIG
	– Inflammation – Pulmonary vascular dysfunction	– Surgical: fenestration, atrioventricular pacing and cardiac transplantation
Plastic bronchitis	– Incompletely understood, most likely multifactorial with aetiology similar to protein-loosing enteropathy PLE	
Fontan failure	– Severely reduced cardiac output due to any Fontan-related complication	– Fontan takedown, Fontan conversion or heart transplantation HTx

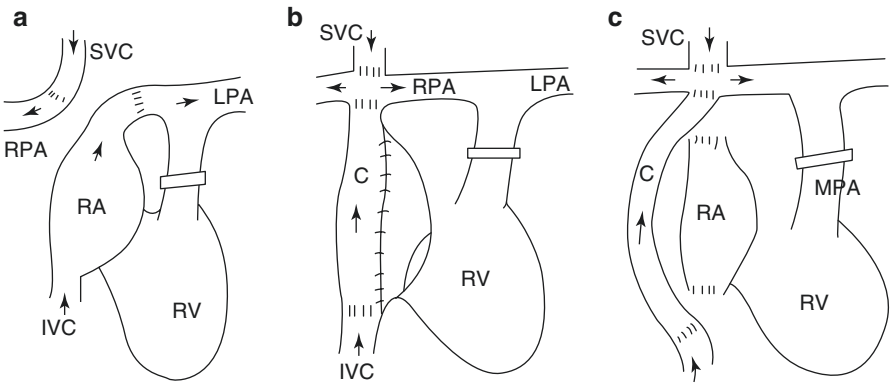

Fig. 7.1 Fontan modifications. (**a**) Classic Fontan (RA–PA), (**b**) lateral tunnel TCPC, (**c**) extracardiac conduit TCPC. *IVC* inferior vena cava, *LPA* left pulmonary artery, *MPA* main pulmonary artery, *RA* right atrium, *RPA* right pulmonary artery, *RV* right ventricle, *SVC* superior vena cava. www.fontanoperation.com

In 1971 Fontan and Baudet published their report describing the first successful surgical repair for tricuspid atresia. The original Fontan operation consisted of a classic Glenn anastomosis between the superior vena cava (SVC) and the right pulmonary artery (PA), closure of the atrial septal defect, insertion of a homograft valve in the inferior vena cava (IVC) ostium and placement of a valved conduit

between the right atrium (RA) and the left PA [5] (Fig. 7.1a). While initially applied to patients with tricuspid atresia, the indications for this operation have been widely extended, as have the criteria for consideration of the Fontan procedure [9].

From the classic Fontan procedure (the right atrium-to-pulmonary artery (RA–PA) anastomosis), there has been considerable evolution in surgical techniques. In 1973, Kreutzer et al. described a large direct anastomosis between the RA appendage and the main PA with its intact pulmonary valve, without the use of a Glenn procedure [10]; in 1978, Björk et al. described an anastomosis between the right atrial appendage and the right ventricular outflow in patients with tricuspid atresia and a relatively small but well-functioning right ventricle (RV) [11]. However, a number of disadvantages of the RA–PA anastomosis became apparent with time, mainly progressive dilatation of the RA secondary to the elevated pressure, right pulmonary vein compression, thromboembolism and supraventricular arrhythmias [12]. Also pulmonary arteriovenous malformations in the right lung were reported and were felt to be caused by the lack of hepatic venous drainage and "hepatic factor" into the right lung [13]. These observations, along with experimental findings of de Leval et al., were the basis for the introduction of the total cavopulmonary connection (TCPC) using the lateral tunnel technique, whereby the RA was baffled with an intra-atrial patch to channel the IVC blood flow to the right PA, which communicated with the left PA. In this way, all but the lateral wall of the RA was excluded from the Fontan pathway and the SVC was sutured directly to the undivided right PA (bidirectional Glenn (BDG)) [14] (Fig. 7.1b). The TCPC was considered to be more energy efficient, and the concept was further extended by Marcelletti et al. who introduced the extra-cardiac conduit, which is the procedure of choice in most centres today [15]. The extra-cardiac conduit consisted of replacement of the intra-atrial route of venous blood by insertion of an extra-cardiac synthetic tube graft connecting the IVC to the right PA (Fig. 7.1c). Thereby, atrial manipulation was minimized, atrial incision and suture lines were eliminated, and the procedure could be performed without cardiopulmonary bypass in some patients.

The superiority of the TCPC compared to the RA–PA anastomosis, with regards to short- and long-term mortality and morbidity, became obvious with time [7]. Furthermore, clear clinical improvement was shown after Fontan conversion from the RA–PA anastomosis to the TCPC [16]. Comparison of the lateral tunnel and the extra-cardiac conduit has shown no difference in mortality [17–19], whereas conflicting data on the prevalence of arrhythmias is available, with studies reporting a lower incidence of arrhythmia in the extra-cardiac conduit TCPC [17, 18], equal risk of arrhythmia between the two techniques [20] or less frequent arrhythmia in the lateral tunnel TCPC [19]. Fenestration and staging of the Fontan procedure has also been introduced in order to improve outcome.

7.1.1 Fenestration

In 1990, Bridges et al. described the use of fenestration as part of the Fontan procedure [21]. The fenestration functions by allowing right-to-left shunt when systemic

venous pressure is elevated, resulting in an increased systemic cardiac output – albeit at the expense of cyanosis – which is preferable in the immediate postoperative period in some patients. It later became clear that creating a fenestration improved survival in high-risk patients [8, 22] and reduced duration of hospital stay, as well as the duration and volume of chest tube drainage [23, 24]. The necessity and proper timing of fenestration closure using cardiac catheterization remain unknown and may be considered in cyanotic patients if test balloon occlusion does not cause critically elevated systemic venous pressure [25]. After fenestration closure, improved oxygenation, reduced need for anticongestive medication and improved somatic growth but higher incidence of tachyarrhythmias have been reported [26, 27].

7.1.2 Staging

One of the major improvements resulting in a significant decrease in morbidity and mortality following the Fontan procedure has been the concept of staging by a preceding BDG or hemi-Fontan operation [28, 29] (Table 7.2). Timing of the BDG procedure has been discussed in several studies, with many highlighting the benefit of performing an "early" Glenn anastomosis between 2 and 6 months of age [30–33]. The optimal timing of Fontan completion remains unknown and is performed in most centres between 2 and 4 years of age [34].

7.2 Fontan Physiology

In the normal biventricular circulation, pulmonary circulation and systemic circulation are connected in series. In the UVH patient, the two circulations are placed in parallel, whereas after the Fontan completion, they are placed in series, but still

Table 7.2 Staged Fontan procedure

Stage	Type of surgery	
1	• Blalock–Taussig shunt	*Aim*: achieve unrestricted systemic outflow and balanced pulmonary blood flow
	• Pulmonary artery banding	*Consequence*: the parallel circuit is maintained, the ventricle is volume overloaded and arterial desaturation persists
	• Norwood-type surgery	
2	• Bidirectional Glenn anastomosis	*Aim*: connect the SVC to the PA and eliminate or restrict other sources of pulmonary blood flow
		Consequence: removes the left-to-right shunt and, thereby, unloads the ventricle. Arterial desaturation persists
3	• Total cavopulmonary connection	*Aim*: connect the IVC to the PA
		Consequence: separated pulmonary and systemic circulation now placed in series. Normal or near-normal saturation

only containing one ventricle, which is placed before the systemic circulation. In other words, the ventricle in the Fontan circuit has to overcome an increased afterload compared to the biventricular circulation, since the ventricle has to overcome both the systemic vascular resistance and the pulmonary vascular resistance (PVR). Due to the lack of a sub-pulmonary ventricle producing a step up in PA pressure and producing pulsatile pulmonary blood flow, a chronic elevation of systemic venous pressure is required to maintain transpulmonary blood flow. Forward pulmonary blood flow is opposed by the resistance created by the Fontan circuit, the main PA branches, the intraparenchymal small pulmonary arteries as well as a high post-capillary pressure often due to diastolic dysfunction of the systemic ventricle or valve dysfunction. Additional factors limiting effective pulmonary blood flow are the presence of a right–left shunt (fenestration, residual intra-atrial leaks in the Fontan pathway, system venous to pulmonary venous collaterals) or the presence of systemic–pulmonary collaterals [35]. Thus, the "normal" haemodynamic status in a Fontan patient is characterized by elevated systemic venous pressure, decreased (in particular during exercise/stress situations) and non-pulsatile pulmonary blood flow, decreased ventricular preload and increased ventricular afterload.

7.2.1 The Single Ventricle

In the normal heart, the RV acts as a pump and drives the systemic venous blood into the pulmonary circulation. The tricuspid valve guards the RA and the systemic veins from the pressure generated in the RV. Therefore, systemic venous pressure remains low (<10 mmHg), while the systolic PA pressure is higher (>15 mmHg). In the Fontan circulation, the systemic venous blood is directly channelled into the PA from the systemic veins. Therefore, creation of a cavopulmonary connection results in a higher systemic venous pressure than normal (10–15 mmHg), since the systemic venous pressure is equal or above the PA pressure [36].

Before birth the single ventricle of a fetus with UVH is enlarged when compared to a normal left ventricle for body surface area BSA) [37]. A normal left ventricle carries 40–45% of fetal cardiac volume output, whereas the single ventricle carries as much as 220–250% of the expected volume output [37]. After birth, the pulmonary and systemic circulation are placed in parallel in an UVH. Consequently, arterial desaturation caused by mixing of venous and arterial blood and continued volume overload to the single ventricle is usually present. This parallel circuit needs to be maintained until the PVR has declined and the SVC and IVC and pulmonary arteries (PA) have grown adequately to perform the Fontan procedure. Meanwhile, the pulmonary circulation often needs to be manipulated through banding of the PA (if no anatomical restriction to pulmonary blood flow is present), or placement of a systemic-to-PA shunt and possibly either discontinuation or banding of the PA. Volume load to the single ventricle will thus be around 250–350% when related to normal for BSA [37]. Consequently, a solid physiological basis for creation of a

cavopulmonary circulation (Fontan circulation) is present, thereby relieving arterial desaturation and volume overload to the single ventricle.

The dramatic volume overload to the single ventricle, in combination with the cyanosis before the BDG or Fontan procedure, may eventually lead to a progressive deterioration of the systemic ventricular function, which is partially reversible [38]. When ventricular volume overload is suddenly removed after the BDG/Fontan operation, geometric alterations occur in the face of relatively stable ventricular mass but a considerable decrease in cavity size. These sudden changes may impair diastolic ventricular function and result in critically low cardiac output postoperatively [39, 40]. A complete Fontan procedure unloads the systemic ventricle to 50–70% of normal if the volume load is related to BSA, but to <50% if related to the size of the severely dilated ventricle [37]. Obviously, a large chronically volume overloaded ventricle should be avoided by restricting pulmonary blood flow early and excessive unloading should be avoided by staged surgery and early unloading of the ventricle at the time of the BDG.

Regarding the role of the ventricular function in relation to cardiac output, it appears that limited cardiac output will only be evident when systolic ventricular function is severely impaired. In most Fontan patients with a reasonable systolic function, it does not seem to play a significant role, whereas an impaired preload reserve is the limiting factor of cardiac output [41]. However, Schmitt et al. found in their study, using magnetic resonance imaging (MRI) catheterization, a significant and adequate decrease in PVR during dobutamine stress along with enhanced pulmonary blood flow [42]. Meanwhile, decreased diastolic compliance and unchanged stroke volume was observed, indicating that diastolic dysfunction might also be a determinant of cardiac output in Fontan patients.

7.2.2 The Pulmonary Circulation and the Role of the PVR

The pulmonary circulation is a key factor in the Fontan-type circulation due to absence of a sub-pulmonary ventricle. The elevated systemic venous pressure, together with the negative intrathoracic pressure during inspiration, are the driving forces for the transpulmonary flow. The lack of a sub-pulmonary ventricle results in a non-pulsatile or severely attenuated pulsatile pulmonary blood flow, although atrial contraction may cause some pulsatile pulmonary flow in case of RA–PA anastomosis or a lateral tunnel [43]. Furthermore, in the absence of a sub-pulmonary ventricle, forward flow in the Fontan circulation is highly dependent on the presence of the following physiological conditions: PVR must be low, the PA should be of adequate size, no significant valvulopathy should be present, and the systemic ventricle must have an adequate systolic and diastolic function. Therefore, it is essential to preserve the above conditions in both the pre- and post-Fontan state.

Table 7.3 Potential reasons for increased PVR in Fontan patients

• Pulmonary hyper- or hypo-perfusion
• Non-pulsatile pulmonary blood flow
• Cyanosis
• Age

A low PVR is crucial for the optimum functioning of the Fontan circulation [44] and a high PVR was shown to be a strong predictor of mortality [45]. The pulmonary blood flow is determined by the transpulmonary pressure gradient and PVR. The transpulmonary gradient, which is the difference between the systemic venous pressure and the pulmonary venous pressure in Fontan patients, shows little variability at rest [41]. Consequently, PVR appears to be the major determinant of transpulmonary blood flow, and influences preload to the systemic ventricle in the absence of a fenestration. As stated, above early restriction of pulmonary blood flow until BDG is of great importance to preserve ventricular function. On the other hand, it is of equal or maybe greater importance to offer sufficient flow at an adequate pressure to the PA in order to ensure continuing lung growth and a high-quality pulmonary vascular bed with low PVR [37]. The different physiology and flow conditions from birth to Fontan completion may affect the pulmonary circulation in different ways, and long-term follow-up has shown that PVR may rise years after Fontan completion (Table 7.3).

7.2.3 Pulmonary Hyper- or Hypo-perfusion

Flow through a circuit is determined by the driving force and the resistance. Before the stage 1 procedure (Table 7.2), flow distribution to the systemic and pulmonary circulation predominantly depends on their respective vascular resistances, and – unless a flow restriction is presented proximal to the pulmonary vascular bed, e.g. pulmonary stenosis – increased pulmonary blood flow will prevail. If left untreated, this may lead to proliferative changes in the pulmonary vascular bed and elevated PVR. In case of reduced pulmonary blood flow due to pre-pulmonary obstruction, the PA and vascular bed may remain underdeveloped, also resulting in raised PVR.

It is impossible to create a Fontan circuit in the neonatal period, since PVR is too high and the vessels used in the cavopulmonary connections are too small. Therefore, the goal of the stage 1 procedure, besides survival, is to provide unobstructed systemic outlet, unobstructed systemic and pulmonary venous return and ensure adequate pulmonary blood flow. Therefore, the outcome of the stage 1 procedure is crucial for achieving a balanced pulmonary and systemic circulation and a good short and long-outcome after Fontan completion.

7.2.4 Non-pulsatile Pulmonary Blood Flow

The lack of pulsatile pulmonary blood flow may result in increased PVR in Fontan patients. It has been shown that pulsatile flow regulates the shear stress-mediated release of many endothelium vasoactive molecules and deregulation of this mechanism may lead to endothelial dysfunction [46].

The non-pulsatile pulmonary blood flow has been shown in animal models simulating Fontan-type circulation to increase PVR through vascular remodelling [47]. This effect is possibly mediated by reduced pulmonary endothelial nitric oxide (NO) expression, which causes vasoconstriction, intimal and medial thickening and consequently increased PVR [48]. The non-pulsatile blood flow has also been shown to have major effects on endothelial function [49], reduced vascular recruitment [50, 51] and lung vessel growth, which in turn influence PVR [52]. Despite several analyses, the physiologic changes in the pulmonary vasculature after Fontan completion, and the underlying pathogenesis of non-pulsatile flow-induced pulmonary hypertension in the Fontan circulation, remain poorly understood.

7.2.5 Cyanosis

Cyanosis is another factor that might affect PVR. Before Fontan completion, all UVH patients are cyanotic, while after Fontan completion, the pulmonary and systemic circulation are separated and most have normal or near-normal oxygen saturation. However, right–left shunts are present in most Fontan patients from, e.g. fenestration, residual intra-atrial leaks in the Fontan pathway, veno-venous collaterals and coronary sinus blood draining to the systemic circulation. The presence of hypoxia is known to cause pulmonary vasoconstriction, resulting in increased PVR.

Besides excessive pulmonary perfusion, non-pulsatile pulmonary blood flow and cyanosis, it has been speculated that increased PVR in Fontan patients might be a result of micro-emboli from the venous system [53], ageing [54], obstructed airways caused by lymphatic dysfunction [55] and prolonged overexpression of vasoconstrictors such as endothelin-1 [56, 57]. A significantly higher plasma level of endothelin-1 has been found in Fontan patients compared to controls [58].

It is important to emphasize that there is still some controversy on how to measure and interpret PVR in the Fontan patient. It was suggested that pulmonary hypertensive vascular disease after the Fontan procedure should be defined as a PVR index more than 3.0 Wood units × m^2 or a transpulmonary gradient more than 6 mmHg – even if the mean PA pressure is much lower than the 25 mmHg used to define pulmonary hypertension [59]. Furthermore, the accuracy of PVR and effective pulmonary blood flow measured in Fontan patients is still low due to the presence of multiple source of pulmonary blood flow and systemic venous or veno-venous collaterals.

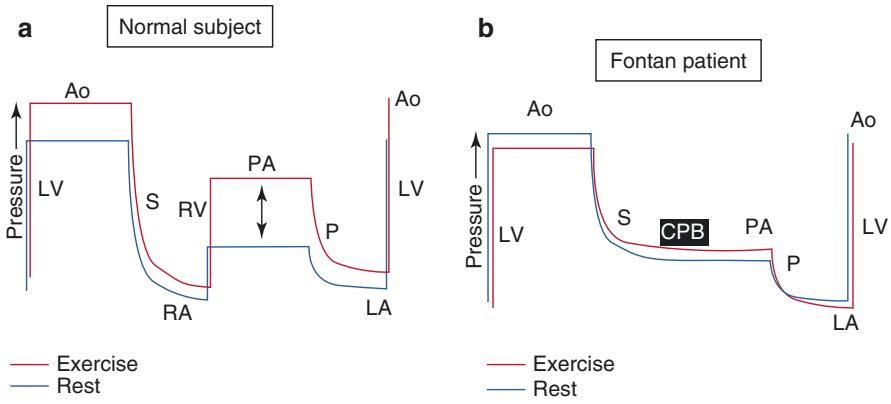

Fig. 7.2 Schematic drawing of pressure and blood flow during rest and during exercise in the biventricular and the Fontan circulation. *Ao* aorta, *CPB* cavopulmonary bypass, *LA* left atrium, *LV* left ventricle, *PA* pulmonary artery, *P* pulmonary circulation, *RA* right atrium, *RV* right ventricle, *S* systemic circulation. Reprint from La Gerche & Gewillig M, Int J Pediatr. 2010. pii: 791291. doi: 10.1155/2010/791291. Epub 2010 Sep 7

7.3 Exercise Physiology in the Fontan Circulation

In the normal biventricular heart, cardiac output increases up to 500% during exercise to meet the muscular metabolic demands [60]. This is achieved by increasing stroke volume and heart rate and by reducing afterload. Augmentation of cardiac output is extremely dependent upon preload reserve. In the biventricular circulation, the RV increases systolic pressure up to 50 mmHg and at the same time PVR falls through release of endothelial NO in response to increased pulsatility of the pulmonary blood flow, thereby securing sufficient increase in systemic ventricular preload [61]. Due to the lack of a sub-pulmonary ventricle to add forward energy to flow through the lungs, the flow return from the pulmonary vascular bed is thereby restricted, resulting in decreased or absent preload reserve to the ventricle (Fig. 7.2) [41]. Consequently, in Fontan patients, minor changes of PVR result in marked changes of cardiac output, and only when severely impaired, the ventricle will influence cardiac output [41].

References

1. Idorn L, Olsen M, Jensen AS, Juul K, Reimers JI, Sorensen K, Johnsen SP, Sondergaard L (2013) Univentricular hearts in Denmark 1977 to 2009: incidence and survival. Int J Cardiol 167:1311–1316
2. Moons P, Sluysmans T, De WD, Massin M, Suys B, Benatar A, Gewillig M (2009) Congenital heart disease in 111 225 births in Belgium: birth prevalence, treatment and survival in the 21st century. Acta Paediatr 98:472–477

3. Ghanayem NS, Berger S, Tweddell JS (2007) Medical management of the failing Fontan. Pediatr Cardiol 28:465–471
4. Jacobs ML, Anderson RH (2006) Nomenclature of the functionally univentricular heart. Cardiol Young 16(Suppl 1):3–8
5. Fontan F, Baudet E (1971) Surgical repair of tricuspid atresia. Thorax 26:240–248
6. Fixler DE, Nembhard WN, Salemi JL, Ethen MK, Canfield MA (2010) Mortality in first 5 years in infants with functional single ventricle born in Texas, 1996 to 2003. Circulation 121:644–650
7. d'Udekem Y, Iyengar AJ, Cochrane AD, Grigg LE, Ramsay JM, Wheaton GR, Penny DJ, Brizard CP (2007) The Fontan procedure: contemporary techniques have improved long-term outcomes. Circulation 116:I157–I164
8. Driscoll DJ (2007) Long-term results of the Fontan operation. Pediatr Cardiol 28:438–442
9. Choussat A, Fontan F, Besse P, Vallot F, Chauve A, Bricaud H (1978) Selection criteria for Fontan's procedure. In: Andersson RH, Shinebourne EA (eds) Pediatric cardiology, 1977. Churchill Livingstone, Edingburgh, pp 559–566
10. Kreutzer G, Galindez E, Bono H, De PC, Laura JP (1973) An operation for the correction of tricuspid atresia. J Thorac Cardiovasc Surg 66:613–621
11. Bjork VO, Olin CL, Bjarke BB, Thoren CA (1979) Right atrial-right ventricular anastomosis for correction of tricuspid atresia. J Thorac Cardiovasc Surg 77:452–458
12. Driscoll DJ, Offord KP, Feldt RH, Schaff HV, Puga FJ, Danielson GK (1992) Five- to fifteen-year follow-up after Fontan operation. Circulation 85:469–496
13. Duncan BW, Desai S (2003) Pulmonary arteriovenous malformations after cavopulmonary anastomosis. Ann Thorac Surg 76:1759–1766
14. de Leval MR, Kilner P, Gewillig M, Bull C (1988) Total cavopulmonary connection: a logical alternative to atriopulmonary connection for complex Fontan operations. Experimental studies and early clinical experience. J Thorac Cardiovasc Surg 96:682–695
15. Marcelletti C, Corno A, Giannico S, Marino B (1990) Inferior vena cava-pulmonary artery extracardiac conduit. A new form of right heart bypass. J Thorac Cardiovasc Surg 100:228–232
16. Deal BJ, Mavroudis C, Backer CL (2007) Arrhythmia management in the Fontan patient. Pediatr Cardiol 28:448–456
17. Azakie A, McCrindle BW, Van AG, Benson LN, Coles J, Hamilton R, Freedom RM, Williams WG (2001) Extracardiac conduit versus lateral tunnel cavopulmonary connections at a single institution: impact on outcomes. J Thorac Cardiovasc Surg 122:1219–1228
18. Robbers-Visser D, Miedema M, Nijveld A, Boersma E, Bogers AJ, Haas F, Helbing WA, Kapusta L (2010) Results of staged total cavopulmonary connection for functionally univentricular hearts; comparison of intra-atrial lateral tunnel and extracardiac conduit. Eur J Cardiothorac Surg 37:934–941
19. Stewart RD, Pasquali SK, Jacobs JP, Benjamin DK, Jaggers J, Cheng J, Mavroudis C, Jacobs ML (2012) Contemporary Fontan operation: association between early outcome and type of cavopulmonary connection. Ann Thorac Surg 93:1254–1260
20. Stephenson EA, Lu M, Berul CI, Etheridge SP, Idriss SF, Margossian R, Reed JH, Prakash A, Sleeper LA, Vetter VL, Blaufox AD (2010) Arrhythmias in a contemporary fontan cohort: prevalence and clinical associations in a multicenter cross-sectional study. J Am Coll Cardiol 56:890–896
21. Bridges ND, Lock JE, Castaneda AR (1990) Baffle fenestration with subsequent transcatheter closure. Modification of the Fontan operation for patients at increased risk. Circulation 82:1681–1689
22. Kim SJ, Kim WH, Lim HG, Lee JY (2008) Outcome of 200 patients after an extracardiac Fontan procedure. J Thorac Cardiovasc Surg 136:108–116
23. Airan B, Sharma R, Choudhary SK, Mohanty SR, Bhan A, Chowdhari UK, Juneja R, Kothari SS, Saxena A, Venugopal P (2000) Univentricular repair: is routine fenestration justified? Ann Thorac Surg 69:1900–1906

24. Lemler MS, Scott WA, Leonard SR, Stromberg D, Ramaciotti C (2002) Fenestration improves clinical outcome of the fontan procedure: a prospective, randomized study. Circulation 105:207–212
25. Baumgartner H, Bonhoeffer P, De Groot NM, de HF DJE, Galie N, Gatzoulis MA, Gohlke-Baerwolf C, Kaemmerer H, Kilner P, Meijboom F, Mulder BJ, Oechslin E, Oliver JM, Serraf A, Szatmari A, Thaulow E, Vouhe PR, Walma E (2010) ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J 31:2915–2957
26. Goff DA, Blume ED, Gauvreau K, Mayer JE, Lock JE, Jenkins KJ (2000) Clinical outcome of fenestrated Fontan patients after closure: the first 10 years. Circulation 102:2094–2099
27. Ono M, Boethig D, Goerler H, Lange M, Westhoff-Bleck M, Breymann T (2006) Clinical outcome of patients 20 years after Fontan operation—effect of fenestration on late morbidity. Eur J Cardiothorac Surg 30:923–929
28. Jacobs ML, Rychik J, Rome JJ, Apostolopoulou S, Pizarro C, Murphy JD, Norwood WI Jr (1996) Early reduction of the volume work of the single ventricle: the hemi-Fontan operation. Ann Thorac Surg 62:456–461
29. Norwood WI, Jacobs ML (1993) Fontan's procedure in two stages. Am J Surg 166:548–551
30. Ghanayem NS, Tweddell JS, Hoffman GM, Mussatto K, Jaquiss RD (2006) Optimal timing of the second stage of palliation for hypoplastic left heart syndrome facilitated through home monitoring, and the results of early cavopulmonary anastomosis. Cardiol Young 16(Suppl 1): 61–66
31. Jaquiss RD, Ghanayem NS, Hoffman GM, Fedderly RT, Cava JR, Mussatto KA, Tweddell JS (2004) Early cavopulmonary anastomosis in very young infants after the Norwood procedure: impact on oxygenation, resource utilization, and mortality. J Thorac Cardiovasc Surg 127:982–989
32. Petrucci O, Khoury PR, Manning PB, Eghtesady P (2010) Outcomes of the bidirectional Glenn procedure in patients less than 3 months of age. J Thorac Cardiovasc Surg 139:562–568
33. Tanoue Y, Sese A, Ueno Y, Joh K, Hijii T (2001) Bidirectional Glenn procedure improves the mechanical efficiency of a total cavopulmonary connection in high-risk fontan candidates. Circulation 103:2176–2180
34. Kaulitz R, Hofbeck M (2005) Current treatment and prognosis in children with functionally univentricular hearts. Arch Dis Child 90:757–762
35. Ciliberti P, Schulze-Neick I, Giardini A (2012) Modulation of pulmonary vascular resistance as a target for therapeutic interventions in Fontan patients: focus on phosphodiesterase inhibitors. Futur Cardiol 8:271–284
36. Sidi D (2005) Cardiac and pulmonary physiology in the functionally univentricular circulation with reference to the total cavo-pulmonary connection. Cardiol Young 15(Suppl 3):26–30
37. Gewillig M, Brown SC, Heying R, Eyskens B, Ganame J, Boshoff DE, Budts W, Gorenflo M (2010) Volume load paradox while preparing for the Fontan: not too much for the ventricle, not too little for the lungs. Interact Cardiovasc Thorac Surg 10:262–265
38. Sluysmans T, Sanders SP, van der Velde M, Matitiau A, Parness IA, Spevak PJ, Mayer JE Jr, Colan SD (1992) Natural history and patterns of recovery of contractile function in single left ventricle after Fontan operation. Circulation 86:1753–1761
39. Cilliers A, Gewillig M (2002) Fontan procedure for univentricular hearts: have changes in design improved outcome? Cardiovasc J S Afr 13:111–116
40. Gewillig M, Daenen W, Aubert A, Van der Hauwaert L (1992) Abolishment of chronic volume overload. Implications for diastolic function of the systemic ventricle immediately after Fontan repair. Circulation 86:II93–II99
41. Gewillig M, Brown SC, Eyskens B, Heying R, Ganame J, Budts W, La GA, Gorenflo M (2010) The Fontan circulation: who controls cardiac output? Interact Cardiovasc Thorac Surg 10:428–433
42. Schmitt B, Steendijk P, Ovroutski S, Lunze K, Rahmanzadeh P, Maarouf N, Ewert P, Berger F, Kuehne T (2010) Pulmonary vascular resistance, collateral flow, and ventricular function in

patients with a Fontan circulation at rest and during dobutamine stress. Circ Cardiovasc Imaging 3:623–631
43. Beghetti M (2010) Fontan and the pulmonary circulation: a potential role for new pulmonary hypertension therapies. Heart 96:911–916
44. Gentles TL, Mayer JE Jr, Gauvreau K, Newburger JW, Lock JE, Kupferschmid JP, Burnett J, Jonas RA, Castaneda AR, Wernovsky G (1997) Fontan operation in five hundred consecutive patients: factors influencing early and late outcome. J Thorac Cardiovasc Surg 114:376–391
45. Griffiths ER, Kaza AK, Wyler von Ballmoos MC, Loyola H, Valente AM, Blume ED, del Nido P (2009) Evaluating failing Fontans for heart transplantation: predictors of death. Ann Thorac Surg 88:558–563
46. Redington AN (2006) The physiology of the Fontan circulation. Prog Pediatr Cardiol 22:179–186
47. Zongtao Y, Huishan W, Zengwei W, Hongyu Z, Minhua F, Xinmin L, Nanbin Z, Hongguang H (2010) Experimental study of nonpulsatile flow perfusion and structural remodeling of pulmonary microcirculation vessels. Thorac Cardiovasc Surg 58:468–472
48. Henaine R, Vergnat M, Bacha EA, Baudet B, Lambert V, Belli E, Serraf A (2013) Effects of lack of pulsatility on pulmonary endothelial function in the Fontan circulation. J Thorac Cardiovasc Surg 146:522–529
49. Kurotobi S, Sano T, Kogaki S, Matsushita T, Miwatani T, Takeuchi M, Matsuda H, Okada S (2001) Bidirectional cavopulmonary shunt with right ventricular outflow patency: the impact of pulsatility on pulmonary endothelial function. J Thorac Cardiovasc Surg 121:1161–1168
50. Idorn L, Hanel B, Jensen AS, Juul K, Reimers JI, Nielsen KG, Sondergaard L (2014) New insights into the aspects of pulmonary diffusing capacity in Fontan patients. Cardiol Young 24:311–320
51. Jaryszak EM, Baumgartner WA Jr, Peterson AJ, Presson RG Jr, Glenny RW, Wagner WW Jr (2000) Selected contribution: measuring the response time of pulmonary capillary recruitment to sudden flow changes. J Appl Physiol (1985) 89:1233–1238
52. Khambadkone S, Li J, de Leval MR, Cullen S, Deanfield JE, Redington AN (2003) Basal pulmonary vascular resistance and nitric oxide responsiveness late after Fontan-type operation. Circulation 107:3204–3208
53. Varma C, Warr MR, Hendler AL, Paul NS, Webb GD, Therrien J (2003) Prevalence of "silent" pulmonary emboli in adults after the Fontan operation. J Am Coll Cardiol 41:2252–2258
54. Kovacs G, Berghold A, Scheidl S, Olschewski H (2009) Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. Eur Respir J 34:888–894
55. Gewillig M (2005) The Fontan circulation. Heart 91:839–846
56. Humbert M, Sitbon O, Simonneau G (2004) Treatment of pulmonary arterial hypertension. N Engl J Med 351:1425–1436
57. Yamagishi M, Kurosawa H, Hashimoto K, Nomura K, Kitamura N (2002) The role of plasma endothelin in the Fontan circulation. J Cardiovasc Surg 43:793–797
58. Inai K, Nakanishi T, Nakazawa M (2005) Clinical correlation and prognostic predictive value of neurohumoral factors in patients late after the Fontan operation. Am Heart J 150:588–594
59. Cerro MJ, Abman S, Diaz G, Freudenthal AH, Freudenthal F, Harikrishnan S, Haworth SG, Ivy D, Lopes AA, Raj JU, Sandoval J, Stenmark K, Adatia I (2011) A consensus approach to the classification of pediatric pulmonary hypertensive vascular disease: report from the PVRI Pediatric Taskforce, Panama 2011. Pulm Circ 1:286–298
60. Vella CA, Robergs RA (2005) A review of the stroke volume response to upright exercise in healthy subjects. Br J Sports Med 39:190–195
61. Argiento P, Chesler N, Mule M, D'Alto M, Bossone E, Unger P, Naeije R (2010) Exercise stress echocardiography for the study of the pulmonary circulation. Eur Respir J 35:1273–1278

Post-capillary Pulmonary Hypertension in ACHD

8

Margarita Brida and Gerhard-Paul Diller

Abbreviations

ACHD	adult congenital heart disease
CHD	congenital heart disease
ccTGA	congenitally corrected transposition of the great arteries
Cpc-PH	combined post-capillary and pre-capillary PH
DPG	diastolic pulmonary pressure gradient
ECG	electrocardiography
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
Ipc-PH	isolated post-capillary PH
LA	left atrium
LHD	left heart disease
LV	left ventricle
LVAD	left ventricle assist device
LVEDP	left ventricular end-diastolic pressure
LVEF	left ventricular ejection fraction

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mPAP	mean pulmonary arterial pressure
PAH	pulmonary arterial hypertension
PH	pulmonary hypertension
PAP	pulmonary arterial pressure
PAWP	pulmonary artery wedge pressure
PVR	pulmonary vascular resistance
RHC	right heart catheterization
SVR	systemic vascular resistance
TGA	transposition of the great arteries
TPG	trans-pulmonary pressure gradient
WHO	World Health Organization
WU	Wood units

8.1 Introduction

Pulmonary hypertension (PH) is a haemodynamic and pathophysiological condition defined as an increase in mean pulmonary arterial pressure (mPAP) at rest $\geqslant$ 25 mmHg as assessed by right heart catheterization (RHC). Haemodynamically PH can be further distinguished into precapillary PH and post-capillary PH [1].

Post-capillary PH represents a group of clinical conditions in which pulmonary artery wedge pressure (PAWP) is elevated above 15 mmHg. This clinical group of post-capillary PH consists of PH due to left heart disease (LHD) and PH with unclear or multifactorial mechanisms. Regarding adult congenital heart disease (ACHD) patients, the LHD can include left ventricular (LV) systolic dysfunction, LV diastolic dysfunction, valvular disease, congenital left heart obstruction, congenital cardiomyopathies and congenital pulmonary vein stenosis. The guidelines also suggest that patients belonging to group 5 of the international PH classification (PH with unclear and/or multifactorial mechanisms) can be classified as having post-capillary PH. This is likely to reflect the fact that many of the conditions within group 5 can cause a rise in post-capillary pressures (e.g. severe pulmonary vein stenosis in fibrosis mediastinitis, diastolic LV dysfunction in chronic renal failure, etc.) (Table 8.1).

Post-capillary PH can also be divided into isolated post-capillary PH (Ipc-PH) and combined post-capillary and pre-capillary PH (Cpc-PH) according to current recommendation guidelines. Distinction is made on the basis of diastolic pulmonary pressure gradient (DPG) and pulmonary vascular resistance (PVR) [1]. The DPG, calculated as the difference between diastolic pulmonary arterial pressure (PAP) and mean PAWP, seems to be a more specific parameter for identifying patients with a Cpc-PH, as it appears to be less sensitive to pulmonary vascular compliance or pulmonary blood flow compared to the more commonly used trans-pulmonary pressure gradient (TPG, the difference between mPAP and mean PAWP) [2–4]. Nevertheless DPG must be considered in the context of PVR and TPG [5, 6].

Table 8.1 Clinical classification of post-capillary PH in ACHD (Adapted from the 2015 ESC/ERS guidelines for the diagnosis & treatment of pulmonary hypertension, Galie N et al.)

Clinical groups of post-capillary PH in ACHD	
PH due to left heart disease	PH with unclear and/or multifactorial mechanisms
LV systolic dysfunction	Coexistent chronic renal failure, pulmonary venous stenosis or other Group 5 condition
LV diastolic dysfunction	
Valvular disease	
Left heart inflow/outflow	
Heart obstruction and cardiomyopathies	
Pulmonary veins stenosis	

LV left ventricle, *PH* pulmonary hypertension, *ACHD* adult congenital heart disease

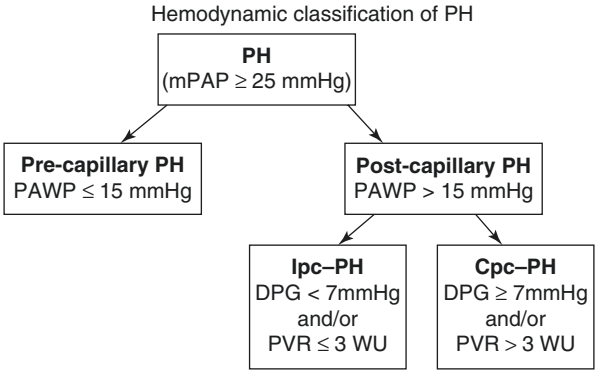

Fig. 8.1 Haemodynamic classification of PH. *PH* pulmonary hypertension, *mPAP* mean pulmonary arterial pressure, *PAWP* pulmonary arterial wedge pressure, *PVR* pulmonary vascular resistance, *DPG* diastolic pressure gradient, *WU* Wood units (Adapted from 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Galie N et al.). *Ipc-PH* isolated post-capillary PH, *Cpc-PH* combined post-capillary and pre-capillary PH

Ipc-PH is defined as postcapillary PH with a normal DPG (lower than 7 mmHg) and normal PVR (less or equal than 3 Wood units) (Fig. 8.1) [1]. In contrast to Cpc-PH, Ipc-PH can be entirely reversible when mean PAWP is normalized, for example, by treating the underlying cause. On the other hand, Cpc-PH often develops as a consequence of long-standing Ipc-PH (e.g. long-standing mitral stenosis) with a progressive rise in DPG and PVR, transforming Ipc-PH into Cpc-PH. This condition has to be distinguished from pulmonary arterial hypertension (PAH), since targeted PAH therapy may be of limited benefit, or even detrimental in this setting, despite the existence of a clear pre-capillary component. Treating the underlying LHD remains the cornerstone of therapy.

While this classification is useful for the initial patient stratification and to further guide assessment and treatment, it is nevertheless simplified, and further important issues need to be addressed.

8.2 Pulmonary Hypertension Due to Left Heart Disease

8.2.1 Epidemiology

LHD is the most common cause of PH and accounts for 65–80% of PH cases. It is classified as World Health Organization (WHO) PH group II according to current guidelines [1]. In this group of patients, PH represents a complication of underlying LHD, and it is associated with disease progression, worsening of symptoms, exercise intolerance and has a negative overall impact on outcome. When compared to PAH, these patients are often older, more likely to be female and present with cardiovascular comorbidities and metabolic syndrome [7, 8].

The prevalence of patients with heart failure (HF) and PH varies greatly depending on patient subsets, definitions used in studies and the methods used to estimate PAP. In HF with reduced ejection fraction (HFrEF), defined as left ventricular ejection fraction less than 40% (LVEF < 40%) [9], the prevalence of PH is reported from 40 to 75% [5, 10, 11]. In the setting of congenital heart disease (CHD), patients with congenitally corrected transposition of the great arteries (ccTGA) and transposition of the great arteries (TGA) after atrial switch operation, both conditions in which the morphological right ventricle is a part of the systemic circulation, often present with reduced ejection fraction and HF symptoms. The morphological right ventricle is not well suited on the long run to support the systemic circulation and, as a result, systemic ventricular dysfunction and HF is a common complication in adulthood. In patients with chronic HF, there is an inverse correlation between the extent of the increase in both PAWP and PAP and survival [12].

In patients with heart failure with preserved ejection fraction (HFpEF), defined as left ventricular ejection fraction equal or more than 50% (LVEF ≥ 50%) [9], recent studies indicate a PH prevalence of 52% to 83% [13, 14]. HF patients, in their majority, present with Ipc-PH, while Cpc-HF is uncommon with a reported prevalence of only 12–14% or less. Cpc-HF is nevertheless associated with decreased survival in comparison to HF with no PH nor Ipc-PH [15].

PH can be seen in the majority of patients with severe symptomatic mitral valve disease and in up to 65% of those with symptomatic aortic stenosis [16, 17]. Surgical aortic valve replacement is the recommended procedure for severe aortic stenosis, but perioperative complications are greater when there is PH preoperatively. However, valve replacement is an effective treatment of PH associated with this condition, and a decrease in PAP can be seen immediately after surgery. Some patients will continue to have persistent PH after the operation, which is associated with a decreased long-term survival [18]. Patients with congenital mitral valve anomalies (such as congenital mitral stenosis with two papillary muscles, parachute

mitral valve with a single papillary muscle, usually seen as a part of Shone complex, double-orifice mitral valve, supravalvar mitral ring, etc. [19]) can also develop PH. In patients with mitral valve disease, the development of post-capillary PH is one of the indications for surgical repair, even though right ventricular dysfunction may occur post-operatively and some centres have used sildenafil as a means of keeping PVR low and allowing the right ventricle to recover [20].

Other lesions, such as baffle stenosis in TGA after atrial switch operation, cor triatriatum sinistrum or Shone complex (multilevel left heart obstruction defined with four obstructive lesions – supravalvular mitral membrane, parachute mitral valve, subaortic stenosis and aortic coarctation [21]), can also lead to post-capillary PH with different incidence. In Shone complex secondary PH is common and often progresses rapidly [22].

No specific genetic linkage has been identified in this group of patients [23].

8.2.2 Pathophysiology

The pathophysiology of PH due to LHD is a complex process, with multiple factors contributing to its development and progression. PH develops in LHD as a result of passive backward transmission of elevated left-sided filling pressures, which occurs as a consequence of systolic or diastolic LV dysfunction, valve disease or obstructive lesions. The elevated left-sided filling pressures result in a rise in pulmonary venous pressures, which tramits backwards into the pulmonary arteries, resulting in post-capillary PH. Therefore, any increase in LV end-diastolic pressure (LVEDP) or PAWP is likely to cause a rise in PAP. This situation, in which DPG, TPG and PVR remain within normal range, was previously called passive PH or pulmonary venous hypertension; at present it is labelled as Ipc-PH.

In some patients, these purely mechanical circumstances of elevated left pulmonary venous pressure and venous congestion might trigger changes in the pulmonary vascular tree, such as decreased nitric oxide (NO) availability, increased expression of endothelin-1, desensitization to natriuretic peptide-induced vasodilatation, infiltration of inflammatory cells, neurogenic or metabolic factors, hypoxia-induced vasoconstriction and growth responses [2, 24]. This results in a further increase in mPAP, due to a rise in PVR. Previously, this group of patients with LHD who have an elevated DPG, TPG and PVR were referred to as mixed, reactive, disproportionate or out-of-proportion PH. However, according to the current guidelines, the preferred term is Cpc-PH [1]. Treatment that can normalise the left-sided pressures, may also normalise PVR, but in some patients the precapillary component may persist. In the latter, elevated pulmonary pressures may lead to structural remodelling, i.e. pulmonary vascular disease mainly in small pulmonary resistance arteries. Histopathological changes include thickening of the alveolar-capillary membrane, medial hypertrophy, intimal and adventitial fibrosis and luminal occlusion in small pulmonary arterioles. Plexiform lesions, considered typical of idiopathic PAH and Eisenmenger syndrome, are usually not found in this setting [13, 25].

Post-capillary PH increases right ventricle afterload. The right ventricle initially becomes hypertrophic and increases its contractility in response to the high PAP, but over time this may not be sufficient. In these circumstances, right ventricular dilatation and dysfunction may occur and ultimately trigger right ventricular failure (maladapted right ventricle/heterometric adaptation, see also chapter 1) [11, 26] (Fig. 8.2). Moreover, it is important to consider additional conditions that can aggravate pre-capillary PH, such as pulmonary embolism or sleep-disordered breathing, especially in patients with Down syndrome.

Additional research in this area is required in order to better understand the pathophysiology of this condition and the factors associated with the development of a significant pre-capillary component in susceptible patients with post-capillary PH and ultimately provide better and more specific treatment options.

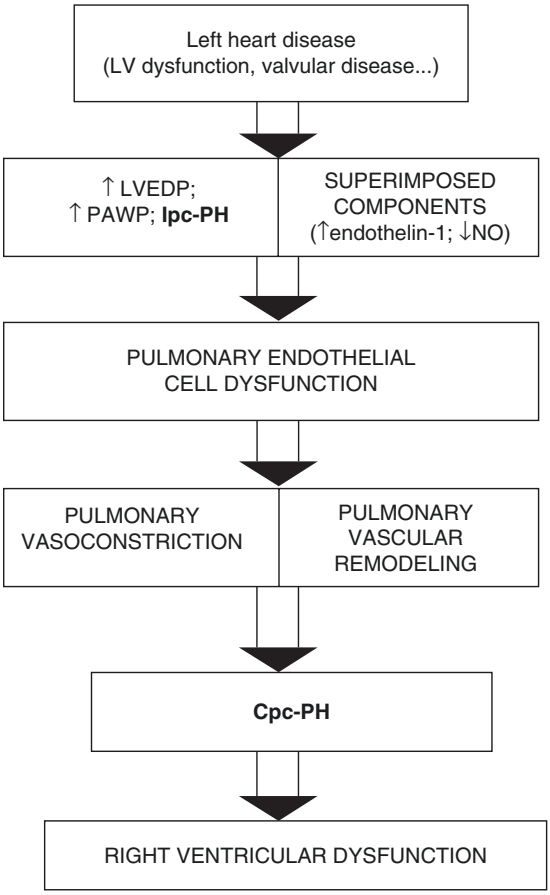

Fig. 8.2 Pathophysiology of pulmonary hypertension due to left heart disease (*LV* left ventricle, *LVEDP* left ventricular end-diastolic pressure, *PAWP* pulmonary arterial wedge pressure, *NO* nitric oxide, *Ipc-PH* isolated post-capillary pulmonary hypertension, *Cpc-PH* combined post-capillary and pre-capillary pulmonary hypertension)

8.2.3 Diagnosis and Evaluation

Patients with post-capillary PH usually present with symptoms of left HF such as breathlessness, orthopnoea, paroxysmal nocturnal dyspnoea, reduced exercise tolerance and fatigue. When compared to PAH patients, this group of patients are usually older, more often hypertensive or have diabetes, are more prone to coronary artery disease and are often overweight. Features of metabolic syndrome and history of HF are common, as well as presentation with atrial fibrillation [1].

All patients suspected to have PH should first undergo clinical evaluation and basic non-invasive testing, and only if indicated additional tests should be performed. A stepwise diagnostic approach incorporates clinical history and physical examination with electrocardiography (ECG) and other imaging techniques. ECG abnormalities, although not specific, are almost always present, and HF is unlikely in patients presenting with a completely normal ECG. In PH due to LHD, signs of LV hypertrophy, left axis deviation and atrial fibrillation can be frequently observed [13].

Echocardiography is the most useful, widely available diagnostic tool and, as such, plays a key role in the initial diagnosis of PH. Moreover echocardiography can easily detect systolic dysfunction of the systemic ventricle in patients with pulmonary hypertension and heart failure with reduced ejection fraction (PH-HFrEF) or valve disease. Systemic ventricular dysfunction is, indeed, quite common in ACHD as a result of previous or ongoing hemodynamic lesions and prior surgery. Moreover, patients with TGA after atrial switch operation, ccTGA and unoperated univentricular heart anatomy are prone to systemic ventricular failure and severe systemic atrioventricular valve regurgitation [27, 28].

Echocardiography also helps to discriminate HFrEF from HFpEF. Echocardiographic key structural alterations in HFpEF in non-congenital patients are: enlarged left atrial volume index (LAVI) > 34 mL/m^2 or a left ventricular mass index (LVMI) >115 g/m^2 for males and >95 g/m^2 for females. Further key findings include an E/e' $\geq$ 13 and a mean e' septal and lateral wall <9 cm/s [9]. In the setting of CHD, assessing diastolic dysfunction can be challenging, especially in conditions presenting with a reduced LV preload (e.g. patients with a Fontan procedure).

In the case of mild PH in the presence of significant LHD, further evaluation of the PH is usually not required. However, when PH is significant and may impact on the choice of treatment, echocardiography alone is not sufficient to support a treatment decision, and cardiac catheterization is required. Moreover, RHC is indicated in patients with PH due to LHD if organ transplantation is considered [1]. RHC is best performed electively, in a compensated stable condition.

When performing RHC for any of the above reasons, it is crucial to obtain a complete set of pulmonary haemodynamics. This includes measurements of systolic, diastolic and mPAP, right atrial pressure, cardiac output/cardiac index and mixed venous oxygen saturation; calculation of TPG, DPG and PVR; and interpretation of pulmonary haemodynamics in relation to systemic vascular resistance, PVR/SVR ratio.

Left-sided filling pressure is determined either as LVEDP, left atrial pressure or PAWP; in post-capillary PH, left-sided filling pressure is elevated (>15 mmHg) in comparison to pre-capillary PH. In post-capillary PH, the elevation in PAWP leads to a "proportionate" increase of the mPAP, maintaining a normal TPG, DPG and low PVR (Ipc-PH).

Distinction between post-capillary and PAH is essential, as it has direct implications on further treatment, e.g. on the use of PAH therapies, which are not indicated in post-capillary PH. As mentioned previously, differentiating pre-capillary PH from post-capillary PH is especially challenging in patients with HFpEF. Echocardiographic findings are not always conclusive and can be difficult to interpret. Even on invasive assessment, many patients with PH-HFpEF may have reduced PAWP below 15 mmHg due to diuretic treatment [30–32]. Acute volume challenge (e.g. a fluid bolus of 500 mL) may help to discriminate patients with PAH from those with LV diastolic dysfunction [33]. In patients with LV diastolic dysfunction, i.e. HFpEF, even small changes in volume are associated with a significant increase in filling pressures, thus, "volume challenge" may unmask occult post-capillary PH. Based on current data, this approach appears to be safe, and a PAWP >18 mmHg may be considered as an abnormal response to fluid [34]. Similarly, exercise testing may also help in uncovering post-capillary PH. A steep diastolic pressure–volume relation and high PAWP at low workload play a key role in exercise limitation [35, 36]. At present, even though potentially useful, both of these tests lack proper standardization and normal values, limiting their use in clinical practice.

8.2.4 Therapy

The primary goal of therapy in post-capillary PH is to treat the underlying heart condition. This includes repair of the congenital heart defect, such as valvular heart disease, and aggressive medical treatment of patients with impaired systemic ventricular function [1]. In settings such as TGA after atrial switch operation, the intra-atrial tunnels (baffles) can obstruct pulmonary venous drainage and lead to PH. Symptomatic patients with baffle stenosis should undergo catheter intervention when possible or surgical repair if intervention is not possible [37]. Catheter interventions are also a treatment option in other ACHD, such as in patients with pulmonary vein stenosis [38]. In general, better postoperative and long-term results can be expected when treatment of the underlying condition is performed before the development of significant PH, especially Cpc-PH.

HF is a frequent problem in the ACHD population. Three neurohormonal antagonists (angiotensin-converting enzyme inhibitors, mineralocorticoid receptor antagonists and beta blockers) form the basis for treating HFrEF due to acquired heart disease with a proven impact on survival in this setting [9]. However, as the pathophysiology of ACHD patients differs from the failing "normal" circulation, extrapolation of results from published studies to ACHD patients may be difficult, particularly in patients with systemic right ventricles or a Fontan circulation. The

few available data on HF treatment in ACHD patients are often not conclusive and are derived from small patient numbers. Cardiac resynchronization therapy (CRT) has gained increasing interest for use in ACHD patients with congestive HF. There is, as yet, little evidence on which to base indications and outcomes [37]. Additional risk factors for the development of PH, such as features of metabolic syndrome and concomitant disorders such as COPD, sleep apnoea syndrome and pulmonary embolism should be identified and treated.

In contrast to HFrEF, no treatment has yet been shown convincingly to reduce morbidity or mortality in HFpEF. However, these patients are often highly symptomatic and an important aim of therapy is to alleviate symptoms and improve well-being, often with the use of diuretics [9].

Despite the high prevalence of PH in LHD, the major focus of research over the past decades has been on PAH, and no specific therapy for post-capillary is available. In all patients with post-capillary PH, and especially Ipc-PH, targeted PAH therapy (prostanoids, endothelin receptor antagonists (ERA), phosphodiesterase-5 inhibitors (PDE-5 inhibitors)) is generally not indicated and could potentially be harmful. Lowering PVR and increasing pulmonary blood flow with PAH-specific therapy may lead to an increase in PAWP, pulmonary oedema and cardiac decompensation. It is, therefore, mandatory to establish a precise diagnosis and distinguish between PAH and post-capillary PH before starting treatment. Of note, long-term data from carefully designed clinical studies are required in this field, since some smaller studies have shown potential benefits in some post-capillary PH patients treated with sildenafil, even though other studies have not confirmed this [39, 40].

Heart transplantation may be indicated in severe LHD that cannot be adequately managed with standard therapeutic approach. An increased PVR is a risk factor for right ventricular failure after transplantation. During the preoperative assessment, testing with sodium nitroprusside or other vasodilators is useful to identify patients who may be candidates of heart transplantation alone. In patients with severe and fixed PH, heart-lung transplantation is indicated.

The implantation of an LV assist device (LVAD) has been shown to lower pulmonary pressures through LV unloading and may allow patients with PH-HFrEF to be eligible for orthotopic heart transplantation [41–44]. According to current HF guidelines, an LVAD should be considered in pharmacologically irreversible PH with a subsequent re-evaluation to establish suitability for heart transplantation [9].

8.3 Pulmonary Venous Stenosis

PH can develop in the setting of pulmonary vein stenosis, which can cause an increase in pulmonary pressure through a rise in post-capillary pressure in the affected segment. Evaluation for stenotic pulmonary veins is mandatory in patients with apparently unexplained severe pulmonary hypertension. It is crucial not to misdiagnose these patients as PAH.

Approximately one half of patients with primary pulmonary vein stenosis have also some type of associated cardiac defect. It is, therefore, imperative that the evaluation of patients with all forms of CHD specifically include evaluation of the pulmonary veins [45]. Pulmonary vein stenosis in ACHD patients may occur after surgical repair of anomalous pulmonary venous return. Clinically significant stenosis occurs postoperatively in ≈10% of patients after repair of total anomalous pulmonary venous return [46, 47]. The echocardiographic finding of turbulent flow on colour Doppler should raise the suspicion of pulmonary vein stenosis [48]. Non-invasive tests, e.g. echocardiography, magnetic resonance imaging and/or CT angiography, are generally sufficient to diagnose pulmonary vein stenosis. As a result of the raised awareness of pulmonary vein stenosis, more cases are being diagnosed before progression to severe PH. A raised PAP has been reported to be an independent predictor of death in these patients, while early diagnosis may lead to improved survival [49]. Treatment options include surgical repair and percutaneous intervention. Unfortunately there has been limited success with either option [50, 51], with a high degree of recurrent stenosis after catheter interventions [52, 53].

Conclusion

Post-capillary PH is a complication of conditions that increase left atrial and pulmonary venous pressures. In ACHD such conditions include systemic ventricular dysfunction, congenital left-sided outflow tract obstruction, left-sided valve disease and pulmonary vein stenosis. Post-capillary PH can be divided into Ipc-PH and a Cpc-PH. It is mandatory for post-capillary PH to be distinguished from PAH since, the benefits of PAH therapies have not been formally established for post-capillary PH and may even prove harmful in some patients. The primary goal of therapy in post-capillary PH remains to treat the underlying heart disease.

References

1. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M, Aboyans V, Vaz Carneiro A, Achenbach S, Agewall S, Allanore Y, Asteggiano R, Paolo Badano L, Albert Barbera J, Bouvaist H, Bueno H, Byrne RA, Carerj S, Castro G, Erol C, Falk V, Funck-Brentano C, Gorenflo M, Granton J, Iung B, Kiely DG, Kirchhof P, Kjellstrom B, Landmesser U, Lekakis J, Lionis C, Lip GY, Orfanos SE, Park MH, Piepoli MF, Ponikowski P, Revel MP, Rigau D, Rosenkranz S, Voller H, Luis Zamorano J (2016) 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 37:67–119
2. Vachiery JL, Adir Y, Barbera JA, Champion H, Coghlan JG, Cottin V, De Marco T, Galie N, Ghio S, Gibbs JS, Martinez F, Semigran M, Simonneau G, Wells A, Seeger W (2013) Pulmonary hypertension due to left heart diseases. J Am Coll Cardiol 62:D100–D108

3. Naeije R, Vachiery JL, Yerly P, Vanderpool R (2013) The transpulmonary pressure gradient for the diagnosis of pulmonary vascular disease. Eur Respir J 41:217–223
4. Gerges C, Gerges M, Lang MB, Zhang Y, Jakowitsch J, Probst P, Maurer G, Lang IM (2013) Diastolic pulmonary vascular pressure gradient: a predictor of prognosis in "out-of-proportion" pulmonary hypertension. Chest 143:758–766
5. Tampakakis E, Leary PJ, Selby VN, De Marco T, Cappola TP, Felker GM, Russell SD, Kasper EK, Tedford RJ (2015) The diastolic pulmonary gradient does not predict survival in patients with pulmonary hypertension due to left heart disease. JACC Heart Fail 3:9–16
6. Tampakakis E, Tedford RJ (2015) Reply: characterization of pulmonary hypertension in heart failure using the diastolic pressure gradient: the conundrum of high and low diastolic pulmonary gradient. JACC Heart Fail 3:426–427
7. Thenappan T, Shah SJ, Gomberg-Maitland M, Collander B, Vallakati A, Shroff P, Rich S (2011) Clinical characteristics of pulmonary hypertension in patients with heart failure and preserved ejection fraction. Circ Heart Fail 4:257–265
8. Robbins IM, Newman JH, Johnson RF, Hemnes AR, Fremont RD, Piana RN, Zhao DX, Byrne DW (2009) Association of the metabolic syndrome with pulmonary venous hypertension. Chest 136:31–36
9. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 37(27):2129–2200
10. Miller WL, Grill DE, Borlaug BA (2013) Clinical features, hemodynamics, and outcomes of pulmonary hypertension due to chronic heart failure with reduced ejection fraction: pulmonary hypertension and heart failure. JACC Heart Fail 1:290–299
11. Ghio S, Gavazzi A, Campana C, Inserra C, Klersy C, Sebastiani R, Arbustini E, Recusani F, Tavazzi L (2001) Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. J Am Coll Cardiol 37:183–188
12. Kjaergaard J, Akkan D, Iversen KK, Kjoller E, Kober L, Torp-Pedersen C, Hassager C (2007) Prognostic importance of pulmonary hypertension in patients with heart failure. Am J Cardiol 99:1146–1150
13. Rosenkranz S, Gibbs JS, Wachter R, De Marco T, Vonk-Noordegraaf A, Vachiery JL (2016) Left ventricular heart failure and pulmonary hypertensiondagger. Eur Heart J 37:942–954
14. Shapiro BP, McGoon MD, Redfield MM (2007) Unexplained pulmonary hypertension in elderly patients. Chest 131:94–100
15. Gerges M, Gerges C, Pistritto AM, Lang MB, Trip P, Jakowitsch J, Binder T, Lang IM (2015) Pulmonary hypertension in heart failure. Epidemiology, right ventricular function, and survival. Am J Respir Crit Care Med 192:1234–1246
16. Faggiano P, Antonini-Canterin F, Ribichini F, D'Aloia A, Ferrero V, Cervesato E, Pavan D, Burelli C, Nicolosi G (2000) Pulmonary artery hypertension in adult patients with symptomatic valvular aortic stenosis. Am J Cardiol 85:204–208
17. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M (2012) Guidelines on the management of valvular heart disease (version 2012). Eur Heart J 33:2451–2496
18. Melby SJ, Moon MR, Lindman BR, Bailey MS, Hill LL, Damiano RJ Jr (2011) Impact of pulmonary hypertension on outcomes after aortic valve replacement for aortic valve stenosis. J Thorac Cardiovasc Surg 141:1424–1430
19. Banerjee A, Kohl T, Silverman NH (1995) Echocardiographic evaluation of congenital mitral valve anomalies in children. Am J Cardiol 76:1284–1291

20. Goodale F Jr, Sanchez G, Friedlich AL, Scannell JG, Myers GS (1955) Correlation of pulmonary arteriolar resistance with pulmonary vascular changes in patients with mitral stenosis before and after valvulotomy. N Engl J Med 252:979–983
21. Shone JD, Sellers RD, Anderson RC, Adams P Jr, Lillehei CW, Edwards JE (1963) The developmental complex of "parachute mitral valve," supravalvular ring of left atrium, subaortic stenosis, and coarctation of aorta. Am J Cardiol 11:714–725
22. Brauner RA, Laks H, Drinkwater DC Jr, Scholl F, McCaffery S (1997) Multiple left heart obstructions (shone's anomaly) with mitral valve involvement: long-term surgical outcome. Ann Thorac Surg 64:721–729
23. Oudiz RJ (2007) Pulmonary hypertension associated with left-sided heart disease. Clin Chest Med 28:233–241, x
24. ten Freyhaus H, Dagnell M, Leuchs M, Vantler M, Berghausen EM, Caglayan E, Weissmann N, Dahal BK, Schermuly RT, Ostman A, Kappert K, Rosenkranz S (2011) Hypoxia enhances platelet-derived growth factor signaling in the pulmonary vasculature by down-regulation of protein tyrosine phosphatases. Am J Respir Crit Care Med 183:1092–1102
25. Delgado JF, Conde E, Sanchez V, Lopez-Rios F, Gomez-Sanchez MA, Escribano P, Sotelo T, Gomez de la Camara A, Cortina J, de la Calzada CS (2005) Pulmonary vascular remodeling in pulmonary hypertension due to chronic heart failure. Eur J Heart Fail 7:1011–1016
26. Melenovsky V, Hwang SJ, Lin G, Redfield MM, Borlaug BA (2014) Right heart dysfunction in heart failure with preserved ejection fraction. Eur Heart J 35:3452–3462
27. Piran S, Veldtman G, Siu S, Webb GD, Liu PP (2002) Heart failure and ventricular dysfunction in patients with single or systemic right ventricles. Circulation 105:1189–1194
28. Khairy P, Landzberg MJ, Lambert J, O'Donnell CP (2004) Long-term outcomes after the atrial switch for surgical correction of transposition: a meta-analysis comparing the mustard and senning procedures. Cardiol Young 14:284–292
29. Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbely A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL (2007) How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the heart failure and echocardiography associations of the european society of cardiology. Eur Heart J 28:2539–2550
30. Frost AE, Farber HW, Barst RJ, Miller DP, Elliott CG, McGoon MD (2013) Demographics and outcomes of patients diagnosed with pulmonary hypertension with pulmonary capillary wedge pressures 16 to 18 mm hg: insights from the reveal registry. Chest 143:185–195
31. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, Strickland W, Neelagaru S, Raval N, Krueger S, Weiner S, Shavelle D, Jeffries B, Yadav JS (2011) Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet 377:658–666
32. Prasad A, Hastings JL, Shibata S, Popovic ZB, Arbab-Zadeh A, Bhella PS, Okazaki K, Fu Q, Berk M, Palmer D, Greenberg NL, Garcia MJ, Thomas JD, Levine BD (2010) Characterization of static and dynamic left ventricular diastolic function in patients with heart failure with a preserved ejection fraction. Circ Heart Fail 3:617–626
33. Robbins IM, Hemnes AR, Pugh ME, Brittain EL, Zhao DX, Piana RN, Fong PP, Newman JH (2014) High prevalence of occult pulmonary venous hypertension revealed by fluid challenge in pulmonary hypertension. Circ Heart Fail 7:116–122
34. Fujimoto N, Borlaug BA, Lewis GD, Hastings JL, Shafer KM, Bhella PS, Carrick-Ranson G, Levine BD (2013) Hemodynamic responses to rapid saline loading: the impact of age, sex, and heart failure. Circulation 127:55–62
35. Maeder MT, Thompson BR, Brunner-La Rocca HP, Kaye DM (2010) Hemodynamic basis of exercise limitation in patients with heart failure and normal ejection fraction. J Am Coll Cardiol 56:855–863
36. Paulus WJ (2010) Culprit mechanism(s) for exercise intolerance in heart failure with normal ejection fraction. J Am Coll Cardiol 56:864–866

37. Baumgartner H, Bonhoeffer P, De Groot NM, de Haan F, Deanfield JE, Galie N, Gatzoulis MA, Gohlke-Baerwolf C, Kaemmerer H, Kilner P, Meijboom F, Mulder BJ, Oechslin E, Oliver JM, Serraf A, Szatmari A, Thaulow E, Vouhe PR, Walma E (2010) Esc guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J 31:2915–2957
38. Seale AN, Daubeney PE, Magee AG, Rigby ML (2006) Pulmonary vein stenosis: initial experience with cutting balloon angioplasty. Heart 92:815–820
39. Lewis GD, Lachmann J, Camuso J, Lepore JJ, Shin J, Martinovic ME, Systrom DM, Bloch KD, Semigran MJ (2007) Sildenafil improves exercise hemodynamics and oxygen uptake in patients with systolic heart failure. Circulation 115:59–66
40. Lewis GD, Shah R, Shahzad K, Camuso JM, Pappagianopoulos PP, Hung J, Tawakol A, Gerszten RE, Systrom DM, Bloch KD, Semigran MJ (2007) Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. Circulation 116:1555–1562
41. Etz CD, Welp HA, Tjan TD, Hoffmeier A, Weigang E, Scheld HH, Schmid C (2007) Medically refractory pulmonary hypertension: treatment with nonpulsatile left ventricular assist devices. Ann Thorac Surg 83:1697–1705
42. Nair PK, Kormos RL, Teuteberg JJ, Mathier MA, Bermudez CA, Toyoda Y, Dew MA, Simon MA (2010) Pulsatile left ventricular assist device support as a bridge to decision in patients with end-stage heart failure complicated by pulmonary hypertension. J Heart Lung Transplant 29:201–208
43. Pauwaa S, Bhat G, Tatooles AJ, Aggarwal A, Martin M, Kumar A, Modi H, Pappas PS (2012) How effective are continuous flow left ventricular assist devices in lowering high pulmonary artery pressures in heart transplant candidates? Cardiol J 19:153–158
44. Zimpfer D, Zrunek P, Sandner S, Schima H, Grimm M, Zuckermann A, Wolner E, Wieselthaler G (2007) Post-transplant survival after lowering fixed pulmonary hypertension using left ventricular assist devices. Eur J Cardiothorac Surg 31:698–702
45. Breinholt JP, Hawkins JA, Minich LA, Tani LY, Orsmond GS, Ritter S, Shaddy RE (1999) Pulmonary vein stenosis with normal connection: associated cardiac abnormalities and variable outcome. Ann Thorac Surg 68:164–168
46. Hancock Friesen CL, Zurakowski D, Thiagarajan RR, Forbess JM, del Nido PJ, Mayer JE, Jonas RA (2005) Total anomalous pulmonary venous connection: an analysis of current management strategies in a single institution. Ann Thorac Surg 79:596–606; discussion 596–606
47. Caldarone CA, Najm HK, Kadletz M, Smallhorn JF, Freedom RM, Williams WG, Coles JG (1998) Relentless pulmonary vein stenosis after repair of total anomalous pulmonary venous drainage. Ann Thorac Surg 66:1514–1520
48. Latson LA, Prieto LR (2007) Congenital and acquired pulmonary vein stenosis. Circulation 115:103–108
49. Holt DB, Moller JH, Larson S, Johnson MC (2007) Primary pulmonary vein stenosis. Am J Cardiol 99:568–572
50. Yun TJ, Coles JG, Konstantinov IE, Al-Radi OO, Wald RM, Guerra V, de Oliveira NC, Van Arsdell GS, Williams WG, Smallhorn J, Caldarone CA (2005) Conventional and sutureless techniques for management of the pulmonary veins: evolution of indications from postrepair pulmonary vein stenosis to primary pulmonary vein anomalies. J Thorac Cardiovasc Surg 129:167–174
51. Devaney EJ, Chang AC, Ohye RG, Bove EL (2006) Management of congenital and acquired pulmonary vein stenosis. Ann Thorac Surg 81:992–995; discussion 995–996
52. Tomita H, Watanabe K, Yazaki S, Kimura K, Ono Y, Yagihara T, Echigo S (2003) Stent implantation and subsequent dilatation for pulmonary vein stenosis in pediatric patients: maximizing effectiveness. Circ J 67:187–190
53. Mendelsohn AM, Bove EL, Lupinetti FM, Crowley DC, Lloyd TR, Fedderly RT, Beekman RH 3rd (1993) Intraoperative and percutaneous stenting of congenital pulmonary artery and vein stenosis. Circulation 88:Ii210–Ii217

Part II

The Diagnosis of Pulmonary Hypertension in Adult Congenital Heart Disease

9 Physical Examination and Electrocardiography in Patients with Pulmonary Arterial Hypertension Due to Congenital Heart Disease: Initial Clinical Assessment

Margherita Ministeri, Natali Chung, and Konstantinos Dimopoulos

Abbreviations

AEPC	Association for European Paediatric Cardiology
AO	aorta
AP	aortopulmonary
AR	aortic regurgitation
ASD	atrial septal defect
AVSD	atrioventricular septal defect
BP	blood pressure
CHD	congenital heart disease
CPET	cardiopulmonary exercise test
CT	computed tomography
CXR	chest X-ray
ECG	electrocardiogram
ERS	European Respiratory Society
ESC	European Society of Cardiology
Hb	haemoglobin
ISHLT	International Society for Heart & Lung Transplantation
JVP	jugular venous pressure
LA	left atrium
LAVV	left atrioventricular valve
LV	left ventricle

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LVH	left ventricular hypertrophy
PA	pulmonary artery
PaO_2	arterial partial pressure of oxygen
PAH–CHD	pulmonary arterial hypertension related to congenital heart disease
PAH	pulmonary arterial hypertension
PDA	patent ductus arteriosus
PH	pulmonary hypertension
PR	pulmonary regurgitation
PS	pulmonary stenosis
PVD	pulmonary vascular disease
PVR	pulmonary vascular resistance
RA	right atrium
RBBB	right bundle branch block
RV	right ventricle
RVH	right ventricular hypertrophy
$SatO_2$	oxygen saturations
TGA	transposition of great arteries
TOF	tetralogy of Fallot
TR	tricuspid regurgitation
VCO_2	carbon dioxide production
VE	ventilation

9.1 Basics of History Taking and Physical Examination in CHD

The initial evaluation of a patient with pulmonary arterial hypertension (PAH) in the context of congenital heart disease (CHD) is usually accomplished by history taking, physical examination (including inspection, palpation and auscultation), electrocardiography (ECG), chest radiography and exercise testing (cardiopulmonary exercise test (CPET) or 6-min walk test (6MWT)). The weight of the information gained from these different techniques varies with the type and severity of the disease. However, the selection of appropriate diagnostic tests and management choices heavily depend on skilful history taking and the physical examination.

The clinical scenarios in pulmonary arterial hypertension related to congenital heart disease (PAH–CHD) are extremely variable, depending on the wide range and complexity of the underlying cardiac anatomy and physiology and a multitude of adaptive mechanisms. PAH can develop at any stage of a CHD patient's life [1, 2]. In some patients, PAH develops in childhood, and pulmonary arterial pressures may never drop in neonatal life, usually as a result of a large post-tricuspid shunt. In others, PAH may persist after late repair or may indeed develop later in life, e.g. in patients with a pre-tricuspid shunt. In exceptional cases, PAH may even develop after timely repair of a defect, in the absence of significant residual haemodynamic lesions or in the presence of a small intracardiac defect, which would not have been expected to trigger the development of pulmonary vascular disease (PVD) (see classification of PAH–CHD, Chaps. 1 and 2).

Careful and meticulous interrogation of the patient is essential for obtaining a complete history. Key components are the assessment of the chief complaint and other recent medical history, with emphasis on the onset, duration and timing of symptoms. Past medical history should include a detailed description of the underlying anatomical defect, coexisting disease and medical therapy. In PAH–CHD, particular focus should be placed on previous surgery or other interventions: surgical reports should be reviewed with regard to the perioperative haemodynamics, intraoperative anatomy, reparative technique and final outcome. Other causes of pulmonary hypertension (PH) should also be investigated for and excluded, including evidence of previous thromboembolism, Raynaud phenomenon, dysphagia, travel history, the use of anorexigens, sleep apnoea or history of respiratory disease.

Family and genetic history (genetic/chromosomal disease), along with the prenatal/birth/postnatal history, can give clues on the underlying CHD and predisposition to PAH. Maternal exposure to teratogens, prematurity, low birth weight, cyanosis, hypoxic spells and squatting during childhood are strong indicators of CHD. Information about physical and cognitive development, recurrent lower respiratory infections or other lung injury are not infrequent in CHD, especially children with a large left-to-right shunt, and may contribute to the development of PH. Diminished exercise tolerance from an early age, with a young patient unable to keep up with his peers, is often encountered in CHD, with or without PAH.

9.2 The Symptoms of PAH

The most common symptoms reported by a PAH–CHD patient are entirely non-specific:

- *Dyspnoea*, usually on mild-to-moderate efforts, can be quantified using the modified Borg dyspnoea scale (see chapter on 23 palliative care) and disease-specific quality of life (QoL) scores. The pathogenesis of dyspnoea in heart failure remains unclear. In patients with PAH–CHD, especially those with Eisenmenger syndrome, dyspnoea is likely to be related to the significant ventilation (VE)/perfusion mismatch (physiological dead space) caused by the right-to-left shunt and reduced pulmonary blood flow. Paul Wood, in 1958, observed that Eisenmenger syndrome patients with a patent ductus arteriosus (PDA) were less symptomatic compared to those with a ventricular septal defect or atrial septal defect (VSD or ASD). Based on this observation, he proposed that breathlessness in Eisenmenger syndrome is due to a low arterial oxygen saturation in the blood passing through the chemoreceptors of the head and neck.
- *Fatigue* is common in PAH–CHD and can be defined as physical and/or mental exhaustion triggered by stress, medication, overwork or mental and physical illness or disease.
- *Light-headedness and syncope*. The latter is a concern in PAH. Syncope on effort suggests significant inability of patients to increase their cardiac output and an

inability to sustain cerebral blood flow. It is an adverse prognostic marker, requiring aggressive treatment. For this reason, syncope is included in the WHO functional classification for PH patients (Table 9.1).

- *Chest pain* is not uncommon in PAH and PAH–CHD. It can originate from the myocardium of the hypertrophied and hypoperfused RV, but compression of the left main coronary artery by a dilated hypertensive pulmonary trunk should always be suspected and treated promptly (Figs. 9.1.and 9.2). Massive dilatation of the pulmonary artery (PA) can also lead to dissection or rupture, producing

Table 9.1 WHO functional classification of PH, modified after the New York Heart Association functional classification

WHO functional classification for PH	
Class I	Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or near syncope
Class II	Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope
Class III	Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain or near syncope
Class IV	Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity

WHO World Health Organization

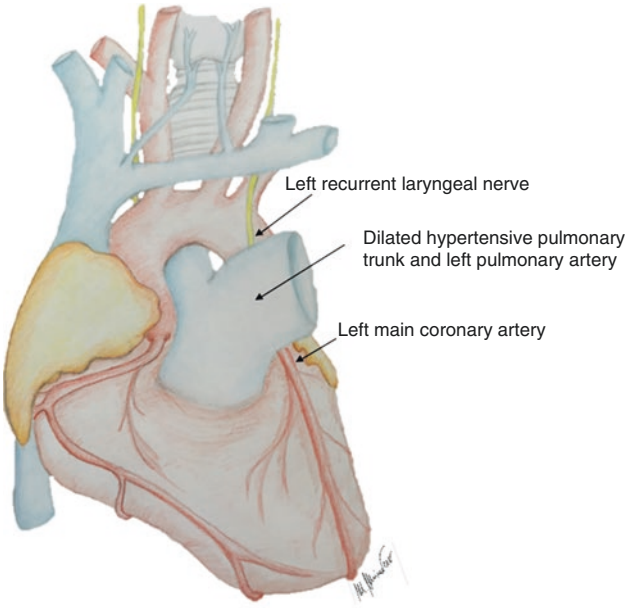

Fig. 9.1 Anatomical relation between the left recurrent laryngeal nerve, the left main coronary artery and a dilated hypertensive pulmonary trunk

massive haemoptysis and death. In situ thrombi developing within the enlarged pulmonary arteries (PAs) of Eisenmenger patients may rarely dislodge and cause peripheral pulmonary embolism and pulmonary infarction, which can present with chest pain.

- *Hoarseness* (Ortner syndrome or cardiovocal syndrome) is observed in some PAH–CHD patients with severely dilated PAs, especially patients with Eisenmenger syndrome (Fig. 9.1, note the proximity of the recurrent laryngeal nerve to the dilated PA).
- *Symptoms related to systemic complications* (renal dysfunction, gout, gallstones) or bleeding (manifested as easy bruising, gingival bleeding, haemoptysis, etc.) are not uncommon in cyanotic PAH–CHD patients (see Chap. 15).

9.3 Visual Inspection

Valuable information can be gained by an initial "head to toe" inspection of PAH–CHD patients [3]. This should include:

- General appearance and nutritional state
- Abnormalities in the facies, stature or extremities compatible with known genetic syndromes
- Colour of the skin (cyanosis, pallor, jaundice)
- Clubbing of toes and/or fingers

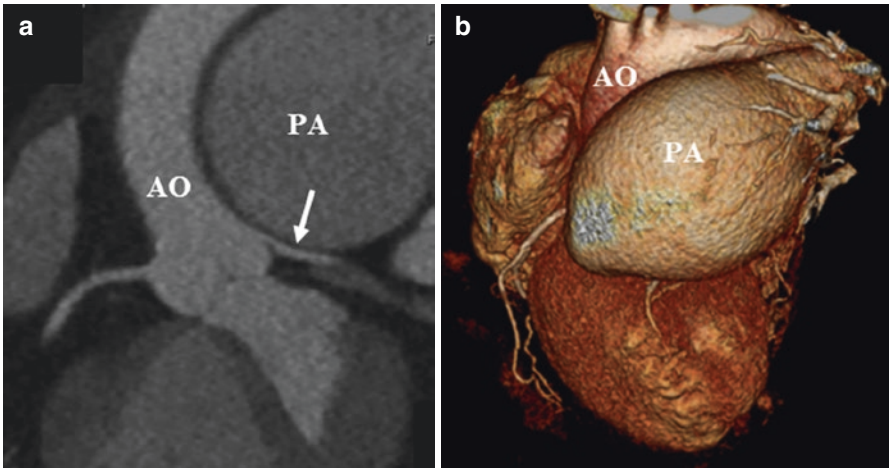

Fig. 9.2 Compression of the left main coronary artery by a dilated hypertensive pulmonary trunk. Coronary CT scan (**a**) and 3D reconstruction of the heart and massively dilated pulmonary artery (**b**). Extrinsic compression of the left main stem and left anterior descending coronary artery from the enlarge pulmonary artery is seen in (**a**) (*arrow*). The pulmonary artery is massively dilated (**b**) in this patient with Eisenmenger syndrome, who presented with typical chest pain and a troponin rise. *AO* ascending aorta, *PA* main pulmonary artery

- Respiratory rate, dyspnoea and the use of accessory respiratory muscles
- Sweating
- Chest and back inspection for the identification of any deformities and prior surgical scars
- The presence of peripheral oedema
- Inspection of the jugular venous waveform and estimation of pressure
- The presence of petechiae or purpura, suggestive of a low platelet count (common in Eisenmenger patients, especially those with Down syndrome)

Chromosomal, hereditary or nonhereditary syndromes are common in PAH–CHD patients and are known to be associated with certain congenital heart defects (Table 9.2). Approximately 40–50% of children with Down syndrome have a congenital heart defect (see Chap. 18) and are prone to developing PVD prematurely.

Table 9.2 Major genetic syndromes associated with cardiovascular abnormalities, which can be associated with PAH–CHD

Disorders	Aetiology	Cardiac defect	Major features
Down syndrome	Trisomy 21	Frequent (40–50%); AVSD, VSD	Hypotonic, flat facies, slanted palpebral fissure, small eyes, mental deficiency, simian crease
Holt-Oram syndrome (cardiac-limb syndrome)	Autosomal dominant	Frequent; ASD, VSD	Defects or absence of the thumb or radius
Patau's syndrome	Trisomy 13	Very common (80%); VSD, PDA, dextrocardia	Low birth weight, central facial anomalies, polydactyly, chronic haemangiomas, low-set ears, visceral and genital anomalies
Edwards syndrome	Trisomy 18	Very common (90%); VSD, PDA, PS	Low birth weight, microcephaly, micrognathia, rocker-bottom feet, closed fists with overlapping fingers
Di George syndrome	Microdeletion of 22q11.2	Frequent; interrupted aortic arch, truncus arteriosus, VSD, PDA, TOF	Hypertelorism, short philtrum, downslanting eyes, hypoplasia or absence of thymus and parathyroid, hypocalcaemia, deficient cell-mediated immunity
CHARGE association	Unknown	Common (65%); TOF, truncus arteriosus, aortic arch anomalies (e.g. vascular ring, interrupted aortic arch)	Coloboma, heart defects, choanal atresia, growth or mental retardation, genitourinary anomalies, ear anomalies, genital hypoplasia

Table 9.2 (continued)

Disorders	Aetiology	Cardiac defect	Major features
Carpenter's syndrome	Autosomal recessive	Frequent (50%); PDA, VSD, PS, TGA	Brachycephaly with variable craniosynostosis, mild facial hypoplasia, polydactyly and severe syndactyly ("mitten hands")
Ellis–van Creveld syndrome (chondroectodermal dysplasia)	Autosomal recessive	Frequent (50%); ASD, single atrium	Short stature of prenatal onset, short distal extremities, narrow thorax with short ribs, polydactyly, nail hypoplasia, neonatal teeth
Zellweger's syndrome (cerebrohepatorenal syndrome)	Autosomal recessive	Frequent; PDA, VSD or ASD	Hypotonia, high forehead with flat facies, hepatomegaly, albuminuria
VATER association (VATER/VACTERL syndrome)	Sporadic	Common (>50%); VSD, other defects	Vertebral anomalies, anal atresia, congenital heart defects, tracheoesophageal fistula, renal dysplasia, limb anomalies (e.g. radial dysplasia)
Cri du chat syndrome	Partial deletion, short arm of chromosome 5	Occasional (25%); variable CHD (VSD, PDA, ASD)	Catlike cry in infancy, microcephaly, downward slant of palpebral fissures
Rubella syndrome	Maternal rubella infection during the first trimester	Frequent (>95%); PDA and PA stenosis	Triad of the syndrome: deafness, cataract and CHD. Others include intrauterine growth retardation, microcephaly, microphthalmia, hepatitis, neonatal thrombocytopenic purpura
Fetal alcohol syndrome	Ethanol or its byproducts	Occasional (25–30%); VSD, PDA, ASD, TOF	Prenatal growth retardation, microcephaly, short palpebral fissure, mental deficiency, irritable infant or hyperactive child
Fetal warfarin syndrome	Exposure to warfarin	Occasional (15–45%); TOF, VSD	Facial asymmetry and hypoplasia, hypoplasia or aplasia of the pinna with blind or absent external ear canal (microtia), ear tags, cleft lip or palate, epitubular dermoid, hypoplastic vertebrae

Patients with Patau's syndrome (trisomy 13) or Edwards syndrome (trisomy 18) very commonly present with a VSD or PDA. Abnormalities of the digits are found in association with an ASD or VSD in patients with Holt–Oram syndrome. On the other hand, patients with Noonan syndrome are often born with pulmonary stenosis, which protects the pulmonary circulation from developing PAH in the presence of a large VSD. They can, however, develop restrictive cardiomyopathy, which can cause post-capillary PH (see Chap. 8).

Cyanosis is common in PAH–CHD and is a fundamental feature of Eisenmenger syndrome. There are two types of cyanosis:

- Peripheral cyanosis, which results from a low cardiac output or peripheral vasoconstriction.
- Central cyanosis, which is the result of right-to-left shunting, occurring when there is severe PH in patients with a congenital heart disease (PAH–CHD) or other types of PAH (e.g. idiopathic PAH) with a patent foramen ovale. Other causes of central cyanosis include intrapulmonary shunting and VE–perfusion mismatch in the presence of parenchymal lung disease. The presence of cyanosis in an adult with CHD is not always an expression of PAH. Patients with an intracardiac defect and severe pulmonary stenosis or raised right ventricular end-diastolic pressure (e.g. Ebstein anomaly of the tricuspid valve) and those with complex CHD may also develop cyanosis in the absence of PH.

When assessing cyanosis, the physician should make a note of the severity and distribution. While central cyanosis commonly affects the entire body, there are conditions in which this is not the case. Differential cyanosis and differential clubbing are typical in patients with Eisenmenger syndrome due to a large PDA: the upper half part of the body is "pink" and the lower half is cyanotic (Fig. 9.3). To detect differential cyanosis, oxygen saturations should be measured in sites that receive blood flow from both pre-ductal (right hand) and post-ductal (foot) vessels. It is preferable to use the right (rather than left) upper extremity, since the left subclavian artery arises close to the ductus arteriosus and may receive desaturated blood.

Reversed differential cyanosis occurs when oxygen saturation is lower in the right hand compared to the feet. It is a feature of the Taussig–Bing anomaly (double outlet RV with anterior and dextroposition of the aorta and sub-pulmonary VSD) in which unoxygenated blood from the right ventricule goes into the ascending aorta and upper extremities, while oxygenated left ventricular blood enters the pulmonary trunk through the sub-pulmonary VSD and flows through a nonrestrictive PDA to the lower extremities. This can also be observed in transposition of the great arteries with a PDA and elevated pulmonary vascular resistance (PVR) or in transposition of the great arteries with PDA and pre-ductal aortic interruption or coarctation but is rarely seen in adults due to poor survival.

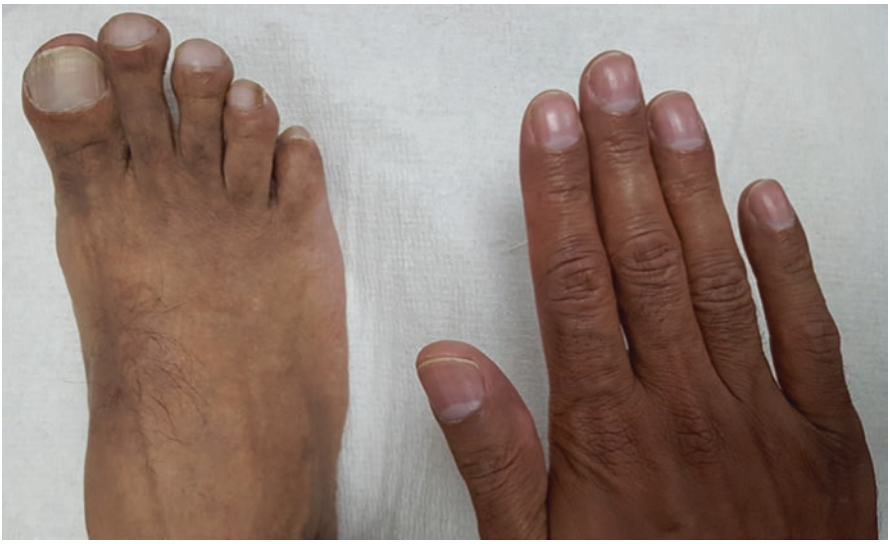

Fig. 9.3 Differential cyanosis and clubbing between the right hand and foot in a patient with Eisenmenger PDA. In this patient, oxygen saturation was normal in the right hand but low in the toes. Digital clubbing follows this pattern and is only present in the toes

Cyanosis may not be present at rest but develop on exercise in PAH–CHD. This may be suspected based on the cardiac anatomy and the presence of a raised haemoglobin concentration (secondary erythrocytosis). Exercise testing in these cases (CPET or 6MWT) is diagnostic.

The precordium should be assessed for bulging and pulsations of the chest, which may suggest chronic cardiac enlargement. A parasternal heave is a precordial impulse that may be seen or palpated and occurs in the setting of right ventricular dilatation or hypertrophy. A depressed line along the bottom of the rib cage where the diaphragm attaches, Harrison's groove, may be indicative of "stiff" lungs (poor pulmonary compliance) and is present in patients with a large left-to-right shunt.

A crude estimate of central venous pressure can be obtained by observing the internal jugular vein. With the patient lying with the upper trunk elevated at 45°, the vertical distance between the blood column within the vein (highest pulsation) and the imaginary straight line across the manubrium of the sternum (angle of Louis) should not exceed 2 cm. In a patient with significant PAH, the jugular vein may be distended, with a prominent A wave or V wave (in the presence of severe tricuspid regurgitation (TR)) (see Chap. 14, Fig. 9.1, for the pressure waveform). The systemic arterial pulse, on the other hand, may be reduced, and the pulse pressure may be narrow due to low cardiac output.

9.4 Palpation

In a slim patient with PAH, it is possible to appreciate an RV lift or tap on the left parasternal area secondary to the enlarged RV, which displaces the left ventricle (LV) from the apex. Palpation in the second left intercostal space can detect a dilated hypertensive pulmonary trunk and the pulmonary closure sound. In patients with dextrocardia, the RV impulse is located along the right sternal border, with the cardiac apical impulse in the fifth right intercostal space along the right midclavicular line. Depending on the severity of congestive heart failure and fluid overload, hepatomegaly may be present, with palpable pulsations of the liver (TR), an abnormal abdominal–jugular reflex, ascites and pitting oedema.

9.5 Auscultation

Auscultation in PAH–CHD reflects the severity of the PH and associated lesions [4]. In Eisenmenger syndrome, auscultation is as follows:

- The pulmonary component of the second heart sound (P2) is loud.
- The S2 may be single or may split narrowly due to decreased capacitance of the pulmonary vascular bed and RV dysfunction.
- An ejection click may be heard and is caused by flow in the dilated and hypertensive pulmonary trunk.
- An early diastolic decrescendo murmur of pulmonary regurgitation (PR) is often present along the mid-left sternal border (see Graham-Steell murmur).
- A holosystolic murmur of TR may be audible at the lower left sternal border and increases in intensity during active inspiration (Rivero-Carvallo sign). Amplification depends on whether the RV is functionally capable of converting the inspiratory increase in venous return, into an increase in stroke volume and regurgitant flow. In advanced RV failure, this ability is lost and the Rivero-Carvallo sign is not present.
- A third and fourth heart sound can be audible, expression of right ventricular failure.

Careful auscultation can aid the physician to distinguish between Eisenmenger syndrome and less severe forms of PAH–CHD such as those with left-to-right shunting [5]:

- Restrictive VSDs produce a soft, high-frequency, holosystolic murmur in the fourth intercostal space at the left parasternal border.
- In the presence of a post-tricuspid shunt (VSD, PDA or aortopulmonary window), which allows large volumes of left-to-right shunt (hence, there is no significant PH), a mid-diastolic flow rumble across the mitral valve indicates a pulmonary-to-systemic flow ratio (Qp/Qs) of at least 2. As PVD progresses, murmurs associated with the shunt become softer and shorter, and murmurs associated with right ventricular and PA dilatation (TR and PR) become more prominent.

– If a large pre-tricuspid shunt is present (ASD, partial anomalous pulmonary venous drainage without sequestration, systemic to right atrial shunt), a diastolic flow murmur across the tricuspid valve is indicative of a large Qp/Qs.

9.6 Blood Pressure and Peripheral Oxygen Saturations

Ideally, every patient should have their blood pressure (BP) measured as part of the physical examination. A high BP can be detrimental to PAH–CHD patients, and secondary causes of systemic hypertension (e.g. aortic coarctation) should be sought and excluded. A low BP may reflect a low cardiac output, medication, dehydration or peripheral vasodilatation. Attention should be made to use the correct arm for measuring BP in patients with previous Blalock–Taussig shunts (subclavian artery to PA) and those with aortic coarctation involving the left subclavian artery (or an aberrant right subclavian artery).

Peripheral oxygen saturation (SpO_2) is measured in clinic by means of a pulse oximeter and can easily confirm or exclude the presence of cyanosis. SpO_2 measurements must be obtained after the patient has rested in a supine or sitting position for at least 5 min (ideally silent). Oximetry can also be used during exercise testing to unmask right-to-left shunting, which may not be present at rest. Caution should be taken in interpreting SpO_2 in patients who drop their saturation below 70%, as pulse oximeters become less accurate at such low saturations. Sequential measurement of SpO_2 on the left and right hand and toes allows the differentiation between pre-ductal and post-ductal shunts in PAH–CHD patients with a right-to-left shunt (see differential cyanosis).

9.7 ECG

The ECG is able to detect right ventricular hypertrophy (RVH) quite accurately and is, thus, helpful in conditions of RV pressure overload. It is, however, less reliable in detecting RV dilatation due to volume overload, as opposed to the chest X-ray (CXR), which is helpful in diagnosing volume overload but not hypertrophy. The two tests are, therefore, complementary and, together, are an essential part of the cardiac evaluation.

In CHD, the presence of ECG abnormalities can provide useful clues regarding not only the type of defect, but also the haemodynamic status of patients with PAH–CHD (Table 9.3) [6].

In CHD patients with left-to-right shunting, the ECG trace is influenced by the severity of the shunt and the PVR. The presence of left atrial enlargement, left ventricular or biventricular enlargement (Katz-Wachtel phenomenon) and q waves in the lateral precordial leads suggests volume overload due to a post-tricuspid shunt in the absence of significant PH. In pre-tricuspid shunts, an incomplete right bundle branch block (RBBB) pattern (with rsR' in V1) and right axis deviation suggest volume overload without a significant rise in PVR (Fig. 9.4, also see ASD section below).

Table 9.3 Chest X-ray and ECG features that may help distinguish volume vs. right ventricular pressure overload (and PH), i.e. patients with left-to-right shunting and/or mild PH vs. patients with severe PH and pulmonary vascular disease (PVD)

		Features suggestive of volume overload due to a left-to-right shunt	Features suggestive PVD
ECG	P wave	Left atrial enlargement in a pre- but especially post-tricuspid shunt	Signs of right atrial enlargement
		Right atrial enlargement in a pre-tricuspid shunt	
	QRS	Incomplete right bundle branch block (RBBB) pattern (with rsR' in V1) with rightward QRS axis in a pre-tricuspid shunt	Right ventricular hypertrophy
			Rightward QRS axis
Chest X-ray	Cardiac size	Left ventricular enlargement in a post-tricuspid shunt	Heart size may be normal or mildly enlarged, apex lifted as the right ventricular hypertrophy
		Right chamber enlargement in a pre-tricuspid shunt	
	Atrial enlargement	Enlarged left atrium in a post- (and pre-) tricuspid shunt	Enlarged right atrium
		Enlarged right atrium in pre-tricuspid shunt	
	Lung vascularity	Increased vascularity across the lung fields (plethora)	Prominent main and hilar pulmonary arteries with peripheral pruning and oligaemic peripheral lung fields

PVD pulmonary vascular disease

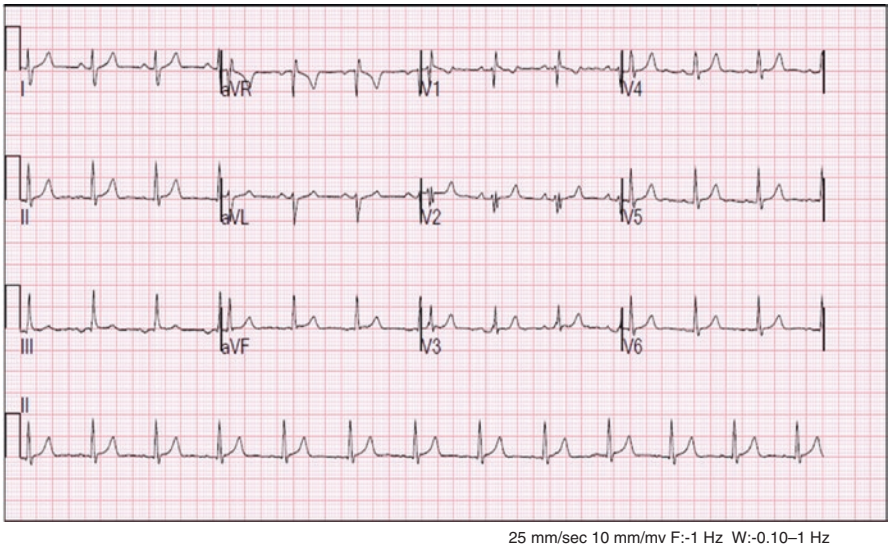

Fig. 9.4 ECG of a patient with a large left-to-right shunt due to a large atrial septal defect

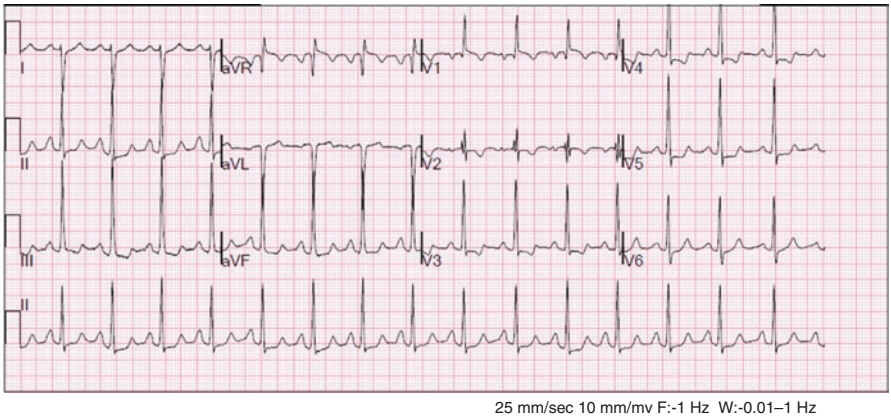

Fig. 9.5 ECG of large post-tricuspid shunt (PDA) with severe PAH

Right atrial dilatation with prominent right ventricular forces (high positive voltage in right precordial leads) and the absence of q waves in the lateral leads are expressions of significant PH (Fig. 9.5). RVH reflects the increase in PVR and is more prominent in cases with severe and long-standing PH. Reduced compliance of the hypertrophied RV often results in right atrial dilatation, seen as tall peaked P waves. In addition, RVH produces abnormalities in the QRS axis, the QRS voltage, the R/S ratio and the T axis:

- Changes in the QRS axis: the QRS axis is usually directed towards the ventricle that is hypertrophied; hence, in the presence of right pressure overload, there is right axis deviation.
- Changes in QRS voltage: considering that anatomically, the RV occupies the right and anterior aspect of the heart, and RV hypertrophy causes an increase in the (positive) forces of the QRS complex, i.e. tall R wave voltages in aVR and III and increased S voltages in lead I. In the horizontal plane, tall R waves in V4R, V1 and V2 or deep S waves in V5 and V6 are typically seen.
- Changes in R/S ratio: the R/S ratio represents the relative electromotive force of opposing ventricles in a given lead. An increase in the R/S ratio in right precordial leads suggests RVH.
- Changes in the T wave axis: changes in the T wave axis are seen in severe ventricular hypertrophy with relative ischaemia of the hypertrophied myocardium. In the presence of other criteria of ventricular hypertrophy, a wide QRS-T angle (i.e. >90°) with the T wave axis outside the normal range indicates a "strain" pattern. When the T wave axis remains in the normal quadrant (0 to +90°), a wide QRS-T axis angle alone indicates a possible "strain" pattern.

9.8 Chest X-Ray

A CXR is readily available and provides valuable information on cardiovascular anatomy and pulmonary vasculature. Signs of previous sternotomy or thoracotomy are also useful in reconstructing the surgical history of the patient and the potential contribution of lung restriction to dyspnoeic symptoms, while different radiographic features can help determine the presence, severity and cardiac adaptation to PAH–CHD (Table 9.3) [6, 7, 22]. Signs of PAH in CHD include (Fig. 9.6):

- Enlargement and calcification of the pulmonary trunk and its proximal branches.
- Clear lung fields (oligaemia).
- Signs of RV hypertrophy: the apex of the heart is pushed upwards (right ventricular-type apex); the heart size is normal or enlarged and reflects the degree of right ventricular failure.
- RA enlargement varies from a slight convexity at the right lower cardiac border, to striking enlargement provoked by right ventricular failure and TR.
- Further information on the CXR and other radiology is provided in Chap. 10.

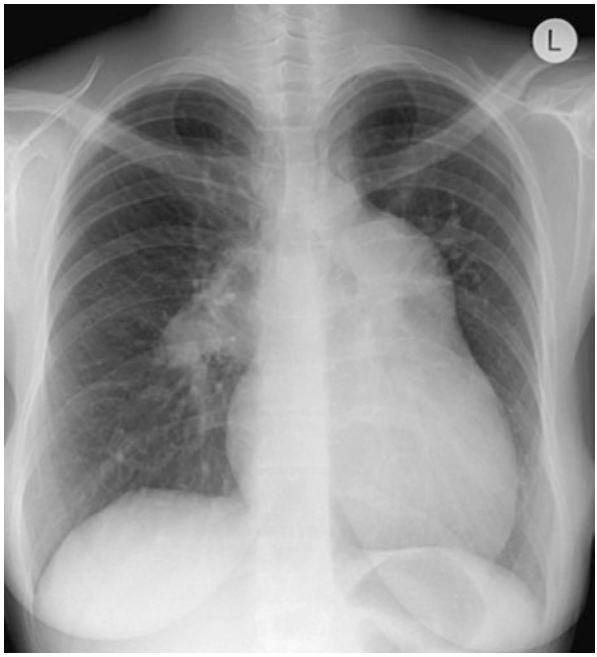

Fig. 9.6 Chest X-ray of PAH in a patient who developed PAH after VSD closure. Notice the prominent central pulmonary arteries with oligaemia in the periphery and a mildly enlarged heart with the apex shape suggestive of RV dilatation

9.9 Six-Minute Walk Test

The 6MWT is a submaximal timed distance test and is the standard test for PAH patients. The main response variable in this type of exercise testing is the distance covered at a patient's own pace within 6 min. A healthy 40-year-old person can cover approximately 600 m in 6 min, decreasing by 50 m per decade thereafter [8]. Oxygen saturations can also be recorded by portable pulse oximetry. The 6MWT reflects ordinary daily activities and is easy to perform in clinic. It is a submaximal test for healthy individuals and those with mild functional impairment but can become a maximal test in highly symptomatic patients. Indeed, the 6-min walking test distance correlates well with peak oxygen consumption (VO_2) measured during CPET in highly symptomatic patients [9]. It is commonly used to assess the response to PAH therapies and is the only test approved by the US Food and Drug Administration (FDA) as an endpoint for prospective clinical trials in this population [10, 11]. Correlation with peak VO_2 appears to be best when distance is adjusted for patient weight (distance weight) [12]. Reproducibility of repeat 6MWTs also depends on adequate standardization of the protocol used. An important learning effect has also been described and should be considered when comparing the first with subsequent tests [13].

9.10 CPET

CPET is a powerful tool for the simultaneous objective evaluation of the cardiovascular, respiratory and muscular systems under conditions of controlled metabolic stress (see also Chap. 13). In fact, the subjective assessment of exercise intolerance using the New York Heart Association (NYHA) classification appears to underestimate the severity of functional impairment in CHD. A linear relationship exists between NYHA class and peak VO_2 across the spectrum of CHD, but many asymptomatic CHD patients show dramatically lower peak VO_2 values compared with normal controls [14]. Cyanosis and PH significantly affect exercise capacity. Objective data confirm that Eisenmenger and complex patients with cyanosis are impaired significantly in their ability to exercise, expressed as very low values of peak VO_2 and limited ventilatory response to exercise in the form of an extremely high VE/carbon dioxide production (VCO_2) slope (Fig. 9.7) [15]. The effect of the PH and right-to-left shunting is obvious from the onset of exercise, when VO_2 fails to increase because of the inability to sufficiently increase pulmonary blood flow [16]. In these patients, an increase in (systemic) cardiac output is obtained through shunting, at the expense of further systemic desaturation. An abrupt, exaggerated increase in VE occurs almost at the onset of exercise, resulting in alveolar hyperventilation, a rise in VCO_2 and a drop in VO_2. This accounts for the transient increase in the respiratory quotient (the ratio between VCO_2 and VO_2) often encountered in these patients at the start of exercise.

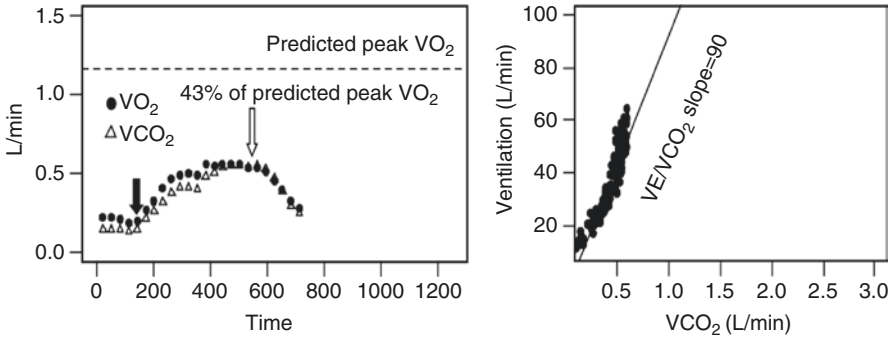

Fig. 9.7 Cardiopulmonary exercise test results from a patient with Eisenmenger syndrome. CPET in a mildly symptomatic 52-year-old woman with Eisenmenger physiology. She exercised for 6.3 min and reached a peak VO_2 of 11.2 mL/kg/min, which was 43% of predicted. The VE/VCO_2 slope was 90, which is severely raised. Her resting saturations were 90% and decreased to 45% at peak exercise, when she became light-headed and had to stop. Heart rate response was appropriate (89–151 bpm), but blood pressure response was suboptimal (128/82 to 142/80 mmHg). In this case, the cardiopulmonary exercise test revealed significant exercise intolerance and severe ventilatory inefficiency. Despite near-normal resting oxygen saturations, severe desaturation occurred and was likely the cause of termination of exercise. Moreover, the significant right-to-left shunt caused a significant ventilation–perfusion (V/Q) mismatch and stimulation of peripheral and central chemoreceptors, leading to an increase in ventilation, disproportionate to CO_2 production. *VO2* oxygen consumption, *VCO2* carbon dioxide production, *VE* ventilation

Although VE is increased, ventilatory efficiency is significantly impaired, as suggested by very high values of the VE/VCO_2 slope in cyanotic patients [17]. Pulmonary hypoperfusion, an increase in physiological dead space through right-to-left shunting, and enhanced ventilator reflex sensitivity are potential mechanisms contributing to the ventilatory inefficiency and the failure to meet oxygen requirements [17]. The inefficiency of the ventilatory response to exercise in cyanotic patients is likely to lead to the early onset of dyspnoea and exercise limitation in Eisenmenger patients. However, the exaggerated ventilatory response in these patients appears appropriate from a chemical point of view. In fact, hyperventilation succeeds in maintaining near-normal arterial PCO_2 and pH levels in the systemic circulation, at least during mild-to-moderate exertion, despite significant right-to-left shunting [18].

The effect of cyanosis on exercise capacity and VE is difficult to distinguish from that of PH. Significant ventilatory inefficiency and an exaggerated ventilatory response to exercise have been described in patients with idiopathic PH in the absence of right-to-left shunting [19, 20]. In Eisenmenger patients, the ventilatory response to exercise is exacerbated by the right-to-left shunt, which contributes to the physiological dead space and allows stimulation of chemoreceptors in the systemic circulation.

9.11 Specific Congenital Lesions

In order to appreciate the effect of PH on the clinical findings of patients with specific congenital lesions, it is necessary to understand the usual presentation of individual lesions prior to the development of PH.

9.12 Atrial Septal Defect

An ASD is a direct communication between the atrial chambers. In the absence of a condition causing increased RV end-diastolic pressure (e.g. pulmonary stenosis or PH) or obligatory right-to-left shunting (e.g. tricuspid atresia), the direction of the shunt through an ASD is from left to right, and the magnitude of the shunt is determined by the size of the defect and the relative compliance of the RV and LV. Because the compliance of the RV is normally greater than that of the LV, a left-to-right shunt is present, even in older patients. The magnitude of the shunt is reflected in the degree of cardiac enlargement: the right atrium (RA), RV and main PA and its branches are volume overloaded and, therefore, became dilated. These findings are translated into the clinical examination. In the presence of a large left-to-right shunt (and hence no significant PH), there is (Fig. 9.8):

- A hyperdynamic cardiac impulse at the left sternal border during expiration.
- A widely (fixed) split S2 is the cardinal feature in ASDs and is the result of the large shunt that prolongs ejection leading to delayed closure of the pulmonary valve. Moreover, the large shunt tends to abolish respiration-related variations in systemic venous return, resulting in a fixed S2. RBBB is also often present and may delay the electrical depolarization of the RV and, hence, RV contraction, resulting in delayed closure of the pulmonary valve.
- A soft systolic crescendo–decrescendo ejection murmur at the left upper sternal border, resulting from the increased blood flow passing through the pulmonary valve. No heart murmur is caused by the ASD because of the low pressure gradient between the atria and the cardiac cycle.
- An early to mid-diastolic murmur at the left lower sternal border, reflecting increased blood flow across the tricuspid valve, secondary to the left-to-right shunt.
- No cyanosis with normal SpO_2.
- The ECG reflects the RV dilatation, which prolongs the RV depolarization time. The outflow tract of the RV is the last part of the heart to depolarize and, because of its length, produces a peculiar QRS complex characterized by an rsR' in right precordial leads, expression of the rightward, superior and anterior direction of the terminal force of the QRS. This is the ECG hallmark of the ASD, identified commonly but improperly as incomplete RBBB (Fig. 9.4). The QRS axis is vertical with clockwise depolarization and deviates further to the left when PH

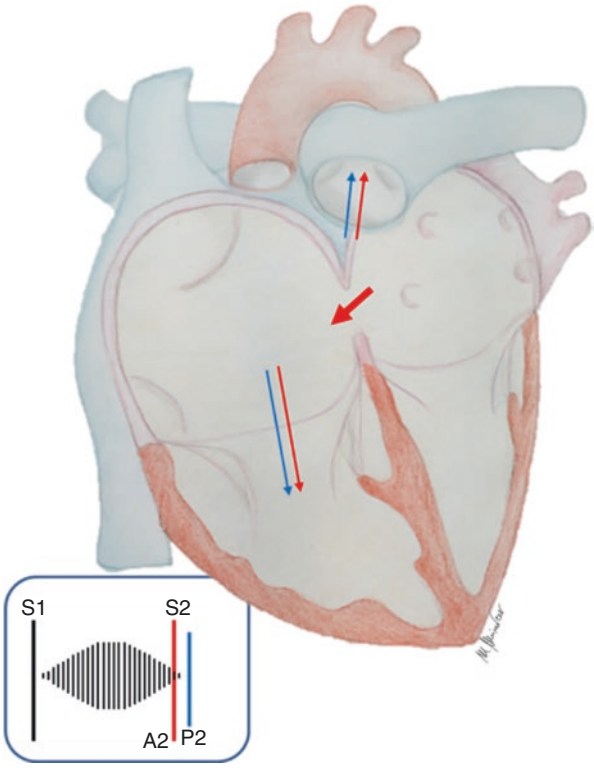

Fig. 9.8 Large ASD with left-to-right shunt. Significant enlargement of the right heart chambers and the main pulmonary artery. On the left the typical phonocardiogram. See text for explanation

develops. Patients with a superior sinus venosus ASD can have an abnormal P wave axis (outside the normal range of 0–60°). Extreme right or left QRS axis deviation (superior QRS axis) is seen in patients with a primum ASD (part of the spectrum of atrioventricular septal defects (AVSDs)).

- The CXR (Fig. 9.9) suggests enlargement of the RA, RV and PA, as well as an increase in pulmonary vascular markings (plethoric lungs). The left atrium (LA) may become enlarged but not as much as the RA, because the increased pulmonary venous return to the LA does not stay within that chamber but is shunted to the RA. The absence of significant left atrial enlargement, together with plethora vs. pulmonary venous congestion, are helpful X-ray signs for differentiating an ASD vs. right heart dilatation secondary to left heart disease (e.g. long-standing mitral stenosis or LV diastolic dysfunction).

Patients with an ASD may remain asymptomatic through childhood and beyond. Many may develop PH, which is purely related to the large shunt and is associated with a normal PVR. Very rarely does PVD develop in patients with an isolated ASD. Down patients and patients born at high altitude are more prone to develop PVD in the context of an ASD. In Down patients, other causes for PH, e.g. sleep apnoea, should be excluded before intrinsic reactivity of the vascular bed is blamed for the development of PH.

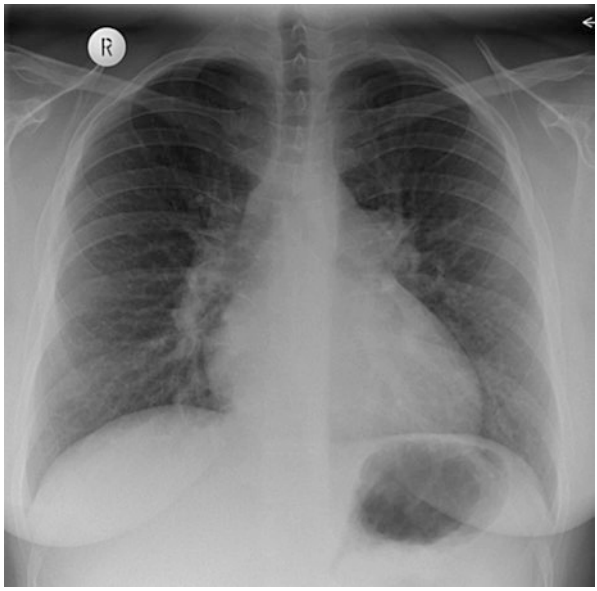

Fig. 9.9 Chest X-ray of a large pre-tricuspid left-to-right shunt (ASD); see text for explanation

If PH develops in a patient with an ASD, the left-to-right shunt decreases in volume proportionate to the severity of the PH. As a result, the features during clinical examination change and resemble those of idiopathic PAH:

- A dominant A wave in the jugular venous pressure (JVP).
- A narrow S2.
- The pulmonic component of the S2 is accentuated.
- The systolic murmur shortens or disappears.
- A diastolic murmur due to the shunt can no longer be heard, but PR may develop.

The patient may develop cyanosis, especially during exercise, due to the reversal shunt across the ASD. In patients with an ASD, it is important to distinguish cyanosis due to PVD from a streaming phenomenon within the heart, e.g. platypnea–orthodeoxia, i.e. desaturation in the upright position, which may be caused by a prominent Eustachian valve directing flow through an ASD or patent foramen ovale (PFO).

On CXR, the hypertensive proximal PAs can become aneurysmal with intraluminal (in situ) thrombosis and look strikingly enlarged and possibly calcified. The remaining peripheral lung fields appear black (pruning).

9.13 Ventricular Septal Defect

A VSD is one of the most common types of CHD. In a heart with normal segmental anatomy and without significant obstruction to pulmonary blood flow or increased PVR, a large VSD will allow significant left-to-right shunting. The magnitude of the

shunt is determined by the size rather than location of the defect, the relative ratio of the resistances of the pulmonary and systemic vascular beds and the presence and severity of obstruction in either the right or left ventricular outflow tract. In the case of a large VSD, the resistance offered by the defect itself is minimal, and the amount of left-to-right shunt depends largely on PVR: the lower the PVR, the greater the left-to-right shunt. This type of shunt is called a dependent shunt (as opposed to obligatory shunt).

VSDs can be classified as restrictive (when RV and pulmonary arterial systolic pressures are significantly lower to those in the LV and aorta) or nonrestrictive (allowing near equalization of pressures between the LV and RV). Small "restrictive" VSDs do not usually have haemodynamic or other clinical consequences. They are associated with a loud holosystolic murmur (evidence of a significant pressure gradient between the two ventricles) and do not lead to the development of PVD. Generally, shunting through restrictive VSDs occurs mainly in systole, when the pulmonary valve is open; thus, they do not cause RV dilatation. However, larger restrictive VSDs may allow significant left-to-right shunting and volume overload of the LV.

A large, nonrestrictive VSD causes significant left-to-right shunting immediately after birth, when PVR falls abruptly. The right cardiac chambers and pulmonary vessels are exposed to a chronic pressure and volume overload, as is the LA and LV, resulting in enlargement of the main PA, LA and LV as well as an increase in pulmonary vascular markings. These pathophysiological changes related with the large left-to-right shunt are translated into the clinical examination, as follows (Fig. 9.10a):

- A systolic thrill may be present at the left lower sternal border.
- A precordial bulge and hyperactivity are present with a large-shunt VSD.
- The intensity of the P2 is normal with a small shunt, while it is moderately increased with a large shunt.
- The left-to-right shunt produces a grade 2–5/6 systolic murmur, audible at the third or fourth intercostal space to the left of the sternum. It may be holosystolic or early systolic.
- With a moderate-to-large shunt, an apical diastolic rumble may be present because of increased flow through the mitral valve during diastole.
- With an infundibular VSD, a grade 1–3/6 early diastolic decrescendo murmur of AR may be audible due to prolapse of an aortic cusp through the VSD.

The ECG shows left ventricular hypertrophy (LVH) of the volume overload type and sometimes left atrial hypertrophy/dilatation. A large VSD usually results in biventricular hypertrophy.

When a large left-to-right shunt is present, the CXR shows cardiomegaly of varying degrees and involves mainly the LA, LV but also the RV due to the rise in RV pressure. Pulmonary vascularity is increased. The degree of cardiomegaly and the increase in pulmonary vascular markings directly relate to the magnitude of the left-to-right shunt.

When a moderate/large VSD is left untreated, irreversible changes take place in the pulmonary arterioles, producing PVD and, potentially, Eisenmenger

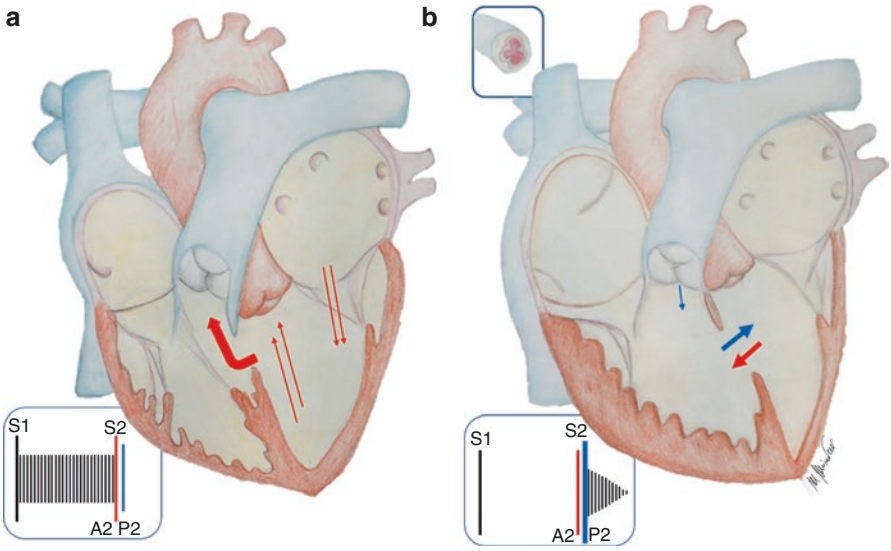

Fig. 9.10 Pathophysiological and phonocardiogram changes in the presence of VSD, before (**a**) and after developing of PAH with Eisenmenger physiology (**b**)

physiology. PVD may begin to develop as early as 6–12 months of age in patients with large VSDs (earlier in patients with Down syndrome), but right-to-left shunting (Eisenmenger syndrome) often does not develop until teenage years.

When Eisenmenger syndrome occurs, striking changes take place in the heart size, clinical findings and ECG. As the PVR rises, the magnitude of the left-to-right shunt decreases. As the pressure gradient between the ventricles diminishes, so does the intensity of the systolic murmur until, in Eisenmenger patients, it disappears. The P2 is loud and the S2 may appear single. A long decrescendo diastolic murmur beginning after the S2 is often present, in keeping with PR (Fig. 9.10b). Note that in patients with no PH, the diastolic murmur of PR becomes shorter as the severity of the regurgitation increases and often ceases in mid-diastole when RV and PA pressures equalize. In patients with systemic levels of PA pressure, the murmur is always long as diastolic RV and PA pressures are unlikely to equalize. When PVR reaches systemic levels, the VSD shunt is small and becomes bidirectional causing cyanosis. The LV and LA cease to be overloaded and heart size decreases, but the PAs continue enlarging and RVH is the predominant feature on ECG.

9.14 Patent Ductus Arteriosus and Aortopulmonary Window

A PDA, most common in preterm infants, is caused by the persistence of the normal fetal vascular channel between the PA and the aorta. The aortopulmonary window develops when the septum between the aorta and PA does not fully form.

The haemodynamics of a PDA are similar to those of a VSD. Both are post-tricuspid shunts, and the magnitude of left-to-right shunting is determined by the resistance offered by the ductus (i.e. its diameter, length and tortuosity) and the PVR (especially when the PDA is large). This is a dependent shunt.

On clinical examination, a characteristic continuous murmur (machinery-like quality) may be audible due to a significant pressure gradient between the aorta and the PA in both systole and diastole, with left-to-right shunt occurring in both phases of the cardiac cycle. Very small PDAs may not be audible (silent duct) and are incidental findings on echocardiography. Moreover, in a small PDA with limited shunting, the LV and LA overload is minimal; therefore, ECG and CXR findings are often normal.

In the case of an aortopulmonary window or a PDA with a significant (large) shunt, a continuous murmur is typically present (described for a PDA above) and may be associated with an apical diastolic flow rumble, the result of relative stenosis of the mitral valve (increased transmitral flow due to the shunt). P2 slightly increases in intensity but may not be heard when there is a loud continuous murmur. The ECG shows evidence of LVH. Enlargement of the LA and LV, a large ascending aorta and PA and increased pulmonary vascular markings can be seen on CXR.

When unrepaired or repaired "late", an aortopulmonary window or large PDA is complicated by PVD. As PVR rises, the diastolic flow through the ductus (or window) diminishes and may even cease. This causes the diastolic component of the murmur to disappear, leaving only a holosystolic murmur. As PVR rises further and reaches systemic levels, the shunt becomes bidirectional, and cyanosis appears (Eisenmenger syndrome). Cyanosis affects the entire body in the case of an AP window or is differential, i.e. only affecting the lower half of the body in the case of a PDA. On auscultation, the continuous murmur or apical rumble disappears (no significant left-to-right shunt or pressure gradient between the aorta and PA). The S2 is single and loud, and other signs of Eisenmenger syndrome (previously described for patients with a VSD) can be present. The ECG shows pure RVH as the LV is no longer overloaded. As there is little shunting in Eisenmenger syndrome, the heart size may return to normal on CXR, and peripheral pulmonary vascularity decreases, but the central hilar vessels and the main PA are greatly dilated due to the severe PH.

9.15 AVSD

AVSDs are the result of abnormal development of the endocardial cushions and are the most common type of CHD in Down syndrome. The haemodynamic implications of an AVSD depend on the type of AVSD (complete or partial) and specifically the size of the VSD. The magnitude of the left-to-right shunt through the ASD and VSD is determined by the level of PVR and the diastolic properties of the RV. In complete AVSD, the large left-to-right shunt through the VSD causes volume overload of the LA and LV (see VSD section). Additional volume overload of the LV can be due to significant left atrioventricular valve (LAVV) regurgitation. Shunting through the ASD can also cause volume overload of the RA and RV. Physical examination is characterized by a hyperactive precordium and systolic murmurs relating

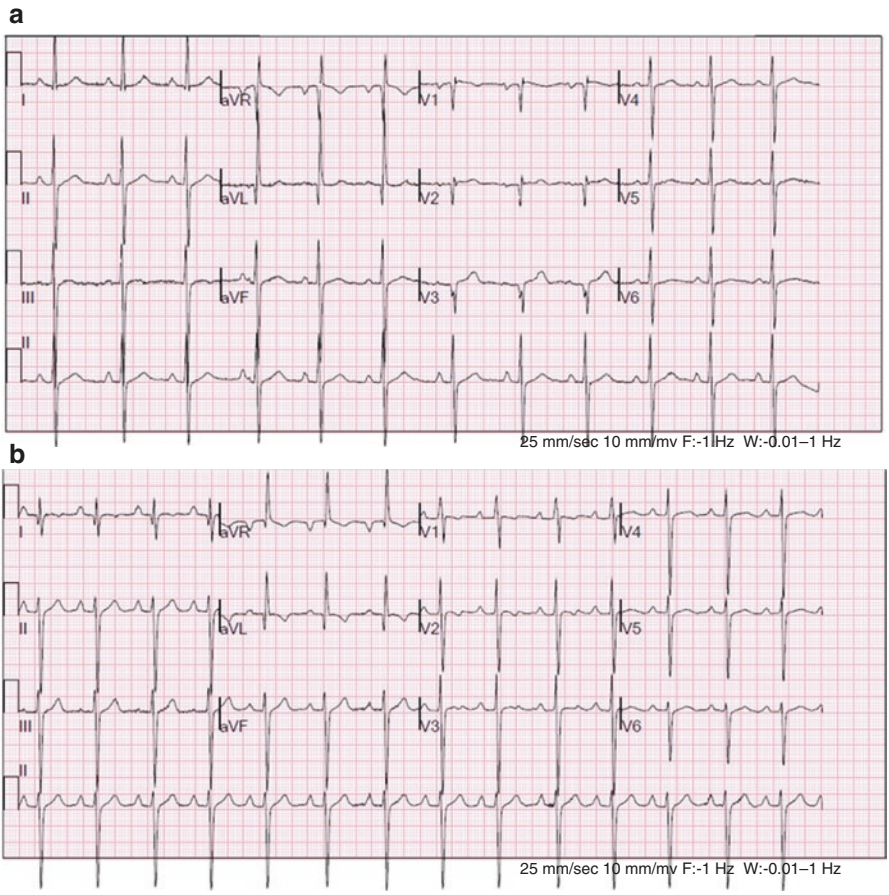

Fig. 9.11 ECG of patients with a complete AVSD, *before* (**a**) and *after* (**b**) developing significant PAH

to the VSD and LAVV regurgitation, with a loud and narrowly split S2, apical and/or tricuspid diastolic rumble and, often, signs of congestive heart failure.

The ECG also reflects these changes as LVH plus RVH and occasional biatrial hypertrophy. A "superior" QRS axis (QRS axis −20 to −150°) is characteristic of AVSDs and is often associated with a prolonged PR interval (first-degree AV block) (Fig. 9.11). The abnormal QRS axis and PR interval are not the result of the haemodynamic abnormalities mentioned but rather of the position of the atrioventricular node and bundle of His within the heart: the atrioventricular node area is displaced posteriorly and inferiorly, and the bundle branches are more posterior compared to normal.

Biatrial and biventricular enlargement is seen on the CXR in complete AVSDs.

If not repaired in a timely fashion (within the first few months of life in patients with Down syndrome), PVD develops (see large VSD or PDA). When PVR reaches systemic levels, the features of Eisenmenger syndrome appear.

Box 9.1 Cyanosis

Cyanosis is the bluish discolouration of the skin and mucosas that occurs when the absolute concentration of reduced haemoglobin in the peripheral blood exceeds 5 g/100 mL (or 3.4 g/dL in arterial blood). In patients with normal haemoglobin levels, cyanosis is detectable when arterial saturations fall below 85%. However, as the occurrence of cyanosis depends on the absolute concentration of reduced haemoglobin rather than the ratio between reduced and oxygenated haemoglobin, it depends on the concentration of Hb in the blood: for the same level of oxygen saturations, cyanosis is less obvious in patients with anaemia and more obvious in patients with high Hb concentration (e.g. polycythaemia or secondary erythrocytosis). For this reason, the clinical evaluation of cyanosis has to take into consideration Hb concentration (Fig. 9.12).

Cyanosis may occur due to desaturation of arterial blood (secondary to right-to-left shunting or parenchymal lung disease) or due to increased oxygen extraction by peripheral tissues (with normal arterial saturation) causing cyanosis of the fingers and toes (e.g. congestive heart failure, peripheral vasoconstriction).

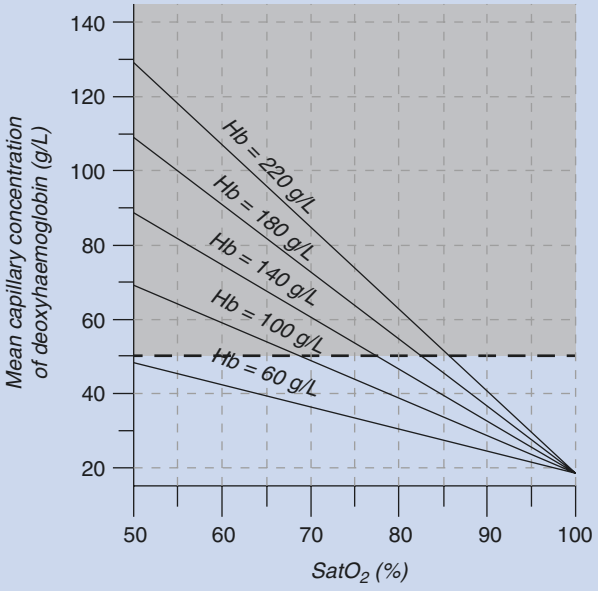

Fig. 9.12 The relation between capillary deoxyhaemoglobin (reduced haemoglobin) concentration and oxygen saturations ($SatO_2$), for various haemoglobin (Hb) concentrations. Assuming that cyanosis appears at a capillary deoxyhaemoglobin concentration of 50 g/L, patients with 80% oxygen saturations will be cyanotic when their Hb concentration is at the expected levels (>180–200 g/L; see Chap. 15). However, when their Hb concentration drops below 140 g/L, they will not be cyanotic despite having low $SatO_2$. Therefore, lack of cyanosis in Eisenmenger patients with saturations in the 80s should raise the alarm of an inappropriately low Hb (due to bleeding, iron deficiency, etc.), which results in significantly reduced oxygen delivery to peripheral tissues. Modified from Martin L, Khalil H: How much reduced hemoglobin is necessary to generate central cyanosis? Chest 1990;97:182–5

Cyanosis associated with desaturation of arterial blood is called central cyanosis: it is best detected in highly vascularized tissues through which blood flow is fast, with little arteriovenous difference (e.g. lips and other mucosas). Cyanosis due to increased oxygen extraction in peripheral tissues and normal arterial blood saturations is called peripheral cyanosis (Table 9.4). Other more rare

Table 9.4 Central versus peripheral cyanosis

	Central cyanosis	Peripheral cyanosis
Arterial pO_2	Decreased: <70 mmHg (<95%)	Normal: >70 mmHg (>95%)
Venous pO_2	Decreased proportionally with decreased arterial saturation	Reduced: <30 mmHg
Systemic A–V oxygen difference	Normal: ≈40%	Increased: >60%
Site of detection	Highly vascularized tissue, such as the lips, mucous membrane, through which blood flow is brisk. The patients' extremities are warm	Distal extremities and circumoral or periorbital areas where the blood has a sluggish movement. The extremities are often cool or clammy
Causes	• *Inadequate alveolar ventilation:*	• *Increased deoxygenation in the capillaries:*
	– Central nervous system depression	– Circulatory shock
	– Inadequate ventilatory drive (e.g. obesity, Pickwickian syndrome)	– Congestive heart failure
	– Obstruction of the airway, congenital or acquired	– Vasoconstriction from cold
	– Structural changes in the lungs and/or ventilation-perfusion mismatch (e.g. pneumonia, cystic fibrosis, hyaline membrane disease, pulmonary oedema, congestive heart failure)	– Venous obstruction
	– Weakness of the respiratory muscles	– Elevated venous pressure
	• *Desaturated blood bypassing effective alveolar units:*	– Polycythaemia
	– Intracardiac right-to-left shunt (i.e. cyanotic congenital heart defect)	
	– Intrapulmonary shunt (e.g. pulmonary atrioventricular fistula, chronic hepatic disease resulting in multiple microvascular fistulas in the lungs)	
	– PH with the resulting right-to-left shunt at the atrial, ventricular or ductal levels (e.g. Eisenmenger syndrome, persistent PH of the newborn)	
Response to hyperoxia test	• Positive in the presence of lung disease	• Negative
	• Negative in the presence of right-to-left cardiac shunting lesion	

causes of cyanosis, such as methaemoglobinaemia and sulphaemoglobinaemia, should be kept in mind. Pseudocyanosis is bluish discolouration of the skin and mucosas not relating to hypoxemia or vasoconstriction. Examples of pseudocyanosis include exposure to drugs (e.g. amiodarone) or metals (e.g. silver).

When cyanosis is present, the physician should note its severity degree and distribution (e.g. throughout the body, only on the lower or upper half of the body). Cyanosis can be detected in various parts of the body including the nail beds, lips, oral mucosa and conjunctivae. The tip of the tongue is the best place to look for cyanosis, because the colour of the tongue is not affected by ethnic background, and the circulation can never become sluggish enough to cause peripheral cyanosis. When in doubt, pulse oximetry is helpful.

In the presence of central cyanosis, the hyperoxia test is useful in distinguishing cardiac from noncardiac causes of central cyanosis (Fig. 9.13), especially lung (airways) disease [21]. Although it is mostly used in the paediatric population in the setting of PH, it could help to rule out hypoxia-related PH.

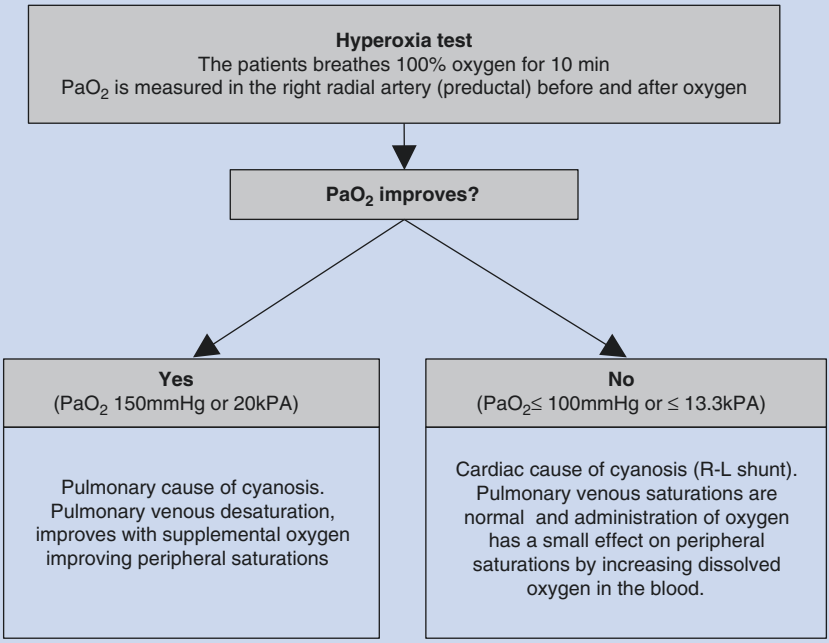

Fig. 9.13 The hyperoxia test to distinguish cardiac from pulmonary causes of cyanosis. Arterial blood gases are required as a pulse oximeter may not detect increases in arterial partial pressure of oxygen (PaO_2)

Box 9.2 Clubbing and Hypertrophic Osteoarthropathy

Long-standing arterial desaturation results in clubbing of the fingernails and toenails. When fully developed, clubbing is characterized by a widening and thickening of the distal phalanges of the fingers and toes and convex fingernails with loss of the angle between the nail and nail bed (Fig. 9.3). Reddening and shininess of the terminal phalanges are seen in the early stages of clubbing. Clubbing appears earliest and most noticeably in the thumb.

Clubbing is caused by soft tissue growth under the nail bed as a consequence of central cyanosis. The mechanism for the soft tissue growth is unclear. One hypothesis is that megakaryocytes present in the systemic venous blood may be responsible for the change. In the normal circulation, platelets are formed from the cytoplasm of the megakaryocytes by fragmentation during their passage through the pulmonary circulation. The cytoplasm of megakaryocytes contains growth factors (e.g. platelet-derived growth factor and transforming growth factor β). In patients with right-to-left shunts, megakaryocytes enter the systemic circulation, become trapped in the capillaries of the digits and release growth factors, which in turn cause clubbing.

References

1. Galiè N, Humbert M, Vachiery J-L et al (2016) 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 37(1):67–119
2. Dimopoulos K, Wort SJ, Gatzoulis MA (2014) PH related to congenital heart disease: a call for action. Eur Heart J 35(11):691–700
3. Braunwald E, Perloff JK (2001) Physical examination of the heart and circulation. In: Braunwald E, Zipes DP, Libby P (eds) Heart disease, 6th edn. WB Saunders, Philadelphia, pp 5–81
4. Perloff JK (1967) Auscultatory and phonocardiographic manifestations of PH. Prog Cardiovasc Dis 9:303
5. Pelech AN (1999) Evaluation of the pediatric patient with a cardiac murmur. Pediatr Clin N Am 46:167–188
6. Park MK, Guntheroth WG (1992) How to read pediatric ECGs, 3rd edn. Mosby, St. Louis
7. Amplatz K, Moller JH (1992) Radiology of congenital heart disease. Mosby-Year Book, St. Louis
8. Cooper CB, Storer TW (2001) Testing methods. In: Exercise testing and interpretation. Cambridge University Press, Cambridge, pp 51–92
9. Niedeggen A, Skobel E, Haager P et al (2005) Comparison of the 6-minute walk test with established parameters for assessment of cardiopulmonary capacity in adults with complex congenital cardiac disease. Cardiol Young 15(4):385–390
10. Hoeper MM, Oudiz RJ, Peacock A et al (2004) End points and clinical trial designs in PAH: clinical and regulatory perspectives. J Am Coll Cardiol 43:48S–55S

11. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories (2002) ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 166:111–117
12. Oudiz RJ, Barst RJ, Hansen JE et al (2006) Cardiopulmonary exercise testing and six-minute walk correlations in PAH. Am J Cardiol 97(1):123–126
13. Wu G, Sanderson B, Bittner V (2003) The 6-minute walk test: how important is the learning effect? Am Heart J 146(1):129–133
14. Diller GP, Dimopoulos K, Okonko D et al (2005) Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. Circulation 112(6):828–835
15. Ponikowski P, Francis DP, Piepoli MF et al (2001) Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. Circulation 103:967–972
16. Sietsema KE, Cooper DM, Perloff JK et al (1988) Control of ventilation during exercise in patients with central venous-to-systemic arterial shunts. J Appl Physiol 64(1):234–242
17. Dimopoulos K, Okonko DO, Diller GP et al (2006) Abnormal ventilatory response to exercise in adults with congenital heart disease relates to cyanosis and predicts survival. Circulation 113:2796–2802
18. Glaser S, Opitz CF, Bauer U et al (2004) Assessment of symptoms and exercise capacity in cyanotic patients with congenital heart disease. Chest 125(2):368–376
19. Oudiz RJ, Sun XG (2002) Abnormalities in exercise gas exchange in primary PH. In: Wasserman K (ed) Cardiopulmonary exercise testing and cardiovascular health. Futura, Armonk, pp 179–190
20. Sun XG, Hansen JE, Oudiz RJ et al (2001) Exercise pathophysiology in patients with primary PH. Circulation 104(4):429–435
21. Jones RW, Baumer JH, Joseph MC, Shinebourne EA (1976) Arterial oxygen tension and response to oxygen breathing in differential diagnosis of congenital heart disease in infancy. Arch Dis Child 51:667
22. Amplatz K (2000) Plain film diagnosis of congenital heart disease. In: Moller JH, Hoffman JIE (eds) Pediatric cardiovascular medicine. Churchill Livingstone, New York, pp 143–155

The Role of Plain Chest Radiography and Computed Tomography

10

Edward D. Nicol and Michael B. Rubens

Abbreviations

ASD	atrial septal defect
AVSD	atrioventricular septal defect
BMI	body mass index
CHD	congenital heart disease
CMR	cardiac magnetic resonance
CT	computed tomography
CTPA	CT pulmonary angiogram
CXR	chest X-ray
HRCT	high-resolution computed tomography
IVC	inferior vena cava
LV	left ventricle
PA	pulmonary artery
PAH	pulmonary arterial hypertension
PAH–CHD	pulmonary arterial hypertension related to congenital heart disease
PDA	patent ductus arteriosus
PH	pulmonary hypertension

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PVOD	pulmonary veno-occlusive disease
RA	right atrium
RV	right ventricle
VSD	ventricular septal defect

10.1 Introduction

X-ray imaging remains a key component of the investigation of patients with pulmonary hypertension (PH) and pulmonary arterial hypertension (PAH) with plain chest radiography and computed tomography (CT) allowing assessment of cardiac and thoracic pathology. CT has advanced significantly in the last 10–15 years with the advent of rapid acquisition, multi-detector CT scanners that now enables enhanced spatial and temporal resolution, which means that cardiac structures can be accurately visualized [1]. This has extended the traditional role of CT beyond that of assessment of the lung parenchyma and CT angiography has evolved into a modality that can provide both anatomical and functional cardiothoracic imaging and is of particular value to patients with congenital heart disease (CHD). This chapter outlines the role of plain radiography and CT in the management of patients with PAH, especially those with PAH related to CHD (PAH-CHD).

10.2 Plain Radiography

At the time of presentation, about 90% of patients with idiopathic PAH have an abnormal chest X-ray (CXR), although a normal chest radiograph does not exclude the presence of PH, and in cases in which PAH is secondary to acquired or CHD or to lung disease, the CXR may assist in the differential diagnosis [2].

The cardinal sign of PAH on the CXR is dilatation of the central pulmonary arteries (PAs) and relative reduction in size (often referred to as "pruning") of the peripheral blood vessels (Fig. 10.1). In cases where there has been long-standing, severe PAH, calcified atheroma may be visible in the central PAs (Fig. 10.2). Signs of right heart chamber enlargement may also be seen in advanced cases of PAH (Fig. 10.3) [3].

When PAH is associated with or is secondary to CHD (PAH–CHD), an unusually small aortic knuckle suggests a shunt at atrial level, whereas in ventricular and great vessel-level shunts, the aortic knuckle usually appears normal or prominent. An additional feature in cases of Eisenmenger due to a patent ductus arteriosus (PDA) may be visible calcification of the duct [4].

10.3 Computed Tomography

While echocardiography, both transthoracic echocardiogram (TTE) and transoesophageal echocardiogram (TOE), and cardiac magnetic resonance (CMR) imaging remain the first-line modalities for the assessment of cardiac morphology and

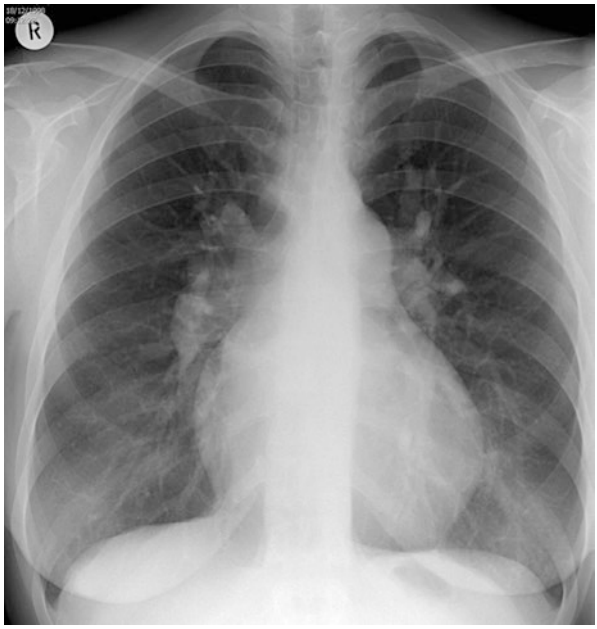

Fig. 10.1 PAH associated with an atrial septal defect (ASD). Note the enlarged central pulmonary arteries (PAs) and peripheral pruning. The heart is mildly enlarged due to right atrial dilatation and right ventricular hypertrophy. Also note that the aortic knuckle is small, a typical finding in so-called Eisenmenger ASD, possibly reflecting a long-standing low cardiac output state

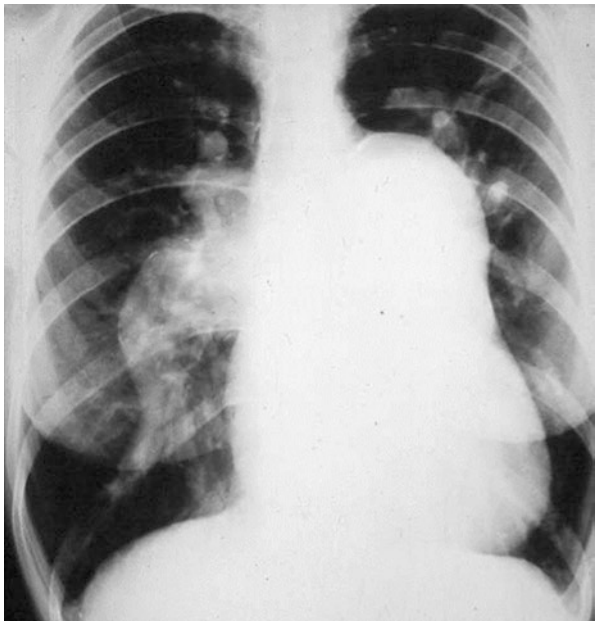

Fig. 10.2 ASD with long-standing severe PAH. Note the curvilinear calcification in the central pulmonary arteries

anatomical localization of a shunt, CT is now able to provide comparable diagnostic yield as CMR (with the exception of flow and tissue characterization), in addition to providing the traditional pulmonary parenchymal and vascular data. As with all imaging modalities, CT is useful, both for determining the underlying aetiology of

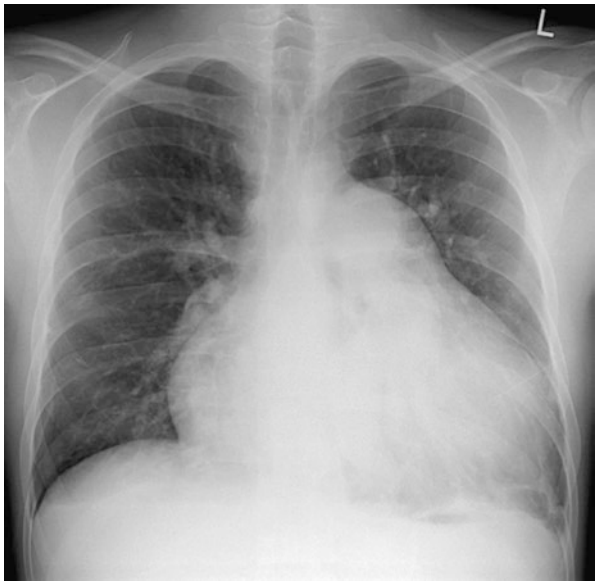

Fig. 10.3 PAH associated with an ASD. Note the enlarged central pulmonary arteries and peripheral pruning. There is gross cardiomegaly due to right atrial dilatation and right ventricular hypertrophy

PAH, and for the monitoring of known disease, including the assessment of complications of PAH, disease progression and assessment prior to consideration of intervention (both percutaneous and surgical) or transplantation [5].

The systematic assessment of PAH–CHD should include the assessment of the PAs (size, ratio with the ascending aorta, detection and quantification of thrombus or calcification, etc.), bronchial arteries and lung parenchyma, in addition to specific detailed assessment of the right heart, cardiac and extra-cardiac shunts, cardiac and coronary morphology.

The comprehensive assessment of both cardiac and thoracic structures with CT requires adaptation of traditional cardiac acquisition protocols to ensure sufficient contrast opacification of both left- and right-sided cardiovascular structures. However, with simple modifications to contrast bolus composition and timing, a single, comprehensive cardiothoracic assessment is relatively easy to achieve [1].

10.4 Pulmonary Artery Assessment

The main indicator of raised PA pressure on contrast-enhanced thoracic CT is dilatation of the main, branch and segmental PAs (Fig. 10.4a). A specific cut-off for defining PA dilatation, which is indicative of PAH remains uncertain in the literature. A pulmonary artery (PA) diameter of 29–30 mm has traditionally been quoted as the upper limit of normal; however, more recent literature would suggest 33 and 36 mm are more specific cut-off values. Normalizing for body surface area does not appear to

add value to these measurements in adults. Branch and segmental PAs should also be assessed, and values of >22.5–25 mm are often quoted for branch PAs (Fig. 10.4a – yellow lines), while segmental PA diameter exceeding that of the associated bronchus in >3 lobes and an artery–bronchus ratio of >1.25 are both used. Clinically, these are seen as the "inverse signet ring sign".

In addition to the size of the PA, other markers of potential PAH include a raised PA–aortic ratio (Fig. 10.4a black–white line ratio). It is argued that this ratio corrects for distensibility throughout the cardiac cycle, patient size and cardiac output, all of which may influence PA size. Again a definitive cut-off is debatable; however, a ratio of >1.0 is suggestive of PAH, while values >1.1 may be more specific. Finding a main PA that is conspicuously larger than the aorta is usually suggestive of PH, and measuring the ratio of the two diameters is of limited additional value. Finally, the so-called "egg and banana sign" (Fig. 10.4b) may be a marker for PH, although this may also be seen in patients with high BMI, with or without PAH.

CT pulmonary angiography (CTPA) is the gold standard test for the assessment of thromboembolic disease, which may be a cause of PH or occur as a result of PH. Eccentric mural thrombus is often associated with calcification of the PA in established chronic PH (Fig. 10.5a). Massive PA dilation may also cause left main coronary artery compression, while increasing the risk of PA dissection. Both of these conditions may present with acute onset chest pain in patients with otherwise low likelihood of significant coronary atheromatous disease. Current guidance from the UK National Institute of Healthcare Excellence (NICE) recommends CT as the first-line investigation in these patients.

Bronchial artery assessment is also important in the assessment of PH, with enlarged and hypertrophied bronchial arteries often developing as a result of the chronically raised PA pressures, and may predispose to hemoptysis (Fig. 10.5b).

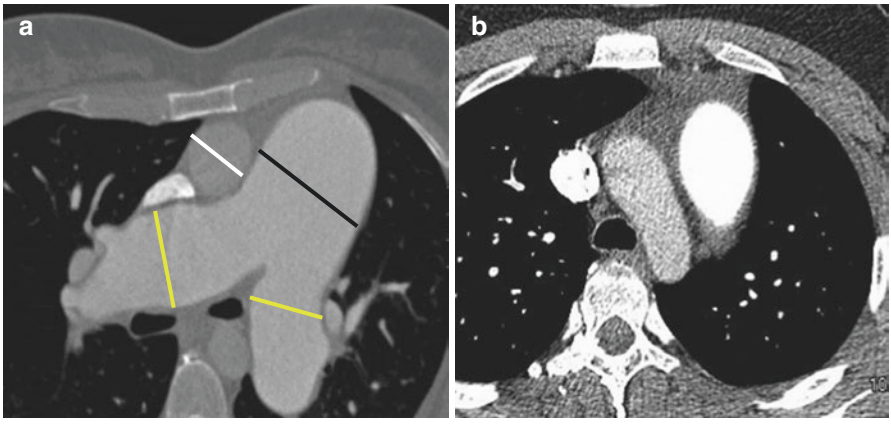

Fig. 10.4 (**a**) CTPA shows enlarged branch pulmonary arteries (*yellow lines*) and increased PA–aortic ratio (*black–white line* ratio). (**b**) CTPA shows the transverse aortic arch and (dilated) MPA on same transaxial CT section, mimicking an egg and a banana

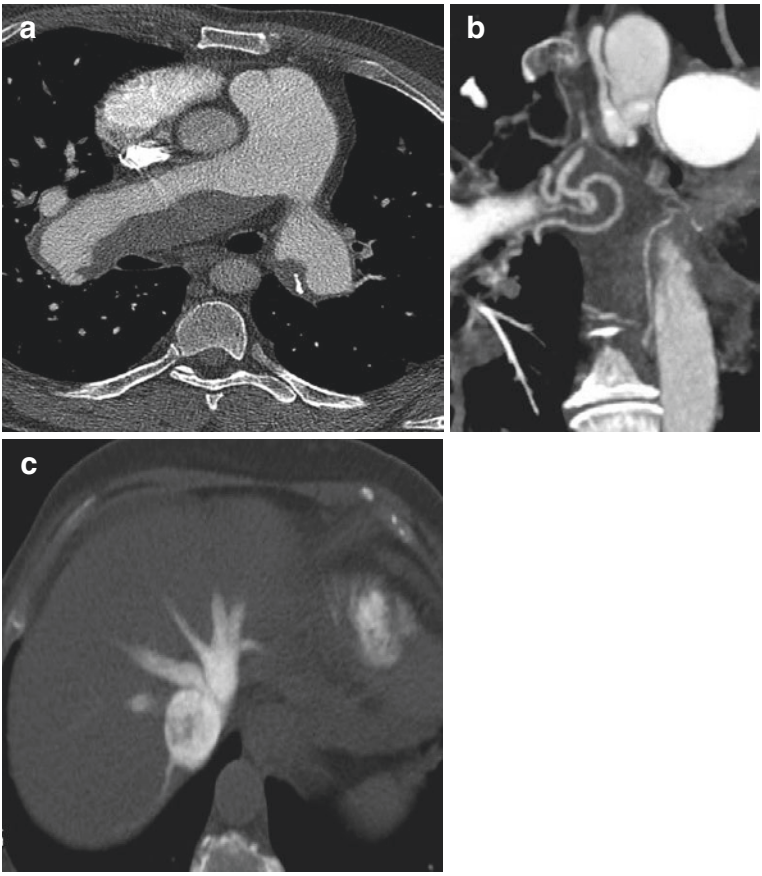

Fig. 10.5 CTPA showing dilated branch PAs with extensive mural thrombus and calcification in the left pulmonary artery (**a**), hypertrophied bronchial arteries (**b**) and dilatation of the IVC and hepatic veins due to tricuspid regurgitation (**c**)

10.5 Lung Parenchyma Assessment

High-resolution CT (HRCT) of the chest (without intravenous contrast medium) provides excellent demonstration of the lung parenchyma, and in cases of PH secondary to lung disease (such as emphysema, bronchiectasis and diffuse fibrosis), it may reveal the underlying diagnosis. There are also specific lung abnormalities that are suggestive of PH regardless of the underlying cause. The most common is a mosaic attenuation pattern, characterised by areas of decreased attenuation adjacent to areas of increased attenuation (Fig. 10.6a), reflecting relative differences in perfusion. A similar appearance may be caused by patchy areas of air trapping, as is seen in various forms of obstructive airway disease. However, in these cases, the mosaicism increases on expiratory scans (Fig. 10.6b).

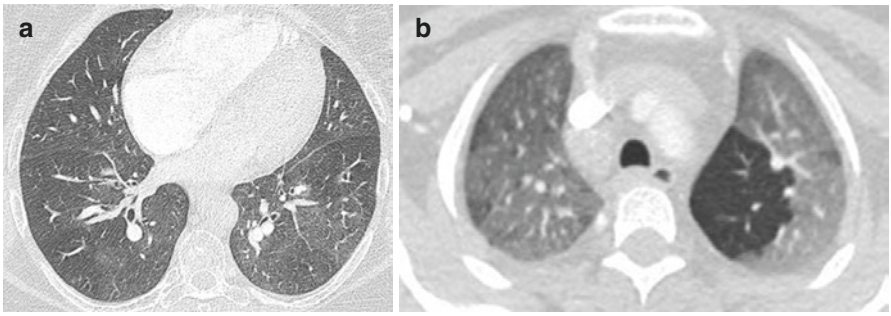

Fig. 10.6 CT scans showing mosaic attenuation of the lung parenchyma due to idiopathic PAH (**a**) and due to air trapping (**b**)

Centrilobular ground-glass nodules are a well-recognised but less common finding on HRCT in all types of PH (Fig. 10.7). Their precise cause is uncertain, but the combination of ground glass, nodules, thickened interlobular septa and possibly pleural effusions in the presence of PH should raise the possibility of pulmonary veno-occlusive disease (PVOD) or pulmonary capillary haemangiomatosis as the possible underlying cause (Figs. 10.8a, b).

Small, serpiginous intrapulmonary vessels related to centrilobular arterioles have been described in Eisenmenger syndrome and idiopathic PAH and are probably due to neovascularity.

10.6 Cardiac Assessment

Traditional cardiac assessment in PH has focussed on morphological changes associated with the increased PA pressure, namely, the size of the right-sided chambers, the degree of right ventricular hypertrophy (RVH) and the presence of hepatic vein dilatation (indicative of severe tricuspid regurgitation) (Fig. 10.5c). However, with the advent of robust cardiovascular CT, this is increasingly used to assess intra- and extra-cardiac shunts (septal defects and PDA), pericardial effusion and coronary anatomy.

10.6.1 Congenital Heart Disease Assessment

Cardiovascular CT is able to match the ability of CMR in CHD, with the exception of flow data and tissue characterization [6]. Of course, the main disadvantage of cardiovascular CT, when compared to CMR, is radiation exposure. However, in patients in whom other imaging modalities have provided insufficient information on cardiovascular anatomy (e.g. the increasing number of CHD patients with pacemakers or defibrillators either for arrhythmia or heart failure, who cannot undergo CMR), claustrophobic patients and patients with underlying conditions that may

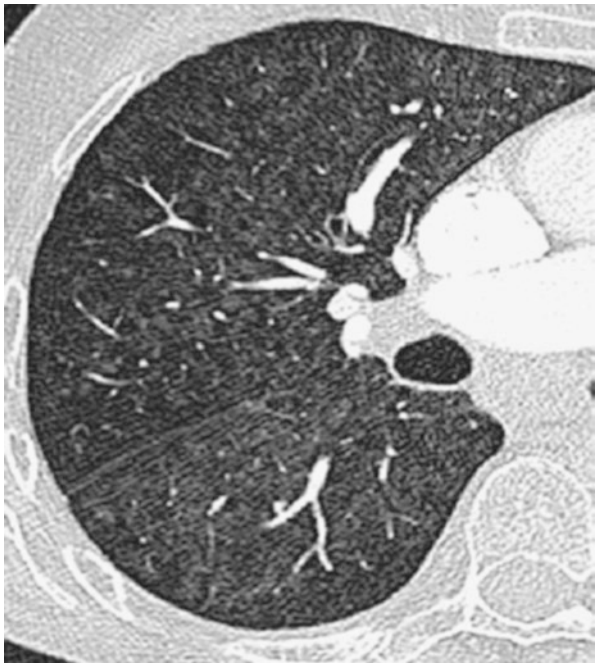

Fig. 10.7 HRCT of patient with idiopathic PAH showing small centrilobular ground-glass nodular opacities

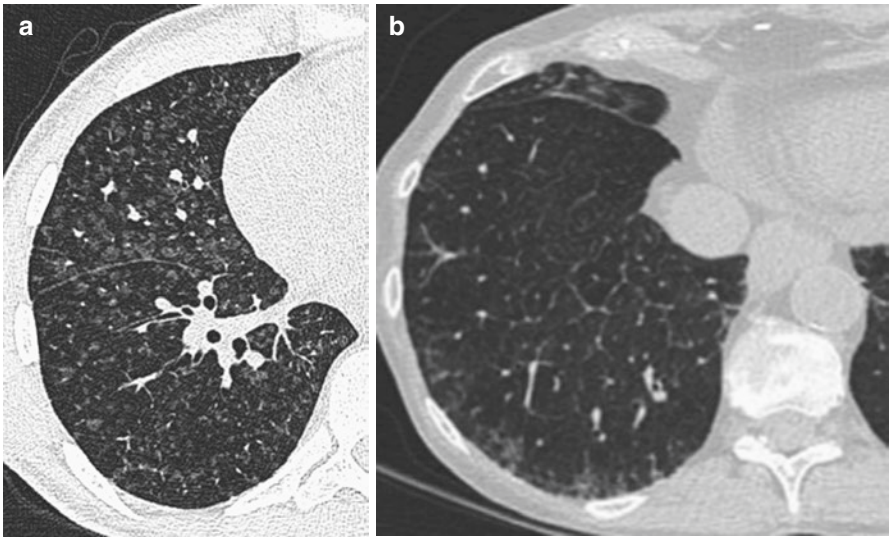

Fig. 10.8 Two cases of pulmonary veno-occlusive disease (PVOD). The first case (**a**) shows predominantly centrilobular nodules, and the second case (**b**) shows a combination of ill-defined nodules and thickened interlobular septa

significantly reduce life expectancy, cardiovascular CT remains an important and valuable tool.

10.6.2 Right Atrial (RA) and Right Ventricular (RV) Assessment

Both the RA and RV may dilate as a result of raised PA pressures (Fig. 10.9a), and most CT signs are largely extrapolated from non-PH patient cohorts. An RV diameter of >45 mm is often quoted as indicative of dilation, with an RV–LV ratio of >1.0 suggestive of significant dilatation, but >1.2 being more specific. Deviation or flattening of the ventricular septum may be seen on either dynamic (multiphase) CT imaging or single-phase analysis. Simple analysis of the RV diameter, however, is fraught with difficulty (due to the lack of a universally accepted method for measurement on axial CT, poor reliability and significant interobserver variability) and is less able to predict the presence of PH when compared to the diameter of the main PA. The interobserver variability is likely to be more pronounced on non-ECG-gated thoracic acquisitions. RV hypertrophy may also be seen on CT with a cut-off >3mm often used to define true RV hypertrophy (Fig. 10.9b). Finally, significant hepatic vein dilatation (Fig. 10.5c) is suggestive of severe tricuspid regurgitation and, in conjunction with other suggestive findings, may indicate significantly raised PA pressures.

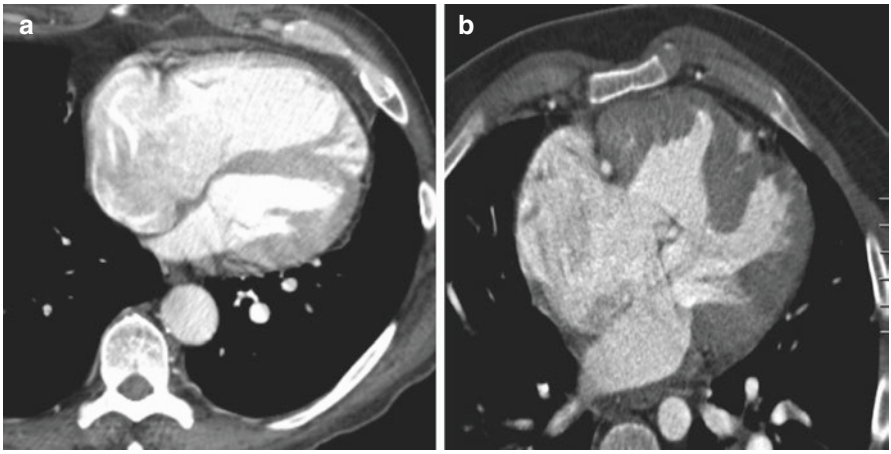

Fig. 10.9 Right atrial and right ventricular dilatation and flattening of the ventricular septum (**a**), right ventricular hypertrophy in a patient with a complete atrio-ventricular septal defect and Eisenmenger syndrome (**b**)

10.6.3 Shunt Assessment

Cardiovascular CT allows full morphological assessment of cardiac shunts, whether a patent foramen ovale (PFO) (Fig. 10.10a), atrial septal defect (ASD) (Fig. 10.10b), ventricular septal defect (VSD) or atrioventricular septal defect (AVSD) (Fig. 10.10c), PDA (Fig. 10.10d) or rarer entities such as aortopulmonary window or more complex CHD (e.g. transposition of great arteries or univentricular circulation). CT also allows full assessment of (anomalous) pulmonary venous return.

10.6.4 Coronary Assessment

CT coronary angiography has, nowadays, become a well-established technique for the exclusion of significant coronary atheromatous disease and is the gold standard investigation for coronary artery anomalies. Indeed, there are several causes of acute chest pain in PAH–CHD, and CT coronary angiography is able to exclude or confirm most of these, including significant coronary atheromatous disease, coronary compression (Fig. 10.11a), aberrant coronary anatomy (which is both common and often complex in patients with CHD, Fig. 10.11b) and other congenital coronary malformations [6].

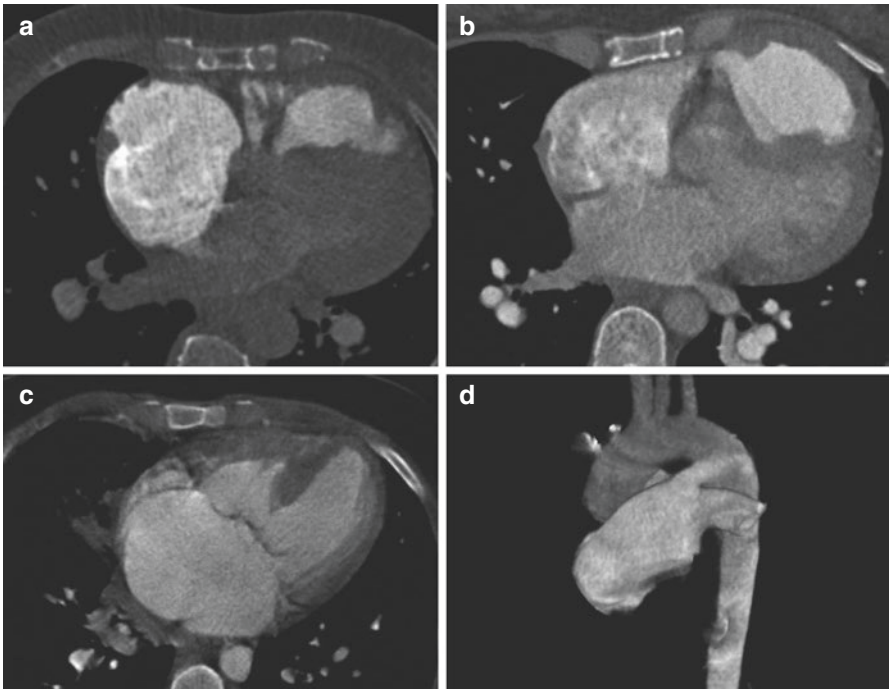

Fig. 10.10 CT showing a patent foramen ovale with right-to-left shunting (**a**), secundum ASD (**b**), complete AVSD (**c**), PDA (**d**)

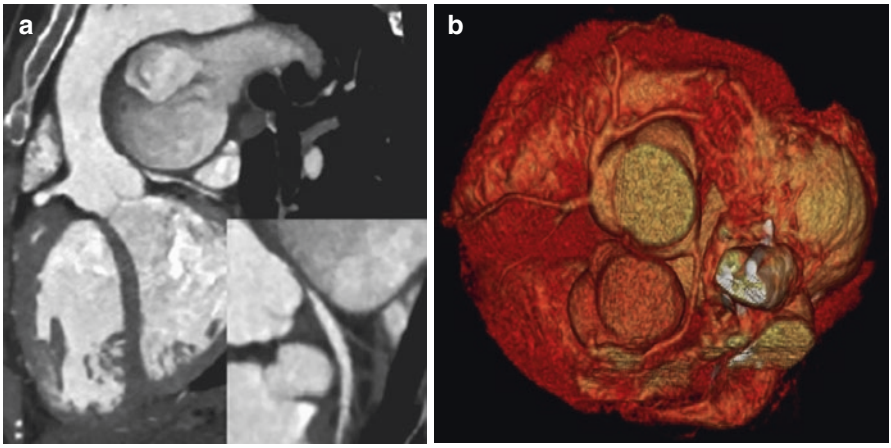

Fig. 10.11 Compression of left main stem coronary artery by a dilated PA (**a**), aberrant origin of left circumflex artery from the right aortic sinus (**b**)

10.6.5 Extended Assessment with Cardiovascular CT

If CMR is contraindicated (due to previous pacemaker insertion, claustrophobia) and biventricular functional assessment is required, this can be delivered by cardiovascular CT, although at increased ionizing radiation dose due to the requirement for retrospective ECG-gated acquisition. Using a tri-phasic contrast protocol, accurate biventricular ejection fractions and volumetric data can be acquired with suitable left and right heart opacification (Fig. 10.12a, b). It should be noted, however, that although calculated ejection fractions are comparable to those obtained by CMR, due to differences in spatial and temporal resolution as well as volumetric analysis techniques, volumetric data are not interchangeable between CT and CMR, with CT systematically overestimating ventricular volumes compared with CMR. Sequential volumetric analysis, therefore, requires the use of one technique only, and this is not routinely performed with CT due to concerns with regard to the cumulative radiation exposure.

10.7 Novel CT Assessment in PH

With novel CT technologies increasingly becoming embedded within clinical practice, a number of additional tools are emerging from within the research field. These include CT assessment of pulmonary distensibility, which appears to have a good inverse relationship with pulmonary capillary wedge pressure, direct assessment of left atrial function and extrapolated CT wedge pressure assessment. Automated fractal analysis of the pulmonary vasculature has been shown to correlate with functional parameters, such as the 6 min walk distance, with both PA tortuosity and the degree of "pruning" correlating with rising PA pressures. Finally, the use of dual energy CT for the assessment of pulmonary perfusion is becoming more

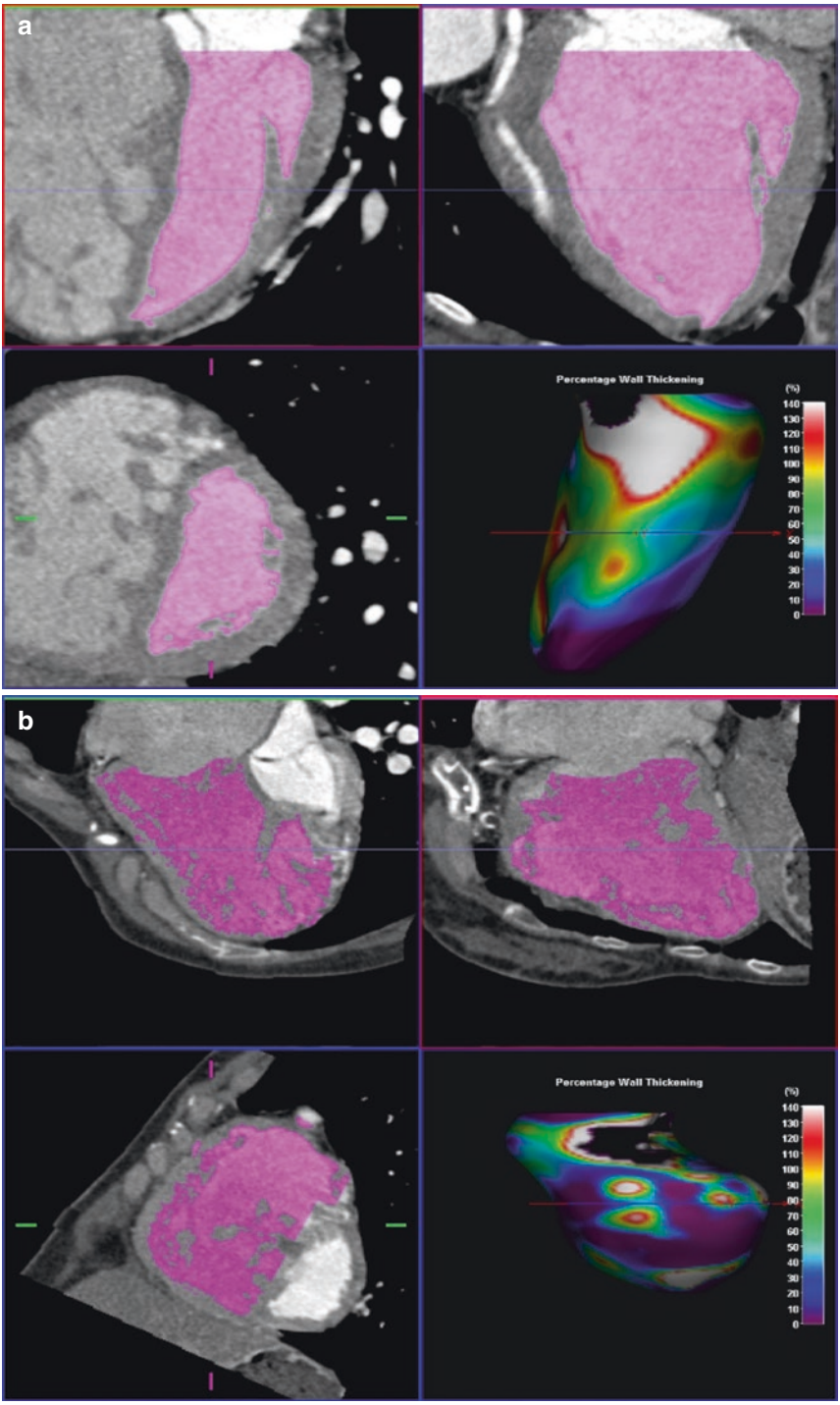

Fig. 10.12 Left (**a**) and right (**b**) ventriculography from CT datasets

established, with increased main PA enhancement and reduced parenchymal enhancement reflecting the degree of perfusion/ventilation mismatch. This may be of particular value in improving the detection of small emboli and in the follow-up of individuals on therapy.

10.8 Summary

Plain radiography remains a cheap and effective first-line investigation in PH. The role of cardiovascular and thoracic CT has expanded significantly in the last 5–10 years, both in the diagnosis and follow-up of PAH. In patients with CHD, cardiovascular CT is particularly valuable for the comprehensive assessment of both the PH and underlying congenital malformations, effectively replacing CMR in those patients who have pacemakers or other contraindications to magnetic assessment. Several automated novel technologies are emerging and are being incorporated into clinical practice, and the role of cardiothoracic CT is likely to increase as the technology improves and the radiation dose falls, thanks to advances in scanner technology.

References

1. Nicol E, Kafka H, Stirrup J, Padley S, Rubens M, Kilner P, Gatzoulis M (2009) A single non-invasive diagnostic test for the assessment of pulmonary hypertension—the role of fast computed tomography in the assessment of severe pulmonary hypertension. Int J Cardiol 136(3):278–288
2. Elena P, Carole D, John V, Susana Hernández M (2012) Pulmonary hypertension: how the radiologist can help. Radiographics 32(1):9–32
3. Dimopoulos K, Giannakoulas G, Bendayan I, Liodakis E, Petraco R, Diller G-P, Piepoli MF, Swan L, Mullen M, Best N, Poole-Wilson PA, Francis DP, Rubens MB, Gatzoulis MA (2013) Cardiothoracic ratio from postero-anterior chest radiographs: a simple, reproducible and independent marker of disease severity and outcome in adults with congenital heart disease. Int J Cardiol 166(2):453–457
4. Perloff JK, Marelli A (2012) Perloff's clinical recognition of congenital heart disease: expert consult—online and print, 6e, 6th edn. Saunders, Philadelphia
5. Devaraj A, Hansell DM (2009) Computed tomography signs of pulmonary hypertension: old and new observations. Clin Radiol 64(8):751–760
6. Sithamparanathan S, Padley SPG, Rubens MB, Gatzoulis MA, Ho SY, Nicol ED (2013) Great vessel and coronary artery anatomy in transposition and other coronary anomalies. J Am Coll Cardiol Img 6(5):624–630

11 Echocardiography in the Diagnosis and Follow-Up of Patients with Pulmonary Arterial Hypertension Associated with Congenital Heart Disease

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Abbreviations

ASD	Atrial septal defect
CHD	Congenital heart disease
IVC	Inferior vena cava
LA	Left atrium
LV	Left ventricle
LVOT	Left ventricular outflow tract
P	Pressure
PH	Pulmonary hypertension
PAH	Pulmonary arterial hypertension
PAP	Pulmonary artery pressure
PVR	Pulmonary vascular resistance
RA	Right atrium
RV	Right ventricle
RVOT	Right ventricular outflow tract
TAPSE	Tricuspid annular plane systolic excursion
Vmax	Maximum velocity
VSD	Ventricular septal defect

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Echocardiography is a widely used tool for the assessment of patients with congenital heart disease (CHD), especially those with pulmonary hypertension (PH), both in terms of diagnosis and follow-up. This investigation has the advantage of being cost-effective, non-invasive and widely available, even though significant training and expertise is required for performing and interpreting echocardiograms in complex CHD and PH. Two-dimensional transthoracic echocardiography is able to demonstrate the intracardiac anatomy and underlying cardiac defects, such as atrial, ventricular or atrioventricular septal defects, a patent ductus arteriosus or aortopulmonary window or more complex conditions. Beyond anatomical features, echocardiography provides information on cardiovascular physiology, which is invaluable when assessing patients with pulmonary arterial hypertension related to CHD (PAH–CHD). In this chapter, we provide an overview of the role of echo in the management of patients with PAH–CHD.

11.1 Classification and Diagnosis of PAH Associated with CHD

PH is defined as an increase in mean pulmonary artery pressure (PAP) to ≥25 mmHg at rest [1], while PAH requires a normal pulmonary wedge pressure and a pulmonary vascular resistance (PVR) >3 Wood units [2]. While the diagnosis of PAH–CHD should be confirmed by cardiac catheterization in most cases, echocardiography is essential in raising the suspicion of PH. PAH-CHD consists of an anatomically and phenotypically heterogeneous group (see also Chap. 2). Recent PH guidelines classify these lesions into four major groups: (1) Eisenmenger syndrome; (2) PAH–CHD with left-to-right shunting; (3) PAH with possibly coincidental, small congenital defects (idiopathic PAH-like physiology); and (4) postoperative PAH–CHD persisting after repair or developing later in life despite timely repair of the congenital heart abnormality [2]. In addition, there are patients with unilateral or segmental PAH and patients with a Fontan-type repair, although these do not fulfil standard criteria for PAH (mean PAP typically <25 mmHg) while having a raised PVR. All CHD patients undergoing routine echocardiography should be thoroughly assessed in terms of underlying cardiac anatomy, physiology and the presence and severity of PH.

Recent PH guidelines provide clear criteria for defining the echocardiograpic probability of PH in symptomatic patients, based on the peak velocity of the tricuspid regurgitation (TR) jet. Moreover, they suggest a series of supporting echocardiographic signs relating to the ventricles, pulmonary arterial Doppler, inferior vena cava (IVC) and right atrium (RA) (Table 11.1). These criteria should be applied with caution in PAH–CHD, as they may not apply to patients with complex anatomy or associated lesions (e.g. right ventricular outflow tract (RVOT) obstruction or atrioventricular valve disease).

11.1.1 Tricuspid Regurgitation

Establishing the cardiac anatomy, especially the atrioventricular and ventriculoarterial relations, is an essential first step before using the TR Doppler to estimate

Table 11.1 Echocardiographic probability in symptomatic patients, according to International Pulmonary Hypertension Guidelines

Echo probability of PH	Peak TR velocity (m/s)	Other echo signs*
Low	≤2.8 or non-measurable	None
Intermediate	≤2.8 or non-measurable	Present
	2.9–3.4	None
High	2.9–3.4	Present
	>3.4	Not required
*Echo signs of PH		
Signs from at least two categories (columns A, B or C) are required		
A. Ventricles	B. Pulmonary artery (PA)	C. IVC and RA
RV/LV basal diameter ratio > 1	RVOT Doppler acceleration time < 105 ms	IVC diameter > 21 mm and decreased inspiratory collapse (<50% sniff, <20% quiet inspiration)
	RVOT Doppler acceleration mid-systolic notch	
LV eccentricity index (systolic or diastolic) >1.1	Early PR velocity > 2.2 m/s	RA area > 18 cm^2 in end-systole
	PA diameter > 25 mm	

The above criteria apply to most non-PAH–CHD and some PAH–CHD patients, depending on underlying cardiac anatomy, direction and severity of shunting and associated lesions (e.g. congenital valve disease). Care and expertise in CHD is, thus, required when applying the above criteria in PAH–CHD patients

PH pulmonary hypertension, *TR* tricuspid regurgitation; *PA* pulmonary artery; *RV* right ventricle; *LV* left ventricle; *RA* right atrium; *IVC* inferior vena cava; *RVOT* right ventricular outflow tract; *PR* pulmonary regurgitation

PAP. Moreover, care should be taken to exclude or account for obstruction within the right ventricle (RV) (e.g. double-chambered RV), the RV outflow tract or pulmonary arteries, all conditions that can raise TR Doppler velocity in the absence of PH. In patients with biventricular circulation and a sub-pulmonary RV, the systolic PAP ($PAP_{systolic}$) can be assessed by measuring peak TR velocity ($V_{max_{TR}}$) using the modified Bernoulli equation (Fig. 11.1a):

$$P_{gradient_{RV-RA}} = P_{systolic_{RV}} - P_{systolic_{RA}} = 4 \times V_{max_{TR}}{}^{2}$$

$$PAP_{systolic} = P_{gradient_{RV-RA}} + P_{RA}$$

where $P_{gradient_{RV-RA}}$ is the peak pressure gradient in systole between the RV and RA and P_{RA} is the estimated RA pressure.

The TR jet should be appreciated from multiple views, always ensuring that the ultrasound beam is parallel to the jet. P_{RA} can be estimated based on the diameter and respiratory variation in diameter of the IVC [3, 4]: An IVC diameter below 2.1 cm that collapses more than 50% with a sniff manoeuvre suggests a normal P_{RA} of 3 mmHg. An IVC diameter above 2.1 cm that collapses less than 50% with a "sniff" or <20% on quiet inspiration suggests a high P_{RA} of 15 mmHg. In scenarios in which the IVC diameter and response to a "sniff" or inspiration do not fit any of the previous situations, an intermediate value of 8 mmHg can be used. In CHD patients with agenesis of the IVC (e.g. left atrial isomerism with azygos continuation of the IVC), other parameters should be used, such as evidence of right heart

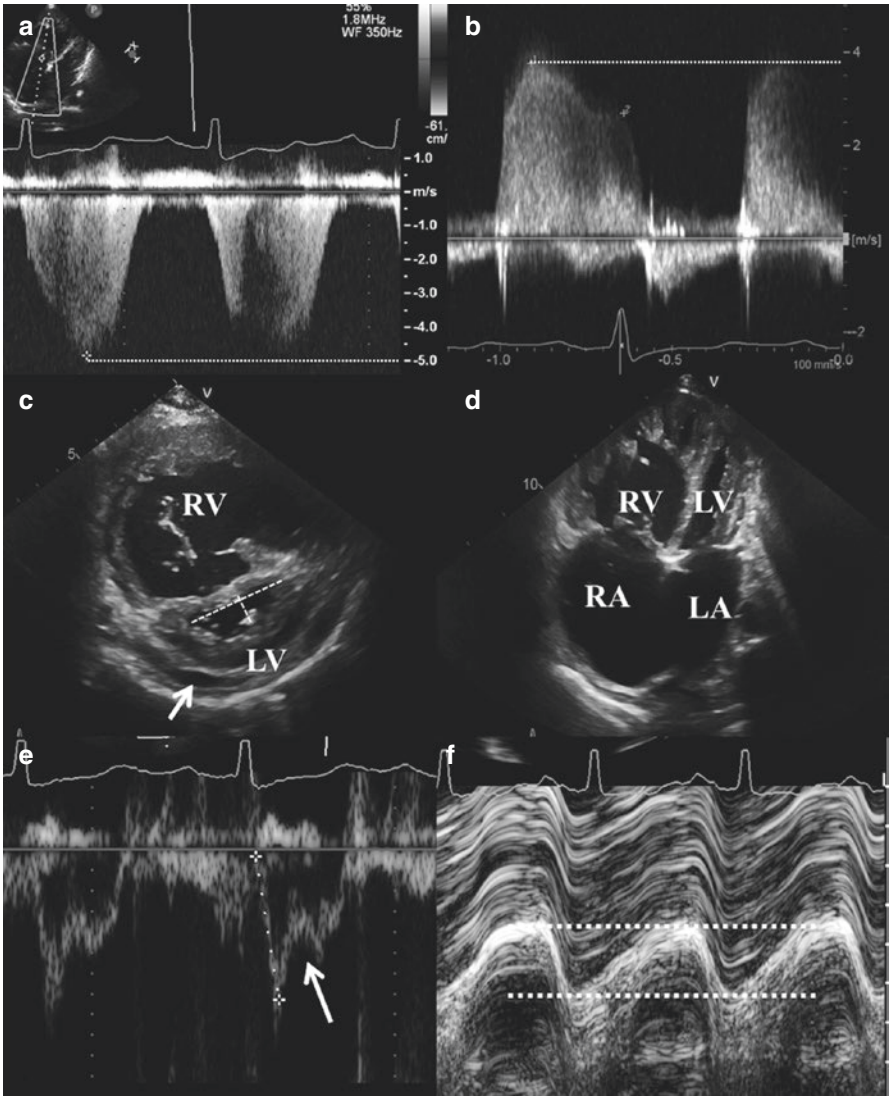

Fig. 11.1 Echocardiographic signs of PH. In (**a**), estimation of the systolic PAP using the Doppler signal of the tricuspid regurgitation (TR) and the modified Bernoulli equation in patients with Eisenmenger syndrome and a large atrial septal defect. A peak TR velocity of 5 m/s equates with a RV–RA gradient in systole of 100 mmHg. Adding the estimated RA pressure (in this case 15 mmHg), the systolic PAP is calculated at 115 mmHg. In (**b**), estimation of the mean PAP using the pulmonary regurgitation (PR) Doppler. The peak early gradient plus the RA pressure provides an estimate of the mean PAP (in this case 58 mmHg + 15 mmHg = 73 mmHg). In (**c**), an example of severe deviation of the ventricular spectrum towards the LV, with a diastolic eccentricity index of 3.7. In (**d**), a four-chamber view of the same patient, demonstrating the large secundum atrial septal defect, severely dilated atria. The RV is dilated and hypertrophied, while the ventricular septum is deviated towards the small underfilled LV. In (**e**), the Doppler of the RV outflow tract, with a short acceleration time (*dotted line*) and a systolic "notch" (*arrow*). In (**f**), the tricuspid annular plane systolic excursion (TAPSE). LV, left ventricle; LA, left atrium; RV, right ventricle; RA, right atrium

failure on physical examination (adding 5 mmHg to right atrial pressure for each sign) or the tricuspid valve E/e' ratio [5]. Of course, P_{RA} can also be estimated by clinical assessment of the jugular venous pressure.

Errors in the estimation of systolic PA pressure are often due to overestimation of P_{RA} with echo, explaining why international guidelines use cut-offs based on TR velocity alone and also why the gold standard for the estimation of PAP remains right heart catheterization. In fact, while estimates of PVR can also be provided with echocardiography using the ratio $V_{\max_{TR}}$ to pulmonary artery Doppler velocity time integral [6], these formulas make assumptions on left atrial pressure and are generally unreliable in CHD.

11.1.2 Pulmonary Regurgitation

The mean PAP can be estimated from the early peak velocity of the pulmonary regurgitation (PR) Doppler using the following formula (Fig. 11.1b) [7].

$$PAP_{\text{mean}} = 4 \times V_{\max_{PR}}{}^{2} + P_{RA}$$

This method is extremely useful in patients with undetectable TR.

11.1.3 Other Echocardiographic Signs of Pulmonary Hypertension

Echocardiographic variables, beyond TR or PR velocities, that may reinforce the suspicion of PH include [4]:

- Flattening of the ventricular septum (Fig. 11.1c). A left ventricular eccentricity index in systole or diastole >1.1 is suggestive of high RV pressures.
- Dilatation of the RA (RA area > 18 cm^2) or the RV (RV/LV basal diameter ratio > 1) (Fig. 11.1d). This sign and the previous signs are of limited use in patients with significant left-to-right shunting at atrial level (or partial anomalous pulmonary venous return), which may also cause RA and/or RV dilatation and cause flattening of the RV septum in the absence of PH. Moreover, RA dilatation may be caused by associated lesions of the tricuspid or right atrioventricular valve, or pulmonary stenosis.
- RV hypertrophy and dysfunction. RV hypertrophy has been defined as RV free wall thickness >0.5 cm measured from the subcostal four-chamber view. It is an indirect sign of chronic increase in RV afterload (not only PH).
- Pulmonary artery Doppler profile and measurements. A spiky (acute, with short time from onset to peak) pulmonary artery Doppler is a sign of severe PAH (Fig. 11.1e). A short PA acceleration time has been shown to correlate reversely with mean PAP [8]. Moreover, a mid-systolic "notch" is a common finding in significant PH, even though not ubiquitously present, and is felt to be the result of waves reflected by the pulmonary circulation.

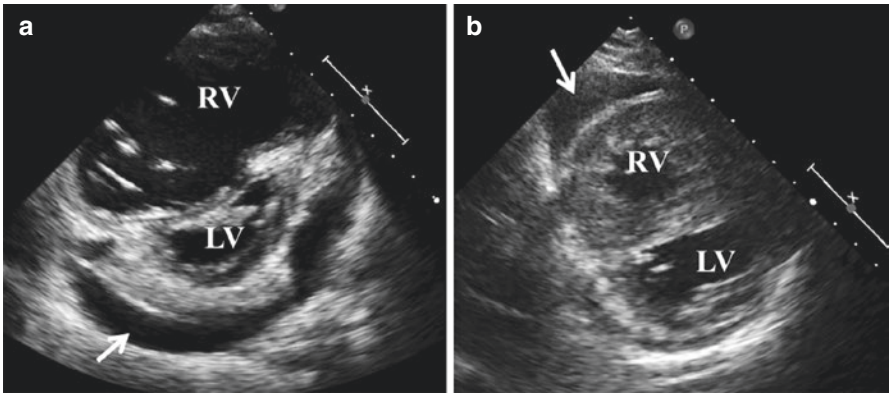

Fig. 11.2 Pericardial effusions in PH. In (**a**) a pericardial effusion (*arrow*) in a patient with severe idiopathic PAH and a very dilated and impaired (failing) RV. In (**b**), a long-standing pericardial effusion (*arrow*) in a patient with Down syndrome and Eisenmenger syndrome, who has a hypertrophied RV with preserved function and no signs on RV failure. LV, left ventricle; RV, right ventricle

- Tricuspid annular plane systolic excursion (TAPSE) is probably the most reproducible measure of (longitudinal) RV function (Fig. 11.1f). Even though not included as a marker of PH and RV function in recent guidelines, it remains one of the most widely used parameters in clinical practice.
- Right-to-left (R-L) shunting. R–L shunting at ventricular (or patent ductus arteriosus) level is evidence of severely raised RV (or PA) pressures, at systemic or suprasystemic levels. For this reason, a low-velocity bidirectional shunt at ventricular, ductal or aortopulmonary window level in cyanotic patients, in the absence of pulmonary stenosis, is deemed diagnostic of Eisenmenger physiology.
- Pericardial effusion. A pericardial effusion is often present in patients with advanced idiopathic PAH and is a sign of RV failure and adverse prognosis (Fig. 11.2a). A pericardial effusion may also be present in advanced PAH–CHD, but its prognostic role may be confounded by comorbidity, especially the presence of Down syndrome (Fig. 11.2b). In fact, many patients with Down syndrome may have small or larger pericardial effusions in the absence of RV failure.

The echocardiographic assessment of PA pressures in PAH–CHD is, thus, both qualitative and quantitative.

11.1.4 Echocardiographic Assessment of PH in Complex CHD

Significant expertise is required when assessing a patient with complex CHD using echocardiography (e.g. univentricular physiology or a systemic RV), as "standard" echocardiographic parameters may not apply.

In patients with a systemic RV, e.g. those with transposition of the great arteries after atrial switch (Mustard or Senning) repair, the sub-pulmonary ventricle is

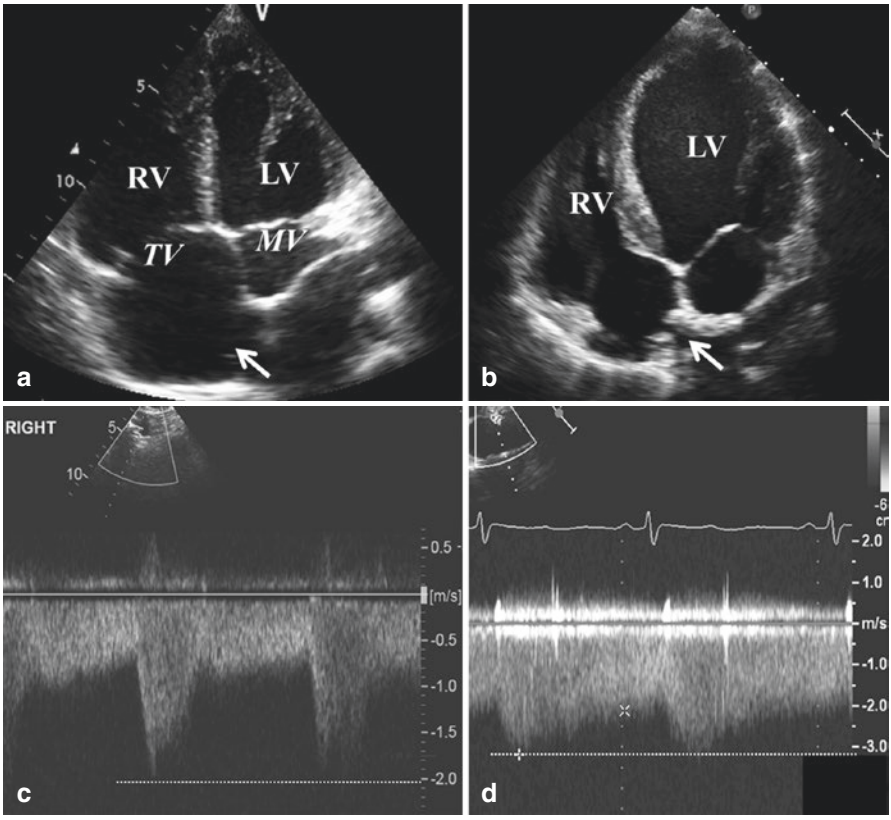

Fig. 11.3 PH in complex CHD. In (**a**), a patient with transposition of great arteries and a previous Mustard (*atrial switch*) procedure. Note the dilated and hypertrophied systemic RV, small sub-pulmonary LV and pulmonary venous pathway (*arrow*) directing flow from the pulmonary veins towards the systemic RV and the systemic circulation. In (**b**), a patient with similar anatomy but severe PH. The sub-pulmonary LV is severely dilated and impaired. In (**c**), the Doppler signal of a modified Blalock–Taussig shunt (connecting the right subclavian artery to the right pulmonary artery). The low peak velocity suggests that pressures in the systemic (subclavian) artery and right pulmonary artery are similar; hence, there is PH in the territory fed by the shunt. In (**d**), Doppler signal from a Waterston shunt (between the ascending aorta and pulmonary artery). The peak velocity is 3.2 m/s, and according to the modified Bernoulli equation, the peak pressure gradient between the aorta and pulmonary artery is approximately 40 mmHg. This is a clear, albeit indirect sign of raised PAP

morphologically left and, in the absence of PH, often appears small, crescent-like and hyperdynamic (Figs. 11.3a and b). PH is not uncommon in this population and may be pre- or, most often, post-capillary. While cardiac catheterization is mandatory for a correct diagnosis (with measurement of a pulmonary wedge and RV end-diastolic pressure), certain echocardiographic changes raise the suspicion of PH. In this situation, the mitral, rather than tricuspid, regurgitation Doppler can be used in a Bernoulli equation to estimate $PAP_{systolic}$. Care should be taken to account for any pulmonary stenosis or Left ventricular outflow tract (LVOT) obstruction. The PR

Doppler estimation of PAP_{mean} can be extremely useful. Moreover, estimation of systemic venous atrial pressure is difficult, and any technique used should account for possible stenosis of the systemic venous pathways.

In patients with unrepaired univentricular circulation, e.g. double inlet left ventricle (LV) or tricuspid atresia, atrioventricular valve regurgitation Doppler does not provide an estimate of $PAP_{systolic}$, but rather systemic ventricular pressure. In these cases, it is particularly important to understand the anatomy and especially define ventriculo-arterial relations. Once the PA and aorta are identified, one should focus on quantifying any degree of pulmonary and sub-pulmonary stenosis. Indeed, severe pulmonary stenosis is likely to have protected the pulmonary circulation from developing pulmonary vascular disease, while mild or moderate Doppler gradients across the pulmonary valve (peak <60 mmHg) should always raise the suspicion of PH. In adult patients with no pulmonary stenosis, systemic levels of PH can be reliably diagnosed with echo in all patients with discordant ventriculo-arterial connection (PA arising from the LV) and patients with concordant ventriculo-arterial connection and a non-restrictive ventricular septal defect (VSD).

When surgical shunts (e.g. Blalock–Taussig shunts) are present, the peak Doppler velocity of the shunt may be used to estimate the pressure difference between the aorta and pulmonary artery fed by the shunt, providing the ultrasound beam is well aligned to the shunt (Fig. 11.3c and d). This is particularly useful in patients with unrepaired pulmonary atresia and major aortopulmonary collateral arteries (MAPCAs), in whom pulmonary vascular disease often develops in areas fed by large collaterals or large surgical shunts (e.g. the Waterston shunt, see also Chapter 6). While invasive catheterization of individual collaterals is the only reliable way to measure pressures in individual lung segments, echocardiography can provide indirect evidence of raised PA pressures: Doppler interrogation through MAPCAs feeding normotensive regions will demonstrate continuous flow with high peak velocities (well above 4 m/s, depending on aortic pressure), while velocities will be substantially lower in significantly hypertensive areas, reflecting the reduced pressure gradient between the aorta and the pulmonary arteries feeding these areas. Obviously, the TR Doppler velocity cannot be used to estimate $PAP_{systolic}$ in patients with unrepaired pulmonary atresia, as the RV is disconnected from the pulmonary circulation.

Finally, patients with a Fontan circulation form a unique and challenging subgroup, in whom standard criteria of detecting PH do not apply. In the Fontan circulation, pulmonary blood flow is driven passively from the systemic venous circulation to the lungs without the interposition of a sub-pulmonary ventricle. Hence, even the slightest increase in PAP and PVR can lead to significant haemodynamic compromise. Accurate estimation of PAP and PVR is impossible by echocardiography in Fontan patients. However, when a surgical fenestration between the Fontan circulation and the left atrium (LA) remains, the Doppler flow velocity of the shunt can be used to approximate the pressure difference between the central venous (Fontan) system and the LA. In the presence of normal left atrial pressures, a flow velocity of the fenestration shunt >1.8 m/s suggests raised pressures in the Fontan circuit:

$$\text{Central venous (Fontan) pressure} = 4V^2 + \text{LA pressure}$$

Even mild increases in LA pressure can result in a significant rise in central venous pressure, hence compromising the Fontan circulation. Therefore, careful assessment of the systolic and diastolic properties of the systemic ventricle and the function of the cardiac valves is also essential when investigating for post-capillary causes of a "failing Fontan" circulation.

11.2 The Assessment of Right Ventricular Function

Once the presence of PH is established in a CHD patient, echocardiography plays an important role in assessing RV (sub-pulmonary ventricular) function at baseline and during follow-up. Indeed, the adaptation (or maladaptation) of the RV to the increased and increasing afterload significantly influences the functional status and prognosis of PH patients (see also Chapter 1). RV function influences management decisions, with regard to the type and intensity of treatment. Of course, when RV hypertrophy and dysfunction are encountered in a CHD patient, other causes of RV pressure overload should be excluded, such as RVOT/pulmonary stenosis.

RV remodelling occurs as a response to the increase in afterload and ranges from adaptive hypertrophy (homeometric adaptation) to RV dilatation and dysfunction (heterometric adaptation) [9]. RV function and the response to pressure overload may also be affected by congenital abnormalities of the RV or previous surgery that might affect myocardial deformation and contractility.

Despite limitations in the assessment of right ventricular dimensions and function by transthoracic echocardiography, guidelines from the American Society of Echocardiography and European Association for Cardiovascular Imaging [10] provide standards of good practice and normal values. Most parameters rely on measurements obtained in the apical four-chamber view, although this provides a two-dimensional view of a more complex anatomical structure. RV function can be appreciated using various parameters, mainly tricuspid annular plane excursion (TAPSE), tissue Doppler imaging peak velocity of the "s" wave at the lateral tricuspid annulus and right ventricular fractional area change.

Three-dimensional transthoracic echocardiography can overcome some of the limitations of two-dimensional assessment (Fig. 11.4) and provide a volumetric assessment of the RV. However, only few studies have validated three-dimensional tools in PH [11, 12], and their applicability to PAH–CHD patients needs further exploring.

A wide range of RV responses to PH can be observed in various types of PAH and even within the adult Eisenmenger cohort (Fig. 11.5). In the latter, the anatomical location of the shunt (pre- vs. post-tricuspid) appears to influence RV adaptations to systemic PA pressures. Patients with pre-tricuspid defects (i.e. atrial septal defects) typically present with a phenotype resembling that of severe idiopathic PH, with a heterometric response manifesting as significant RV dilatation and dysfunction. Eisenmenger patients with a post-tricuspid shunt and especially those with a ventricular or atrioventricular septal defect, on the other hand, often demonstrate better RV adaptation with significant RVH but little RV dilatation and preserved systolic function [13]. It appears that in patients with an unrestricted

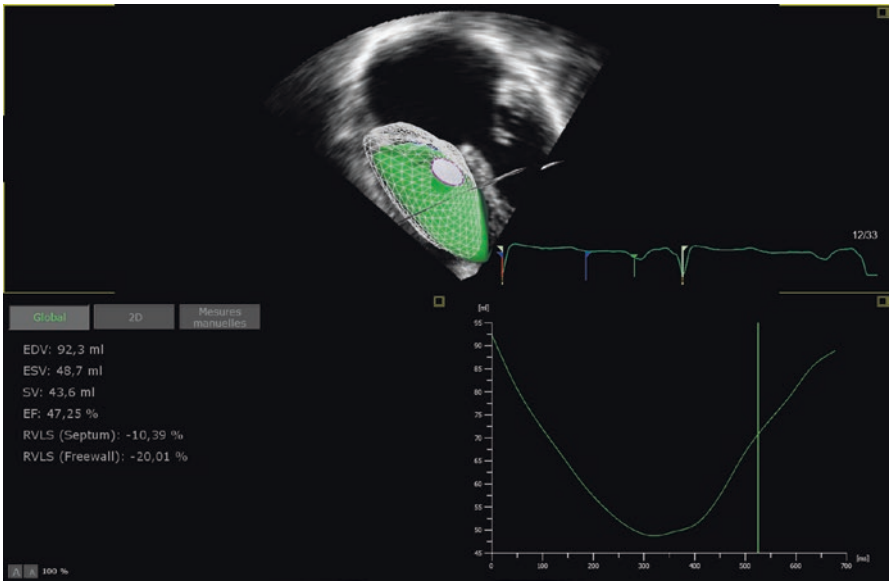

Fig. 11.4 Three-dimensional right ventricular volumetric quantification in a patient with PAH–CHD related to an atrial septal defect

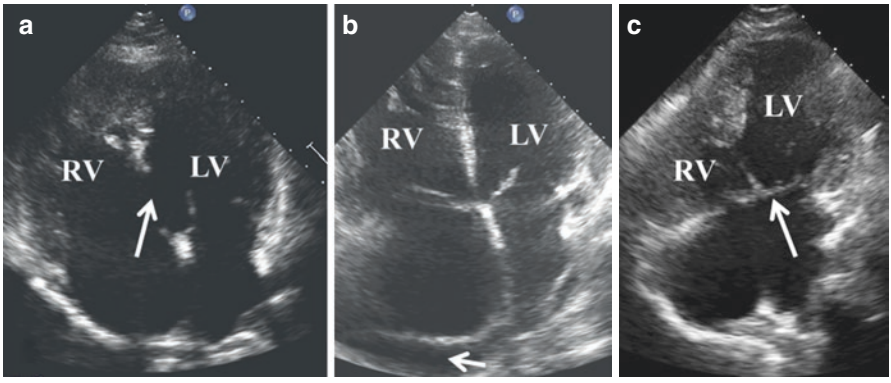

Fig. 11.5 The spectrum of RV adaptation in Eisenmenger syndrome. In (**a**), an Eisenmenger patient with a large ventricular septal defect (*arrow*, outlet with inlet extension) and a severely hypertrophied RV with preserved systolic function and mild–moderate dilatation. The patient is in functional class 2. In (**b**), an Eisenmenger patient with a large patent ductus arteriosus and a maladapted, hypertrophied but severely dilated and impaired RV. The RA is also severely dilated, and there is a pericardial effusion (*arrow*). The patient in severely symptomatic despite PAH therapy. In (**c**), a patient with Down syndrome and Eisenmenger syndrome due to complete atrioventricular septal defect. The RV is not dilated but severely hypertrophied, with a preserved systolic function. Note the single atrioventricular valve (*arrow*). The patient is mildly symptomatic. For an example of an Eisenmenger patient with a pre-tricuspid defect (atrial septal defect), see Fig. 11.1d (note the hypertrophied but severely dilated and impaired RV)

post-tricuspid shunt, both ventricles are working as one contractile unit, ejecting into both the systemic and pulmonary circulations, hence responding better to the elevated RV afterload. RV and LV remodelling, as assessed by speckle-tracking imaging, differ between patients with pre- and post-tricuspid shunt [14]. These differences, especially in RV adaptation, between Eisenmenger patients with pre- and post-tricuspid lesions do appear to influence prognosis and should be taken into account when deciding on their management.

In PAH–CHD patients with more complex anatomy, most of the above considerations do not apply. In patients with systemic RVs and PH, the sub-pulmonary LV and mitral valve may adapt to the high afterload better than a morphological RV and tricuspid valve, with LV dilatation and dysfunction, and mitral regurgitation often developing late. Attention must be paid to changes in the LV shape and dimensions, as well as increases in pulmonary artery size, in order to avoid a delay in the diagnosis of PH. In this situation, the early pulmonary valve regurgitation velocity, which is often detectable even when very mild, is extremely useful in identifying a raised PAP. The complex ventriculo–ventricular interaction between a hypertensive sub-pulmonary LV and a systemic RV makes echocardiographic interpretation difficult, requiring high levels of expertise and careful longitudinal assessment to detect changes over time.

In patients with a univentricular circulation, a rise in PAP is unlikely to have a major, detectable effect on the systemic ventricle. However, ventricular function significantly influences outcome in these patients, and careful monitoring is required. Close monitoring of systemic ventricular function is especially important when PAH therapies are used, in order to detect changes in ventricular size and function relating to additional volume loading secondary to the increase in pulmonary blood flow. In fact, the systemic ventricle is, by default, chronically volume loaded in an unrepaired univenticular heart, as it receives and supplies blood to both the systemic and pulmonary circulation.

11.3 Identifying Undiagnosed CHD in Patients with PH

In patients with known PH, echocardiography is crucial for excluding CHD, especially given the difference in prognosis and management between idiopathic PAH and PAH–CHD. Moreover, the presence of a large left–right shunt has significant implications with regard to the method used to estimate cardiac output and pulmonary blood flow during right heart catheterization (Fick method rather than thermodilution). This impacts significantly on haemodynamic calculations (especially PVR) and hence the management of the patient.

Two-dimensional echocardiography with colour Doppler can, in experienced hands, detect most CHD and document the direction and velocity of shunting across a defect. Moreover, significant RV dilatation with normal or hyperdynamic RV function and preserved velocity time integral across the pulmonary valve (an indicator of normal or increased pulmonary blood flow) are in support of CHD rather than significant PH. In such cases, if the defect is not obvious with transthoracic

echocardiography, other imaging is indicated to exclude an intra- or extra-cardiac shunt (e.g. contrast echocardiography, transoesophageal echocardiography, computed tomography, cardiac magnetic resonance or cardiac catheterization with full oximetry run). Indeed, the diagnosis of CHD may be difficult in adults due to poor acoustic windows, especially in patients with systemic levels of PAP, in whom near equalization of pressures in the systemic and pulmonary circulations results in low-velocity bidirectional shunting that may be difficult to visualize on transthoracic echocardiography. For example, a large patent ductus arteriosus or aortopulmonary window may easily be missed on echocardiography in Eisenmenger patients.

11.4 Patients with Left Heart Disease

Post-capillary PH, i.e. PH related to left heart disease, is likely the most common type of PH in CHD. Left-sided obstructive congenital lesions (e.g. cor triatriatum, supramitral membrane, congenital mitral or aortic stenosis), as well as regurgitant lesions and systemic ventricular dysfunction, can result in a rise in PA pressure. Moreover, systolic or severe left ventricular diastolic dysfunction is not uncommon in older CHD patients who underwent surgical repair of left heart obstructive lesions, tetralogy of Fallot or other CHD "late" in life and those who were operated during the early era of CHD surgery, when myocardial preservation may have been less than optimal. A restrictive cardiomyopathy phenotype can be encountered in patients with Noonan syndrome or endocardial fibroelastosis, while systolic and diastolic dysfunction of the LV is encountered in severe forms of left ventricular non-compaction. Post-capillary PH related to CHD has now been recognized as an entity and classified in group 2 of the PH classification, according to the latest international guidelines: it should not be treated with PAH therapies.

Echocardiography can provide direct and indirect signs of raised left ventricular filling pressures in the setting of structurally heart [15]: left ventricular hypertrophy, dilatation of the LA, changes in the mitral valve Doppler E/A ratio and deceleration time (DT) of early filling velocity, mitral E/e' and pulmonary venous Doppler parameters. In patients with CHD and previous surgery and those with a morphologic RV in the systemic position, the above-mentioned parameters may not be as reliable and should be interpreted with caution and in the context of the clinical presentation.

11.5 Echocardiography for Prognostication and Follow-Up

Several clinical and biological parameters [16–21] have been linked to prognosis in Eisenmenger syndrome patients (see Chap. 21) [22]. RV dilatation and dysfunction, rather than the severity of the PAH, has been closely related to functional class, exercise capacity and survival in PAH [23, 24]. Recent publications have shown that echocardiographic parameters relating mainly to right ventricular function are associated with outcome in Eisenmenger syndrome [25–28]. A TAPSE below 16 mm identified patients at high risk of adverse outcome in a Belgian

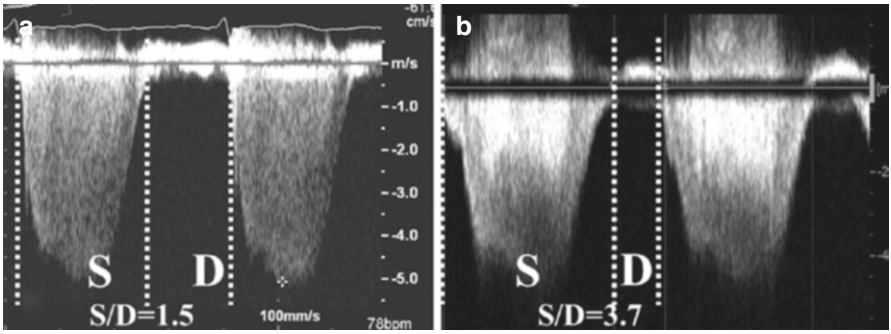

Fig. 11.6 The concept of the systolic-to-diastolic ratio on the tricuspid regurgitation Doppler. Two examples of the systolic-to-diastolic ratio (S/D ratio): a mildly symptomatic (**a**) and a severely symptomatic (**b**) patient with Eisenmenger syndrome. Progressive RV dilatation and dysfunction is associated with a prolongation of the RV systole and shortening of diastole. A reduced filling time contributes to the low cardiac output. This phenomenon is exacerbated by the onset of supraventricular tachycardias, which severely reduce filling time and can be fatal to patients with severe PAH

cohort and was also associated with the presence of pulmonary artery thrombosis. In a large Eisenmenger cohort from the Royal Brompton Hospital (patients with biventricular circulation), a TAPSE below 15 mm identified Eisenmenger patients with a fivefold increased risk of death. Other parameters linked to prognosis included RA area, increased RA/LA area ratio and the ratio of right ventricular effective systolic to diastolic duration (SD_{ratio}), as assessed on the tricuspid valve Doppler (Fig. 11.6):

$$S/D_{\text{ratio}} = \frac{TR\ \text{duration}}{\text{Time from } end \text{ of } TR \text{ to the onset of subsequent } TR \text{ signal}}$$

An echocardiographic composite score, attributing one point to each of the following, TAPSE <15 mm, $S/D_{ratio} \geq 1.5$, right atrial area $\geq 25\ cm^2$ and right atrial/left atrial area ratio ≥ 1.5, was strongly related to mortality. A study in paediatric patients with PH, including idiopathic, repaired CHD and other causes of PAH, has shown that simple RV to left ventricular diameter ratio at end-systole (RV/LV ratio) measured in the standard parasternal short-axis view was significantly related to invasive haemodynamic measures of PH. A RV/LV ratio > 1 was associated with an increased risk of adverse events (need to initiate intravenous prostacyclin therapy, atrial septostomy, death or transplantation) [29].

The role of speckle tracking in CHD is currently expanding. Advanced echocardiographic imaging with 2D and 3D speckle tracking can measure intrinsic myocardial contractility and appears to be less load-dependent than other parameters. Speckle-tracking estimates have been shown to relate to mortality in patients with PH [30, 31]. Few studies have reviewed the ability of speckle tracking to evaluate ventricular function in complex CHD. Using speckle-tracking, cardiac remodelling differs between CHD-PAH patients and other PAH aetiologies: the presence of Eisenmenger syndrome seems to be associated with increased RV free wall

transverse strain and better survival [32]. Further studies are needed to determine its role in the routine assessment of the RV in PAH–CHD.

11.6 The Echocardiographic Follow-Up of PAH–CHD Patients

PAH therapies can have major beneficial effects on RV physiology, paralleling improvements in exercise capacity and quality of life. In a study on 23 Eisenmenger patients, the clinical benefits from treatment with bosentan were more obvious in patients who demonstrated a measurable improvement in their RV myocardial performance index by at least 12% [33]. Moreover, bosentan leads to an improvement in RV systolic function assessed by tissue Doppler imaging (peak tricuspid S wave) as well as diastolic RV function, as assessed by the tricuspid valve E/e' ratio. In another study, bosentan improved left and right ventricular longitudinal strain, as well as right atrial strain, after 24 weeks of therapy [34]. Despite being single-centre studies with a small sample size, the results of these studies help us comprehend the possible underlying mechanisms by which clinical improvement occurs after treatment with PAH therapies and underline the importance of echocardiographic follow-up in Eisenmenger syndrome patients.

11.7 Future Perspectives

Echocardiography can provide extremely useful information in the diagnosis, prognostication and follow-up of PAH–CHD patients. However, as echocardiographic assessment is subject to variability (relating to the acoustic window, intra-operator and inter-operator variability, load dependency of right ventricular function indices), many PH centres consider echocardiography as having a secondary role in the management of PH. This is not so for PAH–CHD patients, in whom echocardiography (together with cardiac catheterization) is fundamental for the diagnosis, management and follow-up. Standard echocardiography, combined with novel techniques such as two-dimensional speckle-tracking imaging, three-dimensional quantification of the RV and three-dimensional myocardial tracking, can provide invaluable information on cardiac physiology and merit further investigation [35, 36].

References

1. Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M et al (2013) Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol 62(25 Suppl):D42–D50
2. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I et al (2016) 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric

and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 37(1):67–119
3. Brennan JM, Blair JE, Goonewardena S, Ronan A, Shah D, Vasaiwala S et al (2007) Reappraisal of the use of inferior vena cava for estimating right atrial pressure. J Am Soc Echocardiogr 20(7):857–861
4. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K et al (2010) Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography. J Am Soc Echocardiogr 23(7):685–713
5. Nageh MF, Kopelen HA, Zoghbi WA, Quinones MA, Nagueh SF (1999) Estimation of mean right atrial pressure using tissue Doppler imaging. Am J Cardiol 84(12):1448–1451. A8
6. Abbas AE, Fortuin FD, Schiller NB, Appleton CP, Moreno CA, Lester SJ (2003) A simple method for noninvasive estimation of pulmonary vascular resistance. J Am Coll Cardiol 41(6):1021–1027
7. Abbas AE, Fortuin FD, Schiller NB, Appleton CP, Moreno CA, Lester SJ (2003) Echocardiographic determination of mean pulmonary artery pressure. Am J Cardiol 92(11):1373–1376
8. Kitabatake A, Inoue M, Asao M, Masuyama T, Tanouchi J, Morita T, Mishima M, Uematsu M, Shimazu T, Hori M, Abe H (1983) Noninvasive evaluation of pulmonary hypertension by a pulsed Doppler technique. Circulation 68:302–309
9. Naeije R, Manes A (2014) The right ventricle in pulmonary arterial hypertension. Eur Respir Rev 23:476–487
10. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L et al (2015) Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 28(1):1–39. e14
11. Maffessanti F, Muraru D, Esposito R, Gripari P, Ermacora D, Santoro C et al (2013) Age-, body size-, and sex-specific reference values for right ventricular volumes and ejection fraction by three-dimensional echocardiography: a multicenter echocardiographic study in 507 healthy volunteers. Circ Cardiovasc Imaging 6(5):700–710
12. Grapsa J, Gibbs JSR, Dawson D, Watson G, Patni R, Athanasiou T et al (2012) Morphologic and functional remodeling of the right ventricle in pulmonary hypertension by real time three dimensional echocardiography. Am J Cardiol 109(6):906–913
13. Moceri P, Kempny A, Liodakis E, Alonso Gonzales R, Germanakis I, Diller GP et al (2015) Physiological differences between various types of Eisenmenger syndrome and relation to outcome. Int J Cardiol 179:455–460
14. Moceri P, Iriart X, Bouvier P, Baudouy D, Gibelin P, Saady R, et al (2016) Speckle-tracking imaging in patients with Eisenmenger syndrome. Arch Cardiovasc Dis 109(2):104–112.
15. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA et al (2009) Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 22(2):107–133
16. Diller GP, Dimopoulos K, Broberg CS, Kaya MG, Naghotra US, Uebing A et al (2006) Presentation, survival prospects, and predictors of death in Eisenmenger syndrome: a combined retrospective and case-control study. Eur Heart J 27(14):1737–1742
17. Diller GP, Alonso-Gonzalez R, Kempny A, Dimopoulos K, Inuzuka R, Giannakoulas G et al (2012) B-type natriuretic peptide concentrations in contemporary Eisenmenger syndrome patients: predictive value and response to disease targeting therapy. Heart 98(9):736–742
18. Tay EL, Peset A, Papaphylactou M, Inuzuka R, Alonso-Gonzalez R, Giannakoulas G et al (2011) Replacement therapy for iron deficiency improves exercise capacity and quality of life in patients with cyanotic congenital heart disease and/or the Eisenmenger syndrome. Int J Cardiol 151(3):307–312
19. Dimopoulos K, Inuzuka R, Goletto S, Giannakoulas G, Swan L, Wort SJ et al (2010) Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension. Circulation 121(1):20–25

20. Van De Bruaene A, Delcroix M, Pasquet A, De Backer J, De Pauw M, Naeije R et al (2011) Iron deficiency is associated with adverse outcome in Eisenmenger patients. Eur Heart J 32(22):2790–2799
21. Van De Bruaene A, De Meester P, Voigt J-U, Delcroix M, Pasquet A, De Backer J et al (2013) Worsening in oxygen saturation and exercise capacity predict adverse outcome in patients with Eisenmenger syndrome. Int J Cardiol 168(2):1386–1392
22. Manes A, Palazzini M, Leci E, Bacchi Reggiani ML, Branzi A, Galie N (2013) Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: a comparison between clinical subgroups. Eur Heart J 35(11):716–724
23. Forfia PR, Fisher MR, Mathai SC, Housten-Harris T, Hemnes AR, Borlaug BA et al (2006) Tricuspid annular displacement predicts survival in pulmonary hypertension. Am J Respir Crit Care Med 174(9):1034–1041
24. Raymond RJ, Hinderliter AL, Willis PW, Ralph D, Caldwell EJ, Williams W et al (2002) Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. J Am Coll Cardiol 39(7):1214–1219
25. Moceri P, Dimopoulos K, Liodakis E, Germanakis I, Kempny A, Diller GP et al (2012) Echocardiographic predictors of outcome in Eisenmenger syndrome. Circulation 126(12): 1461–1468
26. Van De Bruaene A, De Meester P, Voigt J-U, Delcroix M, Pasquet A, De Backer J et al (2012) Right ventricular function in patients with Eisenmenger syndrome. Am J Cardiol 109(8): 1206–1211
27. Ueti OM, Camargo EE, Ueti Ade A, de Lima-Filho EC, Nogueira EA (2002) Assessment of right ventricular function with Doppler echocardiographic indices derived from tricuspid annular motion: comparison with radionuclide angiography. Heart 88(3):244–248
28. Kaul S, Tei C, Hopkins JM, Shah PM (1984) Assessment of right ventricular function using two-dimensional echocardiography. Am Heart J 107(3):526–531
29. Jone P-N, Hinzman J, Wagner BD, Ivy DD, Younoszai A (2014) Right ventricular to left ventricular diameter ratio at end-systole in evaluating outcomes in children with pulmonary hypertension. J Am Soc Echocardiogr 27:172–178
30. Fine NM, Chen L, Bastiansen PM, Frantz RP, Pellikka PA, Oh JK, Kane GC (2013) Outcome prediction by quantitative right ventricular function assessment in 575 subjects evaluated for pulmonary hypertension. Circ Cardiovasc Imaging 6:711–721
31. Smith BCF, Dobson G, Dawson D, Charalampopoulos A, Grapsa J, Nihoyannopoulos P (2014) Three-dimensional speckle tracking of the right ventricle: toward optimal quantification of right ventricular dysfunction in pulmonary hypertension. J Am Coll Cardiol 64:41–51
32. Moceri P, Bouvier P, Baudouy D, Dimopoulos K, Cerboni P, Wort SJ et al (2017) Cardiac remodelling amongst adults with various aetiologies of pulmonary arterial hypertension including Eisenmenger syndrome-implications on survival and the role of right ventricular transverse strain. doi: 10.1093/ehjci/jew277.
33. Kaya MG, Lam Y-Y, Erer B, Ayhan S, Vatankulu MA, Nurkalem Z et al (2012) Long-term effect of bosentan therapy on cardiac function and symptomatic benefits in adult patients with Eisenmenger syndrome. J Card Fail 18(5):379–384
34. Abd El Rahman MY, Rentzsch A, Scherber P, Mebus S, Miera O, Balling G et al (2014) Effect of bosentan therapy on ventricular and atrial function in adults with Eisenmenger syndrome. A prospective, multicenter study using conventional and speckle tracking echocardiography. Clin Res Cardiol 103(9):701–710
35. Haeck ML, Scherptong RW, Marsan NA, Holman ER, Schalij MJ, Bax JJ et al (2012) Prognostic value of right ventricular longitudinal peak systolic strain in patients with pulmonary hypertension. Circ Cardiovasc Imaging 5(5):628–636
36. Hardegree EL, Sachdev A, Villarraga HR, Frantz RP, McGoon MD, Kushwaha SS et al (2013) Role of serial quantitative assessment of right ventricular function by strain in pulmonary arterial hypertension. Am J Cardiol 111:143–148

Cardiovascular Magnetic Resonance

12

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Abbreviations

A	Area
ASD	Atrial septal defect
AVSD	Atrioventricular septal defect
BP	Blood pressure
CHD	Congenital heart disease
CMR	Cardiac magnetic resonance imaging
CTEPH	Chronic thromboembolic pulmonary hypertension
EDV	End diastolic volume
EF	Ejection fraction
ESV	End systolic volume
LA	Left atrium
LAP	Left atrial pressure
LGE	Late gadolinium enhancement
LV	Left ventricle
PA	Pulmonary artery
PAH	Pulmonary arterial hypertension
PAP	Pulmonary artery pressure
PCWP	Pulmonary capillary wedge pressure
PDA	Patent ductus arteriosus

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PVR	Pulmonary vascular resistance
PWV	Pulse wave velocity
Q_p	Pulmonary blood flow
Q_s	Systemic blood flow
RHC	Right heart cardiac catheterisation
RV	Right ventricle
SVR	Systemic vascular resistance
TPG	Transpulmonary gradient

12.1 Introduction

The assessment of pulmonary hypertension in congenital heart disease (CHD) is challenging, partly because this group may have elevated pulmonary pressure caused by a range of haemodynamic mechanisms (sometimes coexisting), including increased pulmonary flow (left-to-right shunts), elevated pulmonary vascular resistance (PVR) or elevated pulmonary venous pressure. Furthermore, prognosis in pulmonary hypertension is strongly influenced by the adaptation of the sub-pulmonary ventricle to increased load – which may also be influenced by coexisting congenital abnormalities or their postsurgical residua. This complexity necessitates careful haemodynamic assessment for which cardiovascular magnetic resonance (CMR) is particularly well suited.

In this chapter, the role of CMR in the assessment of pulmonary hypertension in patients with CHD will be discussed, both in its role in combination with cardiac catheterization and part of multimodality noninvasive imaging.

12.2 Haemodynamic Assessment

As discussed elsewhere in this book, any large intra- or extra-cardiac shunt that allows unrestricted pressure and volume loading of the pulmonary circulation can lead to the development of pulmonary vascular disease and pulmonary arterial hypertension (PAH). PAH is characterized by increased afterload due to pulmonary vasoconstriction and vascular remodelling, the haemodynamic consequences of which are increased vascular resistance, reduced arterial compliance, elevated characteristic impedance and abnormal wave reflections. Early repair of such lesions in childhood aims to prevent this, but occasionally patients present late or develop pulmonary vascular disease after complete repair (See Table 1.1 for Types of PAH associated CHD).

12.3 CMR-Augmented Cardiac Catheterization

Assessment of patients with intra- or extra-cardiac, left-to-right shunts must critically differentiate pulmonary hypertension due to increased pulmonary blood flow from increased PVR due to pulmonary vascular disease.

The mean pressure drop across the lungs (mean pulmonary artery pressure [PAP] – mean left atrial pressure [LAP]) is related to mean pulmonary blood flow (Q_p) and PVR by Ohm's law:

$$\left(PVR \times Q_p\right) + LAP = PAP$$

Consideration of this equation demonstrates that raised PA pressure can occur through elevation of PVR, flow or LAP. Each of these factors, alone or in combination, can cause pulmonary hypertension (mean PA pressure ≥ 25 mmHg).

The importance of accurate haemodynamic assessment can be illustrated using an example of a large sinus venosus atrial septal defect (ASD) with partially anomalous pulmonary venous drainage: mean PAP, 35 mmHg and LAP 5 mmHg (transpulmonary gradient, TPG 30 mmHg). If Q_p is 10 L/min/m^{-2}, the PVR index is 3 Wu × m^2 and PAH is secondary to increased flow, but if Q_p is 3 L/min/m^{-2}, the patient has an elevated PVR index of 10 Wu × m^2 and, therefore, pulmonary vascular disease.

While determination of mean PA and LA pressure (or pulmonary capillary wedge pressure, PCWP) is usually straightforward by right heart catheterization (RHC), the assessment of flow based on Fick or thermodilution is problematic (shunts/valvar regurgitation makes dilution techniques inaccurate, while indirect Fick uses assumed oxygen consumption introducing error). CMR is considered the gold standard for the assessment of great vessel flow. One novel use of CMR is MR-augmented cardiac catheterization, whereby patients undergo RHC followed immediately by CMR with a balloon-tipped catheter (Swan–Ganz) in the branch pulmonary arteries (for mean PA and PCWP measurement) during simultaneous acquisition of CMR flow [1]. Vasodilator testing can also be performed using inhaled nitric oxide (with or without oxygen) with PVR changes easily and reliably assessed.

This approach is particularly useful in patients with combinations of shunts (e.g. ASD and patent ductus arteriosus (PDA)), multiple sources of pulmonary blood flow (systemic to pulmonary collaterals) or valve regurgitation in which conventional techniques are prone to significant errors. However, this approach can be considered in any patient in whom accurate calculation of PVR is critical. While most units do not have the luxury of combined CMR cardiac catheter laboratories, it is feasible to transfer patients from catheter laboratories to CMR suites using a strict operating procedure and safety protocol for this purpose.

12.4 CMR Assessment in Subtypes of CHD-Associated PAH

12.4.1 Eisenmenger Syndrome

Eisenmenger syndrome occurs when elevation of PVR exceeds systemic vascular resistance (SVR), with resultant intra- or extra-cardiac shunt reversal. The presence of net right-to-left shunt can be determined qualitatively using Doppler echocardiography. However, phase-contrast flow imaging by CMR can accurately quantify both pulmonary and systemic blood flow and, therefore, track serial changes in the

ratio of pulmonary-to-systemic cardiac output (Q_p:Q_s) over time or in response to therapy.

As with other forms of PAH, the function and adaptation of the right ventricle (RV) can be assessed by calculating its ejection fraction (EF), which may impart prognostic information and indicate response to therapy. Jensen et al. [2] have recently demonstrated that impaired ventricular function (either right or left impaired EF) was associated with increased mortality in this population (Fig. 12.1). Furthermore, biventricular impairment was associated with worse prognosis in this study; patients with right ventricular ejection fraction (RVEF) and left ventricular ejection fraction (LVEF) in the lowest quartile had significantly higher mortality (hazard ratio = 8.0 [95% CI 2.5–25.1], $p = 0.0004$). An important negative finding of this study was that, apart from EF and resting oxygen saturation, no other clinical parameters (including echocardiographic, laboratory or functional) had prognostic value. It may be that CMR EF was more sensitive than other important parameters when tested with this smaller sample size. It is well understood that the high reproducibility of CMR measures lends itself to the study of rare diseases [3].

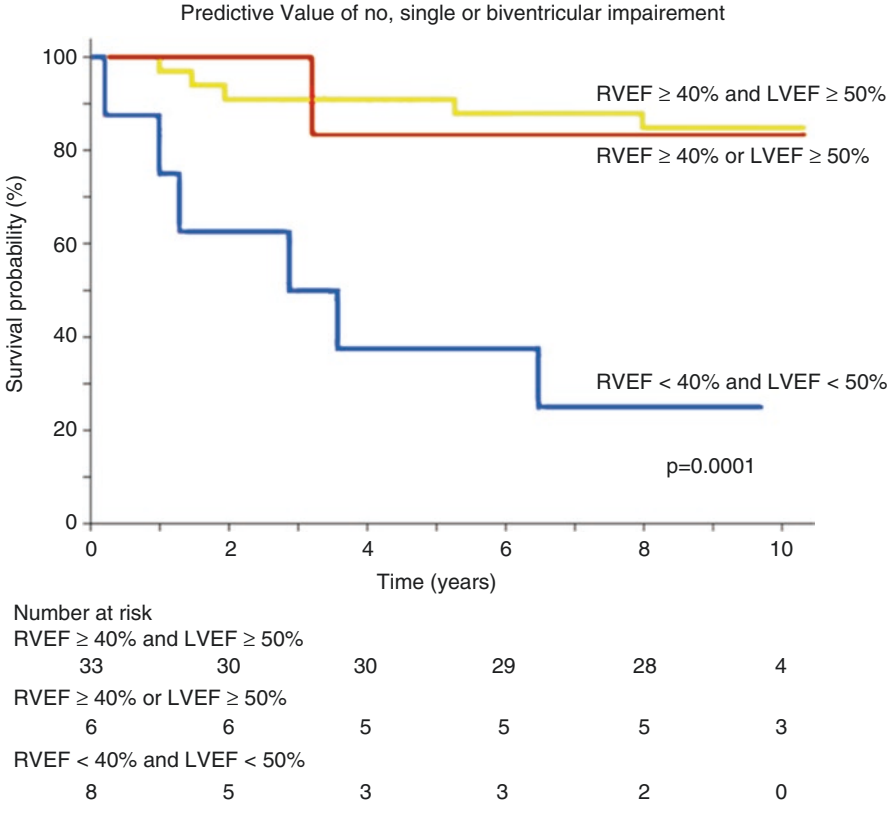

Fig. 12.1 Kaplan–Meier survival curves with the survival distributions of patients with LV or RV impairment (defined as lower quartile EF) versus both RV and LV impairment, adapted from Jensen et al. [2]

These data are also consistent with those from studies of other forms of PAH. In idiopathic PAH, CMR-derived right ventricular end-systolic volume (RVESV), right ventricular end-diastolic volume (RVEDV) and RV mass have been shown to have prognostic value [4, 5]. In children with PAH, including those with CHD, RV, EF and left ventricle (LV) stroke volume index have prognostic value [6].

The study by Jensen et al. [2] highlights the importance of the LV in this condition. In contrast to other forms of PAH, Eisenmenger patients will also often have important abnormalities of this ventricle; for example, if the underlying lesion is an atrioventricular septal defect (AVSD). This necessitates careful assessment of both right and left ventricles. Cine images of the RV and LV long axes and a four-chamber view are acquired to plan a short-axis "stack" covering both ventricles (9–12 slices). RV and LV end-systolic volume (ESV) and end-diastolic volume (EDV) are calculated by Simpson's rule following manual segmentation of the endocardial contours at end diastole and end systole. From these volumes, stroke volume and EF are calculated. Ventricular mass is calculated as the difference between the epicardial and endocardial contours, multiplied by the slice thickness and specific gravity of the ventricular myocardium of 1.05 g/mL. When combined with great vessel flow, volumetric data can also provide accurate quantification of both left and right atrioventricular valve regurgitation. Because the approach incorporates whole-heart coverage, no geometrical assumptions need to be made, which is particularly relevant where there is complex ventricular architecture related to adaptation or maladaptation and, potentially, previous surgery.

The observation of improved survival in Eisenmenger syndrome compared to other forms of PAH is intriguing and remains largely unexplained. However, patients with Eisenmenger syndrome commonly have correspondingly greater RV mass at similar levels of PVR than patients with idiopathic PAH. It is possible that RV adaptation in this condition is a major determinant of increased survival.

The ability to track disease progression and response to therapy may also have value in this population, as previously shown in other forms of PAH. Van de Veerdonk et al. [5] showed that, not only does RVEF predict mortality in PAH, but improvement in RVEF at follow-up is associated with improved outcome, independent of PVR. Further studies on the use of interval CMR in Eisenmenger syndrome are pending.

Chronic cyanosis in Eisenmenger syndrome can contribute to abnormalities in coagulation, which predispose to thrombosis [7]. A site at particular risk of in situ thrombosis is the main pulmonary artery and its branches. Gadolinium-enhanced MR angiography using a coronal 3D fast-field-echo sequence can be used to define pulmonary artery anatomy, which is typically dilated. In patients in whom intravenous (IV) access cannot be obtained or in whom IV gadolinium contrast is contraindicated (e.g. due to renal dysfunction, common in this population), 3D anatomy can be obtained using a diastolic "whole-heart", magnetization-prepared, 3D, balanced, steady-state free precession (SSFP) sequence with navigator respiratory gating. Selected cine images in the pulmonary trunk and branch pulmonary arteries can also be helpful when targeted in response to findings in preliminary imaging. "Whole-heart" data also provides important delineation of intracardiac morphology.

Late gadolinium enhancement (LGE) imaging is a technique whereby T1-weighted, inversion recovery, gradient echo images are acquired approximately 10–15 min following IV injection of gadolinium contrast. Abnormal myocardium (e.g. scar, increased interstitial space, fibrosis) is permeable to contrast and retains it longer than normal tissue. Areas of abnormal myocardium appear bright on LGE imaging, and this has proven useful for the prediction of clinical events in several forms of adult CHD. Common sites of LGE in pulmonary hypertension include the insertion points of the interventricular septum. However, a recent study did not find that LGE provided prognostic information in a large group of mixed aetiology pulmonary hypertension patients, including a small number with CHD-associated PAH [8]. A small study comprising only of Eisenmenger syndrome patients showed that LGE, additional to that at insertion points, was a common finding, but no prognostic value was demonstrated [9]. There is still limited understanding of the role of myocardial fibrosis in these patients, with little data on the use of more modern high-resolution LGE techniques [10]. Further work is needed to apply new interstitial fibrosis CMR measures to the RV [11–14].

12.4.2 Pulmonary Arterial Hypertension Associated with Moderate Systemic-to-Pulmonary Shunts

Some patients with an intra- or extra-cardiac shunt and PAH, due to mild/moderately elevated PVR, will have no cyanosis at rest and maintain a net left-to-right shunt, as SVR still exceeds PVR. Accurate diagnosis in this patient group is challenging and requires a high index of suspicion to identify patients in whom the PAH is disproportionate to the amount of left-to-right shunt, i.e. PVR is raised. Clinical management of this group is difficult, and decisions to close shunts rely on precise estimation of PVR; for this reason, these patients are ideal candidates for CMR-augmented cardiac catheterization.

CMR assessment of this group is similar to that described above, and assessment should concentrate on LV and RV function. Following diagnosis, CMR assessment of Q_p:Q_s (measurement of systemic mean arterial blood pressure (BP) and calculation of SVR can help interpretation) is a valuable way to track progression of pulmonary vascular disease.

12.4.3 Pulmonary Arterial Hypertension with Small Defects or After Repair

Patients with pulmonary hypertension and small cardiac defects, most commonly a small ASD, which would not be expected to produce PAH, are often considered to have idiopathic PAH with a coexistent defect. Although the disease processes and physiology are almost indistinguishable, the presence of an ASD may be beneficial, as it allows maintenance of cardiac output by right-to-left shunting in the presence of a profoundly elevated PVR. Elevated PVR and PAH may also occur in patients many years after repair of CHD defects, even if normal

pulmonary pressures had been confirmed before and early after repair. These patients also tend towards the pattern of idiopathic PAH.

CMR assessment in these patients can, therefore, be modelled on idiopathic PAH. This group of patients should undergo thorough evaluation for other common causes of pulmonary hypertension, in particular group 2 (left heart disease), group 3 (lung disease/hypoxia) and group 4 (chronic thromboembolic pulmonary hypertension, CTEPH). Indeed, CMR contrast-enhanced angiography may be particularly useful for the latter [15–17].

Serial CMR assessment after diagnosis necessarily focuses on biventricular volume and function, which independently predict mortality and treatment failure in idiopathic PAH. RV function can also be used to guide treatment with advanced therapies. Indeed, recent data indicates that changes in CMR volumetric data precede clinical deterioration; worsening RV indices could, therefore, be used as a reason to escalate therapy [18]. However, the impact of such a strategy is yet to be tested.

12.4.4 Pulmonary Arterial Hypertension in the Fontan Circulation

In the Fontan circulation, systemic venous return is directed to the lungs without an interposed sub-pulmonary ventricle. Haemodynamics in the Fontan circulation are interesting: the pulmonary circulation is uniquely exposed to flow with absent or at least severely attenuated pulsatility. Pulsatility of blood flow is important for the shear stress-mediated release of nitric oxide, which lowers PVR and also recruits capillaries. PVR may be elevated in patients following Fontan-type palliation, and, in this setting, even a relatively minimal increase in PVR can have major adverse clinical effects on the pulmonary circulation and cardiac output.

An important element of the Fontan circulation is that systemic function is strongly determined by the inherent preload, limited by the absence of a sub-pulmonary ventricle. CMR, through quantification of pulmonary venous flow and ventricular volumes, can provide valuable information. CMR allows accurate serial quantification of the systemic ventricular function, whether the primary ventricle is morphologically left or right. Cardiac output can be measured directly from flow in the aorta. Atrioventricular valvar regurgitation can be quantified by the difference in volumetric stroke volume and aortic forward flow. CMR is also excellent for detecting intracavitary thrombosis, an important complication of the Fontan circulation. Thrombi can form in the right atrium of an atriopulmonary Fontan circulation or in the blind-ended pulmonary artery after total cavopulmonary connection. Flow measurements in the inflow to the Fontan circulation (superior and inferior vena cava) and outflow (pulmonary veins) also allow quantification of shunting through systemic to pulmonary collateral vessels [19], which can also be imaged by contrast-enhanced angiography. These collaterals have been shown to influence the very short-term outcome (such as length of hospital stay) following total cavopulmonary connection, but their role long term or in the context of the “failing Fontan” remains uncertain.

12.4.5 PAH Secondary to Unexpected Congenital Heart Disease or Left-Sided Disease

Patients may be referred for CMR as part of the diagnostic workup for invasively documented pulmonary hypertension or for dilated pulmonary arteries incidentally diagnosed by other imaging modalities. Unexpected, previously undiagnosed sinus venosus atrial septal defects are not uncommon incidental findings at CMR, and their management is significantly influenced by pulmonary vascular haemodynamics (when PVR is low and surgical repair is possible) and, hence, prognosis (Fig. 12.2).

The presence, severity and underlying cause of left-sided heart disease can also be assessed by CMR, which is the gold standard for quantification of left ventricular volumes, mass and function. Tissue characterization is excellent by CMR and aids greatly in diagnosing the aetiology of left-sided disease [20] (Fig. 12.3).

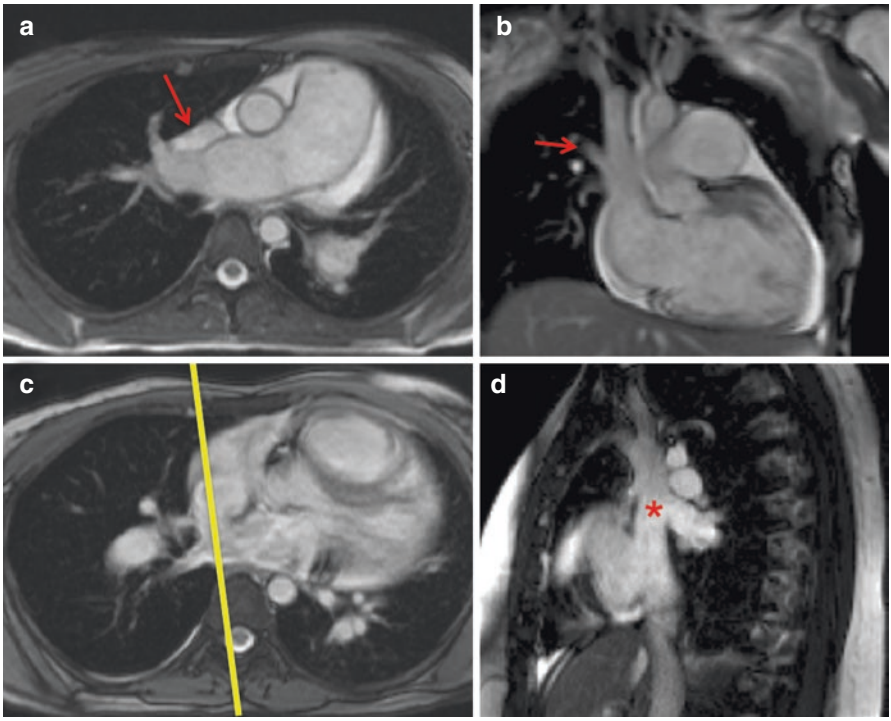

Fig. 12.2 An anomalous right upper pulmonary vein (*red arrow*) is seen passing horizontally and entering the superior vena cava on a transaxial white blood image (**a**). The pulmonary trunk and right pulmonary artery are clearly dilated compared with the aorta; (**b**) the entry of the right pulmonary artery into the superior vena cava is seen in a coronal image. A pericardial effusion can also be noted. The communication, i.e. the sinus venosus atrial septal defect, is seen in the transaxial orientation (**c**), and the yellow line represents the orientation of the image required to achieve the image of the sinus venosus atrial septal defect in (**d**)

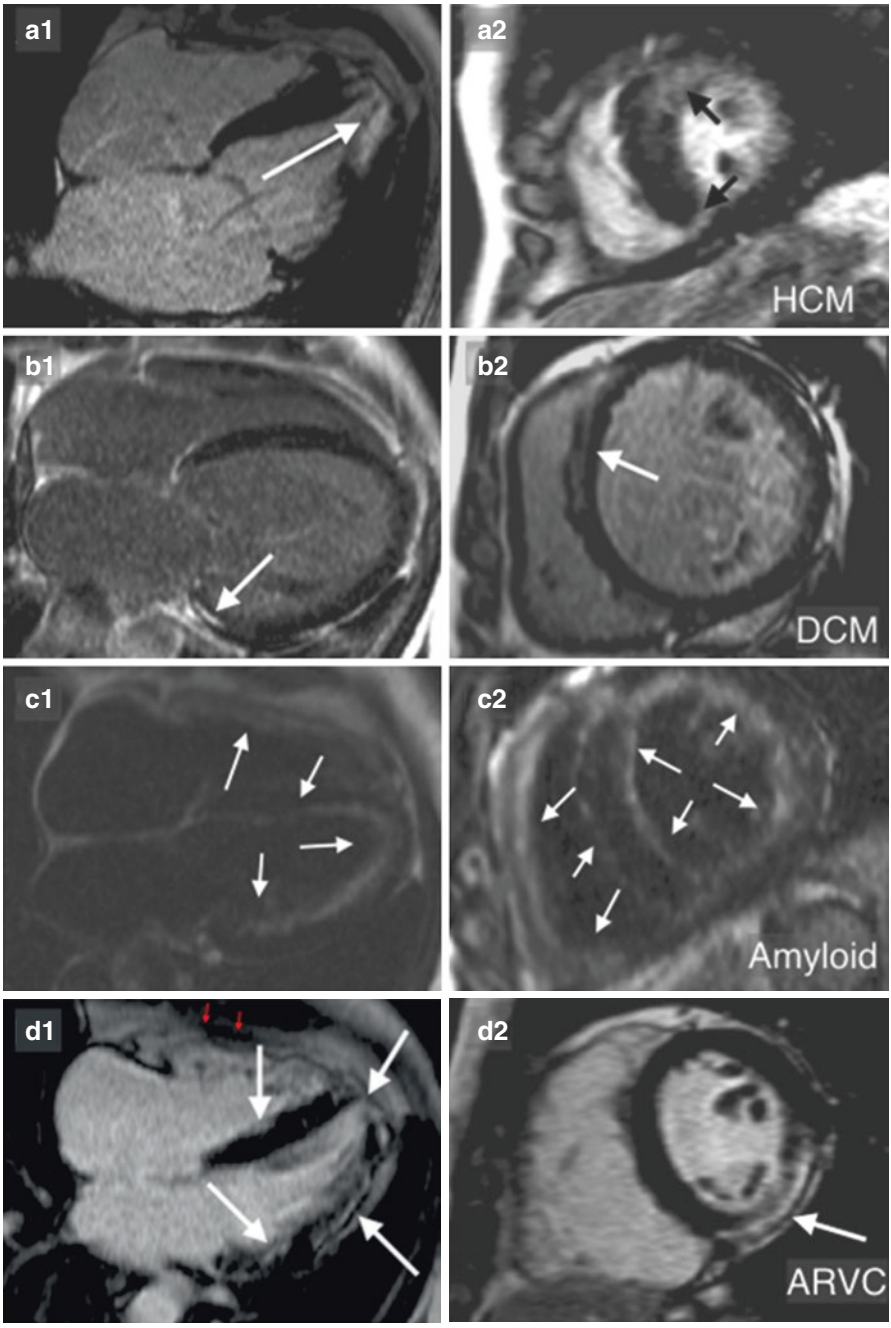

Fig. 12.3 Late gadolinium enhancement (LGE) in non-ischaemic cardiomyopathy. Classic LGE CMR findings in hypertrophic cardiomyopathy (**a**), dilated cardiomyopathy (**b**), arrhythmogenic cardiomyopathy (ARVC) with LV involvement (**c**) and amyloid cardiomyopathy (**d**) are shown in four-chamber (*i*) and short-axis (*ii*) views with areas of LGE arrowed (figure adapted from Babu-Narayan [20])

12.5 Noninvasive CMR Biomarkers of Pulmonary Hypertension

Noninvasive assessment of central pulmonary haemodynamics using CMR is attractive, as it could facilitate both noninvasive diagnosis and ongoing assessment of disease after diagnosis of PAH.

12.5.1 Markers of Raised Pulmonary Artery Pressure and Vascular Resistance

One promising marker is quantification of the curvature of the interventricular septum. The position of the interventricular septum is determined by the instantaneous RV–LV pressure gradient. In health, the LV pressure exceeds RV pressure throughout the cardiac cycle, thus, giving the LV a circular conformation. However, in PAH, this pressure gradient is reduced or even reversed, causing the septum to become either flattened or bow into the LV (Fig. 12.4) [21]. The sensitivity of this marker to acute changes in RV load has been demonstrated by its ability track PA pressure changes during vasodilator testing in children. A similar approach using a multivariable linear regression equation, incorporating septal angle and RV mass, has also been shown to closely approximate PA pressure in adults [22]. These simple approaches are appealing, as they are based upon routinely acquired short-axis cine imaging with simple post-processing. However, the effects of coexisting outflow tract lesions (pulmonary or aortic stenosis), the presence of patch material or bundle branch block must be borne in mind when generalizing to CHD.

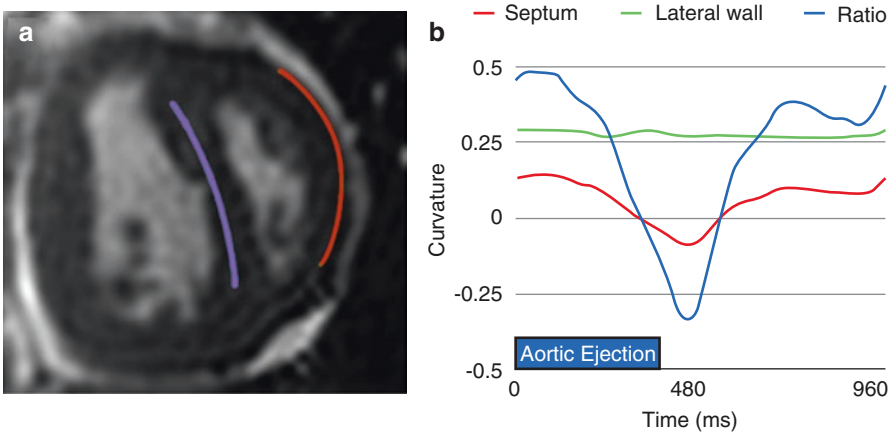

Fig. 12.4 (**a**) Regions of interest applied to the lateral free wall and septum during *left* ventricular bowing. (**b**) Curvature across one cardiac cycle in the septum (*red line*), lateral wall (*green line*) and curvature ratio (*blue line*). The minimum point of curvature ratio (*blue line*) is strongly associated with the mean pulmonary artery pressure (figure adapted from Pandya et al. [21])

Indices of pulmonary artery flow, such as average flow velocity, have been shown to correlate with PAP [23]. 4D phase-contrast flow imaging has been used to image pulmonary artery vortices, which have also been shown to correlate with PAP [24]. 4D flow imaging may also be used to estimate tricuspid regurgitation velocity.

PVR represents the mean, non-pulsatile component of afterload; the additional pulsatile components of afterload include compliance, characteristic impedance (pulse wave velocity (PWV)) and wave reflections.

12.5.2 Compliance

Compliance is defined as a change in volume (ΔV) for a given change in pressure (ΔP). In PAH, the pulmonary arteries are stiffer and compliance is reduced, which contributes to increased afterload. Noninvasive assessment of compliance has been attempted using the relative cross-sectional area change of the pulmonary arteries using CMR. This metric only crudely approximates compliance, as it neglects the ΔP component; however, it has been shown to correlate with PVR and predicts clinical events [25, 26].

12.5.3 Characteristic Impedance and Pulse Wave Velocity

When the RV ejects, it must accelerate blood into the pulmonary artery, overcoming a combination of inertance and vessel compliance. This is the characteristic impedance (Z_c) of the vessel, and governs ventricular load in early systole. The Z_c is directly related to PWV (c) as follows: $Z_c = \rho c / A_d$ where A_d is vessel diastolic area, and ρ is blood density. As can be seen from this equation, ventricular load in early systole is increased in vessels with smaller areas and elevated PWV. Given a stable PWV, a dilated pulmonary artery would decrease load in early systole. PWV relates to the material properties of the vessel: it is the relationship between pulsatile pressure and pulsatile flow measured at the same site in an artery, in the absence of wave reflections. One method that can be used to calculate pulmonary artery PWV is the QA (flow-area) method. This is based upon solution of the water hammer equation and involves measurement of the flow (Q) and cross-sectional area (A) in the pulmonary arteries (ideally branch pulmonary arteries due to the through-plane motion of the pulmonary trunk) using phase-contrast CMR:

$$PWV = \frac{\Delta Q}{\Delta A}$$

This method relies upon measurement during the reflection-free part of early systole (with PWV in m/s, ΔQ in m^3/s and ΔA in m^2). This is a very short interval at the onset of ejection and may last less than 30 ms; therefore, high temporal resolution imaging is required. A proposed implementation measures the gradient of Q against A by linearly regressing the first three unfiltered and uninterpolated points of

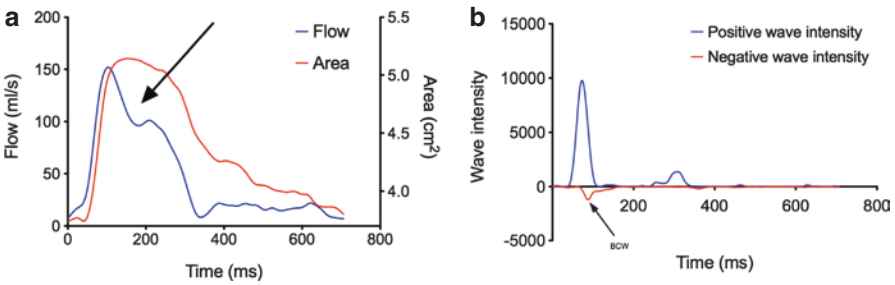

Fig. 12.5 Flow (*blue*) and area (*red*) curves from a phase-contrast MR acquisition in a patient with idiopathic pulmonary arterial hypertension. There is a characteristic notch of the flow curve (*arrow*, panel **a**), which is caused by a negative wave reflection (*arrow*, panel **b**) travelling backwards towards the heart (backwards compression wave, BCW)

the Q and A curves in the first 30 ms of systole [27, 28]. PWV is higher in patients with pulmonary hypertension than in controls [29]. However, the role of this metric in the detection, screening and monitoring of patients is still unknown, and data on pulmonary arterial hypertension related to congenital heart disease (PAH-CHD) is lacking.

12.5.4 Wave Reflections

Arterial wave reflections are caused by abrupt changes in vessel area or compliance and also contribute to RV load. As PAH is characterized by widespread vascular changes, it has been postulated that abnormal wave reflections may be an additional source of increased RV afterload. The influence of wave reflections can be observed qualitatively by inspection of a PAH patient's pulmonary artery flow curve, which shows a typical mid-systolic "notch"; this represents early wave reflections (resulting in reduced peak velocity and earlier time to peak velocity [acceleration time]) [23] (Fig. 12.5). It has recently been shown that CMR can be used to noninvasively quantify wave reflections in the pulmonary circulation using a technique called wave intensity analysis. This method has been shown to differentiate between health and disease and can also identify certain subtypes of PAH [29].

12.5.5 Pitfalls

Pulmonary blood flow is usually measured in the main pulmonary artery. However, in PAH, this is usually dilated. It has been observed that measurements in this location can often be associated with overestimation of blood flow. This can be overcome by measurement of flow in the branch pulmonary arteries (which has the added advantage of providing data for individual lungs). It is also important to acquire additional data to internally validate measurements of pulmonary artery flow (e.g. pulmonary venous flow). Arrhythmia is not infrequent in patients with CHD-associated PAH and can cause difficulties with cardiac gating.

Conclusion

CMR is the gold standard for the assessment of ventricular function, volume and great vessel flow. This is founded upon the low intra- and interobserver variability when using these techniques and its avoidance of ionizing radiation. This precision and reproducibility means that, in clinical trials requiring ventricular indices, fewer patients need to be imaged by CMR than by transthoracic echocardiography [3, 30]. The ability of CMR to simultaneously assess intra- and extracardiac anatomy is of vital importance in patients with CHD. The proven prognostic value of many CMR markers of PAH is very exciting, and CMR will undoubtedly grow in importance for patients with CHD-related PAH.

References

1. Muthurangu V, Taylor A, Andriantsimiavona R, Hegde S, Miquel ME, Tulloh R, Baker E, Hill DL, Razavi RS (2004) Novel method of quantifying pulmonary vascular resistance by use of simultaneous invasive pressure monitoring and phase-contrast magnetic resonance flow. Circulation 110:826–834
2. Jensen AS, Broberg CS, Rydman R, Diller GP, Li W, Dimopoulos K, Wort SJ, Pennell DJ, Gatzoulis MA, Babu-Narayan SV (2015) Impaired right, left, or biventricular function and resting oxygen saturation are associated with mortality in eisenmenger syndrome: a clinical and cardiovascular magnetic resonance study. Circ Cardiovasc Imaging 8(12):e003596. doi:10.1161/CIRCIMAGING.115.003596
3. Bellenger NG, Davies LC, Francis JM, Coats AJ, Pennell DJ (2000) Reduction in sample size for studies of remodeling in heart failure by the use of cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2:271–278
4. Swift AJ, Rajaram S, Campbell MJ, Hurdman J, Thomas S, Capener D, Elliot C, Condliffe R, Wild JM, Kiely DG (2014) Prognostic value of cardiovascular magnetic resonance imaging measurements corrected for age and sex in idiopathic pulmonary arterial hypertension. Circ Cardiovasc Imaging 7:100–106
5. van de Veerdonk MC, Kind T, Marcus JT, Mauritz GJ, Heymans MW, Bogaard HJ, Boonstra A, Marques KM, Westerhof N, Vonk-Noordegraaf A (2011) Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. J Am Coll Cardiol 58:2511–2519
6. Moledina S, Pandya B, Bartsota M, Mortensen KH, McMillan M, Quyam S, Taylor AM, Haworth SG, Schulze-Neick I, Muthurangu V (2013) Prognostic significance of cardiac magnetic resonance imaging in children with pulmonary hypertension. Circ Cardiovasc Imaging 6:407–414
7. Broberg C, Ujita M, Babu-Narayan S, Rubens M, Prasad SK, Gibbs JS, Gatzoulis MA (2004) Massive pulmonary artery thrombosis with haemoptysis in adults with Eisenmenger's syndrome: a clinical dilemma. Heart 90:e63
8. Swift AJ, Rajaram S, Capener D, Elliot C, Condliffe R, Wild JM, Kiely DG (2014) LGE patterns in pulmonary hypertension do not impact overall mortality. JACC Cardiovasc Imaging 7:1209–1217
9. Broberg CS, Prasad SK, Carr C, Babu-Narayan SV, Dimopoulos K, Gatzoulis MA (2014) Myocardial fibrosis in eisenmenger syndrome: a descriptive cohort study exploring associations of late gadolinium enhancement with clinical status and survival. J Cardiovasc Magn Reson 16:32
10. Keegan J, Jhooti P, Babu-Narayan SV, Drivas P, Ernst S, Firmin DN (2014) Improved respiratory efficiency of 3D late gadolinium enhancement imaging using the continuously adaptive windowing strategy (CLAWS). Magn Reson Med 71(3):1064–1074

11. Broberg CS, Chugh SS, Conklin C, Sahn DJ, Jerosch-Herold M (2010) Quantification of diffuse myocardial fibrosis and its association with myocardial dysfunction in congenital heart disease. Circ Cardiovasc Imaging 3:727–734
12. Plymen CM, Sado DM, Taylor AM, Bolger AP, Lambiase PD, Hughes M, Moon JC (2013) Diffuse myocardial fibrosis in the systemic right ventricle of patients late after mustard or senning surgery: an equilibrium contrast cardiovascular magnetic resonance study. Eur Heart J Cardiovasc Imaging 14(10):963–968
13. Heng EL KP, Gatzoulis MA, Moon J, Gatehouse P, Babu-Narayan SV (2015) Pilot data of right ventricular myocardial T1 quantification by free-breathing fat-water separated dark blood saturation-recovery imaging. J Cardiovasc Magn Reson 17(Suppl 1):Q23
14. Heng EL KP, Gatzoulis MA, Moon J, Gatehouse PD, Babu-Narayan SV (2016) Right ventricular T1 mapping by free-breathing fat-water separated dark blood saturation-recovery imaging in repaired tetralogy of Fallot and healthy volunteers. J Cardiovasc Magn Reson 18(Suppl 1):O26
15. Oudkerk M, van Beek EJ, Wielopolski P, van Ooijen PM, Brouwers-Kuyper EM, Bongaerts AH, Berghout A (2002) Comparison of contrast-enhanced magnetic resonance angiography and conventional pulmonary angiography for the diagnosis of pulmonary embolism: a prospective study. Lancet 359:1643–1647
16. Ley S, Ley-Zaporozhan J, Pitton MB, Schneider J, Wirth GM, Mayer E, Duber C, Kreitner KF (2012) Diagnostic performance of state-of-the-art imaging techniques for morphological assessment of vascular abnormalities in patients with chronic thromboembolic pulmonary hypertension (CTEPH). Eur Radiol 22:607–616
17. Rajaram S, Swift AJ, Telfer A, Hurdman J, Marshall H, Lorenz E, Capener D, Davies C, Hill C, Elliot C, Condliffe R, Wild JM, Kiely DG (2013) 3D contrast-enhanced lung perfusion MRI is an effective screening tool for chronic thromboembolic pulmonary hypertension: results from the ASPIRE registry. Thorax 68:677–678
18. van de Veerdonk MC, Marcus JT, Westerhof N, de Man FS, Boonstra A, Heymans MW, Bogaard HJ, Vonk NA (2015) Signs of right ventricular deterioration in clinically stable patients with pulmonary arterial hypertension. Chest 147:1063–1071
19. Odenwald T, Quail MA, Giardini A, Khambadkone S, Hughes M, Tann O, Hsia TY, Muthurangu V, Taylor AM (2012) Systemic to pulmonary collateral blood flow influences early outcomes following the total cavopulmonary connection. Heart 98:934–940
20. Babu-Narayan SV (2010) The role of late gadolinium enhancement cardiovascular magnetic resonance in the assessment of congenital and acquired heart disease. Prog Pediatr Cardiol 28:11–19
21. Pandya B, Quail MA, Steeden JA, McKee A, Odille F, Taylor AM, Schulze-Neick I, Derrick G, Moledina S, Muthurangu V (2014) Real-time magnetic resonance assessment of septal curvature accurately tracks acute hemodynamic changes in pediatric pulmonary hypertension. Circ Cardiovasc Imaging 7(4):706–713. doi:10.1161/CIRCIMAGING.113.001156
22. Swift AJ, Rajaram S, Hurdman J, Hill C, Davies C, Sproson TW, Morton AC, Capener D, Elliot C, Condliffe R, Wild JM, Kiely DG (2013) Noninvasive estimation of PA pressure, flow, and resistance with CMR imaging: derivation and prospective validation study from the ASPIRE registry. JACC Cardiovasc Imaging 6:1036–1047
23. Sanz J, Kuschnir P, Rius T, Salguero R, Sulica R, Einstein AJ, Dellegrottaglie S, Fuster V, Rajagopalan S, Poon M (2007) Pulmonary arterial hypertension: noninvasive detection with phase-contrast MR imaging. Radiology 243:70–79
24. Reiter G, Reiter U, Kovacs G, Kainz B, Schmidt K, Maier R, Olschewski H, Rienmueller R (2008) Magnetic resonance-derived 3-dimensional blood flow patterns in the main pulmonary artery as a marker of pulmonary hypertension and a measure of elevated mean pulmonary arterial pressure. Circ Cardiovasc Imaging 1:23–30
25. Gan CT, Lankhaar JW, Westerhof N, Marcus JT, Becker A, Twisk JW, Boonstra A, Postmus PE, Vonk-Noordegraaf A (2007) Noninvasively assessed pulmonary artery stiffness predicts mortality in pulmonary arterial hypertension. Chest 132:1906–1912

26. Swift AJ, Rajaram S, Condliffe R, Capener D, Hurdman J, Elliot C, Kiely DG, Wild JM (2012) Pulmonary artery relative area change detects mild elevations in pulmonary vascular resistance and predicts adverse outcome in pulmonary hypertension. Investig Radiol 47:571–577
27. Quail MA, Steeden JA, Knight D, Segers P, Taylor AM, Muthurangu V (2014) Development and validation of a novel method to derive central aortic systolic pressure from the MR aortic distension curve. J Magn Reson Imaging 40(5):1064–1070
28. Swillens A, Taelman L, Degroote J, Vierendeels J, Segers P (2013) Comparison of non-invasive methods for measurement of local pulse wave velocity using FSI-simulations and in vivo data. Ann Biomed Eng 41:1567–1578
29. Quail MA, Knight DS, Steeden JA, Taelman L, Moledina S, Taylor AM, Segers P, Coghlan GJ, Muthurangu V (2015) Noninvasive pulmonary artery wave intensity analysis in pulmonary hypertension. Am J Physiol Heart Circ Physiol 308:H1603–H1611
30. Addetia K, Bhave NM, Tabit CE, Gomberg-Maitland M, Freed BH, Dill KE, Lang RM, Mor-Avi V, Patel AR (2014) Sample size and cost analysis for pulmonary arterial hypertension drug trials using various imaging modalities to assess right ventricular size and function end points. Circ Cardiovasc Imaging 7:115–124

Cardiopulmonary Exercise and Six-Minute Walk Testing

13

Graham Stuart and Reza Ashrafi

Abbreviations

ACCP	American College of Chest Physicians
ACHD	Adult Congenital Heart Disease
AT	Anaerobic threshold
ATS	American Thoracic Society
BP	Blood pressure
CO_2	Carbon dioxide
CPEX	Cardiopulmonary exercise testing
DO_2	Peripheral oxygen delivery
HCO_3	Bicarbonate
HF-PEF	Heart failure with preserved ejection fraction
MVV	Maximum voluntary ventilation
NYHA	New York Heart Association
OUER	Oxygen Uptake Extraction Ratio
OUES	Oxygen Uptake Efficiency Slope
PAP	Pulmonary arterial pressure
$PetCO_2$	end tidal CO_2
PH	Pulmonary hypertension
PH–ACHD	Pulmonary hypertension related to Adult Congenital Heart Disease
RER	Respiratory exchange ratio
VCO_2	CO_2 production

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VD	Dead space
VE	Ventilation
VO_2	Oxygen consumption
VT	Tidal volume
WR	Work rate

13.1 Introduction

Cardiopulmonary exercise testing (CPEX) and six-minute walk testing (6MWT) have been available for many decades and are used for diagnosis and prognostic assessment in many cardiology settings including heart failure, quantitation of cardiorespiratory function, preoperative assessment and monitoring of treatment efficacy or symptom deterioration [1]. CPEX/6MWT have been used both separately and in combination in the assessment of pulmonary hypertension (PH) secondary to congenital cardiac disorders [2]. Compared to static lung function tests or a standard treadmill exercise test, CPEX can evaluate dynamic changes in cardiorespiratory function and can obtain functional information on apparently minor lesions at rest, which lead to profound symptoms on exercise. In this chapter, we will look at the background physiology of exercise, the organisation and performance of the test and the use of CPEX/6MWT in diagnosis and prognosis when assessing PH in adult congenital heart disease (PH–ACHD).

13.2 Background Physiology

At the heart of exercise physiology testing is the assessment of two key processes at rest followed by dynamic aerobic exercise and recovery:

- Oxygenated blood delivery to the tissues from the heart
- CO_2 removal from blood through the lungs

These two key processes involve:

- Ventilation of the lungs
- Pulmonary capillary diffusion of O_2 and CO_2
- Movement of oxygenated and deoxygenated blood around the body
- Exchange of O_2 and CO_2 between blood vessels and working muscle

The normal cardiovascular response to exercise is to increase heart rate substantially with an increase in myocardial contractility and shift in the Frank–Starling effect to the left [3]. This leads to an increase in cardiac output and left atrial pressure with transmission of this increased pressure to the pulmonary vasculature. There is also vasoconstriction of arterioles to non-important organs and increased venous return through large muscle groups acting as a pump return. These processes are designed to increase oxygen delivery to metabolically active tissue, in particular, skeletal muscle.

The normal ventilatory response to exercise, in tandem with increased oxygen consumption requirements, is to increase respiratory rate and tidal volume. At higher levels of exercise, the dominant change is an increase in respiratory rate. This increase in rate is accomplished through reduced inspiratory and expiratory times, made possible by activating expiratory muscles and reducing end expiratory lung volume [4]. Exercise also induces an increase in pulmonary capillary recruitment and oxygen diffusion [5]. In the normal patient, unused pulmonary blood vessels dilate on exercise and the ventilation/perfusion ratio falls (from 0.8 at rest to 0.5). The diastolic pulmonary artery pressure changes little, with no major change in pulmonary resistance, but the systolic pulmonary pressure increases significantly (x3 in the normal heart). Thus, the work of the sub-pulmonary ventricle is much greater than that of the systemic ventricle. This can be of major importance in congenital heart disease.

13.2.1 Physiological Response to Exercise in Pulmonary Hypertension

It is difficult to summarise a single set of exercise responses that apply to the wide spectrum of congenital heart conditions associated with PH. In congenital heart patients, there may be restrictions of ventricular filling due to systemic or pulmonary venous anomalies or as a consequence of previous cardiac surgery. A good example of this is seen in patients who have undergone an atrial switch procedure for transposition of the great arteries (Mustard or Senning operation). These patients have an intra-atrial baffle which can constrict at either the systemic or pulmonary venous site. In turn, this can restrict ventricular filling and reduce exercise-related cardiac output. If the pulmonary venous baffle (pathway) is obstructed, this can cause pulmonary venous hypertension which may be corrected by surgical revision of the baffle or transcatheter stent implantation.

During long-term follow-up, around 7% of patients with a Senning or Mustard correction of transposition of the great arteries have PH secondary to pulmonary vascular disease [6]. The precise cause of this is uncertain but may relate to a delay in corrective surgery and the concomitant effect of prolonged cyanosis on the developing pulmonary vasculature. Similarly, patients with a small VSD may present with raised pulmonary vascular resistance. The size of an intracardiac shunt can be difficult to interpret during a resting assessment and a “small” ventricular septal defect detected in an adult may have been much larger in early childhood with partial closure during somatic growth. There may be residual changes to the pulmonary vasculature, which are easily missed during a resting evaluation but may detected during CPEX.

Congenital conditions with even more complex response to exercise include complex pulmonary atresia and the Fontan circulation. In pulmonary atresia, some regions of the lung are subjected to systemic pressure with consequent pulmonary vascular changes, but other regions have stenosed arterial supply and pulmonary resistance is low or normal (see also Chapter 6). Pulmonary vascular disease in the Fontan circulation (see Chapter 7) is yet another unique situation in congenital heart patients where the absence of a sub-pulmonary pump and

dependence on the skeletal muscle pump and systemic ventricular function can make interpretation of the CPEX/6MWT much more complex. In this situation, the pulmonary vascular resistance may be elevated despite the pulmonary artery pressure remaining at a level that would be low in a biventricular circulation. This "relative" PH can be accentuated by environmental factors such as living at high altitude. Consequently, the interpretation of CPEX/6MWT tests in congenital heart patients must be preceded by a detailed echocardiogram and, possibly, haemodynamic assessment to fully assess anatomy and detect any residual anatomic or postsurgical disease.

Despite the above, there are some changes, which are common to many PH–ACHD patients that provide informative data in a CPEX. Due to changes in the pulmonary vasculature, there may be increased pulmonary vascular resistance and pulmonary arterial pressure (PAP) with failure to perfuse alveoli. This leads to increased *V*/*Q* mismatch and an increase in dead-space ventilation. There is also a reduction in cardiac output and reduced pulmonary capillary diffusion of oxygen. In comparison to normal controls, there may be an increase in breathing frequency and volume with reduced partial pressures of CO_2 due to respiratory compensation of the metabolic acidosis, which occurs as a consequence of cyanosis and hypoxia.

These changes can be detected in measurements generated during the CPEX. A clear understanding of the physiology of each measurement enables the observer to understand their usefulness in the assessment of the congenital cardiac patients with PH. This list is not exhaustive and many departments include additional measures of assessment. It is essential for each CPEX lab to have a clear understanding of the normal ranges, sensitivity and utility of individual measures used in their own laboratory. Often, a single measurement is of little value, but an analysis of the pattern of changes combined with the sequential changes that occur over time can be highly informative.

13.2.2 Measurements

13.2.2.1 Oxygen Uptake: Peak VO_2

Oxygen uptake is the volume of oxygen (VO_2) metabolised by the body during exercise. The three stages of oxygen uptake and utilisation include a respiratory stage (ventilation, alveolar-capillary diffusion and binding to haemoglobin), a cardiovascular stage with delivery of oxygen to the skeletal muscles and a muscular stage (diffusion of oxygen from erythrocytes to mitochondria to respiratory chain). VO_2 is a measure of the body's ability to deliver oxygenated blood to the large muscle groups required for exercise and is defined by the Fick equation as the product of stroke volume multiplied by heart rate multiplied by the arteriovenous oxygen (A-VO_2) differential [7]. During exercise in healthy individuals, this value has a linear relationship until it reaches a plateau near maximum exercise capacity although, in clinical practice, maximum exercise capacity may never be reached and the peak VO_2 value is quoted. VO_2 is influenced by age, gender and, to a lesser extent, height. VO_2 is often quoted in mL/kg/min but, in oedematous or obese patients, a dry (or lean) weight should be estimated.

VO_2 during exercise is mainly increased through an increase in cardiac output, which in healthy individuals can be increased by a factor of six [7], but is also due to diversion of blood flow to large muscle groups, pulmonary vasodilation and increased O_2 extraction from muscles (widening the A-VO_2 difference). VO_2 max is the maximum quantity of oxygen, which can be taken up by an individual, but often this level of exercise is not reached, and VO_2 peak (the maximum VO_2 achieved during the exercise) is used. Peak VO_2 will often be reduced in congenital cardiac patients due to their underlying condition at rest, and when PH is present, this will worsen their left ventricular filling/right ventricular performance, thus, suppressing their peak VO_2.

13.2.2.2 Oxygen Pulse

O_2 pulse is calculated by dividing VO_2 by heart rate (VO_2/HR). This reflects the O_2 taken up by the lungs for every heart beat and can be used as a surrogate for stroke volume. In the healthy individual, O_2 pulse rises during the initial phase of exercise before plateauing with the increasing heart rate providing any further rise in cardiac output [8]. O_2 pulse is reported in mL/beat. In the presence of a right–left intracardiac shunt, the O_2 pulse will be reduced reflecting diversion of deoxygenated blood to the systemic circulation rather than severity of disease. Thus, pulse oximetry saturations must be monitored for O_2 pulse to be interpreted correctly. ΔO_2 pulse can be a useful parameter to assess prognosis in PH. This is calculated as the change in VO_2/HR from rest to maximal exercise.

13.2.2.3 VCO_2

This is the amount of CO_2 expired and normally reported in L/min. Most CO_2 is produced through respiration, but at higher workloads with increasing lactate production, some is produced as a response in cell buffering reflected in the equation:

$$\left[\mathrm{H}^{+}\right]+\left[HCO_3\right]\leftrightarrow\left[\mathrm{H}_2CO_3\right]\leftrightarrow\left[CO_2\right]+\left[\mathrm{H}_2\mathrm{O}\right].$$

This is important as CO_2 is much more soluble than O_2, and so there is an assumption that not all measured CO_2 reflects all that is produced during the test assessed using gas analysis.

13.2.2.4 $PetCO_2$

This is the end tidal CO_2 measurement.

13.2.2.5 Minute Ventilation (V_E)

This is the volume of gas exhaled per minute and reflects tidal volume and respiratory frequency. V_E does not normally limit exercise and values >80% of predicted normally imply there is a pulmonary component to exercise limitation.

13.2.2.6 Maximum Voluntary Ventilation (MVV)

This is the maximum amount of air that can be exhaled over 12 s during rapid deep breathing.

13.2.2.7 Anaerobic Threshold (AT)

The stage at which oxygen supply to muscles can no longer be met by increased ventilation is the *anaerobic threshold*. At this point, the muscles revert to anaerobic metabolism, resulting in lactate production. During a CPEX, the AT can be determined when the VE rises exponentially compared with failure or a very slight rise in VO_2 [9]. In congenital cardiac patients and especially those with PH, the AT may be achieved early due to reduced cardiac output and high ventilatory effort.

13.2.2.8 Physiological Dead-Space-to-Tidal Volume Ratio (V_D/V_T)

One of the most important measurements of lung gas exchange efficiency is the V_D/V_T, which measures the fraction of each breath used to ventilate the anatomical dead-space and non-perfused alveoli (physiological dead space).

V_D/V_T is calculated using the Bohr equation, where $PaCO_2$ is the partial pressure of CO_2 in blood measured directly or estimated using Jones formula [10], and $PeCO_2$ is the partial pressure of CO_2 in expired air. This is normally calculated using V_E/VCO_2 ratio.

$$V_D / V_T = \frac{\left(PaCO_2 - PeCO_2\right)}{PaCO_2}.$$

During exercise, several processes affect the V_D/V_T including an increase in tidal volume, bronchodilatation and increased lung perfusion [11]. In normal individuals, these factors tend to lead to a reduction in the V_D/V_T. In PH, recruitment of the vascular bed is near maximal at rest, and so the physiological dead space can't be reduced through extra recruitment, and so V_D/V_T increases in PH.

13.2.2.9 Work Rate (WR)

This is normally described when using cycle ergometers, which use graded resistance measurements and ramp protocols are used to increase the WR gradually. It is normally reported in watts.

13.2.2.10 Respiratory Exchange Ratio (RER)

This is the ratio (VCO_2/VO_2) of carbon dioxide output to oxygen uptake and, primarily, a noninvasive way of assessing the food store being used by the body for energy production with:

RER = 0.7 - metabolism primarily of fats and carbohydrates

RER = 0.8 - metabolism primarily of proteins and carbohydrates

RER = 1.0 and above - metabolism primarily of carbohydrates

Most centres also use this measurement to determine whether a patient has exercised sufficiently (good effort): an RER greater than 1.1 indicates an effective (maximal) exercise stress [1].

13.2.2.11 Alveolar–Arterial Gradient (A-aO_2)

When CPEX or 6MWT is undertaken with blood gas analysis, then a measurement of A-aO_2 may be made, which assesses the difference in alveolar and arterial oxygenation and may give a clue to the cause of hypoxaemia.

A-aO_2 is calculated using arterial blood gas analysis and the following equation:

$$\left(\left(FiO_2\,\%/100\right)\times\left(P_{atm}-P_{H_2O}\right)\right)-\left(P_{aCO_2}/0.8-P_{aO_2}\right).$$

13.2.2.12 Ventilatory Reserve

A measure of ventilatory demand and capacity is assessed using the equation below:

$$\left(V_e\text{peak}/MVV\right)\times 100.$$

13.2.2.13 Ventilatory Efficiency Slope V_E/VCO_2

This is the amount of air required to eliminate 1 L of CO_2. Traditionally a high V_E/VCO_2 slope is associated with poor outcome in heart failure and non-cyanotic congenital heart disease. In cyanosed patients, this has to be interpreted with caution due to the increased ventilatory drive in cyanosis. The normal V_E/VCO_2 slope is <30, but this may be elevated in both heart failure and PH and should be interpreted in the context of the patient's underlying congenital diagnosis.

13.2.2.14 Oxygen Uptake Extraction Ratio (OUER)

This measurement is a ratio of the amount of oxygen consumed, VO_2, to its delivery, DO_2. This measurement can be very useful for assessing oxygen consumption/delivery: to maintain aerobic respiration in the setting of either increased demand or reduced supply, the OUER will increase normally to a maximum of around 70%, with obligatory anaerobic respiration after this.

This can be calculated using the formula:

$$\frac{SaO_2-SvO_2}{SaO_2}$$

A high OUER is normally a sign of oxygen delivery problems or increased demands. Unfortunately this value does require a central venous catheter for measuring central venous oxygen content, SvO_2 [12].

13.2.2.15 Oxygen Uptake Efficiency Slope (OUES)

The OUES reflects the effectiveness of oxygen extraction and utilisation and is derived from the logarithmic relation between VO_2 and minute ventilation [13]. It is effort-independent and is of particular value in the assessment of changes in exercise performance in individuals who are unable to complete a maximal exercise test. It has been shown to correlate with outcome in PH patients [14].

13.3 Diagnostic Utilities of CPEX/6MWT in Congenital Cardiac Patients with Pulmonary Hypertension

In the current UK guidelines, the baseline investigation of choice for PH is a 6MWT, while functional baseline assessment of the patient with CPEX is recommended more specifically for prognostication [15]. We discuss the performance of the two tests below.

13.3.1 6MWT

6MWT is a simple test that can be performed in most outpatient departments and requires a measured distance of 15–30 m, which a patient can walk in a shuttle fashion over 6 min, with total distance recorded by a member of staff (Fig. 13.1). In addition to the distance covered, pre and post blood pressure, heart rate and oxygen saturations should be recorded [16].

Aside from the recordings noted above, the patient should have their level of breathlessness recorded pre- and post-test, using the modified BORG scale (see also Chapter 20):

Score	Level of breathlessness
0	Nil
↓	↓
5	Strong breathlessness
↓	↓
10	Maximum

The 6MWT is cheap, simple and reproducible, with very few technical requirements. The walk area should be clearly marked and free from obstruction for the patient. If supplemental oxygen is needed during the test, the distance at which this is required, time and oxygen saturation should be noted. An example of a supervised test is shown in Fig. 13.1.

13.3.2 Cardiopulmonary Exercise Test

CPEX in congenital cardiac patients with PH has several indications. The most common of these include:

- Assessment of disease severity
- Serial monitoring/assessment of intervention response
- As part of exercise training prescriptions
- Recognition of undiagnosed PH prior to other investigations
- Assessing the contribution of different disease processes to exercise limitation

13.3.3 CPEX Protocol

CPEX studies are performed using a combination of ECG, blood pressure, oxygen saturation monitoring and breath-to-breath gas analysis while exercising on a treadmill or on cycle ergometer. Blood gas and lactate analysis may be added to the list of parameters analysed, but are usually not essential and are unpopular with patients. In a small numbers of mainly research-based papers, a cycle ergometer CPEX has been performed with right heart catheterisation [17].

Fig. 13.1 A patient performing a supervised 6MWT

13.3.3.1 Risks of CPEX

Standard exercise treadmill testing has been reported to have a risk of myocardial infarction or death of 1 per 2500 tests [18]. Compared to this, in the only published safety analysis of CPEX, from the HF-ACTION study, it has been shown that, in 2037 tests, there were no deaths and <0.5 per 1000 major cardiovascular events [19]. Moreover, there are no reported deaths or serious morbidity reported in association with exercise testing in several studies of children and adults with PH and congenital heart disease [20–22].

Absolute and relative contraindications to testing from the American Thoracic Society (ATS) and American College of Chest Physicians (ACCP) position paper are listed in Table 13.1 [23].

There are specific additional features in a congenital population which may pose particular safety concerns and these include:

Table 13.1 Absolute and relative contraindications to CPEX redrawn from the ATS/ACCP position paper

Absolute contraindications	Relative contraindications
Acute myocardial infraction	Left main coronary disease
Unstable angina	Moderate stenotic valvular disease
Uncontrolled arrhythmias with symptoms or compromise	Severe untreated hypertension, e.g. systolic BP greater than 200
Unexplained syncope	Hypertrophic cardiomyopathy
Active endocarditis	Significant pulmonary hypertension
Active myocarditis	Electrolyte imbalances
Severe symptomatic ventricular outflow obstruction	Advance or complicated pregnancy
Uncontrolled heart failure	Arrhythmias
Acute pulmonary embolus	High-grade atrioventricular block
Lower limb thrombosis	
Aortic dissection	
Inability to cooperate	
Respiratory failure	
Uncontrolled asthma	
Oxygen saturation less than 85% without available oxygen for test	
Disorders aggravated by exercise, e.g. infection	

- Patients with repaired coarctation of the aorta may develop significant exercise-induced hypertension, which may make completion of the test difficult.
- Some patients may have significant intracardiac shunts and may become symptomatic on exercise.

13.3.3.2 CPEX Equipment

It is beyond the scope of this short chapter to explain all the equipment used in the CPEX test and the appropriate calibration and maintenance required, but information on this is found in the ATS/ACCP position statement [23].

13.3.3.3 Treadmill Exercise Testing

Treadmill-based exercise tests are familiar to most physicians due to their traditional use in ischemia testing using the Bruce protocol [24]. Moreover, they can be useful for patients who are unable to cycle. In most departments, treadmill CPEX will involve a modified Balke protocol (or similar) where the treadmill speed is kept constant with a constant incremental increase in gradient which is usually well tolerated and allows the patient to approximate their maximum exercise potential [25].

13.3.3.4 Cycle Ergometer

Cycle ergometry is both our own preferred method and the preferred method for most CPEX testing centres worldwide and particularly in PH, where there are very few treadmill CPEX papers [26]. Similar to treadmill testing, incrementally increasing workloads can be introduced. With modern machines, one can utilise an unloaded stage at the start, whereby motor assistance can remove the internal resistance of the

chainset to allow for a very easy first stage for severely limited patients. This may be important in some complex congenital syndromes with skeletal abnormalities and in obese patients. Compared to treadmill testing, cycle ergometry tends to result in a VO_2 maximum value that can be up to 20% less than that achieved using the treadmill [27]; particularly in the PH setting, a variety of measurements were lower during cycle ergometry compared to a treadmill test [26]. One hypothesis for this is that, at higher levels of exercise, the *V-Q* gap increases [26].

In cases where there are lower limb problems that preclude a treadmill or standard cycle ergometry test, a hand cycle test can be used, though with the knowledge that it is likely that only a peak 70% of VO_2 max will be reached [28].

A comparison of cycle ergometry and treadmill CPEX testing is shown in Table 13.2 highlighting some of the reasons that make cycle ergometry dominant in clinical practice [23].

13.3.3.5 The CPEX Test

Prior to the CPEX test, the physician ordering the test should make clear whether they want the test conducted on or off medications that may affect the patient's performance such as beta-blockers or amiodarone. In our centre, we tell patients to have eaten at least 2 h prior to the test a light meal and to arrive in comfortable loose clothes and flat shoes for cycling (Fig. 13.2).

Table 13.2 A comparison of cycle ergometry versus treadmill CPEX

	Treadmill	Cycle ergometry
VO_2 Max	Higher	Lower
Work rate measurement	No	Yes
Blood gas measurement	Hard	Easier
Noise and artefacts	More	Less
Safety	Less Safe	Safer
Weight bearing for obese patients	Higher	Less
Leg muscle strength needed	Higher	Less

Fig. 13.2 A member of staff demonstrating the setup of our paediatric treadmill CPEX area

Table 13.3 Reasons to consider stopping a CPEX early

Ischaemic ECG changes with chest pain
Ventricular arrhythmias
Arrhythmias causing symptoms
High-grade atrioventricular block
Respiratory failure
Dizziness with pre-syncope
Confusion
Fall in BP greater than 20 mmHG
Severe hypertension greater than 220 mmHG systolic
Severe desaturation less than 80% with distress

Prior to the commencement of the test, a haemoglobin value should be noted, and full lung function testing should be performed at rest, including gas transfer; a blood gas may be taken with or without an arterial line being placed for sequential analysis.

Ideally, a CPEX protocol should be selected that allows for 8–12 min of exercise and leads to the test being stopped by the patient for whatever reason they describe (which can often be a valuable insight into the cause of their symptoms). Reasons to consider prematurely stopping a CPEX must be adapted to the clinical history of the patient and can include the reasons listed in Table 13.3.

The test should record continuous BP, oxygen saturations, ECG and all the measurements referenced above at exercise and into the recovery period. Many of the measurements will be compared to age-predicted values. The patient should be observed after the test, until their observations have returned to normal and they feel well enough to leave the department.

13.3.4 Maximal CPEX Tests in Patients with Congenital Cardiac Disease and Pulmonary Hypertension

To interpret the test, it is important to know that the patient has objectively given their best effort and, while no one value can demonstrate this, several features grouped together can help guide the physician; especially as we may not expect a patient with complex congenital cardiac disease to reach their age-predicted maximal values:

- RER greater than 1.1.
- Maximum predicted WR achieved.
- Maximum predicted heart rate achieved.
- Ventilatory limitation evidenced by a V_e/MVV greater than 20% or marked desaturation - greater than 5%.
- Peak predicted VO_2 reached.

An example of the typical nine panel report produced at the end of a CPEX test and post processed using commercially available software is shown in Fig. 13.3.

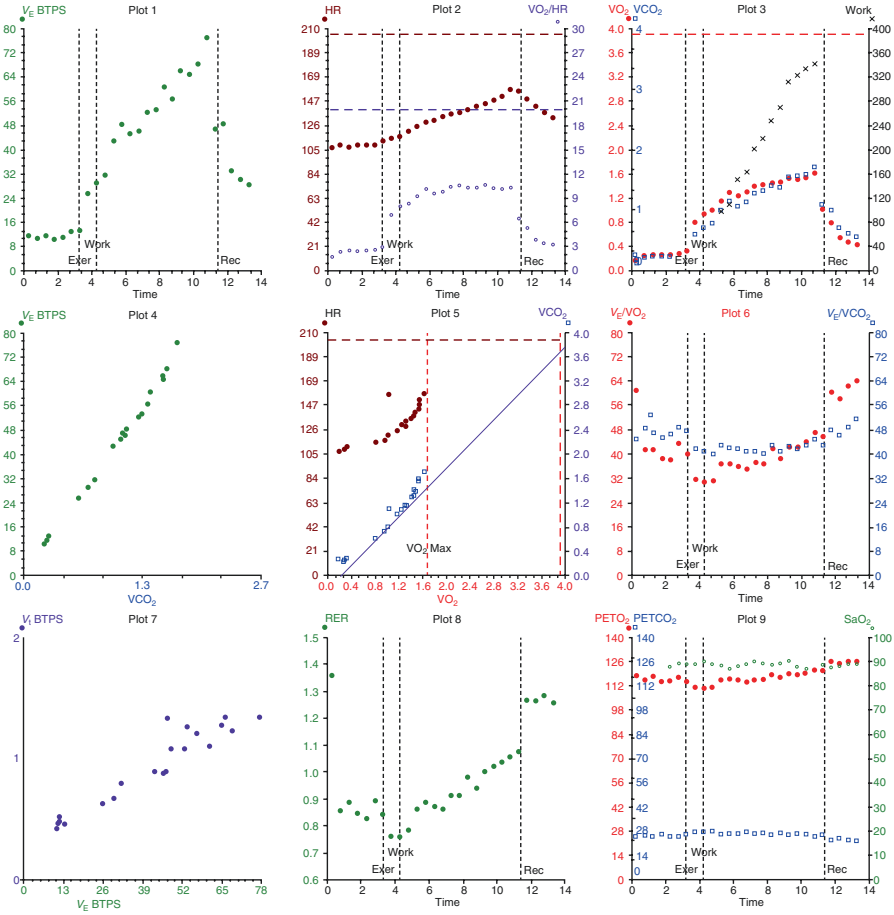

Fig. 13.3 A typical nine panel report used in most CPEX centres

13.4 Interpretation of CPEX/6MWT

Before undertaking a CPEX test or a 6MWT test, it is important to know that the exercise capacity of ACHD patients, even asymptomatic, may be reduced. This varies by diagnosis, with simple coarctation of the aorta having on average nearly twice the peak VO_2 of patients with congenitally corrected transposition of the great arteries [20]. In congenital heart disease, it is important to provide as much clinical information as possible to enable an accurate interpretation of the test results by the reporting physiologist.

13.4.1 Assessment of Disease Severity and Prognostication

One of the most common reasons for the performance of a CPEX in congenital cardiology and PH is assessment of disease severity, both from a prognostic point of view and as a functional assessment of the patient. There are very few studies on CPEX in PH–ACHD, and most of the prognostic information discussed below refers to PH studies, which have included congenital cardiac patients.

Probably the best known and most widely investigated marker of prognosis in PH secondary to congenital cardiac disease is peak VO_2. Peak VO_2 is reduced in congenital heart disease with PH and there is a well-established relationship between reduced peak VO_2 and reduced long term survival. Groepenhoff and colleagues have evaluated the use of CPEX to gain additional prognostic information above that available from 6MWT [29]. They found that CPEX parameters did predict survival in PH, but with only a marginal benefit over and above 6MWT. PH patients with a V_E/VCO_2 slope < 48, VO_2 peak > 13.2 ml/kg/min, ΔO_2 pulse > 3.3 mI/beat, or a 6MWT distance of 400m or above had a higher cumulative survival ($p< 0.05$). However, multivariable regression analysis demonstrated that only ΔO_2 pulse improved the univariate 6MWT prediction model [29]. We, like many centres, advocate the use of VO_2/WR plots, which have been shown to be clearly related to survival, with a suggested cut-off of 5.5 mL/min/watt [30].

The V_E/VCO_2 slope can be a useful prognostic marker in PH–ACHD as, with increasing PH, there is an increase in the *V-Q* mismatch, which leads to reduced arterial oxygen saturations and earlier lactate formation, triggering an increased ventilatory response and an elevation in the V_E/VCO_2 slope. This slope is calculated using linear regression of the V_E plotted against the VCO_2. Proposed cut-offs for the slope associated with a worse prognosis vary in PH–ACHD, with a figure of 51 reported in a paediatric study [31] and 55 for adults [30]; indeed, a markedly elevated slope seems to be associated with worse PH and a worse prognosis. In the overall congenital cardiac population (not just patients with PH), there is a strong link between V_E/VCO_2 slope and survival and has been found to be the most powerful single exercise predictor of mortality [32].

One of the newer markers of reduced survival in a series of patients with PH, including those with congenital cardiac disease, was a reduction in the inspiratory capacity (total lung capacity-functional residual capacity) at rest and during exercise of less than 89% of predicted [33]. This leads to a reduction in the ability of the patient to increase their V_T during exercise, reducing their ventilatory efficiency and increasing the V_D/V_T ratio.

Similarly, OUES in a mixed cohort of PH patients, has been shown to predict outcome with a cut-off of $\leq$0.56 L min^{-1} per log V_e [14].

The 6MWT is a much simpler investigation to perform than CPEX. Although the 6MWT has been used extensively for many years in patients with PH, most data have been derived from primary (now idiopathic) PH or studies of mixed aetiology, as opposed to just congenital heart disease. However, useful markers of disease severity have included:

- A 6MWT distance <322 m is associated with reduced survival [34]; a distance less than 165 m is associated with a low 1-year survival [35, 37].

- Arterial desaturation of greater than 10% is associated with a threefold increase in mortality [36] – though the validity of this in the context of ACHD with shunting is not known.

In a more recent study, Groepenhoff and colleagues found that a failure to improve 6MWT with treatment, failure to improve maximum heart rate by at least four beats, a failure of peak VO_2 to increase by 0.3 mL/min/kg or failure of O_2 pulse to increase by 1 mL/beat is associated with a poorer prognosis [38].

Overall, CPEX and 6MWT are very important in the assessment of disease severity and prognosis for patients with PH and form a key part of the assessment of patients with PH–ACHD. Prognostication is discussed in more detail in Chapter 21.

13.4.2 Serial Monitoring and Assessment of the Response to Treatment

After assessment of disease severity, serial monitoring of disease state and the response to treatment forms the greatest proportion of our CPEX/6MWT workload.

Serial monitoring by 6MWT is a simple task and is often incorporated into the outpatient visit and documented in our institution alongside other observations, such as blood pressure and pulse rate. Analysis of the trend in 6MWT distance provides a clinician with an easy way to monitor exercise capacity over the years and alert them early to deterioration, and an increased mortality risk in the PH–ACHD cohort [39]. Shunting can also be assessed using the 6MWT, assessing resting and peak exercise saturations in Eisenmenger patients, which relate to symptoms and survival [32]. One of the most common indications of the 6MWT is to assess the response to treatment and help diagnose objectively whether a patient is responding adequately. 6MWT can be used to both assess formally the distance achieved by the patient on treatment and also their level of breathlessness while exercising; these trends have proved very valuable in many PH trials [40].

CPEX testing can also be used for trend analysis, but in a more detailed fashion, assessing changes in physiology or response to treatment. Changes in peak VO_2 [41] and reduction in the steepness of the V_E/VCO_2 slope have been used to indicate reduced PAP [42].

13.4.3 Diagnosis of Unrecognised Pulmonary Hypertension in ACHD

Although it is not possible to make a precise diagnosis of PH solely on the basis of data obtained from CPEX or 6MWT, information can be gleaned from these tests, which may suggest PH. Indeed, PH may be missed in noninvasive testing, such as echocardiography, due to poor image quality or when a patient is not known to have congenital cardiac disease.

When compared to normal controls, patients with congenital heart disease often have a reduced peak VO_2 , VO_2/dWR, O_2 pulse, anaerobic threshold and an increase

in the heart rate-VO_2 slope. A variety of factors may suggest superimposed PH. These may be linked to impaired gas exchange, left-sided filling and red cell transit time, though differentiating reduced cardiac output due to the primary cardiac abnormality from PH-related impairment can be impossible.

When the PAP rises, there is an elevation in the V_E/VCO_2 due to an increase in physiological dead space and a reduction in the $PetCO_2$, both of which may suggest PH. This can be assessed quantitatively by measurement of PAP and pulmonary vascular resistance using right heart catheterisation. As compensatory mechanism in PH, there is often an increase in respiratory frequency, with a corresponding reduction in tidal volume and poor gas exchange, reflected in an increase in V_D/V_T.

OUER has been shown to be valuable in assessing exercise intolerance in heart failure with a preserved ejection fraction (HF-PEF) [43]. In PH, calculation of OUER may prove useful when the cause of breathlessness is unclear, as it tends to be lower compared to systolic and diastolic heart failure patients [12].

If the CPEX is being undertaken using arterial blood gas analysis, then A-aO_2 can be calculated and may be significantly increased due to increasing ventilation/perfusion mismatch; this can again suggest PH in the setting of ACHD. As PH worsens, there is a decrease in the transit time of red cells through the pulmonary vasculature; this leads to hypoxaemia and may show up in a CPEX or 6MWT as desaturation [44].

Finally, exercise-induced PH or progressive PH may be uncovered in ACHD patients with known or unknown atrial communications because exercise increases venous return and leads to an increase in right atrial pressure, which can exceed left atrial pressure due to increasing pulmonary vascular resistance. This leads to right to left shunting and desaturation, which in turn leads to a sharp fall in $PetCO_2$ and a more rapid rise in V_e/VO_2 compared to V_e/VCO_2 due to shunting of deoxygenated blood to the systemic circulation [45].

All these factors need to be assessed in context in a patient with PH–ACHD, as interpretation of a single value in patients who can have multiple level shunts and both pulmonary vascular and airways disease can be extremely difficult, even for experts.

13.4.4 Differentiating the Cause of Exercise Limitation: Other Causes of Limitations

Patients with PH–ACHD may have reduced exercise tolerance for many reasons, including their underlying primary cardiac disorder, PH and associated complications or simple physical deconditioning. Exercise testing can help guide the physician in their assessment and help to identify which factor may be amenable to modification and, thus, improvement in the patient's quality of life. Above, we have

discussed some of the specific changes seen in PH, and we will now look at some other common conditions, which may coexist in the PH–ACHD patient and may cause exercise limitation.

13.4.4.1 Deconditioning

One area where exercise testing utilising CPEX has proven of immense value is when assessing patients (including PH-ACHD) for deconditioning as an important component of their exercise intolerance. Indeed, we know that ACHD patients exercise less than their peers, and so deconditioning is a very real problem for many [46]. Using CPEX, there a variety of factors which may help identify deconditioning, such as:

- Poor effort, as evidenced by RER less than 1.1
- Failure for VO_2 to plateau and reach max
- Leftward shift in the HR-VO_2 curve
- Reduced O_2 pulse
- Low anaerobic threshold

Some of these features, such as low anaerobic threshold, may be seen in mild disease states, and it may be that deconditioning can only be confirmed with an appropriate exercise programme and repeat testing. This has proved very useful for many of our ACHD patients.

13.4.4.2 Obesity

Obesity is common in congenital heart disease and can be a major cause of exertional limitation. The exercise consequences of obesity may be observed on CPEX as an increased VO_2 at a relatively low WR in combination with an elevated body mass index. It can be helpful to interpret low or low normal peak VO_2 in light of both actual and ideal (lean) weight. This can help clarify the underlying influence of obesity.

13.4.4.3 Thoracic Disease

In congenital cardiac patients, there are a wide variety of associated syndromes, which may be associated with abnormal lung function, e.g. due to interstitial lung disease or skeletal/thoracic deformities causing restrictive lung defects. This includes the effect of previous cardiac surgery, especially previous thoracotomy. Thoracotomy in early childhood (for the creation of a systemic to pulmonary artery shunt, arterial duct ligation or repair of aortic coarctation), can lead to the development of scoliosis, with consequent respiratory compromise. Some forms of cardiac surgery can also be complicated by damage to the phrenic nerve with unilateral diaphragmatic paralysis. The first step in assessing these patients, as part of the CPEX, is for them to have full lung function testing with gas analysis, whereby restrictive and obstructive lung defects and gas diffusion abnormalities can be identified.

During exercise, VO_2 and VO_2/dWR will be reduced in the context of PH–ACHD; moreover, many of the changes described in other forms of PH are also present in PH-ACHD, such as an increase in V_e/VCO_2 and V_D/V_T ratio, and are consistent with poor ventilatory efficiency. One parameter that can be helpful in distinguishing between the effect of PH and that of thoracic abnormalities is the Ventilatory Threshold (also known as the anaerobic threshold). This is often reduced in thoracic disease and is less affected by PH.

13.4.5 Exercise Training

CPEX is a useful tool for assessing the effects of exercise training. This is also covered in Chapter 20. The benefits of exercise training can also be evaluated quantitatively using sequential 6MWT distance measurement in PH-ACHD patients. CPEX is also extremely valuable in recommending exercise training and should be used to demonstrate an improvement in functional ability and prognostic markers, such as peak VO_2 [22].

Conclusion

Exercise testing using CPEX and the 6MWT is extremely useful in the diagnosis of PH–ACHD, is assessing disease severity and response to treatment, as well as identifying other factors contributing to exercise limitation. While CPEX can provide valuable information on the presence and severity of PH, it should be interpreted in the context of the clinical picture and other non-invasive and invasive investigation in patients with congenital heart disease.

References

1. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF et al (2010) Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation 122(2):191–225
2. Parikh KS, Rajagopal S, Arges K, Ahmad T, Sivak J, Kaul P et al (2015) Use of outcome measures in pulmonary hypertension clinical trials. Am Heart J 170(3):419.e3–429.e3
3. Warburton DE, Haykowsky MJ, Quinney HA, Blackmore D, Teo KK, Humen DP (2002) Myocardial response to incremental exercise in endurance-trained athletes: influence of heart rate, contractility and the Frank-Starling effect. Exp Physiol 87(5):613–622
4. Stickland MK, Butcher SJ, Marciniuk DD, Bhutani M (2012) Assessing exercise limitation using cardiopulmonary exercise testing. Pulm Med 2012:824091
5. Tamhane RM, Johnson RL Jr, Hsia CC (2001) Pulmonary membrane diffusing capacity and capillary blood volume measured during exercise from nitric oxide uptake. Chest 120(6):1850–1856
6. Warnes CA (2006) Transposition of the great arteries. Circulation 114(24):2699–2709
7. Albouaini K, Egred M, Alahmar A, Wright DJ (2007) Cardiopulmonary exercise testing and its application. Heart 93(10):1285–1292
8. Oliveira RB, Myers J, Araujo CG (2011) Long-term stability of the oxygen pulse curve during maximal exercise. Clinics (Sao Paulo) 66(2):203–209

9. Wasserman K, Beaver WL, Whipp BJ (1990) Gas exchange theory and the lactic acidosis (anaerobic) threshold. Circulation 81(1 Suppl):II14–II30
10. Jones NL, Robertson DG, Kane JW (1979) Difference between end-tidal and arterial PCO_2 in exercise. J Appl Physiol Respir Environ Exerc Physiol 47(5):954–960
11. Mohsenifar Z, Ross MD, Waxman A, Goldbach P, Koerner SK (1985) Changes in distribution of lung perfusion and ventilation at rest and during maximal exercise. Chest 87(3):359–362
12. Tolle J, Waxman A, Systrom D (2008) Impaired systemic oxygen extraction at maximum exercise in pulmonary hypertension. Med Sci Sports Exerc 40(1):3–8
13. Baba R (2000) The oxygen uptake efficiency slope and its value in the assessment of cardiorespiratory functional reserve. Congest Heart Fail 6(5):256–258
14. Ramos RP, Ota-Arakaki JS, Alencar MC, Ferreira EV, Nery LE, Neder JA (2014) Exercise oxygen uptake efficiency slope independently predicts poor outcome in pulmonary arterial hypertension. Eur Respir J 43(5):1510–1512
15. National Pulmonary Hypertension Centres of the UK, Ireland (2008) Consensus statement on the management of pulmonary hypertension in clinical practice in the UK and Ireland. Thorax 63(Suppl 2):ii1–ii41
16. Laboratories ATSCoPSfCPF (2002) ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 166(1):111–117
17. Tolle JJ, Waxman AB, Van Horn TL, Pappagianopoulos PP, Systrom DM (2008) Exercise-induced pulmonary arterial hypertension. Circulation 118(21):2183–2189
18. Rodgers GP, Ayanian JZ, Balady G, Beasley JW, Brown KA, Gervino EV et al (2000) American College of Cardiology/American Heart Association Clinical Competence statement on stress testing: a report of the American College of Cardiology/American Heart Association/American College of Physicians—American Society of Internal Medicine Task Force on Clinical Competence. J Am Coll Cardiol 36(4):1441–1453
19. Keteyian SJ, Isaac D, Thadani U, Roy BA, Bensimhon DR, McKelvie R et al (2009) Safety of symptom-limited cardiopulmonary exercise testing in patients with chronic heart failure due to severe left ventricular systolic dysfunction. Am Heart J 158(4 Suppl):S72–S77
20. Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS et al (2005) Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. Circulation 112(6):828–835
21. Abumehdi MR, Wardle AJ, Nazzal R, Charalampopoulos A, Schulze-Neick I, Derrick G et al (2016) Feasibility and safety of cardiopulmonary exercise testing in children with pulmonary hypertension. Cardiol Young 26(6):1144–1150
22. Becker-Grunig T, Klose H, Ehlken N, Lichtblau M, Nagel C, Fischer C et al (2013) Efficacy of exercise training in pulmonary arterial hypertension associated with congenital heart disease. Int J Cardiol 168(1):375–381
23. American Thoracic S (2003) American College of Chest P. ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 167(2):211–277
24. Bruce RA, McDonough JR (1969) Stress testing in screening for cardiovascular disease. Bull N Y Acad Med 45(12):1288–1305
25. Nagle FJ, Balke B, Naughton JP (1965) Gradational step tests for assessing work capacity. J Appl Physiol 20(4):745–748
26. Valli G, Vizza CD, Onorati P, Badagliacca R, Ciuffa R, Poscia R et al (2008) Pathophysiological adaptations to walking and cycling in primary pulmonary hypertension. Eur J Appl Physiol 102(4):417–424
27. Miyamura M, Honda Y (1972) Oxygen intake and cardiac output during treadmill and bicycle exercise. J Appl Physiol 32(2):185–188
28. Martin TW, Zeballos RJ, Weisman IM (1991) Gas exchange during maximal upper extremity exercise. Chest 99(2):420–425
29. Groepenhoff H, Vonk-Noordegraaf A, Boonstra A, Spreeuwenberg MD, Postmus PE, Bogaard HJ (2008) Exercise testing to estimate survival in pulmonary hypertension. Med Sci Sports Exerc 40(10):1725–1732

30. Ferreira EV, Ota-Arakaki JS, Ramos RP, Barbosa PB, Almeida M, Treptow EC et al (2014) Optimizing the evaluation of excess exercise ventilation for prognosis assessment in pulmonary arterial hypertension. Eur J Prev Cardiol 21(11):1409–1419
31. Rausch CM, Taylor AL, Ross H, Sillau S, Ivy DD (2013) Ventilatory efficiency slope correlates with functional capacity, outcomes, and disease severity in pediatric patients with pulmonary hypertension. Int J Cardiol 169(6):445–448
32. Dimopoulos K, Okonko DO, Diller GP, Broberg CS, Salukhe TV, Babu-Narayan SV et al (2006) Abnormal ventilatory response to exercise in adults with congenital heart disease relates to cyanosis and predicts survival. Circulation 113(24):2796–2802
33. Richter MJ, Tiede H, Morty RE, Voswinckel R, Seeger W, Schulz R et al (2014) The prognostic significance of inspiratory capacity in pulmonary arterial hypertension. Respiration 88(1):24–30
34. Miyamoto S, Nagaya N, Satoh T, Kyotani S, Sakamaki F, Fujita M et al (2000) Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. Am J Respir Crit Care Med 161(2 Pt 1):487–492
35. Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS et al (2010) Predicting survival in pulmonary arterial hypertension: insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management (REVEAL). Circulation 122(2):164–172
36. Paciocco G, Martinez FJ, Bossone E, Pielsticker E, Gillespie B, Rubenfire M (2001) Oxygen desaturation on the six-minute walk test and mortality in untreated primary pulmonary hypertension. Eur Respir J 17(4):647–652
37. Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Herve P et al (2002) Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol 40(4):780–788
38. Groepenhoff H, Vonk-Noordegraaf A, van de Veerdonk MC, Boonstra A, Westerhof N, Bogaard HJ (2013) Prognostic relevance of changes in exercise test variables in pulmonary arterial hypertension. PLoS One 8(9):e72013
39. Blok IM, van Riel AC, Schuuring MJ, Duffels MG, Vis JC, van Dijk AP et al (2015) Decrease in quality of life predicts mortality in adult patients with pulmonary arterial hypertension due to congenital heart disease. Neth Hear J 23(5):278–284
40. D'Alto M, Romeo E, Argiento P, Sarubbi B, Santoro G, Grimaldi N et al (2012) Bosentan-sildenafil association in patients with congenital heart disease-related pulmonary arterial hypertension and Eisenmenger physiology. Int J Cardiol 155(3):378–382
41. Wensel R, Opitz CF, Ewert R, Bruch L, Kleber FX (2000) Effects of iloprost inhalation on exercise capacity and ventilatory efficiency in patients with primary pulmonary hypertension. Circulation 101(20):2388–2392
42. Ting H, Sun XG, Chuang ML, Lewis DA, Hansen JE, Wasserman K (2001) A noninvasive assessment of pulmonary perfusion abnormality in patients with primary pulmonary hypertension. Chest 119(3):824–832
43. Williams RG, Pearson GD, Barst RJ, Child JS, del Nido P, Gersony WM et al (2006) Report of the National Heart, Lung, and Blood Institute working group on research in adult congenital heart disease. J Am Coll Cardiol 47(4):701–707
44. Glaser S, Noga O, Koch B, Opitz CF, Schmidt B, Temmesfeld B et al (2009) Impact of pulmonary hypertension on gas exchange and exercise capacity in patients with pulmonary fibrosis. Respir Med 103(2):317–324
45. Sun XG, Hansen JE, Oudiz RJ, Wasserman K (2002) Gas exchange detection of exercise-induced right-to-left shunt in patients with primary pulmonary hypertension. Circulation 105(1):54–60
46. Dua JS, Cooper AR, Fox KR, Graham SA (2007) Physical activity levels in adults with congenital heart disease. Eur J Cardiovasc Prev Rehabil 14(2):287–293

Cardiac Catheterization

14

Massimo Chessa

Abbreviations

PH	Pulmonary hypertension
RHC	Right heart catheterisation

14.1 Introduction

Right heart catheterization (RHC) is required to confirm the diagnosis of pulmonary hypertension (PH) and pulmonary arterial hypertension (PAH), to assess the severity of the haemodynamic impairment and to test the vasoreactivity of the pulmonary circulation (Table 14.1) [1–3].

Hoeper et al. [4] reported on a multicentre 5-year retrospective and 6-month prospective evaluation of serious adverse events in patients with PH undergoing right heart catheterization, with or without pulmonary vasoreactivity testing or pulmonary angiography. When performed in experienced centres, RHC in patients with PH appears to be associated with a low morbidity (1.1%) and mortality (0.055%). Full right and left cardiac catheterization is usually required in patients with congenital heart disease (CHD) and can be more challenging due to anatomic issues and multiple previous procedures.

The variables that must be recorded and calculated during RHC are summarized in Table 14.2.

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Table 14.1 Recommendations for right heart catheterization, according to the international pulmonary hypertension guidelines [1]

Statement	Class of recommendation	Level of evidence
RHC is indicated in all patients with pulmonary arterial hypertension to confirm the diagnosis and to evaluate the severity and when PAH specific drug is considered	I	C
RHC should be performed for confirmation of efficacy of pulmonary arterial hypertension-specific drug therapy	IIa	C
RHC should be performed for confirmation of clinical deterioration and as baseline for the evaluation of the effect of treatment escalation and/or combination therapy	IIa	C

RHC right heart catheterization

Table 14.2 Essential data to be acquired/calculated during invasive haemodynamic assessment

Parameters measured	• Heart rate, haemoglobin concentration, height and weight
	• Oxygen saturations (high and low SVC, IVC, RA, RV, PA, SA)
	• When the patient is on oxygen with an $FiO_2 > 30\%$, pO_2 is also required in some or all of the above sites
	• Oxygen consumption (VO_2): measured or extrapolated from nomograms
	• Right atrial pressure
	• Right ventricular pressure
	• Pulmonary artery pressure
	• Pulmonary arterial wedge pressure, or left atrial pressure, or left ventricular end-diastolic pressure
	• Systemic arterial blood pressure
	• Response to acute vasodilator, when indicated (in iPAH or PAH–CHD with a L–R shunt to assess operability)
Parameters calculated	• Body surface area
	• Mixed venous saturations
	• Cardiac output/index or pulmonary (Q_p) and systemic (Q_s) blood flow in patients with a shunt
	• Q_p/Q_s ratio
	• Pulmonary vascular resistance (PVR)
	• Systemic vascular resistance (SVR)
	• Pulmonary-to-systemic resistance ratio (PVR/SVR)

IVC inferior vena cava, *PA* pulmonary artery, *RA* right atrium, *RV* right ventricle, *SA* systemic artery, *SVC* superior vena cava, *iPAH* idiopathic pulmonary arterial hypertension

14.1.1 How to Perform a Cardiac Catheter

Cardiac catheterization in CHD patients is usually performed in the catheter lab, under local anaesthesia. The most frequent venous access is the femoral, jugular, arm (basilica or cephalic) or, less frequently, subclavian vein. Vascular access problems are not infrequent in adult congenital heart disease (ACHD), due to multiple previous catheterization procedures or anatomy (e.g. left atrial isomerism with azygos continuation of the inferior vena cava (IVC)). Therefore, unusual or multiple vascular accesses may be needed in certain patients [5].

Different catheters can be used to reach the heart chambers and blood vessels, where blood samples can be taken and pressures can be measured. Ideally, all blood samples should be obtained simultaneously; if contaminated by an air bubble or not immediately analysed, errors in measurement may occur. It is important to remember that oximeters become less accurate in measuring oxygen saturations when haemoglobin concentration is above 20 g/dL; in this situation, it may be better to send samples to blood gas analysis [5, 6].

Blood samples are best acquired with the patient breathing spontaneously room air, or ventilated with air or a gas mixture containing no more than 30% oxygen ($FiO_2 < 30\%$). If oxygen-rich gas is being given (>30% oxygen), then the saturations alone are not enough to provide an accurate estimation of pulmonary blood flow, as a significant amount of oxygen may be present in dissolved form, especially in the pulmonary venous sample. The arterial and pulmonary saturations are estimated by direct collection of samples. If the pulmonary veins cannot be reached (e.g. through an atrial septal defect), they may be assumed to have oxygen saturation values of 98% (if the patients is not receiving supplemental oxygen and has no significant parenchymal lung disease or intrapulmonary shunts). The left atrial saturation can be assumed to be equal to that in the pulmonary veins, provided there is no right-to-left shunt at atrial level causing systemic desaturation [5, 7]. The calculation of systemic blood flow (systemic cardiac output, Q_s) requires the measurement of mixed venous saturation (MVS). A value intermediate between superior vena cava (SVC) and IVC may be used to estimate MVS. The following formula is often utilized:

$$MVS = \frac{3 \times SVC + 1 \times IVC}{4}.$$

The right atrial saturations may be used as a surrogate of MVS in the absence of an atrial septal defect. Pulmonary arterial saturations may be used as a surrogate of MVS if there is no evidence of a shunt. It is important to remember that IVC saturation varies depending on where the sample is obtained: the ideal sampling site is at the level of the diaphragm, to ensure that hepatic venous blood is taken into account. In the presence of a shunt and/or tricuspid regurgitation causing regurgitation of blood into the IVC, many operators will use high SVC saturations as MVS, because it has been demonstrated that MVS approximates more closely SVC than IVC saturations [5, 7].

14.1.2 Estimation of Pulmonary Blood Flow and Cardiac Output [6–10]

When all the saturations have been collected, systemic (Q_s) and pulmonary flow (Q_p) and their ratio (Q_p/Q_s) can be calculated. The most common methods for obtaining these are thermodilution and the method conceived by Adolph Fick (Fick method). Both are based on assumptions and have limitations.

14.1.2.1 The Thermodilution Method

First introduced in the 1950s, the principle of thermodilution determines the rate and extent of thermal changes in the bloodstream after upstream injection of a fixed volume of fluid at a set temperature. This method is valid when no shunt is present. A special balloon-tipped floatation catheter is placed in the pulmonary artery, which has a thermistor mounted on its distal end and a proximal port opening into the right atrium. A small, predefined amount (10 cm^3) of normal saline or dextrose solution is injected rapidly into the right atrium. A cardiac chamber (right ventricle) should be interposed between the injection site and the sampling site to allow complete mixing of the solution with blood. Changes in blood temperature are recorded by the thermistor, and the rate and extent of temperature change is proportional to the blood flow within the right heart. The procedure should be repeated several times, and three consecutive estimates should be taken and averaged. There should be less than a 10% variation between the three samples [5].

14.1.2.2 The Fick Method

The most commonly used method for calculating Q_p and Q_s in congenital cardiology is the one described by Adolph Fick in 1870. The basic principle of the Fick method is that flow is proportional to the difference in concentration of an indicator (in our case oxygen) in the blood that enters and leaves an organ (in our case the lungs) during steady state. Therefore, by calculating pulmonary arterial and pulmonary venous oxygen content, together with oxygen consumption, one can calculate pulmonary blood flow using the following formula called *the Fick equation*. Flow calculations based on Fick's principle can be applied to both pulmonary and systemic blood flows:

$$Q_p\left(\frac{\text{L}}{\text{min}}\right) = \frac{VO_2\left(\frac{\text{L}}{\text{min}}\right)}{PVO_2 \text{ content} - PAO_2 \text{ content}}$$

$$Q_s\left(\frac{\text{L}}{\text{min}}\right) = \frac{VO_2\left(\frac{\text{L}}{\text{min}}\right)}{AoO_2 \text{ content} - MVO_2 \text{ content}}$$

where VO_2 = oxygen consumption, PVO_2 content = pulmonary venous oxygen content, PAO_2 content = pulmonary arterial oxygen content, AoO_2 content = aortic oxygen content and MVO_2 content = mixed venous oxygen content.

Oxygen consumption (VO_2) can be measured directly (direct Fick method) or extrapolated from readily available tables (indirect Fick method, Appendix 1). Indirect Fick is significantly less accurate than direct Fick, but despite this, it is widely used. In the ideal setting, VO_2 should be measured rather than assumed. VO_2 can be measured, using a traditional hood: the process involves a gas pump that extracts all exhaled air and passes it through a mixing system, which measures oxygen content. The difference between inhaled oxygen content and exhaled oxygen content, with a known flow by the pump, enables estimation of VO_2. This assumes that no exhaled air is lost, that mixing is effective and that volume of exhaled air equals volume of inhaled. There are modern indirect calorimeters that can be used for this purpose (e.g. CCM Express®) [10].

The denominator of the Fick equation is the arteriovenous oxygen content difference across an organ (the lung or systemic circulation). To calculate the arterial and venous oxygen content (mL O_2/L), we need to know the blood's oxygen-carrying capacity: this is the maximum amount of oxygen that either an arterial or venous sample can bind and can be calculated using the following formula:

$$\mathrm{O_2\ carrying\ capacity}\left(\frac{mL\ O_2}{\mathrm{L}}\right) = Hb\left(\frac{g}{\mathrm{L}}\right)\times 1.39\left(\frac{mL\ O_2}{gHb}\right)$$

Alternative values of 1.34 and 1.36 instead of 1.39 have also been used.

The oxygen content of the blood is the amount of oxygen in that specific sample (either arterial or venous) and can be estimated by the following formulas [9, 10]:

$$\mathrm{Arterial\ O_2\ content}\left(\frac{mL\ O_2}{\mathrm{L}}\right) = \mathrm{O_2\ carrying\ capacity}\left(\frac{mL\ O_2}{\mathrm{L}}\right)\times \mathrm{SatO_{2\ arterial}}(\%)$$

$$\mathrm{Venous\ O_2\ content}\left(\frac{mL\ O_2}{\mathrm{L}}\right) = \mathrm{O_2\ carrying\ capacity}\left(\frac{mL\ O_2}{\mathrm{L}}\right)\times \mathrm{SatO_{2\ venous}}(\%)$$

where $\mathrm{SatO_{2\ arterial}}$ is arterial O_2 saturation and $\mathrm{SatO_{2\ venous}}$ is venous O_2 saturation.

Finally, the effective pulmonary blood flow (Q_{ep}) is the amount of deoxygenated blood pumped to the lungs:

$$Q_{ep}\left(\frac{\mathrm{L}}{\mathrm{min}}\right) = \frac{VO_2\left(\frac{\mathrm{L}}{\mathrm{min}}\right)}{PVO_2\ \text{content} - MVO_2\ \text{content}}$$

$Q_{ep} = VO_2$/(pulmonary venous O_2 content – mixed venous O_2 content).

In a biventricular heart with no shunting, Q_{ep} is equivalent to Q_p.

Calculation of the pulmonary-to-systemic flow ratio (Q_p/Q_s) can estimate the magnitude of shunts, using the following equation:

$$Q_p / Q_s = \frac{\mathrm{SatO_{2\ Ao}} - \mathrm{SatO_{2\ MV}}}{\mathrm{SatO_{2\ PV}} - \mathrm{SatO_{2\ PA}}}$$

where $\mathrm{SatO_{2\ Ao}}$, $\mathrm{SatO_{2\ MV}}$, $\mathrm{SatO_{2\ PV}}$ and $\mathrm{SatO_{2\ PA}}$ are aortic, mixed venous, pulmonary venous and pulmonary arterial oxygen saturations.

A Q_p/Q_s between 1 and 1.5 is considered a small left-to-right shunt and of relatively small clinical consequence. A $Q_p/Q_s > 1.8$ indicates a large left-to-right shunt, while a $Q_p/Q_s < 1$ indicates a net right-to-left shunt [5].

14.1.3 Pressure Evaluation and Waveforms

Pressure changes within the cardiac chambers and vessels are generally recorded through membrane transducers transforming the pressure signal into an electrical signal, which is filtered, amplified, and displayed as a change in pressure over time.

The pressure transducer is outside the body, and the pressure waveform is transmitted to it through a column of fluid within the intravascular catheter and circuit. Table 14.3 contains tips for the accurate acquisition of intracardiac pressures (Fig. 14.1) [5].

Table 14.3 Tips for accurate pressure acquisition [5]

Step 1: check setup	Check transducer levelling, zeroing and calibration
	Select appropriate fluid-filled catheter (short, large bore, stiff, with side holes or end hole)
	Ensure connections are tight between catheter(s) and transducer(s); avoid fluid leakage
	Remove all air bubbles from the circuit
Step 2: acquisition	Assess the morphology of the acquired waves, closely correlating to the ECG. Remember to consider the patient's rhythm when you examine your waveforms Non-sinus rhythm can drastically alter not only atrial waveform morphology but also absolute ventricular pressures and systolic flows
	Check for artefacts that can distort waveform tracing (e.g. over- or under-damping)
	Check an arterial blood gas to confirm normocapnia and a normal pH and rule out respiratory pathology
	Measure pressures at end expiration
	Obtain pressure waveform data before injecting contrast or giving fluids. Avoid dehydrating the patient prior to the procedure

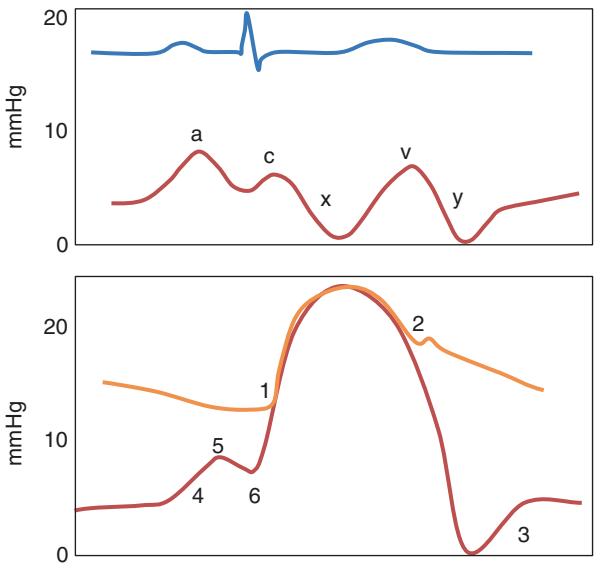

Fig. 14.1 *Top panel*, ECG and right atrial pressure waveform. *Bottom panel*, right ventricular (*red*) and pulmonary artery (*yellow*) waveforms. See text for explanation of annotation. Courtesy of Dr. K. Dimopoulos

14.1.3.1 The Right Atrium

Normal right atrial (RA) pressure is 2–8 mmHg.

The normal waveform has two major positive waves (*a* and *v*) and two negative descents (*x* and *y*). The *a* wave is generated from the pressure rise following atrial contraction and, hence, follows the *P* wave on the ECG by approximately 80 ms. It is normally the dominant wave but is absent in patients with atrial fibrillation. High *a* waves can occur when atrial emptying into the ventricle is restricted, e.g. with tricuspid (or right atrioventricular) valve stenosis or with a noncompliant right ventricular chamber.

The *x* descent occurs due to atrial relaxation and the downward motion of the atrioventricular junction during the early phase of ventricular systole. A *c* wave may occasionally be observed as a small positive deflection during early ventricular systole and interrupts the *x* descent, following the *a* wave by a time that equals the PR interval on the ECG. Accordingly, patients with first-degree atrioventricular block may have increased *c* waves. As right atrial relaxation continues and pressure declines after the *c* wave, the *x* descent is now termed *x′* [5, 6].

The positive *v* wave deflection is generated by passive venous filling of the atrium, while the tricuspid valve is closed, the peak of the wave occurring at the end of ventricular systole, which corresponds to the end of the *T* wave in the ECG. The *y* descent that follows reflects the fall in RA pressure when the atrioventricular valve opens and rapid emptying into the ventricle occurs.

Breathing affects the waveforms, especially in patients with lung disease: during inspiration, the chest expands and intrathoracic pressure becomes negative. This negative pressure is transmitted to the RA, and RA pressure falls during inspiration. Right atrial pressures are best taken at end expiration, avoiding Valsalva manoeuvres [5, 6].

14.1.3.2 The Right Ventricle

Normal right ventricular systolic pressure is 20–30 mmHg and end-diastolic 2–8 mmHg.

When the RV contracts and pressure within it exceeds that in the pulmonary artery (Fig. 14.1, point 1), the pulmonary valve opens and blood exits the chamber. This occurs in most instances immediately after the onset of the QRS complex on the ECG. Thereafter, pressure begins to fall, and when below the pulmonary arterial pressure, the pulmonary valve closes (Fig. 14.1, point 2). In diastole, there is an early and late ventricular filling positive deflection (Fig. 14.1, points 3 and 4), and when atrial contraction occurs, an *a* wave is visible on the ventricular waveform (Fig. 14.1, point 5). The end-diastolic pressure (Fig. 14.1, point 6) is the pressure just prior to ventricular contraction and falls within the QRS complex [5, 6].

14.1.3.3 The Pulmonary Artery

The normal PA systolic pressure is 17–32 mmHg, diastolic pressure is 4–13 mmHg and mean PA pressure ranges between 12 and 16 mmHg. International PH guidelines define PH as a mean PAP ≥ 25 mmHg and provide a classification of all the reasons for an elevated PAP pressure (see Chap. 2, [2, 5, 6]).

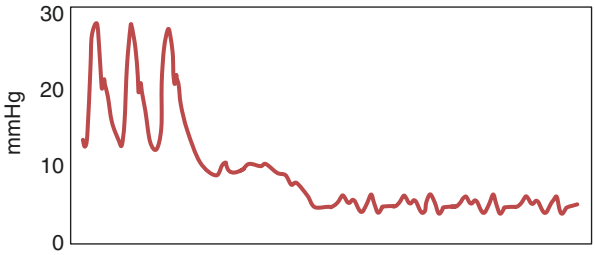

Fig. 14.2 Pulmonary artery to pulmonary capillary wedge pressure. Courtesy of Dr. K. Dimopoulos

14.1.3.4 The Pulmonary Capillary Wedge Pressure

Mean pulmonary capillary wedge (PCWP) values normally range between 2 and 12 mmHg.

The PCWP pressure approximates left atrial pressure. In the absence of pulmonary venous obstruction or mitral valve disease, PCWP reflects end-diastolic LV pressure.

Remember that an adequate recording of PCWP is essential for the diagnosing of PH due to left heart disease (post-capillary PH). To measure the PCWP, a balloon-tipped end-hole catheter is manoeuvred into a distal pulmonary artery and, with balloon inflation, occludes the vessel and blocks flow distal to the balloon (Fig. 14.2). When assessing the PCWP, the operator should be careful to avoid balloon overinflation, which can cause "overshooting" or "overwedging" and a falsely high PCWP pressure. Similar to RA pressure, the PCWP varies during the respiratory cycle [3, 5].

14.1.3.5 The Left Atrium

Normal mean left atrial pressure ranges between 5 and 12 mmHg.

The left atrial pressure waveform has essentially the same shape as that described for the right atrial pressure waveform, but the pressure is normally slightly higher, with a dominant *v* wave.

14.1.3.6 The Left Ventricle

Normal LV pressure is between 90 and 140 mmHg during systole and 5–12 mmHg at end-diastole.

The peak systolic pressure should equal that of the ascending aorta, unless there is subvalvular, valvular or supravalvular aortic stenosis: in this case, LV pressure exceeds that of the aorta. The LV end-diastolic pressure (LVEDP) is a simplified but valuable marker for LV diastolic function. When LVEDP is elevated (>12 mmHg), it suggests poor diastolic ventricular properties and/or LV failure. When a reliable PCWP or direct LA pressure cannot be obtained during RHC, operators should proceed to an arterial access and measure LVEDP [5, 10].

14.1.3.7 The Aorta

Normal aortic systolic pressure is 90–140 mmHg and diastolic pressure is 60–90 mmHg.

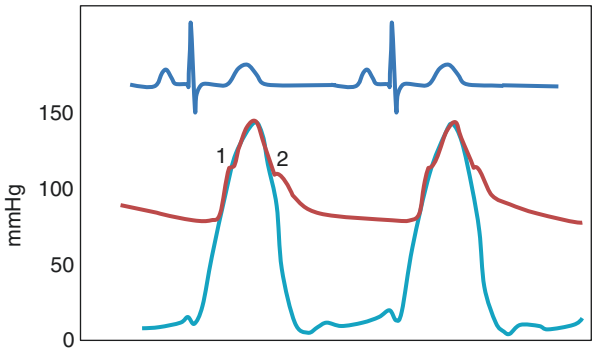

Fig. 14.3 Aortic (*red*) and left ventricular (*light blue*) pressure waveforms. Courtesy of Dr. K. Dimopoulos

The waveform has a rapid upstroke and a presystolic rise in pressure just before the aortic valve opens (anacrotic notch; see Fig. 14.3, point 1). Peak aortic pressure and a clear dicrotic notch (Fig. 14.3, point 2) caused by the closure of the aortic valve occur as pressure decays. Under normal conditions, peak LV and aortic pressure are equal. In older patients, increased systolic aortic pressure results from stiffness of the aorta and large arteries, whereas increased stroke volume may raise aortic pressure in adolescents and young adults [5].

14.1.4 Pulmonary and Systemic Vascular Resistance

Resistance calculations [3, 5, 6, 10] are most important when performing a cardiac catheter in a patient with PH, and especially patients with congenital heart defects.

The first concept we must remember is that resistance in a vascular circuit is equal to the difference in pressure between the two ends of the circuit, divided by the flow running through the circuit. For the right heart, the pulmonary vascular bed determines pulmonary vascular resistance (PVR) and can be calculated by the following equation:

$$PVR = \frac{\text{mean } PAP - \text{mean } LAP}{Q_{\text{p}}}$$

where PAP means pulmonary artery pressure, LAP means left atrial pressure and Q_{p} means pulmonary blood flow. When a direct mean LAP cannot be obtained, PCWP or LVEDP should be used instead.

Similarly, systemic vascular resistance (SVR) can be calculated as follows:

$$SVR = \frac{\text{mean } AoP - \text{mean } RAP}{Q_{\text{s}}}$$

where AoP means aortic pressure, RAP means right atrial pressure and Q_s means systemic blood flow.

Resistance units are commonly expressed as mmHg/L/min, also referred to as Wood units (WU).

Resistance units can also be expressed as dyne × s × cm^{-5}. To convert WU to dyne × s × cm, one must multiply by 80. if Q_p and Q_s are indexed for body surface area, indexed resistance is calculated and expressed as WU × m^2.

Haemodynamic definitions of pulmonary hypertension are reported in Part 1, Chap. 2.

14.1.5 Response to Acute Vasodilator

During cardiac catheterization in a patient with idiopathic PAH, heritable PAH and PAH associated with anorexigen use, vasoreactivity testing should be performed, to identify patients who may benefit from long-term therapy with calcium channel blockers (CCBs). Recommendations for vasoreactivity testing for this purpose are summarized in Table 14.4. Acute vasodilator challenge should only be performed with short-acting, safe and easy-to-administer drugs, with no or limited systemic effects (Table 14.5). A positive acute response (positive acute responder) is defined as a reduction of mean PAP ≥ 10 mmHg to reach an absolute value of mean PAP ≤ 40 mmHg with an increased or unchanged cardiac output (Q_p) [1, 3].

Table 14.4 Recommendations for vasoreactivity testing for the purpose of identifying patients with idiopathic PAH who may be candidates for calcium channel blocker therapy [1]

Statement	Class of recommendation	Level of evidence
Vasoreactivity testing is indicated in patients with IPAH, heritable PAH and PAH associated with anorexigen use to detect patients who can be treated with high doses of a CCB	I	C
A positive response to vasoreactivity testing is defined as a reduction of mean PAP ≥ 10 mmHg to reach an absolute value of mean PAP ≤ 40 mmHg with an increased or unchanged CO	I	C
Vasoreactivity testing should be performed only in referral centres	IIa	C
Vasoreactivity testing should be performed using nitric oxide as vasodilator	IIa	C
Vasoreactivity testing may be performed in other types of PAH)	IIb	C
Vasoreactivity testing may be performed using i.v. epoprostenol or i.v. adenosine	IIb	C
The use of an oral or i.v. CCB in acute vasoreactivity testing is not recommended	III	C
Vasoreactivity testing to detect patients who can be safely treated with high doses of a CCB is not recommended in patients with other PH groups (groups 2, 3, 4 and 5)	III	C

Table 14.5 The most commonly used agents for pulmonary vasoreactivity tests [1]

Drug	Route	Half-life	Dose range[a]	Increments[b]	Duration[c]
Epoprostenol	Intravenous	3 min	2–12 ng/kg/min	2 ng/kg/min	10 min
Adenosine	Intravenous	5–10 s	50–350 mg/kg/min	50 mg/kg/min	2 min
Nitric oxide	Inhaled	15–30 s	10–20 p.p.m	–	5 min[d]

[a]Initial dose and maximal tolerated dose suggested (maximal dose limited by side effects such as hypotension, headache, flushing, etc.)
[b]Increments of dose by each step
[c]Duration of administration on each step
[d]For NO, a single step within the dose range is suggested

Vasoreactivity testing is also performed in patients with CHD with borderline PVR, to assess reversibility and aid in the decision to repair or not a cardiac defect. Unfortunately, evidence-based thresholds for deciding operability are still lacking, and the value of vasoreactivity testing in this setting remains controversial and is extensively discussed elsewhere in this book (Chapters 1, 4 and 17).

Appendix 1

Charts of estimation of oxygen consumption [6]

Male patients													
Age	Heart rate (bpm)												
	50	60	70	80	90	100	110	120	130	140	150	160	170
3	155	159	163	167	171	175	178	182	186	190			
4	149	152	156	160	163	168	171	175	179	182	186		
6	141	144	148	151	155	159	162	167	171	174	178	181	
8	136	141	144	148	152	156	159	163	167	171	175	178	
10	130	134	139	142	146	149	153	157	160	165	169	172	176
12	128	132	136	140	144	147	151	155	158	162	167	170	174
14	127	130	134	137	142	146	149	153	157	160	165	169	172
16	125	129	132	136	141	144	148	152	155	159	162	167	
18	124	127	131	135	139	143	147	150	154	157	161	166	
20	123	126	130	134	137	142	145	149	153	156	160	165	
25	120	124	127	131	135	139	143	147	150	154	157		
30	118	122	125	129	133	136	141	145	148	152	155		
35	116	120	124	127	131	135	139	143	147	150			
40	115	119	122	126	130	133	137	141	145	149			

Female patients													
Age	Heart rate (bpm)												
	50	60	70	80	90	100	110	120	130	140	150	160	170
3	150	153	157	161	165	169	172	176	180	183			
4	141	145	149	152	156	159	163	168	171	175	179		
6	130	134	137	142	146	149	153	156	160	165	168	172	
8	125	129	133	136	141	144	148	152	155	159	163	167	
10	118	122	125	129	133	136	141	144	148	152	155	159	163
12	115	119	122	126	130	133	137	141	145	149	152	156	160
14	112	116	120	123	127	131	134	133	143	146	150	153	157
16	109	114	118	121	125	128	132	136	140	144	148	151	
18	107	111	116	119	123	127	130	134	137	142	146	149	
20	106	109	114	118	121	125	128	132	136	140	144	148	
25	102	106	109	114	118	121	125	128	132	136	140		
30	99	103	106	110	115	118	122	125	129	133	136		
35	97	100	104	107	111	116	119	123	127	130			
40	94	98	102	105	109	112	117	121	124	128			

References

1. Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G (2009) ESC Committee for Practice Guidelines (CPG). Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 30(20):2493–2537. doi:10.1093/eurheartj/ehp297
2. Badesch DB, Champion HC, Sanchez MA, Hoeper MM, Loyd JE, Manes A, McGoon M, Naeije R, Olschewski H, Oudiz RJ, Torbicki A (2009) Diagnosis and assessment of pulmonary arterial hypertension. J Am Coll Cardiol 54:S55–S66
3. Chemla D, Castelain V, Hervé P, Lecarpentier Y, Brimioulle S (2002) Haemodynamic evaluation of pulmonary hypertension. Eur Respir J 20:1314–1331
4. Hoeper MM, Lee SH, Voswinckel R, Palazzini M, Jais X, Marinelli A, Barst RJ, Ghofrani HA, Jing ZC, Opitz C, Seyfarth HJ, Halank M, McLaughlin V, Oudiz RJ, Ewert R, Wilkens H, Kluge S, Bremer HC, Baroke E, Rubin LJ (2006) Complications of right heart catheterization procedures in patients with pulmonary hypertension in experienced centers. J Am Coll Cardiol 48(12):2546–2552
5. Jones JPS, Benson L (2015) Hemodynamics: pressures and flows. In: Butera G, Chessa M, Eicken A, Thomson J (eds) Cardiac catheterization for congenital heart disease. Springer, Milan
6. Bergersen L, Foerster S, Marshall AC, Meadows J (eds) (2009) Congenital heart disease: the catheterization manual. Springer, New York
7. Rutledge J, Bush A et al (2010) Validity of the LaFarge equation for estimation of oxygen consumption in ventilated children with congenital heart disease younger than 3 years—a revisit. Am Heart J 160(1):109–114
8. Li J (2013) Accurate measurement of oxygen consumption in children undergoing cardiac catheterization. Catheter Cardiovasc Interv 81(1):125–132
9. Gossl M, Rihal CS (2010) Cardiac shunt calculations made easy: a case-based approach. Catheter Cardiovasc Interv 76(1):137–142
10. Wilkinson JL (2001) Haemodynamic calculations in the catheter laboratory. Heart 85(1):113–120

Part III

Management of Pulmonary Hypertension in Adult Congenital Heart Disease

15 Conservative Management and Recommendations for Pulmonary Arterial Hypertension Related to Congenital Heart Disease

Heba Nashat, Samantha J. Fitzsimmons, Carl Harries, Konstantinos Dimopoulos, and S. John Wort

Abbreviations

ACE	Angiotensin converting enzyme
ARB	Angiotensin receptor blocker
ASD	Atrial septal defect
BNP	B-type natriuretic protein
CHD	Congenital heart disease
CI	Cardiac Index
CO_2	Carbon dioxide
CPET	Cardiopulmonary exercise test
CT	Computed tomography
CTCA	Computed tomography coronary angiogram
CTPA	Computed tomography pulmonary angiogram
CVE	Cerebrovascular events
DCCV	Direct current cardioversion
ECG	Electrocardiogram
ERCP	Endoscopic retrograde cholangiopancreatography
ES	Eisenmenger syndrome
ET	Exercise training
ICD	Implantable cardioverter defibrillator

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ID	Iron deficiency
INR	International normalized ratio
iPAH	Idiopathic pulmonary arterial hypertension
LA	Left atrium
LV	Left ventricle
MCH	Mean corpuscular haemoglobin
MCV	Mean corpuscular volume
PA	Pulmonary artery
PAH	Pulmonary arterial hypertension
PH	Pulmonary hypertension
PRV	Polycythemia rubra vera
PVR	Pulmonary vascular resistance
QoL	Quality of life
RA	Right atrium
RAAS	Renin-angiotensin-aldosterone system
RAP	Right atrial pressure
RV	Right ventricle
RVAD	Right ventricular assist device
SVR	Systemic vascular resistance
TAPSE	Tricuspid annular plane systolic excursion
TOE	Transesophageal echocardiogram
VE	Minute volume
VF	Ventricular fibrillation
VO2	Volume of oxygen
VSD	Ventricular septal defect
VT	Ventricular tachycardia
WHO FC	World Health Organization functional class
6MWT	6 minute walk distance

15.1 Introduction

The incidence of pulmonary arterial hypertension (PAH) in congenital heart disease varies geographically, but, overall, up to 10% of adults with CHD may eventually develop PAH. PAH–CHD is a disease process that is the result of numerous pathomechanistic pathways affecting the pulmonary vascular bed and leading to a rise in pulmonary vascular resistance (PVR), right heart failure and premature death [1, 2]. Depending on the type of underlying defect or previous repair (timing and method used), patients can present with diverse anatomy and pathophysiology [3]. On one end of the spectrum are PAH patients who have small, insignificant shunt lesions and those with previous surgical or interventional repair of cardiac defects. These patients share clinical similarities to idiopathic PAH (iPAH). At the other end of the spectrum is Eisenmenger syndrome (ES). ES is characterized by pulmonary arterial pressure elevated to near-systemic levels with shunt reversal and cyanosis

[3, 4]. It is a multisystem disorder driven by slow progressive chronic hypoxemia and the persistence of a shunt, resulting in coagulation disorders, iron deficiency (ID) anaemia, renal dysfunction, hypertrophic osteoarthropathy, paradoxical emboli and heart failure. Differences between various types of PAH–CHD are not purely academic, but significantly impact on presentation, treatment and outcome [3, 5, 6].

There is growing evidence on the benefits of PAH therapies in the PAH–CHD population, which are now widely used by specialist services [7]. Despite the advances in pharmacotherapy, the morbidity and mortality of PAH–CHD remain high [2]. Moreover, the PAH–CHD population is quite heterogeneous with various subgroups posing different management challenges [3]. For example, patients with Down syndrome make up a large proportion of the Eisenmenger population and often present with early and more aggressive disease than their non-Down counterparts with equivalent lesions yet are underrepresented in the literature and tend to be more challenging in their management [8, 9].

Supportive measures, anticipation of potential systemic complications and avoidance of old unproven practices are as important as specific pharmacological therapy in PAH–CHD. Current guidelines recommend regular consultations with experienced physicians in the area of CHD and pulmonary hypertension (PH) [6, 10]. Routine considerations include adequate contraception, importance of endocarditis prophylaxis and up-to-date immunization against influenza and pneumococcal infections [11]. Pregnancy is contraindicated in women with PAH and is discussed in more detail in Chap. 19 [12]. Drug treatment, up until the era of PAH therapies, largely consisted of medication such as diuretics, anti-arrhythmics, digoxin, β-blockers and aldosterone antagonists, which will be discussed later in this chapter [7].

This chapter will cover the approach to conservative management of PAH–CHD, with a specific focus on ES.

15.2 Systemic Complications in PAH–CHD

The complications of PAH–CHD are variable and depend on the underlying heart defect, age, repair status and degree and direction of shunting (Fig. 15.1) [6]. Those who develop ES are typically cyanosed; the chronic hypoxemia, together with slow cardiac output and PAH, has significant multisystem effects (see also Chap. 3) [13–19]. A vast spectrum of signs and symptoms are encountered, including dyspnoea, fatigue, dizziness and headaches, with a high morbidity and mortality compared to the general population and CHD patients without PH [6, 15]. Cardiac arrhythmias and heart failure are important late complications and a frequent cause of death in these patients. While lung transplantation with shunt closure (if this is still present) or heart and lung transplantation is considered the definitive treatment for PAH–CHD, few patients are transplanted due to the scarcity of donors and multi-organ failure, which is common in later stages of the disease [20]. Therefore, alternative therapeutic options are needed to address the complications of PAH–CHD [7, 21].

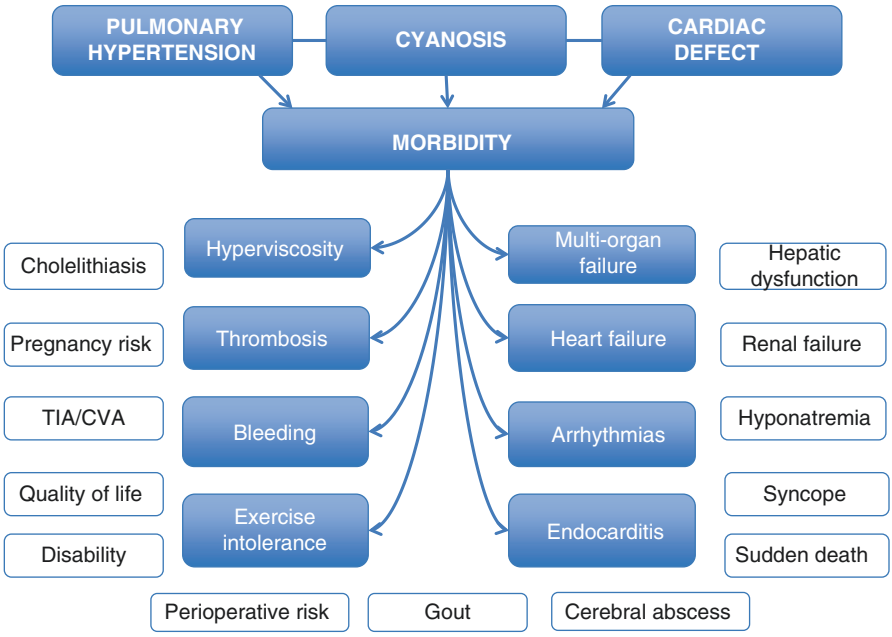

Fig. 15.1 Systemic complications of Eisenmenger syndrome. The vast spectrum of signs, symptoms and systemic complications encountered in Eisenmenger syndrome are related, not only to the presence of severe pulmonary hypertension but also the coexistence of significant cyanosis and the cardiac defect, which may be simple or complex [5]

15.2.1 Haematological Disorders

15.2.1.1 Erythrocytosis and Venesections

Secondary erythrocytosis due to increased erythropoietin production is a physiological response to chronic hypoxemia. The degree of cyanosis is inversely related to the red cell count: the lower the oxygen saturation, the higher the red cell count and haematocrit in iron-replete patients [13]. While an increase in haematocrit increases blood viscosity, the latter depends on several factors, which include red blood cell mass and morphology, aggregation and dispersion of blood cells, plasma viscosity, temperature and shear stress [22]. Erythrocytosis also leads to increased shear stress, which affects the balance between circulating vasodilators and vasoconstrictors [23]. Secondary erythrocytosis is an appropriate, adaptive response to chronic hypoxemia, and in turn results in increased blood viscosity, but rarely causes hyperviscosity symptoms. The symptoms of hyperviscosity in ES include headache, dizziness, visual disturbances, altered mental status, tinnitus and fatigue. They are non-specific and may overlap with other conditions, such as ID anaemia, heart failure and cerebral infection.

Prophylactic or routine venesections to maintain a haematocrit level within an arbitrary predetermined level (haematocrit <65%) for the prevention of cerebrovascular events or reduction of symptoms presumed due to hyperviscosity are

rarely required. Indeed, this is one of the major misconceptions in the management of patients with cyanotic CHD [24, 25]. Routine venesections can result in significant ID anaemia, impaired oxygen transport capacity and reduced exercise tolerance [22]. ID anaemia is common among patients with ES. If there is evidence of ID, especially when haemoglobin concentration is well below the level expected for the oxygen saturations, it should be treated with close monitoring of blood count to avoid an excessive increase in red cell count, which is, however, rare [26].

Distinction should be made between the secondary erythrocytosis encountered in Eisenmenger patients and the primary erythrocytosis typical of polycythemia rubra vera (PRV). The association between the latter and cerebrovascular events is well established, and treatment guidelines recommend routine venesections and/or the use of cytoreductive therapy to maintain a haematocrit below 45%, hence reducing the risk of thrombosis in patients with PRV. The risk of cerebrovascular events in patients with PRV is increased because of multiple factors, including thrombocytosis, impaired fibrinolytic activity, platelet activation, leukocyte activation, endothelial damage and increased whole blood viscosity [27]. In contrast to PRV, erythrocytosis in patients with cyanotic congenital heart disease is typically associated with a low (or low-normal) platelet count and a predisposition to bleeding. There is, as yet, no clear association between secondary erythrocytosis in ES and the risk of major cerebrovascular events (CVEs) [26, 28].

Adults who undergo repeat venesections are at risk of developing ID and microcytic circulating erythrocytes. These microcytic erythrocytes resist deformation in high shear rates in the microcirculation, which in turn can increase the risk of hyperviscosity symptoms and CVEs in adults with cyanotic heart disease and secondary erythrocytosis [29, 30]. Therefore, the short-term potential benefit of venesections in lowering haematocrit may result in chronic ID, with an increased risk of hyperviscosity symptoms and CVEs. Dehydration can rapidly increase the haematocrit level and precipitate or aggravate the symptoms of hyperviscosity. In such cases, initial treatment is volume replacement, not venesection.

Bearing in mind potential hazards, the indications for venesection are limited to two circumstances: (1) in patients with moderate-to-severe hyperviscosity symptoms due to secondary erythrocytosis, in the absence of dehydration or ID anaemia. (2) Venesection may be considered preoperatively for autologous blood donation and for boosting platelet production [23]. When indicated, venesection should be performed following certain safety measures, in an experienced setting. At the offset, baseline vital signs should be documented and repeated every 15 min for the first hour after the procedure. While the venesection is taking place, the volume removed should be replaced simultaneously with isotonic saline to avoid sudden shifts in volume status, which can reduce preload and cause syncope or decompensation. Air filters should be used to avoid air emboli. The procedure should be stopped immediately if the patient experiences hypotension, desaturation, palpitations/arrhythmias or pre-syncope/syncope. If hyperviscosity symptoms persist beyond 24 h from venesection, other causes for the symptoms should be

investigated, such as reassessment of volume status or the presence of a cerebral abscess (when neurological symptoms are present). If symptoms persist, in the absence of other causes, a second venesection can be performed within 48 h, but is rarely required and should be avoided [23].

15.2.1.2 Haemostatic Abnormalities

Haemostatic abnormalities extend beyond compensatory erythrocytosis and are common and complex in cyanotic patients. These include dysregulation in platelet production and the coagulation cascade.

Thrombocytopenia is very common in cyanotic patients. There is a positive correlation between platelet count and oxygen saturation and an inverse relationship with haemoglobin/haematocrit levels [31]. Four pathogenetic mechanisms are potentially responsible for the thrombocytopenia encountered in cyanotic patients: (1) decreased platelet production, (2) decreased megakaryocyte production, (3) increased platelet destruction and (4) increased platelet activation. In 1893, Aschoff proposed that megakaryocytes, originating in the bone marrow, migrate into the bloodstream and, because of their size, lodge into the pulmonary capillary bed where maturation takes place, leading to platelet production. In patients with a right-to-left shunt, megakaryocytes can bypass the lung and, hence, circumvent this maturation process [31].

Abnormal coagulation has also been described in ES patients. Vitamin K-dependent clotting factors (factors II, VII, IX, X) and factor V are reduced. Increased fibrinolytic activity and depletion of von Willebrand factor, which is acquired, contribute to the bleeding tendency seen in these patients [32]. Acquired von Willebrand disease is usually associated with prolonged bleeding times, but in cyanotic patients bleeding times are paradoxically shorter and may not reflect an underlying bleeding disorder, a phenomenon that is not completely understood.

15.2.1.3 Bleeding, Thrombosis and Anticoagulation

Given the abnormalities described above, patients with ES are at risk both for bleeding and thrombosis. Haemoptysis is common among ES patients, usually of minor volume and, fortunately, not a common mode of death nowadays. It is an external manifestation of an intrapulmonary haemorrhage and does not reflect the extent of bleeding. Major haemoptysis is a medical emergency and always requires urgent evaluation by a multidisciplinary team, following an ABC protocol (protecting airway, breathing and circulation). General diagnostic and therapeutic aspects include hospital admission, discontinuation of pharmacotherapy that may induce bleeding, appropriate imaging to identify the site and source of bleeding and volume repletion [33]. Rupture of large bronchial arteries, aortopulmonary collateral or an aneurysm of the pulmonary artery (PA) is often fatal (Fig. 15.2). As bleeding is not uncommon in ES, strategies to prevent its occurrence should be considered (Table 15.1).

Other common sources of bleeding (Table 15.2) include epistaxis, menorrhagia and gastrointestinal blood loss, all of which require a multidisciplinary approach and may require investigations (e.g. endoscopy) that should be performed in a tertiary PH and CHD centre to minimize complications.

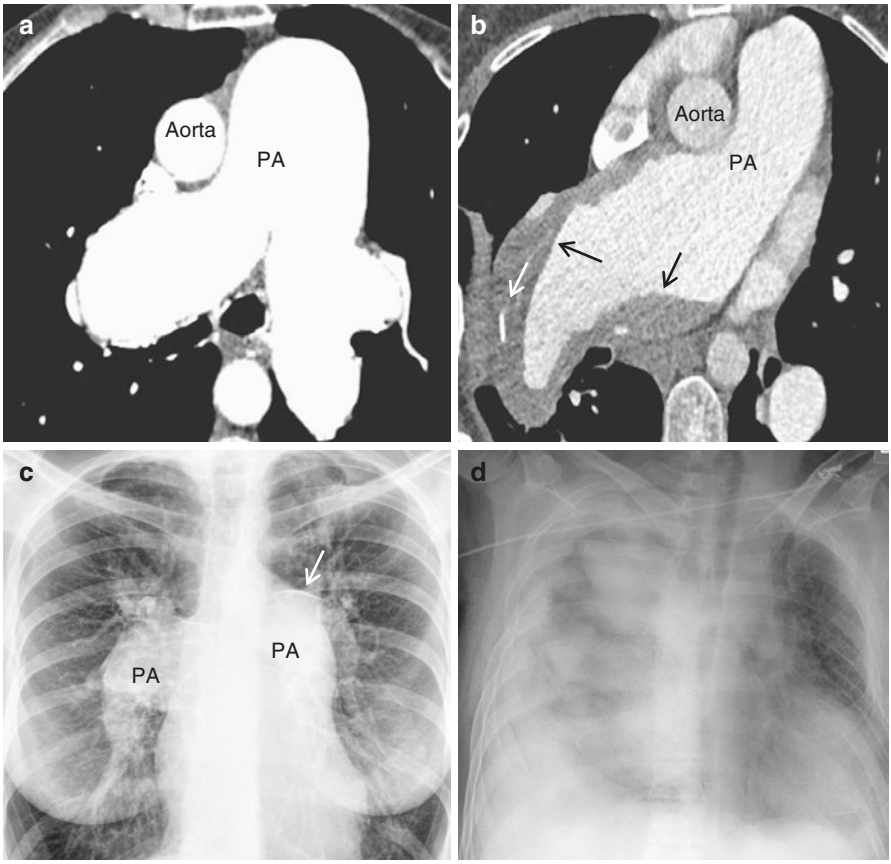

Fig. 15.2 Computed tomography images of patients with Eisenmenger syndrome due to a large ASD (**a**) demonstrating significant pulmonary artery (PA) dilatation when compared to the aorta and in situ thrombus (*black arrow*) in the PAs (**b**). The chest radiograph (**c**) shows large PAs in a patient with Eisenmenger syndrome due to an ASD and PA calcification (*white arrow*). PA dilatation can result in pulmonary artery rupture and haemorrhage (**d**)

Thrombosis is also common in patients with ES [34, 35]. Contributing factors include coagulation abnormalities, stasis of blood in dilated chambers and vessels, atherosclerosis, endothelial injury, pro-thrombotic material (artificial valves, conduits, pacemaker leads) and atrial arrhythmias. The factors contributing to an increase in bleeding tendency do not appear to protect patients from thrombus formation. Laminated thrombi in large, partially calcified and aneurysmal pulmonary arteries are common and occur in up to 30% of patients with ES (Fig. 15.2) [36, 37]. A retrospective analysis of 34 patients with ES by Silversides et al. found 21% of patients with proximal PA thrombus. These patients were more likely to be female and have lower oxygen saturations [34]. In a different study, in situ thrombosis in pulmonary arteries was related to older age, biventricular dysfunction, poor

Table 15.1 Strategies for preventing bleeding

• Limit the use of anticoagulation to the following indications:
– Atrial arrhythmia
– Thromboembolic events
– Mechanical valve prosthesis
– In situ thrombosis
– Advanced heart failure
• Meticulous surveillance of anticoagulation
– Maintain INR within a prespecified therapeutic range
– Monitor regularly
– Citrate adjusted sample[a]
• Prompt treatment of respiratory tract infections
• Up-titration of PAH therapies
• Bronchial artery embolization for recurrent haemoptysis

Suggested strategies for preventing bleeding in patients with Eisenmenger syndrome

[a]Citrate-adjusted samples are required in patients with high haematocrit levels; otherwise INR levels can be underestimated

Table 15.2 Types of bleeding in patients with Eisenmenger syndrome

• **Minor bleeding**
– Skin bruising
– Mucocutaneous bleeding (gingival)
– Epistaxis (can become major)
– Menorrhagia (can become major)
– Mild haemoptysis (due to respiratory tract infection)
• **Major bleeding**
– Haemoptysis, can be due to:
PA dissection or rupture
Bronchial artery rupture
– Iatrogenic/surgical bleeding
Endoscopy (upper and lower GI)
Endoscopic interventions (e.g. ERCP/ sphincterotomy)
Cardiac catheterization resulting in PA dissection/ rupture
– Spontaneous gastrointestinal bleeding
– Cerebral bleeding (e.g. secondary to abscess)

PA pulmonary artery, *ERCP* endoscopic retrograde cholangiopancreatography

functional class and dilatation of pulmonary arteries, with concomitant "sluggish" pulmonary blood flow. In this study, the degree of cyanosis or coagulation parameters did not differ between patients with and without thrombus formation in the central pulmonary arteries [35].

Current guidelines suggest that patients with ES with coexisting conditions, such as atrial fibrillation or intrapulmonary thrombi, in the absence of haemoptysis,

should be anticoagulated [10]. With the use of warfarin, the narrow therapeutic index requires meticulous and regular monitoring. In ES patients, particularly those with higher haematocrit levels, the amount of sodium citrate in the test tubes needs to be adjusted to the haematocrit for accurate INR measurements. There are, however, currently no clinical data to support the routine use of anticoagulation or aspirin in this population. Oral anticoagulants are associated with an increase in ID anaemia in this group, and patients should be routinely assessed and treated when iron deficient [38]. There are no data on the use of novel oral anticoagulants in ES, and the limited availability of direct reversing agents has limited their use in these patients who are prone to bleeding.

15.2.1.4 Iron Deficiency Anaemia

There is no universally accepted definition of ID in this patient group. Tay et al. defined ID in their study a serum ferritin <30 μg/L or a serum ferritin <50 μg/L and a transferrin saturation of <15%. However this definition of ID was derived from acyanotic patients [39]. Earlier, Spence et al. suggested a threshold of serum ferritin ≤15 μg/L and a transferrin saturation ≤15% as their definition for ID in cyanotic patients [40]. In patients with left ventricular failure, ID was defined as serum ferritin <100 μg/L or serum ferritin 100–299 μg/L and a transferrin saturation <20%, possibly to account for a chronic inflammatory state [41].

The causes of ID anaemia in cyanotic patients are multiple: hematologic disorders, bleeding or extrinsic factors such as dietary intake or medication. ID is common in ES and other cyanotic CHD, found in 20–37% of patients [13]. Anaemia is often not recognized in cyanotic patients, as haemoglobin levels, which should be in the range of 18–24 g/dL, may drop to levels that are normal for the general population but not for patients with chronic cyanosis [24]. The typical microcytosis of ID (mean corpuscular volume (MCV) ≤80 fl) is often absent in cyanotic patients with ID [42]. Haemoglobin concentration, MCV and mean corpuscular haemoglobin (MCH) are, hence, not reliable for the diagnosis of ID in this cohort, and parameters reflecting iron metabolism should be used, including ferritin and transferrin saturation. Soluble transferrin receptor assay, when available, is also extremely useful for identifying ID [42].

ID can have a multitude of deleterious effects on cyanotic CHD and ES. Reduced oxygen carrying capacity and delivery to peripheral tissues may impair exercise tolerance [43, 44]. In a review of 162 patients, Ammash et al. sought to determine the frequency of spontaneous cerebrovascular events in cyanotic congenital heart disease and possible contributing factors. In their study, 41 patients had ID with microcytosis (MCV < 82 fl), and among these, 11 had a cerebrovascular event (p = 0.004), thereby demonstrating the strong association between ID anaemia, microcytosis and cerebrovascular events [28].

Data on the management of ID in cyanotic CHD and ES is limited, but there is evidence to support iron supplementation. In a study of 25 patients, replenishing iron stores lead to an improvement in quality of life (QoL) and exercise capacity expressed as 6-min walk distance (6MWT) [39]. Current guidelines recommend

that iron supplementation should be considered in patients who are iron deficient, but do not provide a clear indication on how aggressively this should be pursued. Tay et al. used a protocol in their study incorporating a dosing strategy (mainly oral, with IV supplementation only when patients were intolerant to oral supplements) that is used in many PH centres (Fig. 15.3) [39]. While gradual oral iron replacement is preferred, gastric absorption is often impaired in PAH and side effects are common; hence intravenous iron administration should be considered. Refractory secondary erythrocytosis, precipitating or aggravating symptoms of hyperviscosity, is a concern, but is very rare in our experience. Van De Bruaene et al. suggested close monitoring of patients with resting oxygen saturations <83% receiving iron supplementation [38].

Overall, ID is strongly related to adverse outcomes, particularly in patients on anticoagulants and those receiving routine venesections. In view of the high prevalence of ID in patients with PAH, annual (or more frequent) testing is recommended and iron supplementation (oral or intravenous) should be considered in accordance to local policies [10, 40].

15.2.2 Oxygen Therapy and Air Travel

Oxygen is a strong pulmonary vasodilator and has been shown to reduce PVR in patients with PAH; yet there are no randomized data to suggest that long-term oxygen therapy is beneficial in ES. While low resting saturations (below 85%) are

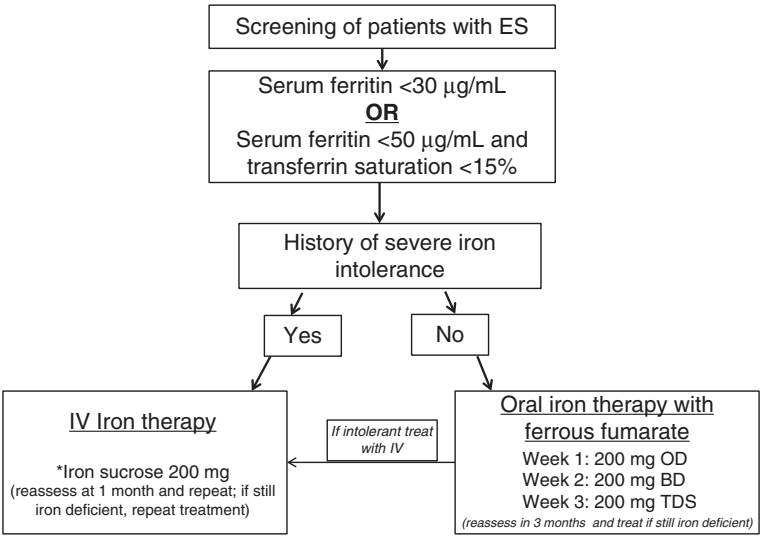

Fig. 15.3 Suggested protocol for treatment of iron deficiency anaemia in patients with Eisenmenger syndrome. *Alternative intravenous infusions can be used, such as ferric carboxymaltose (Adapted from Tay et al. [24])

associated with an adverse outcome in ES [45], this is likely to reflect disease severity, and long-term oxygen therapy in the setting of ES remains controversial. Indeed, hypoxemia in ES is the result of right–left shunting (intra- or extra-cardiac) and cannot be corrected by oxygen supplementation. There is only one prospective randomized controlled study evaluating the effects of nocturnal oxygen in 23 adults with ES. These patients received tailored doses of oxygen for at least 8 h per day and were followed up for 2 years. The authors concluded that oxygen therapy in this cohort had no impact on exercise capacity, haematology variables, quality of life or survival [46]. Some patients may benefit symptomatically from oxygen supplementation, and it remains at the physicians' discretion to prescribe oxygen, as long as it does not limit the patient's ability to remain physically and socially active. In patients with intense hypoxemia and dyspnoea at rest and loss of vital capacity or those awaiting transplantation, oxygen therapy may provide some symptomatic benefit. The risks of oxygen therapy should, of course, be taken into account and include desiccation of nasal mucosa, epistaxis, sleep disturbance and the burden of the oxygen cylinder when traveling/walking.

Unnecessary restrictions to air travel impact on an individual's quality of life. Concerns on the safety of travel in commercial aircraft for ES patients are not based on any strong evidence. A Dutch group addressed this concern by designing a study of cyanotic and healthy individuals assessed during simulated and actual flights [47]. Commercial air travel was well tolerated, and the decrease in oxygen saturation during ascent was similar in both cyanotic and healthy controls. They concluded that atmospheric pressure changes during air travel were not detrimental to patients with cyanotic heart disease. Broberg et al. confirmed that ES patients tolerated travel on commercial aircrafts well in a retrospective study [48]. Therefore, it does not appear that ES patients should be advised against air travel. There is also little evidence on the use of in-flight supplemental oxygen, even though this could be made available in an as-required basis. It is worth noting that the low humidity in commercial aircrafts can cause dehydration, which can be pro-thrombotic; therefore patients are advised to remain well hydrated, keep their legs extended and periodically walk on long-haul flights.

Travel to high altitude in a non-pressurized cabin, such as cable cars or other transport, may be safe, but a gradual ascent on land is important and a time for acclimatization may be wise. Exercise at high altitude must be limited and is usually restricted by symptoms. Some patients who are not acclimatized may not tolerate long stays in high altitude [23].

15.2.3 Gout

Hyperuricemia is another complication of ES and is the result of increased production of uric acid and reduced renal clearance. Renal hypoperfusion, reinforced by a high filtration fraction, enhances urate reabsorption and causes secondary hyperuricemia [49]. Uric acid levels rise in proportion to the haemodynamic severity in ES, and hyperuricemia is independently associated with an adverse outcomes. Administration of uricosuric or uricostatic agents is indicated in patients with

recurrent gouty arthritis. In the acute phase, symptoms can be relieved by oral colchicine or intra-articular corticosteroids, where indicated. Asymptomatic hyperuricemia is not an indication for routine drug therapy [50].

15.2.4 Cholelithiasis

There are two types of gallstones: cholesterol and pigment or bilirubinate. In ES, there is an increased turnover of heme due to the erythrocytosis, resulting in increased concentration of unconjugated bilirubin in the bile. This, in turn, contributes to a higher incidence of calcium bilirubinate gallstones in this cohort.

If complicated by an infection, acute cholecystitis is a serious complication for ES patients, as it can be further complicated by bacteraemia, acute abdomen and haemodynamic instability. It is recommended that ES patients with cholecystitis/symptomatic cholelithiasis be referred to a specialist centre where they can be managed by a multidisciplinary team experienced in managing ES. If surgery is unavoidable, a cardiac anaesthetist experienced in PAH and ES should perform the anaesthesia. As general anaesthesia carries significant risks in ES, minimally invasive procedures are often preferred: endoscopic retrograde cholangiography (ERCP) and papillotomy should be attempted, where possible. A laparoscopic approach with insufflation of carbon dioxide (CO_2) in the abdomen and reduction in venous return may not be tolerated in ES patients. With open cholecystectomy, adequate postoperative pain management is important to minimize haemodynamic instability, but may prove difficult (see below).

15.2.5 Noncardiac Surgery and Endocarditis Prophylaxis

PAH, CHD and ES are known risk factors for perioperative complications [51]. Patients with PAH are often counselled against elective surgery because of the risk of early and sudden postoperative deaths. In PAH, the right ventricle (RV) cannot accommodate large alterations in preload or afterload induced by fluid shift, anaesthetic medication, insufflation of gas in the abdomen during laparoscopic procedures or autonomic changes precipitated by hypoxia or hypercapnia, which are magnified by stress or pain. RV ischemia, resulting in worsening RV function, can be precipitated by systemic hypotension and arrhythmias during surgery [52]. Therefore, the choice of anaesthetic is crucial for patients with PAH. The same principles of risk management apply to ES.

The two main principles of perioperative risk management are the prevention of systemic hypotension and avoidance of an increase in pulmonary arterial pressure (PH crisis). Specific risks during surgery include arrhythmias, thromboembolism, bleeding and sudden changes in systemic vascular resistance. Close monitoring, optimization of systemic blood pressure, pain control, oxygenation and ventilation, avoidance of exacerbating factors and use of vasopressors and pulmonary vasodilators, as necessary, are essential elements of perioperative management. In a study of 33 ES patients undergoing general or regional anaesthesia, 26% experienced

profound hypotension and 17% a drop in oxygen saturation. The authors found that vasopressor agents given during induction significantly reduced the incidence of hypotension [53].

Patients with an underlying cardiac condition, which includes any cyanotic CHD, are at higher risk of infective endocarditis and should receive prophylaxis. This, however, only applies to high-risk procedures, which are mainly invasive dental procedures, and not for respiratory tract procedures, gastrointestinal/urogenital or skin/soft tissue procedures [11].

15.2.6 Exercise Training

This subject will be discussed in greater detail in Chap. 20. Exercise intolerance is a common feature of ACHD, affecting approximately one third of patients [54]. Those with cyanosis or PH are among the most limited, as demonstrated by 6-min walk testing [55, 56]. During exercise endothelial nitric oxide production rises proportional to ventilation, and PVR declines to limit elevation in mean PA pressure [57]. PH patients are unable to sufficiently increase their pulmonary blood flow on exercise, while right-to-left shunting may boost the systemic cardiac output, but at the expense of further systemic desaturation and physiological dead space [58–60].

Exercise training (ET) should not be discouraged in ES. In patients with severe heart failure, regular training improves endothelial function in systemic vessels and improves long-term outcome [61, 62]. Impaired skeletal muscle function has been described in CHD and is a potential target for rehabilitation/ET [63]. Mild to moderate aerobic activity and low-level resistance exercise can be performed safely in most clinically stable patients. The recommendation for patients with ES is low dynamic sport leisure activities with a low isometric (static) component, while competitive sports are contraindicated (see also Chapter 20). Highly isometric exercise (e.g. weight lifting) should be avoided. Patients with a persistent shunt should avoid scuba diving [64].

15.2.7 Heart Failure, Diuretics and Cardiovascular Drugs

RV failure is a major determinant of morbidity and mortality in PAH (see Chapter 1 on RV adaptation to PAH). RV maladaptation to the high afterload caused by PAH often results in RV distension and dysfunction, with an inability to adapt to large fluid shifts [65]. Moreover, ventricular interdependence, myocardial ischemia and tricuspid regurgitation further impact on cardiac output and central venous pressures, leading to reduced oxygen delivery and multi-organ failure. Decreasing oxygen saturation in patients with cyanotic CHD further exacerbates organ failure [66].

The management of RV failure in patients with PAH, and especially ES, is challenging. Genetic studies have confirmed that, during cardiac morphogenesis, the RV and left ventricle (LV) originate from different progenitor cells at different sites [67].

It may be for this reason that drugs routinely used for non-congenital heart failure patients, such as β-blockers, have no proven benefit in RV failure due to PAH.

Patients presenting in acutely decompensated heart failure should be managed in a critical care environment with the appropriate initial investigations (Table 15.3) and monitoring, with the aim of identifying and reversing precipitating factors, such as alveolar hypoxia, hypercapnia, acidaemia and sepsis (Table 15.4, Fig. 15.4) [68, 69]. Additionally adverse prognostic indicators in acute RV failure should be identified and addressed (Table 15.5) [10, 14, 33, 68–71].

The mainstay of treatment is optimal fluid balance, and neither hypovolaemia nor hypervolaemia is well tolerated and can contribute to a low cardiac output. Loop diuretics can be used to reduce RV preload and distension, which in turn improves RV function, RV-LV interdependence and LV compliance, thereby improving cardiac output [66]. RV distension activates the renin–angiotensin–aldosterone system (RAAS) and may cause secondary hyperaldosteronism; thus, the use of an aldosterone antagonist, such as spironolactone, may be helpful [72]. Increasing doses of pulmonary vasodilators can reduce RV afterload and improve RV function and cardiac output. In patients who are severely decompensated, intravenous (prostanoids, sildenafil) or inhaled (prostanoids, nitric oxide) pulmonary vasodilators may be considered [66, 73, 74].

Table 15.3 Initial investigations in patients presenting with RV failure

Clinical history
Progression of breathlessness, oedema, orthopnoea
Change in WHO FC, 6MWD
Cessation of medication or poor compliance
Quality of life score (e.g. EMPHASIS-10)
New-onset arrhythmia
Examination
Weight gain, tachycardia, hypotension, raised JVP, oedema, ascites
Signs of endocarditis (Osler's nodes, splinter haemorrhages, Janeway lesions, new murmurs)
Deep venous thrombosis
RV function assessment
ECG showing RV strain, arrhythmia, ischemia
Rising BNP [71]
Echocardiography [68]
RA area ≥ 25 mm^2
Pericardial effusion
TAPSE < 15 mm
Ratio of RA to LA area ≥ 1.5
Ratio of RV effective systolic to diastolic duration ≥1.5
Haemodynamic on RHC
RAP > 14 mmHg
Lower than expected PA pressures may indicate a failing RV

Initial investigations in patients with PAH presenting with signs of right ventricular failure
WHO FC World Health Organization Functional Class, *6MWD* 6-min walk distance, *JVP* jugular venous pressure, *SBE* subacute bacterial endocarditis, *RV* right ventricle, *BNP* B-type natriuretic protein, *RA* right atrium, *LA* left atrium, *TAPSE* tricuspid annular plane systolic excursion, *RHC* right heart catheterization, *RAP* right atrial pressure, *PA* pulmonary artery

Table 15.4 Reversible causes of heart failure in PAH–CHD

Electrolyte or metabolic imbalance, iron deficiency. Check:	
	Biochemistry, liver, thyroid function
	Haemoglobin, iron studies
Infection. Perform:	
	Septic screen (blood, urine, sputum)
	Consider CT brain to rule out cerebral abscess
Arrhythmia:	
	ECG to rule out new-onset arrhythmia
Pulmonary embolism. Consider:	
	CTPA, avoid if impaired renal function
	D-dimer (limited value in ES)
Myocardial ischemia:	
	Serial troponins and ECG
	CTCA to exclude compression of coronary arteries from dilated PA
Exacerbation of underlying lung disease:	
	Scoliosis due to previous surgery, also associated with cyanotic heart disease
	Sleep-disordered breathing

Potential reversible causes in patients presenting with RV failure and PAH–CHD
CT computed tomography, *CTPA* CT pulmonary angiogram, *CTCA* CT coronary angiogram, *PA* pulmonary arteries

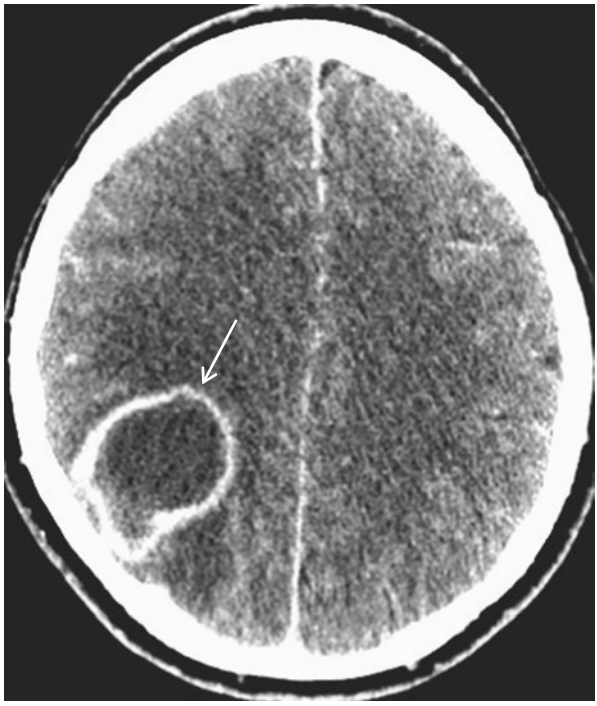

Fig. 15.4 Cerebral abscess (*arrow*) with signs of peri-lesional oedema and midline shift in a patient with VSD and ES presenting with syncope and fever

Table 15.5 Adverse prognostic markers in patients with PAH–CHD (see also Chap. 21) [69]

Signs of RV failure
Syncope
Rapid progression of symptoms
WHO FC III or IV at presentation
6MWD < 300 m
CPET: low peak VO_2
Hypotension
Hyponatremia
Renal dysfunction
BNP > 300 ng/L
RA area ≥ 25 cm^2, RA/LA area > 1.5
TAPSE < 1.5 cm
Pericardial effusion
RAP >15 mmHg
CI <2 L/min/m^2

Clinical indicators that may suggest adverse prognosis in patients with PAH–CHD
RV right ventricle, *WHO FC* World Health Organization Functional Class, *6MWD* 6-min walk distance, *CPET* cardiopulmonary exercise test, VO_2 volume of oxygen, *VE* minute volume, *BNP* B-type natriuretic protein, *RA* right atrium, *RAP* right atrial pressure, *CI* cardiac index

When RV systolic pressure is near or above systemic pressure, right coronary artery perfusion may be affected and cause ischemia in a hypertrophied RV. In this situation, vasoconstrictors can be used to reduce RV preload and increase systemic pressure to maintain adequate coronary perfusion [75]. Inotropes such as dobutamine and dopamine (β-1 agonists) can be used to increase cardiac output. Alternatively milrinone (a phosphodiesterase 3 inhibitor) can be used to avoid the chronotropic effect of β-1 agonists. As they may cause systemic vasodilatation, such agents may need to be combined with a vasoconstrictor [66, 73, 74].

In patients with end-stage RV failure not responding to conventional therapy, extracorporeal life support may be considered as a bridge to transplantation. Assist devices used as a bridge to transplant therapy in heart failure are limited in PAH. Physiological haemodynamics, specifically elevated PVR, hinder their use as right ventricular assist devices (RVADs), increase pulmonary arterial and capillary pressure and may have detrimental effects [76].

It must be noted that certain conventional therapies for heart failure can be harmful in patients with ES and PAH–CHD. β-Blockers and calcium channel blockers are generally contraindicated in PAH due to their negative inotropic effect on the RV, which may be poorly tolerated [77]. Unlike left-sided heart failure, β-blockers have not been shown to improve RV function in PAH. They can be used in specialist PAH centres for other indications such as prevention of recurrent arrhythmias in small doses. While neurohormonal activation is present in PAH [19, 78], only aldosterone antagonists are used in these patients; ACE

inhibitors and ARBs should be avoided in patients with ES as they may reduce the SVR and enhance a right-to-left shunting, causing a worsening in cyanosis [79]. They may also cause hypotension, which can preclude the use of PAH therapies. In a recent German registry of 153 patients with ES and various cardiac anatomies, approximately 35% were on diuretics, 25% on digoxin, 10% on ACE-i/ARBs, 18% on β-blockers, 18% on oral anticoagulation and 25% on aspirin. There was no significant association between conventional medical treatment (diuretics, digoxin, ACE-i/ARBs) and outcome. Patients with more complex CHD were more likely to be on additional conventional therapies compared to ES patients with simple defects [80].

15.2.8 Renal Dysfunction and Hyponatremia

Renal dysfunction is common among patients with PAH–CHD and can affect up to two thirds of adults with ES [16]. The mechanisms are multifactorial and complex. Both functional and structural abnormalities of the kidneys can occur in PAH–CHD. In heart failure, the low cardiac output results in decreased perfusion of vital organs, including kidneys. Consequent activation of the RAAS (through cardiac distension and reduced renal flow) is an attempt to preserve renal perfusion and glomerular flow. However, this compensatory mechanism promotes sodium and water retention, potentially causing further deterioration in cardiac and renal function [81]. In cyanotic patients it is postulated that chronic hypoxia affects renal function directly and indirectly through the increase in blood viscosity [40].

Renal dysfunction can cause a deterioration in cardiac function though water retention and by aggravating hypertension and anaemia. Moderate or severe renal impairment (glomerular filtration rate < 60 mL min^{-1} 1.73 m^{-2}) has been shown to be associated with a threefold increase in mortality in cyanotic patients [16]. Routine, periodic screening of renal function is indicated, and agents that may aggravate renal dysfunction (e.g. contrast media, antibiotics, diuretics) should be avoided, or their doses should be adjusted accordingly.

Hyponatremia (<136 mmol/L) is common in patients with acquired congestive heart failure, as a result of water retention in excess of sodium stores [82]. Hyponatremia is an established prognostic marker in acquired heart failure and ischemic heart disease [83]. Neurohormonal activation, present in abundance in patients with CHD, is important in the pathogenesis of hyponatremia [78]. In a review of 1004 adults with CHD of varied cardiac anatomy and physiology, 20% of patients with ES were found to be hyponatremic compared to 15% in the overall group [14]. The authors discovered that hyponatremia was associated with a threefold increased risk of death in the overall group, independent of renal function and use of diuretics. Measuring sodium levels should be part of the periodic assessment of these patients, as it is a simple, cheap but powerful marker of mortality in CHD [14].

15.2.9 Arrhythmias

Arrhythmias are common in patients with PAH and are often associated with clinical deterioration and major adverse events, such as hospitalization or death [84]. The onset of an arrhythmia may be a signal of acute decompensation or progressive deterioration, and the risk associated with arrhythmias in PAH is significantly higher compared to patients with less severe cardiac conditions.

The most common arrhythmias in PAH–CHD patients are supraventricular tachycardias and often arise due to atrial distention or scar tissue from previous surgery [13]. The incidence of supraventricular tachycardias, including atrial flutter and fibrillation, is reported at 2.8% per annum in patients with PAH [85]. In more advanced PAH, atrial arrhythmias have a 5-year cumulative frequency of approximately 25% [37]. In the acute setting, in symptomatic but haemodynamically stable patients, initial management includes addressing haematological, biochemical or endocrinological causes for the tachyarrhythmia, such as thyroid dysfunction, anaemia or electrolyte disturbances. In stable patients, amiodarone may be used to attempt cardioversion, with close monitoring of parameters of systemic perfusion. However, prompt direct current cardioversion (DCCV) is preferable, especially if the arrhythmia is causing haemodynamic compromise or there is evidence of systemic hypoperfusion in patients not responding to adenosine. DCCV requires general anaesthesia or sedation, which carries significant risks in patients with PAH; therefore senior anaesthetic input is required. Where the time of onset of arrhythmia exceeds 48 h in a haemodynamically stable patient, intra-atrial thrombus should be excluded by transesophageal echocardiogram (TOE) before attempting rhythm restoration. Rate-controlling drug therapy, such as β-blockers, may be poorly tolerated due to their negatively inotropic effects on the RV, but are often used in small doses. Often, medication such as amiodarone, with less of an inotropic effect, is favoured. However, clear recommendations on the use of β-blockers and other antiarrhythmic cannot be made in view of the lack of evidence in patients with PAH–CHD. Catheter ablation can be considered in cases of recurrent atrial arrhythmias and can often be performed under local anaesthesia [86].

Malignant tachycardias, such as ventricular tachycardia (VT), are not as common as supraventricular arrhythmias in PAH. In one study of 132 witnessed cardiac arrests in patients with PAH, only 8% were due to ventricular fibrillation (VF) [87]. The PAH–CHD population has a higher incidence of malignant arrhythmias due to their underlying cardiac defect or previous surgical scarring. In patients who survive a sustained VT or VT/VF arrest, extrinsic compression of the coronary arteries by a dilated PA should be excluded. Other potential precipitating factors, such as a prolonged QT interval or electrolyte imbalances, should be ruled out or corrected. Implantable cardioverter defibrillators (ICDs) may be considered for secondary prevention, but implantation is not without risks, including infection, bleeding and the risks of sedation to test the device. Subcutaneous ICDs are an attractive option in those with no venous access to the heart. The indications for an ICD should be weighed against the overall survival prospects and the patient's wishes (see Chap. 23) [88, 89].

Conclusion

Advances in the diagnosis of CHD and its surgical and medical management have significantly increased the number of patients surviving into adulthood. The best approach to PAH–CHD is prevention, through timely repair of the defect. However, patients do still develop PAH–CHD, and the morbidity and mortality in this group remains high due to the multisystem complications described in this chapter. Supportive measures, anticipation and expert management of potential systemic complications and avoidance of old unproven practices are as important as specific pharmacological therapy in PAH–CHD. The optimum management for these patients is in centres with both PAH and ACHD expertise or a shared care model between specialist PAH and ACHD centres.

References

1. Engelfriet PM, Duffels MG, Moller T et al (2007) Pulmonary arterial hypertension in adults born with a heart septal defect: the Euro Heart Survey on adult congenital heart disease. Heart 93(6):682–687
2. Diller GP, Kempny A, Alonso-Gonzalez R et al (2015) Survival prospects and circumstances of death in contemporary adult congenital heart disease patients under follow-up at a large tertiary centre. Circulation 132(22):2118–2125
3. Dimopoulos K, Giannakoulas G, Wort SJ, Gatzoulis MA (2008) Pulmonary arterial hypertension in adults with congenital heart disease: distinct differences from other causes of pulmonary arterial hypertension and management implications. Curr Opin Cardiol 23(6):545–554
4. Ramjug S, Hussain N, Hurdman J et al (2016) Pulmonary arterial hypertension associated with congenital heart disease: comparison of clinical and anatomic-pathophysiologic classification. J Heart Lung Transplant 35(5):610–618
5. D'Alto M, Diller GP (2014) Pulmonary hypertension in adults with congenital heart disease and Eisenmenger syndrome: current advanced management strategies. Heart 100(17):1322–1328
6. Dimopoulos K, Wort SJ, Gatzoulis MA (2014) Pulmonary hypertension related to congenital heart disease: a call for action. Eur Heart J 35(11):691–700
7. Dimopoulos K, Inuzuka R, Goletto S et al (2010) Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension. Circulation 121(1):20–25
8. King P, Tulloh R (2011) Management of pulmonary hypertension and down syndrome. Int J Clin Pract Suppl 174:8–13
9. Dimopoulos K, Kempny A (2016) Patients with down syndrome and congenital heart disease: survival is improving, but challenges remain. Heart 102(19):1515–1517
10. Galie N, Humbert M, Vachiery JL et al (2016) 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 37(1):67–119
11. Habib G, Lancellotti P, Antunes MJ et al (2015) 2015 ESC guidelines for the management of infective endocarditis: the task force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 36(44):3075–3128

12. Bedard E, Dimopoulos K, Gatzoulis MA (2009) Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? Eur Heart J 30(3): 256–265
13. Diller GP, Dimopoulos K, Broberg CS et al (2006) Presentation, survival prospects, and predictors of death in Eisenmenger syndrome: a combined retrospective and case-control study. Eur Heart J 27(14):1737–1742
14. Dimopoulos K, Diller GP, Petraco R et al (2010) Hyponatraemia: a strong predictor of mortality in adults with congenital heart disease. Eur Heart J 31(5):595–601
15. Dimopoulos K, Okonko DO, Diller GP et al (2006) Abnormal ventilatory response to exercise in adults with congenital heart disease relates to cyanosis and predicts survival. Circulation 113(24):2796–2802
16. Dimopoulos K, Diller GP, Koltsida E et al (2008) Prevalence, predictors, and prognostic value of renal dysfunction in adults with congenital heart disease. Circulation 117(18):2320–2328
17. Alonso-Gonzalez R, Borgia F, Diller GP et al (2013) Abnormal lung function in adults with congenital heart disease: prevalence, relation to cardiac anatomy, and association with survival. Circulation 127(8):882–890
18. Scognamiglio G, Kempny A, Price LC et al (2014) C-reactive protein in adults with pulmonary arterial hypertension associated with congenital heart disease and its prognostic value. Heart 100(17):1335–1341
19. Kempny A, Diller GP, Alonso-Gonzalez R et al (2015) Hypoalbuminaemia predicts outcome in adult patients with congenital heart disease. Heart 101(9):699–705
20. Ross HJ, Law Y, Book WM et al (2016) Transplantation and mechanical circulatory support in congenital heart disease: a scientific statement from the American Heart Association. Circulation 133(8):802–820
21. Christie JD, Edwards LB, Kucheryavaya AY et al (2010) The registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult lung and heart-lung transplant report—2010. J Heart Lung Transplant 29(10):1104–1118
22. Broberg CS, Bax BE, Okonko DO et al (2006) Blood viscosity and its relationship to iron deficiency, symptoms, and exercise capacity in adults with cyanotic congenital heart disease. J Am Coll Cardiol 48(2):356–365
23. Oechslin E, Mebus S, Schulze-Neick I et al (2010) The adult patient with eisenmenger syndrome: a medical update after Dana point part III: specific management and surgical aspects. Curr Cardiol Rev 6(4):363–372
24. Oechslin E (2004) Hematological management of the cyanotic adult with congenital heart disease. Int J Cardiol 97(Suppl 1):109–115
25. Silversides CK, Salehian O, Oechslin E et al (2010) Canadian cardiovascular society 2009 consensus conference on the management of adults with congenital heart disease: complex congenital cardiac lesions. Can J Cardiol 26(3):e98–117
26. Perloff JK, Marelli AJ, Miner PD (1993) Risk of stroke in adults with cyanotic congenital heart disease. Circulation 87(6):1954–1959
27. Kwaan HC, Wang J (2003) Hyperviscosity in polycythemia vera and other red cell abnormalities. Semin Thromb Hemost 29(5):451–458
28. Ammash N, Warnes CA (1996) Cerebrovascular events in adult patients with cyanotic congenital heart disease. J Am Coll Cardiol 28(3):768–772
29. Linderkamp O, Klose HJ, Betke K et al (1979) Increased blood viscosity in patients with cyanotic congenital heart disease and iron deficiency. J Pediatr 95(4):567–569
30. Hoffmann A, Chockalingam P, Balint OH et al (2010) Cerebrovascular accidents in adult patients with congenital heart disease. Heart 96(15):1223–1226
31. Lill MC, Perloff JK, Child JS (2006) Pathogenesis of thrombocytopenia in cyanotic congenital heart disease. Am J Cardiol 98(2):254–258
32. Perloff JK, Rosove MH, Child JS, Wright GB (1988) Adults with cyanotic congenital heart disease: hematologic management. Ann Intern Med 109(5):406–413
33. Dimopoulos K, Giannakoulas G, Bendayan I et al (2013) Cardiothoracic ratio from postero-anterior chest radiographs: a simple, reproducible and independent marker of disease severity and outcome in adults with congenital heart disease. Int J Cardiol 166(2):453–457

34. Silversides CK, Granton JT, Konen E, Hart MA, Webb GD, Therrien J (2003) Pulmonary thrombosis in adults with Eisenmenger syndrome. J Am Coll Cardiol 42(11):1982–1987
35. Broberg CS, Ujita M, Prasad S et al (2007) Pulmonary arterial thrombosis in Eisenmenger syndrome is associated with biventricular dysfunction and decreased pulmonary flow velocity. J Am Coll Cardiol 50(7):634–642
36. Perloff JK, Hart EM, Greaves SM, Miner PD, Child JS (2003) Proximal pulmonary arterial and intrapulmonary radiologic features of Eisenmenger syndrome and primary pulmonary hypertension. Am J Cardiol 92(2):182–187
37. Daliento L, Somerville J, Presbitero P et al (1998) Eisenmenger syndrome. Factors relating to deterioration and death. Eur Heart J 19(12):1845–1855
38. Van De Bruaene A, Delcroix M, Pasquet A et al (2011) Iron deficiency is associated with adverse outcome in Eisenmenger patients. Eur Heart J 32(22):2790–2799
39. Tay EL, Peset A, Papaphylactou M et al (2011) Replacement therapy for iron deficiency improves exercise capacity and quality of life in patients with cyanotic congenital heart disease and/or the Eisenmenger syndrome. Int J Cardiol 151(3):307–312
40. Spence MS, Balaratnam MS, Gatzoulis MA (2007) Clinical update: cyanotic adult congenital heart disease. Lancet 370(9598):1530–1532
41. Anker SD, Comin Colet J, Filippatos G et al (2009) Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med 361(25):2436–2448
42. Kaemmerer H, Fratz S, Braun SL et al (2004) Erythrocyte indexes, iron metabolism, and hyperhomocysteinemia in adults with cyanotic congenital cardiac disease. Am J Cardiol 94(6):825–828
43. Suedekum NA, Dimeff RJ (2005) Iron and the athlete. Curr Sports Med Rep 4(4):199–202
44. McLane JA, Fell RD, McKay RH, Winder WW, Brown EB, Holloszy JO (1981) Physiological and biochemical effects of iron deficiency on rat skeletal muscle. Am J Phys 241(1): C47–C54
45. Saha A, Balakrishnan KG, Jaiswal PK et al (1994) Prognosis for patients with Eisenmenger syndrome of various aetiology. Int J Cardiol 45(3):199–207
46. Sandoval J, Aguirre JS, Pulido T et al (2001) Nocturnal oxygen therapy in patients with the Eisenmenger syndrome. Am J Respir Crit Care Med 164(9):1682–1687
47. Harinck E, Hutter PA, Hoorntje TM et al (1996) Air travel and adults with cyanotic congenital heart disease. Circulation 93(2):272–276
48. Broberg CS, Uebing A, Cuomo L, Thein SL, Papadopoulos MG, Gatzoulis MA (2007) Adult patients with Eisenmenger syndrome report flying safely on commercial airlines. Heart 93(12):1599–1603
49. Ross EA, Perloff JK, Danovitch GM, Child JS, Canobbio MM (1986) Renal function and urate metabolism in late survivors with cyanotic congenital heart disease. Circulation 73(3):396–400
50. Oya H, Nagaya N, Satoh T et al (2000) Haemodynamic correlates and prognostic significance of serum uric acid in adult patients with Eisenmenger syndrome. Heart 84(1):53–58
51. McLaughlin VV, Archer SL, Badesch DB et al (2009) ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation task force on expert consensus documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. Circulation 119(16): 2250–2294
52. Ammash NM, Connolly HM, Abel MD, Warnes CA (1999) Noncardiac surgery in Eisenmenger syndrome. J Am Coll Cardiol 33(1):222–227
53. Bennett JM, Ehrenfeld JM, Markham L, Eagle SS (2014) Anesthetic management and outcomes for patients with pulmonary hypertension and intracardiac shunts and Eisenmenger syndrome: a review of institutional experience. J Clin Anesth 26(4):286–293
54. Dimopoulos K, Diller GP, Piepoli MF, Gatzoulis MA (2006) Exercise intolerance in adults with congenital heart disease. Cardiol Clin 24(4):641–660. vii
55. Kempny A, Dimopoulos K, Alonso-Gonzalez R et al (2013) Six-minute walk test distance and resting oxygen saturations but not functional class predict outcome in adult patients with Eisenmenger syndrome. Int J Cardiol 168(5):4784–4789

56. Kempny A, Dimopoulos K, Uebing A et al (2012) Reference values for exercise limitations among adults with congenital heart disease. Relation to activities of daily life—single centre experience and review of published data. Eur Heart J 33(11):1386–1396
57. Verges S, Flore P, Favre-Juvin A, Levy P, Wuyam B (2005) Exhaled nitric oxide during normoxic and hypoxic exercise in endurance athletes. Acta Physiol Scand 185(2):123–131
58. Ikawa S, Shimazaki Y, Nakano S, Kobayashi J, Matsuda H, Kawashima Y (1995) Pulmonary vascular resistance during exercise late after repair of large ventricular septal defects. Relation to age at the time of repair. J Thorac Cardiovasc Surg 109(6): 1218–1224
59. Oelberg DA, Marcotte F, Kreisman H, Wolkove N, Langleben D, Small D (1998) Evaluation of right ventricular systolic pressure during incremental exercise by Doppler echocardiography in adults with atrial septal defect. Chest 113(6):1459–1465
60. Mocellin R (1986) Sports fitness in pulmonary hypertension. Wien Klin Wochenschr 98(21):735–739
61. Hambrecht R, Fiehn E, Weigl C et al (1998) Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. Circulation 98(24):2709–2715
62. Goret L, Reboul C, Tanguy S, Dauzat M, Obert P (2005) Training does not affect the alteration in pulmonary artery vasoreactivity in pulmonary hypertensive rats. Eur J Pharmacol 527(1–3):121–128
63. Sandberg C, Thilen U, Wadell K, Johansson B (2015) Adults with complex congenital heart disease have impaired skeletal muscle function and reduced confidence in performing exercise training. Eur J Prev Cardiol 22(12):1523–1530
64. Kaemmerer H, Mebus S, Schulze-Neick I et al (2010) The adult patient with Eisenmenger syndrome: a medical update after dana point part I: epidemiology, clinical aspects and diagnostic options. Curr Cardiol Rev 6(4):343–355
65. Greyson CR (2010) The right ventricle and pulmonary circulation: basic concepts. Rev Esp Cardiol 63(1):81–95
66. Granton J, Mercier O, De Perrot M (2013) Management of severe pulmonary arterial hypertension. Semin Respir Crit Care Med 34(5):700–713
67. Zaffran S, Kelly RG, Meilhac SM, Buckingham ME, Brown NA (2004) Right ventricular myocardium derives from the anterior heart field. Circ Res 95(3):261–268
68. Moceri P, Dimopoulos K, Liodakis E et al (2012) Echocardiographic predictors of outcome in Eisenmenger syndrome. Circulation 126(12):1461–1468
69. Gatzoulis MA, Beghetti M, Landzberg MJ, Galie N (2014) Pulmonary arterial hypertension associated with congenital heart disease: recent advances and future directions. Int J Cardiol 177(2):340–347
70. Sztrymf B, Souza R, Bertoletti L et al (2010) Prognostic factors of acute heart failure in patients with pulmonary arterial hypertension. Eur Respir J 35(6):1286–1293
71. Diller GP, Alonso-Gonzalez R, Kempny A et al (2012) B-type natriuretic peptide concentrations in contemporary Eisenmenger syndrome patients: predictive value and response to disease targeting therapy. Heart 98(9):736–742
72. Bansal S, Lindenfeld J, Schrier RW (2009) Sodium retention in heart failure and cirrhosis: potential role of natriuretic doses of mineralocorticoid antagonist? Circ Heart Fail 2(4):370–376
73. Hoeper MM, Granton J (2011) Intensive care unit management of patients with severe pulmonary hypertension and right heart failure. Am J Respir Crit Care Med 184(10):1114–1124
74. Price LC, Wort SJ, Finney SJ, Marino PS, Brett SJ (2010) Pulmonary vascular and right ventricular dysfunction in adult critical care: current and emerging options for management: a systematic literature review. Crit Care 14(5):R169
75. Tayama E, Ueda T, Shojima T et al (2007) Arginine vasopressin is an ideal drug after cardiac surgery for the management of low systemic vascular resistant hypotension concomitant with pulmonary hypertension. Interact Cardiovasc Thorac Surg 6(6):715–719
76. Punnoose L, Burkhoff D, Rich S, Horn EM (2012) Right ventricular assist device in end-stage pulmonary arterial hypertension: insights from a computational model of the cardiovascular system. Prog Cardiovasc Dis 55(2):234–243. e232

77. Peacock A, Ross K (2010) Pulmonary hypertension: a contraindication to the use of {beta}-adrenoceptor blocking agents. Thorax 65(5):454–455
78. Bolger AP, Sharma R, Li W et al (2002) Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease. Circulation 106(1):92–99
79. Trojnarska O (2007) Heart failure in the adult patient with congenital heart disease. Cardiol J 14(2):127–136
80. Diller GP, Korten MA, Bauer UM et al (2016) Current therapy and outcome of Eisenmenger syndrome: data of the German National Register for congenital heart defects. Eur Heart J 37(18):1449–1455
81. Magri P, Rao MA, Cangianiello S et al (1998) Early impairment of renal hemodynamic reserve in patients with asymptomatic heart failure is restored by angiotensin II antagonism. Circulation 98(25):2849–2854
82. Anand IS, Ferrari R, Kalra GS, Wahi PL, Poole-Wilson PA, Harris PC (1989) Edema of cardiac origin. Studies of body water and sodium, renal function, hemodynamic indexes, and plasma hormones in untreated congestive cardiac failure. Circulation 80(2):299–305
83. Parameshwar J, Keegan J, Sparrow J, Sutton GC, Poole-Wilson PA (1992) Predictors of prognosis in severe chronic heart failure. Am Heart J 123(2):421–426
84. Ruiz-Cano MJ, Gonzalez-Mansilla A, Escribano P et al (2011) Clinical implications of supraventricular arrhythmias in patients with severe pulmonary arterial hypertension. Int J Cardiol 146(1):105–106
85. Tongers J, Schwerdtfeger B, Klein G et al (2007) Incidence and clinical relevance of supraventricular tachyarrhythmias in pulmonary hypertension. Am Heart J 153(1):127–132
86. Showkathali R, Tayebjee MH, Grapsa J et al (2011) Right atrial flutter isthmus ablation is feasible and results in acute clinical improvement in patients with persistent atrial flutter and severe pulmonary arterial hypertension. Int J Cardiol 149(2):279–280
87. Hoeper MM, Galie N, Murali S et al (2002) Outcome after cardiopulmonary resuscitation in patients with pulmonary arterial hypertension. Am J Respir Crit Care Med 165(3):341–344
88. Chubb H, Rosenthal E (2016) Implantable cardioverter-defibrillators in congenital heart disease. Herzschrittmacherther Elektrophysiol 27(2):95–103
89. Bedair R, Babu-Narayan SV, Dimopoulos K et al (2015) Acceptance and psychological impact of implantable defibrillators amongst adults with congenital heart disease. Int J Cardiol 181:218–224

Pulmonary Vasodilators in Patients with Pulmonary Arterial Hypertension Related to Congenital Heart Disease

16

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Abbreviations

ASD	atrial septal defect
CTEPH	chronic thromboembolic pulmonary hypertension
PAH	pulmonary arterial hypertension
PAH–CHD	pulmonary arterial hypertension associated with congenital heart disease
PAH–CTD	pulmonary arterial hypertension associated with connective tissue disease
PAH–HIV	pulmonary arterial hypertension associated with human inmunodeficiencyvirus
PDA	patent ductus arteriosus
VSD	ventricular septal defect

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16.1 Introduction

PAH associated to CHD (PAH–CHD) is a very heterogeneous population, ranging from patients with Eisenmenger syndrome, the extreme end of the spectrum, to patients in whom the congenital heart defect is more of an incidental finding. Unfortunately the majority of PAH–CHD patients have been excluded from the randomized controlled trials, and drug therapies are mainly based on clinical expertise rather than strong evidence. Table 16.1 summarizes the most important trials performed in pulmonary arterial hypertension and details the number and type of PAH associated with CHD included in each trial. The industry-run trials that did include PAH–CHD patients only included those with postoperative (post-repair) pulmonary hypertension. BREATHE-5 was the only trial focusing on patients with Eisenmenger syndrome [5]. Following BREATHE-5, smaller investigator-led studies have also focused on the Eisenmenger population.

This chapter will focus on the role of PAH therapies in PAH–CHD.

Table 16.1 Randomized controlled trials in pulmonary arterial hypertension

Author	Year	Drug	N	Aetiology	Number (%) and type of CHD
Barst et al. [1]	1996	Epoprostenol	41	iPAH	None
Olschewski et al. [2]	2002	Iloprost	203	iPAH, PAH–CTD, CTEPH, appetite suppressant	None
Simonneau et al. [3]	2002	Treprostinil	469	iPAH, PAH–CHD	109(23.2%)
				PAH–CHD	Postoperative PAH
					Eisenmenger
Galiè et al. [4]	2005	Sildenafil	278	iPAH, PAH–CTD, PAH–CHD	6(2.2%)
					Postoperative PAH
Galiè et al. [5]	2006	Bosentan	54	Eisenmenger	Bidirectional or reversed shunt
Galiè et al. [6]	2008	Ambrisentan	202 + 192	iPAH, PAH–CTD, PAH–HIV, appetite suppressant	None
Galiè et al. [7]	2009	Tadalafil	405	iPAH, PAH–CTD, PAH–HIV, appetite suppressant, PAH–CHD	32(7.9%) ASD (sat > 88%)
					15(3.7%) Postoperative PAH (VSD, PDA)
Pulido et al. [8]	2013	Macitentan	742	iPAH, PAH–CTD, PAH–HIV, appetite suppressant, drug-related PAH, PAH–CHD	62(8.4%)
					Postoperative PAH
Ghofrani et al. [9]	2013	Riociguat	443	iPAH, PAH–CTD, PAH–HIV, appetite suppressant, amphetamine-related PAH, PAH–CHD	35(8%)
					Postoperative PAH

16.2 Pulmonary Vasodilators in PAH-CHD

16.2.1 Endothelin Receptor Antagonists

Endothelin-1 (ET-1) is a peptide produced primarily by vascular endothelial cells and is a powerful vasoconstrictor and mitogen for smooth muscle. ET-1 binds to two types of receptors, endothelin-A (ET_A) and endothelin-B (ET_B) receptors: ET_A receptors are found in smooth muscle cells, whereas ET_B receptors are localized on both endothelial cells and smooth muscle cells. Activation of ET_A and ET_B receptors on smooth muscle cells mediates the vasoconstrictive and mitogenic effects of ET-1. Stimulation of endothelial ET_B receptors promotes ET-1 clearance and activation of nitric oxide (NO) and prostacyclin release. Activation of the ET-1 system has been demonstrated in both plasma and lung tissues of PAH patients.

Endothelin receptor antagonists include bosentan, ambrisentan and macitentan. These agents block the ET-1 receptors, reducing the deleterious effects of ET-1 (vasoconstriction, proliferation, inflammation and fibrosis). Bosentan and macitentan are competitive antagonists at the ET_A and ET_B receptors, while ambrisentan is more selective for the ET_A receptor.

Bosentan is the most investigated drug in PAH–CHD: it still is the only drug investigated in a large industry-led randomized controlled trial in patients with Eisenmenger syndrome. The *Bosentan Randomized Trial of Endothelin Antagonist Therapy-5* (*BREATHE-5*) was a 16-week, multicentre, randomized, double-blind, placebo-controlled study evaluating the effect of bosentan on systemic pulse oximetry (primary safety endpoint) and pulmonary vascular resistance (PVR) (primary efficacy endpoint). It included 54 patients aged >12 years, in the World Health Organization (WHO) functional class III and 6-min walk distance (6MWD) between 150 and 450 m, with oxygen saturation between 70% and 90%. All patients had Eisenmenger syndrome, but patients with a patent ductus arteriosus and those with complex congenital heart disease were excluded. The placebo-corrected effect on systemic pulse oximetry was 1.0% (95% confidence interval (CI) −0.7 to 2.8), demonstrating that bosentan did not worsen oxygen saturations. Compared with placebo, bosentan significantly reduced PVR (−472.0 dyne s cm^{-5}; $p = 0.0383$). The mean pulmonary arterial pressure decreased by 5.5 mm Hg ($p = 0.0363$), and the exercise capacity increased by 53.1 m ($p = 0.0079$) after 12 weeks of treatment. Thirty patients, who completed the BREATHE-5 study, were included in an open-label extension study for an additional 24 weeks [10], which demonstrated that the improvement in exercise capacity and functional class was maintained at 40 weeks. The above results were independent of the shunt location (pre- or post-tricuspid) [11]. Subsequent non-randomized studies suggested that the effect of bosentan was lost longer term [12–14], after about 2 years; however, recent data have addressed this point, showing prolonged beneficial effect of bosentan treatment on exercise capacity, stroke volume and quality of life [15, 16]. Diller et al. [15] recently reported on a cohort of 79 Eisenmenger patients treated with pulmonary vasodilators, 55 (69.6%) of whom with bosentan as first-line therapy, for a median follow-up

of 3.3 years (range 0.2–8.9 years): 6MWD increased early after initiation of treatment, with a plateau after approximately 3 years and no obvious trend towards a deterioration on average during longer-term follow-up. Vis et al. [16] also evaluated the long-term effect of bosentan on exercise capacity and quality of life in 64 patients with Eisenmenger syndrome. They reported a significant improvement in 6MWD at 6 months (+41 m; $p = 0.002$), which was maintained after 2.5 years ($p = 0.003$).

Ambrisentan is a selective endothelin receptor antagonist approved for idiopathic PAH (iPAH) and PAH associated with connective tissue disease (PAH–CTD). Patients with PAH–CHD were not included in the main randomized placebo-controlled studies of ambrisentan (ARIES-1 and ARIES-2) [6]; therefore, there is no randomized data on the effect of ambrisentan in this population. However, Zuckerman et al. [17] evaluated the short (mean 163 ± 57 days) and longer-term (mean 2.5 ± 0.5 years) effects of ambrisentan in a cohort of 17 consecutive patients with Eisenmenger syndrome. At short-term follow-up, there was a significant improvement in exercise capacity (6MWD: 389 ± 74 to 417 ± 77 m, $p = 0.03$), while oxygen saturations at rest and during exercise were maintained. At longer-term follow-up, compared to baseline and short-term follow-up, exercise capacity, oxygen saturations, functional class and haemoglobin concentration remained stable.

Macitentan is a new dual endothelin receptor antagonist recently approved for the treatment of patients with iPAH, heritable PAH and PAH–CTD, drug abuse, toxins or human immunodeficiency virus. Although the pivotal trial [8] included 62 patients with PAH–CHD, these were only patients with postoperative PAH. Patients with Eisenmenger syndrome were excluded. A trial of macitentan in Eisenmenger syndrome is under way.

Clinical trials specific to patients with PAH–CHD are required to examine the efficacy and safety of both macitentan and ambrisentan in the PAH–CHD population.

16.2.2 Drugs Acting on the Nitric Oxide Pathway

PAH is associated with impaired production of the endothelium-derived vasodilator NO. In healthy individuals, NO acts on smooth muscle cells to induce vasodilation and inhibit proliferation by increasing production of the secondary messenger cyclic guanosine monophosphate (cGMP) via activation of soluble guanylate cyclase (sGC) [18, 19]. The NO pathway can be targeted at different levels with PAH-specific therapies (Fig. 16.1). However, data on the efficacy of these drugs in PAH–CHD is patchy.

16.2.2.1 Nitric Oxide

Nitric oxide is a potent endogenous, endothelium-derived vasodilator that directly relaxes vascular smooth muscle through stimulation of GC (sGC) and increased

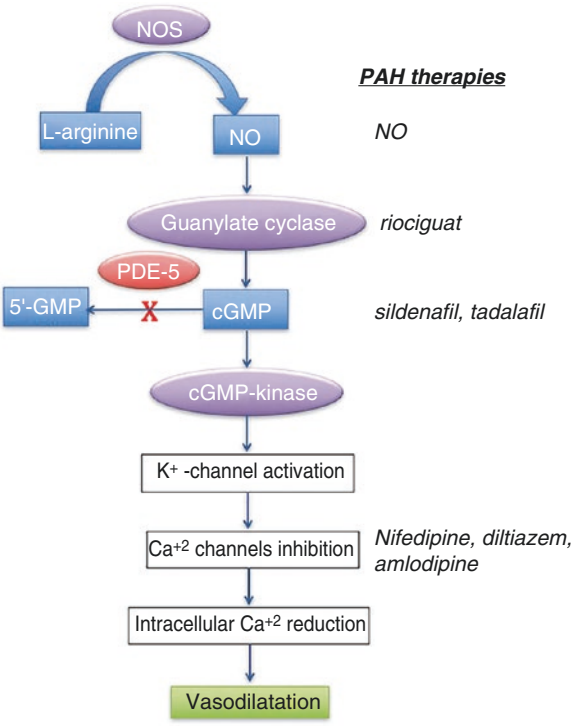

Fig. 16.1 Nitric oxide pathway and different PAH therapies. Outline of the nitric oxide (NO) metabolism pathway. Using L-arginine, NO synthases (NOS) produce NO. The NO activates soluble and membrane-bound guanylate cyclases, which synthesize cyclic guanylate monophosphate (cGMP), which subsequently activates cGMP kinase. This enzyme induces a reduction in intracellular calcium (Ca^{+2}) concentration through activation of potassium (K^{+}) channels and subsequent Ca^{+2} channel inhibition, resulting in vasodilation. The cGMP is degraded by phosphodiesterase (PDE)

production of intracellular cGMP. NO is mainly used to test vasoreactivity in patients with PAH. Since calcium channel blockers are not indicated in patients with PAH–CHD, the latest International ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension do not recommend vasoreactivity testing in this population [20]. However, NO may play a role in decompensated patients with PAH–CHD in the acute setting (intensive care), where NO may be one of the few available treatments.

Budts et al. [21] showed in 23 patients with PAH–CHD, including Eisenmenger patients, that inhaled NO is safe and is associated with a dose-dependent increase in circulating cGMP concentrations, mainly when used at 80 ppm. In addition, Barst et al. [22] reported the outcomes of 353 patients with PAH–CHD included in the REVEAL registry, of whom 151 had Eisenmenger syndrome. In this

cohort, the presence of acute vasoreactivity was an independent predictor of survival at 4 years from enrolment. Therefore, NO may also play a role in assessing the long-term prognosis of patients with PAH–CHD, but further studies are needed.

16.2.2.2 Phosphodiesterase Type 5 Inhibitors

Another strategy for increasing the activity of endogenous NO in PAH is to enhance NO-dependent cGMP-mediated pulmonary vasodilatation, through inhibition of the breakdown of cGMP by phosphodiesterase 5 (PDE-5). Sildenafil and tadalafil have been the lead substances in this group of agents, showing both acute and long-term beneficial effects in patients with iPAH [4, 7]. However, evidence on the use of PDE-5 inhibitors in patients with PAH–CHD is weaker than that for endothelin receptor antagonists.

Although patients with PAH–CHD were included in the pivotal trials with PDE-5 inhibitors (Table 16.1), they rarely represented more than 10% of the total population, and, typically, these trials only included patients with postoperative pulmonary hypertension (PAH which developed at any point after repair of a cardiac shunt), excluding other types of PAH–CHD. However, there are observational studies supporting the efficacy of sildenafil in this population [23–25]. Zhang et al. [25] reported on the effect of sildenafil in an open-label study on 84 Eisenmenger treated for 1 year. The authors showed significant improvement in pulmonary haemodynamics, including pulmonary vascular resistance (−474.0 dyne s cm^{-5} m^2, $p < 0.0001$) and mean pulmonary artery pressure (−4.7 mmHg, $p < 0.001$), as well as in symptoms, peripheral oxygen saturation and 6MWD (+56 m, $p < 0.001$). Sildenafil was well tolerated, and the reported adverse events were not different or more frequent than those seen in the iPAH population. In a prospective, open-label, multicentre trial, Zeng et al. [24] studied the effect of sildenafil in a cohort of 55 patients with PAH–CHD. The authors only included patients with simple lesions (atrial septal defect (ASD), ventricular septal defect (VSD) and patent ductus arteriosus (PDA)). After 12 weeks of treatment, there was a significant improvement in 6MWD in all groups (ASD, +58.8 m, $p < 0.001$; VSD, +42.5 m, $p = 0.006$; PDA, +56.6 m, $p = 0.006$), as well as a significant reduction in pulmonary vascular resistance (ASD, −412.6 dyne s cm^{-5}, $p < 0.001$; VSD, −453.3 dyne s cm^{-5} m^2, $p < 0.001$; PDA, −694.9 dyne s cm^{-5} m^2, $p = 0.046$) with no significant changes in systemic vascular resistance or systemic arterial pressure. In addition, Tay et al. [23] showed that sildenafil improved both quality of life and exercise capacity in a small cohort of 12 patients with Eisenmenger syndrome after 12 weeks of treatment.

Mukhopadhyay et al. [26] reported in a small observational study in a cohort of 16 symptomatic Eisenmenger patients that treatment with tadalafil for 12 weeks reduced pulmonary vascular resistance and improves oxygen saturations, WHO functional class and 6MWD, suggesting that tadalafil works in this population. Subsequently, the same group assessed in a randomized, double-blind, crossover trial the effect of tadalafil in a cohort of 28 patients with Eisenmenger syndrome. The study showed a significant improvement of 6MWD (+46.4 m, $p < 0.001$) as

well as a significant reduction in PVR (−7.3 dyne s cm^{-5}, $p < 0.001$) which led to a significant improvement in WHO functional class [27].

16.2.2.3 Soluble Guanylate Cyclase (sGC) Stimulators

Riociguat is a sGC stimulator that acts directly on sGC, stimulating the enzyme and increasing sensitivity to low levels of NO [28]. Riociguat has a dual mode of action, sensitizing sGC to endogenous NO and also directly stimulating sGC via a different binding site, independently of NO. This leads to vasodilation through the relaxation of smooth muscle cells. Riociguat has recently been approved for treatment of PAH in Europe and the USA. Approval of riociguat for the treatment of PAH was based on a pivotal, randomized, placebo-controlled phase III trial, Pulmonary Arterial Hypertension sGC Stimulator Trial-1 (PATENT-1) [29], which demonstrated that riociguat was well tolerated and significantly improved 6MWD, PVR, N-terminal of the prohormone of brain natriuretic peptide (NT-proBNP) levels, WHO functional class, time to clinical worsening and Borg dyspnoea score. Furthermore, the PATENT-2, an open-label extension study to PATENT-1, showed sustained improvements in exercise capacity and functional capacity at 2 years. The PATENT-1 trial included 35 patients with persistent/recurrent PAH after complete repair of the congenital heart disease (postoperative PAH) and the outcome of these patients have been recently reported by Rosenkranz et al. [30] in a post hoc analysis. They showed that after 12 weeks of treatment, riociguat improved 6MWD (+39 m) and WHO functional class and reduced PVR (−250 dyne s cm^{-5}) and NT-proBNP levels in these patients.

16.2.3 Drugs Acting on the Prostacyclin Pathway

Prostacyclin (PGI_2) is produced in endothelial cells and binds to endothelial prostacyclin receptors, leading to an increase cyclic adenosine monophosphate (cAMP) resulting in vasodilatory and antiproliferative effects. PAH patients have reduced levels of endogenous PGI_2 and reduced expression of PGI_2 synthase in the lung [31, 32]. Several PAH-specific therapies have been developed that target the PGI_2 pathway. While prostacyclin is not routinely used as PAH therapy in patients with PAH–CHD, there is data supporting its use in this setting.

16.2.3.1 Intravenous Prostacyclin: Epoprostenol

The first study on intravenous prostacyclin in patients with PAH–CHD was performed in the late 1990s, when oral PAH therapies were not yet available. This study included 20 treatment-naïve patients with PAH–CHD (children and adults) and showed a significant reduction in pulmonary vascular resistance indexed (−1040 dyne s cm^{-5} m^2, $p < 0.01$) and mean pulmonary artery pressure (−16 mmHg, $p < 0.01$) after a year of treatment. It also showed a significant improvement in cardiac index (+2.4 L min^{-1} m^{-2}) and New York Heart Association (NYHA) functional class. There was also an improvement in 6MWD, but this was not statistically significant (+52 m, $p = 0.13$). In this study, drug-related complications were similar to

those seen in patients with iPAH, and no instances of catheter sepsis were reported [33]. More recently, Fernandes et al. [34] reported on the effect of intravenous prostacyclin in a cohort of eight severely symptomatic patients with Eisenmenger syndrome. After 3 months of treatment, there was a significant improvement in 6MWD (+327 m, $p = 0.01$), NYHA functional class and oxygen saturation, which increased from 69 to 84% ($p = 0.01$). There was also a significant reduction in pulmonary vascular resistance (-1600 dyne s cm^{-5} m^2, $p = 0.04$) and a low complication rate.

The downside of using intravenous prostacyclin in this population is the theoretical higher risk of systemic emboli, mainly in patients with an unrepaired defect and right-to-left shunting. Special care should be taken with air bubbles in this population, and the use of air filters in the central line is recommended. Moreover, patients with Eisenmenger syndrome are prone to infection due to a chronic immunodeficient status. Although none of the aforementioned studies showed an increased risk of catheter sepsis in PAH–CHD, the sample size was rather small, and emphasis is put on aseptic technique when manipulating the central line in this cohort of patients. While patients with Eisenmenger syndrome are at an increased risk of thrombosis, prophylactic anticoagulation is not routinely recommended, even in the presence of a central line. Close monitoring of the platelet count is recommended when starting prostacyclin in all patients, especially those with Eisenmenger syndrome.

16.2.3.2 Subcutaneous Prostacyclin: Treprostinil

There are not many studies reporting on the use of subcutaneous prostacyclin in patients with PAH–CHD. However, this population was well represented in the pivotal study of treprostinil in PAH [3]. The treprostinil study is a 12-week, double-blind, placebo-controlled, multicentre trial in 470 patients with PAH, either idiopathic or associated with connective tissue disease or congenital systemic-to-pulmonary shunts. The study included mainly patients in NYHA functional class III, and a quarter of the patients had PAH–CHD. After 12 weeks, exercise capacity improved significantly in the overall population (+16 m, $p = 0.006$), independent of the aetiology. This improvement was even more noticeable in patients that walked less than 150 m at baseline, in whom 6MWD improved by 51 m, $p = 0.002$. There was also significant improvement in haemodynamics, with a reduction in pulmonary vascular resistance and increase in cardiac index. The most common side-effect attributed to treprostinil was infusion site pain (85%), leading to premature discontinuation from the study in 8% of patients. There is an ongoing randomized controlled trial of treprostinil in patients with PAH–CHD. This trial is currently recruiting patients and hopefully will shed light on the management of this challenging population.

16.2.3.3 Inhaled Prostacyclin: Iloprost

Data on inhaled prostacyclin in patients with PAH–CHD is also scanty and based on observational studies. Cha et al. [35] recently assessed the effects of iloprost in adult patients with PAH–CHD (EIGER study). The EIGER study was a prospective, multicentre, observational study, which included 18 patients with Eisenmenger syndrome treated with iloprost for 24 weeks. The study showed a significant improvement in 6MWD (+80.4 m, $p = 0.032$), as well as in quality of life and right ventricular function. However, there was no improvement in haemodynamics. Yang et al. [36] also recently reported on a cohort of 12 patients with Eisenmenger syndrome treated

with iloprost for an average of 18 months: there was a significant improvement in 6MWD (+93.6 m, $p = 0.013$), NYHA functional class and oxygen saturation, both at rest and exercise. There was also a reduction in mean pulmonary artery pressure, but this was not statistically significant. The main reported side effects of iloprost were mild headache and dyspnoea, no different from those reported in patients with iPAH.

In summary, although the evidence is scanty, prostacyclins should be considered part of the therapeutic armamentarium for patients with PAH–CHD, especially when oral therapies fail.

16.2.4 Calcium Channel Blockers

The role of calcium channel blockers has not been established in this population, and there are concerns with regard to systemic vasodilatation and the negative inotropic effect of some of these drugs. Therefore, although recent data suggest that evidence of vasoreactivity is associated with a better prognosis in PAH–CHD patients [37], there is currently no indication for routinely performing vasoreactivity testing in this setting for the assessment of prognosis or for assessing eligibility to calcium channel blocker therapy (see also chapters 14.1.5 and 16.1.2.1).

16.2.5 Combination Therapy

There is hardly any evidence on the use of combination therapy in PAH–CHD. The only randomized double-blind crossover study included 21 Eisenmenger patients and showed no significant improvement in exercise capacity in stable Eisenmenger patients who started on sildenafil in addition to bosentan [38]. Although methodologically robust, it is likely that the study was negative because the patients received the second drug while stable. More recently, two more observational studies in patients deteriorating on targeted PAH monotherapy were able to demonstrate significant improvements in exercise capacity and haemodynamics after adding a second agent [39, 40]. Therefore, combination therapy is recommended in PAH associated with CHD patients when deteriorating on monotherapy. The latest ESC/ERS guideline for the diagnosis and treatment of pulmonary hypertension recommendation for combination therapy in this population is IIb, level of evidence C; however, this recommendation is based on the above-mentioned randomized controlled trial. In addition, one might speculate that early initiation of pulmonary vasodilators in patients with PAH–CHD might reduce disease progression. This remains to be proven.

16.3 Treatment Goals in PAH Associated with CHD

The overall treatment goal in patients with PAH is achieving a status of good or acceptable exercise capacity and quality of life, improving or preserving right ventricular function and improving outcome. This means bringing or keeping patients in WHO functional class I–II, whenever possible. The latest ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension have modified the

Table 16.2 Monitoring and prognostication in patients with Eisenmenger syndrome

Better prognosis	Determinants of prognosis	Worse prognosis
No	Right ventricular failure	Yes
No	Syncope	Yes
I, II	WHO functional class	III, IV
>350 m	6MWD	<300 m
>85%	Oxygen saturation	<85% or a drop >2% per year
Transferrin saturation >20%	Iron deficiency	Transferrin saturation <20%
Normal or near normal	BNP plasma levels	>30 pmol/L
TAPSE ≥ 1.5 cm	Echocardiogram	TAPSE < 1.5 cm
RA area < 25 cm^2		RA area ≥ 25 cm^2
RA/LA ratio < 1.5		RA/LA ratio > 1.5
RAP < 8 mmHg and CI ≥ 2.5 L/min/m^2	Haemodynamics	RAP >15 mmHg and CI ≤ 2.0 L/min/m^2

BNP brain natriuretic peptide, *CI* cardiac index, *LA* left atrium, *RA* right atrium, *RAP* right atrial pressure, *TAPSE* tricuspid annular plane systolic excursion, *WHO* World Health Organization, *6MWD* 6-min walk distance. Adapted from Gatzoulis et al. [41]

treatment goals based on a low, moderate or high risk of mortality at 1 year (Table 13 of the ESC/ERS guidelines) [20]. These goals might apply to some patients with PAH–CHD but are difficult to apply to Eisenmenger patients who are those at the most severe end of the spectrum, and different management goals should be considered. In a recent publication, Gatzoulis et al. [41] proposed treatment goals specific for this population (Table 16.2).

16.4 Management of Specific PAH–CHD Populations

16.4.1 Segmental Pulmonary Hypertension

Lung perfusion in some patients with complex CHD relies on major aortopulmonary collaterals (MAPCAs), leading to differential pulmonary blood flow across the lung fields (see Chap. 6). Lung areas supplied by large MAPCAs are often "hyperperfused", thus, at risk of developing pulmonary vascular disease, which is not homogeneous across the lung: this entity is called "segmental pulmonary hypertension". This a very unusual haemodynamic condition, which has now been included in group 5 in the latest ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension [20].

The diagnosis of PH in this setting requires a high degree of suspicion and great expertise to understand whether low oxygen saturations in patients with MAPCAs are attributable to segmental PH or inadequate lung perfusion as a result of inadequate pulmonary blood flow from MAPCAs, MAPCA stenosis or thrombosis [42]. The presence of a low flow velocity when interrogating collaterals using Doppler echocardiography should alert to the presence of segmental pulmonary hypertension. Unfortunately, the definitive diagnosis requires cardiac catheterization with selective cannulation of MAPCAs and should be performed in specialized centres.

There are some observational studies supporting treatment of patients with segmental PH using PAH therapies. In a small retrospective, multicentre, case series of patients with segmental pulmonary hypertension, Schuuring et al. [43] reported a significant improvement in 6MWD (+62 m, $p = 0.03$) and NYHA functional class after 12 months of treatment. Nevertheless, further larger and prospective studies are needed to confirming the efficacy and safety of PAH-specific therapy in this setting [42].

16.4.2 Patients with a Fontan Circulation

The Fontan procedure involves routing systemic venous blood flow to the pulmonary arteries without the interposition of a ventricle. In these patients the (effectively single) ventricle pumps blood through the body, with the systemic venous return passively entering the pulmonary circulation. Thus, low pulmonary vascular resistance is paramount in this setting. Although several factors determine cardiac output in patients with Fontan circulation, pulmonary vascular resistance appears to be a major determinant [44]. Pulmonary vascular resistance increases physiologically with increasing age, eventually leading to failure of the Fontan circulation. There is no clear cut-off for diagnosing PH in this population; however, a mean pulmonary artery pressure at rest >15 mmHg is felt to be high enough to preclude Fontan conversion (from an older atriopulmonary Fontan to total cavopulmonary connection). Invasive estimates of pulmonary vascular resistance in the presence of very low pulmonary blood flow and/or multiple sources of blood flow to the lung are often challenging to obtain.

PAH therapies aimed at reducing pulmonary vascular resistance are an attractive option for patients with a failing Fontan circulation due to an increase pulmonary vascular resistance. However, available data are contradictory. Sildenafil has been tested in different studies in this population. Giardini et al. [45] reported in a cohort of 27 patients with Fontan circulation that sildenafil improves peak oxygen consumption, pulmonary blood flow and cardiac index 1 h after administration. Unfortunately this effect has not been confirmed in subsequent randomized controlled trials. In a double-blind, placebo-controlled, crossover trial conducted in children and young adults after Fontan surgery, Goldberg et al. [46] studied the effects of sildenafil after 6 weeks of treatment. There was a significant reduction in respiratory rate and minute ventilation at peak exercise. There was also a significant decrease in the ventilatory equivalent of carbon dioxide at anaerobic threshold. However, there was only a trend for improved oxygen consumption at the anaerobic threshold, with no improvement at peak exercise.

Bosentan has also been studied in patients with Fontan circulation, again with contradictory results. In a cohort of 42 patients with Fontan circulation, Schuuring et al. [47] reported that 6 months of treatment with bosentan improved neither exercise capacity nor quality of life, but there was an increase in NT-proBNP. More recently, Hebert et al. [48] randomized 75 stable patients with Fontan circulation to bosentan or placebo. After 12 weeks there was a significant improvement in peak oxygen consumption, exercise time and NYHA functional class in the bosentan group. In addition, side effects were mild and there was no significant difference in both groups.

In summary, although some studies have suggested a positive effect of PAH therapies in patients with Fontan circulation, there is still insufficient evidence to support routine use in this population, and further studies are warranted before therapeutic recommendations can been made.

Conclusions

Overall, the number of patients with PAH–CHD followed in tertiary referral centres is increasing. Fortunately, the field has seen significant progress over the last two decades, resulting in improved survival and quality of life for patients. However, the complexity of some of these patients makes their management challenging, requiring close collaboration between specialist and non-specialist centres to provide the best care possible.

References

1. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB et al (1996) A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med 334(5):296–301
2. Olschewski H, Simonneau G, Galie N, Higenbottam T, Naeije R, Rubin LJ et al (2002) Inhaled iloprost for severe pulmonary hypertension. N Engl J Med 347(5):322–329
3. Simonneau G, Barst RJ, Galie N, Naeije R, Rich S, Bourge RC et al (2002) Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med 165(6):800–804
4. Galie N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D et al (2005) Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med 353(20):2148–2157
5. Galie N, Beghetti M, Gatzoulis MA, Granton J, Berger RM, Lauer A et al (2006) Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. Circulation 114(1):48–54
6. Galie N, Olschewski H, Oudiz RJ, Torres F, Frost A, Ghofrani HA et al (2008) Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. Circulation 117(23):3010–3019
7. Galie N, Brundage BH, Ghofrani HA, Oudiz RJ, Simonneau G, Safdar Z et al (2009) Tadalafil therapy for pulmonary arterial hypertension. Circulation 119(22):2894–2903
8. Pulido T, Rubin LJ, Simonneau G (2014) Macitentan and pulmonary arterial hypertension. N Engl J Med 370(1):82–83
9. Ghofrani HA, Simonneau G, Rubin LJ, Authors of C, Patent (2013) Riociguat for pulmonary hypertension. N Engl J Med 369(23):2268
10. Gatzoulis MA, Beghetti M, Galie N, Granton J, Berger RM, Lauer A et al (2008) Longer-term bosentan therapy improves functional capacity in Eisenmenger syndrome: results of the BREATHE-5 open-label extension study. Int J Cardiol 127(1):27–32
11. Berger RM, Beghetti M, Galie N, Gatzoulis MA, Granton J, Lauer A et al (2010) Atrial septal defects versus ventricular septal defects in BREATHE-5, a placebo-controlled study of pulmonary arterial hypertension related to Eisenmenger's syndrome: a subgroup analysis. Int J Cardiol 144(3):373–378
12. Apostolopoulou SC, Manginas A, Cokkinos DV, Rammos S (2007) Long-term oral bosentan treatment in patients with pulmonary arterial hypertension related to congenital heart disease: a 2-year study. Heart 93(3):350–354

13. Diller GP, Dimopoulos K, Kaya MG, Harries C, Uebing A, Li W et al (2007) Long-term safety, tolerability and efficacy of bosentan in adults with pulmonary arterial hypertension associated with congenital heart disease. Heart 93(8):974–976
14. van Loon RL, Hoendermis ES, Duffels MG, Vonk-Noordegraaf A, Mulder BJ, Hillege HL et al (2007) Long-term effect of bosentan in adults versus children with pulmonary arterial hypertension associated with systemic-to-pulmonary shunt: does the beneficial effect persist? Am Heart J 154(4):776–782
15. Diller GP, Alonso-Gonzalez R, Dimopoulos K, Alvarez-Barredo M, Koo C, Kempny A et al (2013) Disease targeting therapies in patients with Eisenmenger syndrome: response to treatment and long-term efficiency. Int J Cardiol 167(3):840–847
16. Vis JC, Duffels MG, Mulder P, de Bruin-Bon RH, Bouma BJ, Berger RM et al (2013) Prolonged beneficial effect of bosentan treatment and 4-year survival rates in adult patients with pulmonary arterial hypertension associated with congenital heart disease. Int J Cardiol 164(1):64–69
17. Zuckerman WA, Leaderer D, Rowan CA, Mituniewicz JD, Rosenzweig EB (2011) Ambrisentan for pulmonary arterial hypertension due to congenital heart disease. Am J Cardiol 107(9):1381–1385
18. Arnold WP, Mittal CK, Katsuki S, Murad F (1977) Nitric oxide activates guanylate cyclase and increases guanosine 3':5'-cyclic monophosphate levels in various tissue preparations. Proc Natl Acad Sci U S A 74(8):3203–3207
19. Ignarro LJ, Buga GM, Wood KS, Byrns RE, Chaudhuri G (1987) Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. Proc Natl Acad Sci U S A 84(24):9265–9269
20. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A et al (2016) 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 37(1):67–119
21. Budts W, Van Pelt N, Gillyns H, Gewillig M, Van De Werf F, Janssens S (2001) Residual pulmonary vasoreactivity to inhaled nitric oxide in patients with severe obstructive pulmonary hypertension and Eisenmenger syndrome. Heart 86(5):553–558
22. Barst RJ, Ivy DD, Foreman AJ, McGoon MD, Rosenzweig EB (2014) Four- and seven-year outcomes of patients with congenital heart disease-associated pulmonary arterial hypertension (from the REVEAL registry). Am J Cardiol 113(1):147–155
23. Tay EL, Papaphylactou M, Diller GP, Alonso-Gonzalez R, Inuzuka R, Giannakoulas G et al (2011) Quality of life and functional capacity can be improved in patients with Eisenmenger syndrome with oral sildenafil therapy. Int J Cardiol 149(3):372–376
24. Zeng WJ, Lu XL, Xiong CM, Shan GL, Liu ZH, Ni XH et al (2011) The efficacy and safety of sildenafil in patients with pulmonary arterial hypertension associated with the different types of congenital heart disease. Clin Cardiol 34(8):513–518
25. Zhang ZN, Jiang X, Zhang R, Li XL, Wu BX, Zhao QH et al (2011) Oral sildenafil treatment for Eisenmenger syndrome: a prospective, open-label, multicentre study. Heart 97(22):1876–1881
26. Mukhopadhyay S, Sharma M, Ramakrishnan S, Yusuf J, Gupta MD, Bhamri N et al (2006) Phosphodiesterase-5 inhibitor in Eisenmenger syndrome: a preliminary observational study. Circulation 114(17):1807–1810
27. Mukhopadhyay S, Nathani S, Yusuf J, Shrimal D, Tyagi S (2011) Clinical efficacy of phosphodiesterase-5 inhibitor tadalafil in Eisenmenger syndrome—a randomized, placebo-controlled, double-blind crossover study. Congenit Heart Dis 6(5):424–431
28. Grimminger F, Weimann G, Frey R, Voswinckel R, Thamm M, Bolkow D et al (2009) First acute haemodynamic study of soluble guanylate cyclase stimulator riociguat in pulmonary hypertension. Eur Respir J 33(4):785–792
29. Ghofrani HA, Galie N, Grimminger F, Grunig E, Humbert M, Jing ZC et al (2013) Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med 369(4):330–340

30. Rosenkranz S, Ghofrani HA, Beghetti M, Ivy D, Frey R, Fritsch A et al (2015) Riociguat for pulmonary arterial hypertension associated with congenital heart disease. Heart. 101(22):1792–1799
31. Christman BW, McPherson CD, Newman JH, King GA, Bernard GR, Groves BM et al (1992) An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension. N Engl J Med 327(2):70–75
32. Tuder RM, Cool CD, Geraci MW, Wang J, Abman SH, Wright L et al (1999) Prostacyclin synthase expression is decreased in lungs from patients with severe pulmonary hypertension. Am J Respir Crit Care Med 159(6):1925–1932
33. Rosenzweig EB, Kerstein D, Barst RJ (1999) Long-term prostacyclin for pulmonary hypertension with associated congenital heart defects. Circulation 99(14):1858–1865
34. Fernandes SM, Newburger JW, Lang P, Pearson DD, Feinstein JA, Gauvreau K et al (2003) Usefulness of epoprostenol therapy in the severely ill adolescent/adult with Eisenmenger physiology. Am J Cardiol 91(5):632–635
35. Cha KS, Cho KI, Seo JS, Choi JH, Park YH, Yang DH et al (2013) Effects of inhaled iloprost on exercise capacity, quality of life, and cardiac function in patients with pulmonary arterial hypertension secondary to congenital heart disease (the Eisenmenger syndrome) (from the EIGER study). Am J Cardiol 112(11):1834–1839
36. Yang SI, Chung WJ, Jung SH, Choi DY (2012) Effects of inhaled iloprost on congenital heart disease with Eisenmenger syndrome. Pediatr Cardiol 33(5):744–748
37. D'Alto M, Romeo E, Argiento P, Santoro G, Sarubbi B, Gaio G et al (2010) Pulmonary vasoreactivity predicts long-term outcome in patients with Eisenmenger syndrome receiving bosentan therapy. Heart 96(18):1475–1479
38. Iversen K, Jensen AS, Jensen TV, Vejlstrup NG, Sondergaard L (2010) Combination therapy with bosentan and sildenafil in Eisenmenger syndrome: a randomized, placebo-controlled, double-blinded trial. Eur Heart J 31(9):1124–1131
39. D'Alto M, Romeo E, Argiento P, Sarubbi B, Santoro G, Grimaldi N et al (2012) Bosentan-sildenafil association in patients with congenital heart disease-related pulmonary arterial hypertension and Eisenmenger physiology. Int J Cardiol 155(3):378–382
40. Diller GP, Alonso-Gonzalez R, Kempny A, Dimopoulos K, Inuzuka R, Giannakoulas G et al (2012) B-type natriuretic peptide concentrations in contemporary Eisenmenger syndrome patients: predictive value and response to disease targeting therapy. Heart 98(9):736–742
41. Gatzoulis MA, Beghetti M, Landzberg MJ, Galie N (2014) Pulmonary arterial hypertension associated with congenital heart disease: recent advances and future directions. Int J Cardiol 177(2):340–347
42. D'Alto M, Diller GP (2014) Pulmonary hypertension in adults with congenital heart disease and Eisenmenger syndrome: current advanced management strategies. Heart 100(17):1322–1328
43. Schuuring MJ, Bouma BJ, Cordina R, Gatzoulis MA, Budts W, Mullen MP et al (2013) Treatment of segmental pulmonary artery hypertension in adults with congenital heart disease. Int J Cardiol 164(1):106–110
44. Gewillig M, Brown SC, Eyskens B, Heying R, Ganame J, Budts W et al (2010) The fontan circulation: who controls cardiac output? Interact Cardiovasc Thorac Surg 10(3):428–433
45. Giardini A, Balducci A, Specchia S, Gargiulo G, Bonvicini M, Picchio FM (2008) Effect of sildenafil on haemodynamic response to exercise and exercise capacity in fontan patients. Eur Heart J 29(13):1681–1687
46. Goldberg DJ, French B, McBride MG, Marino BS, Mirarchi N, Hanna BD et al (2011) Impact of oral sildenafil on exercise performance in children and young adults after the fontan operation: a randomized, double-blind, placebo-controlled, crossover trial. Circulation 123(11):1185–1193
47. Schuuring MJ, Vis JC, van Dijk AP, van Melle JP, Vliegen HW, Pieper PG et al (2013) Impact of bosentan on exercise capacity in adults after the fontan procedure: a randomized controlled trial. Eur J Heart Fail 15(6):690–698
48. Hebert A, Mikkelsen UR, Thilen U, Idorn L, Jensen AS, Nagy E et al (2014) Bosentan improves exercise capacity in adolescents and adults after fontan operation: the TEMPO (treatment with endothelin receptor antagonist in fontan patients, a randomized, placebo-controlled, double-blind study measuring peak oxygen consumption) study. Circulation 130(23):2021–2030

Perspectives on Shunts in Pulmonary Arterial Hypertension: From Interventions to Create Shunts to the Concept of "Treat-and-Repair"

17

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Abbreviations

CHD	Congenital heart disease
LV	Left ventricle/ventricular
PA	Pulmonary artery/arterial
PAH	Pulmonary arterial hypertension
PAH–CHD	PAH related to congenital heart disease
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
Qp:Qs	Ratio of pulmonary-to-systemic flow
RA	Right atrial
RHF	Right heart failure
RV	Right ventricle/ventricular
WU	Wood units

17.1 Introduction

Medical therapy for pulmonary arterial hypertension (PAH) has evolved dramatically over the past two decades. A subset of patients, however, still develops progressive right heart failure (RHF) despite aggressive use of available medications. Options for these patients are largely limited to mechanical interventions. Such interventions fall into three main categories: creation of a communication to allow right-to-left

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shunting, device implantation or transplantation. This chapter will review the first two approaches. It should be highlighted that the available options carry high risk of periprocedural demise and do not address the underlying pathophysiology of pulmonary vascular remodelling. As such, they are reserved for severely ill patients without alternative options and are usually seen as a temporizing measure in anticipation of eventual transplantation. These interventions are not commonly performed. It should be evident, then, that both the decision to proceed and the technical performance of these procedures should be limited to a small number of referral centres that also perform or have close links to a lung transplantation centre.

From the converse perspective, a subset of patients born with an intracardiac or intravascular shunt lesion develops PAH. Some manifest as Eisenmenger syndrome: severe, irreversible PAH with markedly elevated pulmonary vascular resistance (PVR) and resulting bidirectional or right-to-left shunting. Others develop a more moderate degree of pulmonary vascular remodelling. The presence of a shunt lesion in patients with significant pulmonary vascular disease is considered advantageous, as it provides a relief outlet to prevent clinical RHF and patients with such a shunt appear to have better long-term prognosis than those with a repaired defect and residual or persistent PAH. With the advent of effective medical therapy for PAH, there is, however, increasing interest in whether some patients may benefit from medical treatment followed by repair of their underlying congenital heart defect (the "treat-and-repair" concept). Defect closure can be dangerous in PAH–CHD patients with moderate-to-severe pulmonary vascular disease, but may improve symptoms over the medium term in others with very mild forms of PAH. It is still unclear how to identify patients who may benefit from such an approach, versus those who are likely to suffer adverse long-term consequences of progressive RHF after closing the shunt.

17.2 Interventional Approaches to Pulmonary Arterial Hypertension

17.2.1 Creating Shunts in Those Without

17.2.1.1 Rationale

RHF develops in a subset of PAH patients, manifesting haemodynamically as a combination of high right heart filling pressures and low cardiac index. Simply put, the right ventricle (RV) is unable to eject an adequate volume of blood through the high-resistance pulmonary circulation at normal filling pressures. While the primary pathophysiology may be pulmonary vascular disease and elevated PVR, there is heterogeneity in right heart response to elevated PVR. RHF may develop in patients with only modestly elevated PVR, while others remain compensated despite severely elevated PVR. Therefore, the cardiac response (adaptation) to elevated pulmonary impedance is an appealing independent target for intervention.

While attention focuses on RV function, several specific consequences of RV dysfunction and dilatation deserve mention. The first is adverse ventricular

interaction. The dilated, hypertensive, hypertrophied RV sustains prolonged systolic contraction in response to increased pulmonary impedance; this results in end-systolic motion of the ventricular septum towards the left ventricular (LV) cavity [1]. The result is impaired early diastolic LV filling and lower LV end-diastolic volume. This limits stroke volume in the context of stable ejection fraction. The second important consequence is tricuspid regurgitation. The tricuspid valve, given its septal attachments, is more prone to regurgitation with ventricular dilatation or dysfunction than is the mitral valve. The third consequence is RV ischaemia. This relates to increased oxygen demand on the hypertrophied, hypertensive, dilated RV with its single coronary supply. Right coronary artery flow normally occurs during both systole and diastole, since there is a large pressure gradient between the aorta and RV cavity throughout the cardiac cycle. As a result of the markedly elevated systolic RV pressure in patients with PAH, coronary flow acquires a predominantly diastolic pattern, akin to that seen normally in coronaries perfusing the LV. These sequelae of severe RV dysfunction have pivotal ramifications for mechanical interventions in end-stage PAH: even modest changes in RV geometry and function may have striking effects on overall clinical status, because of improved ventricular interaction, tricuspid regurgitation and balance between myocardial oxygen demand and supply.

The main goal of creating a shunt lesion in patient with PAH who does not have a shunt is to off-load the RV. However, any right-to-left shunt will cause systemic hypoxemia. Candidates for these procedures have low cardiac output, and the arteriovenous oxygen content difference tends to be high, with low mixed venous saturation. Hence, for any given volume of shunted blood, the degree of systemic hypoxemia will be greater in patients with a low rather than normal cardiac output. In addition, many patients with severe PAH have some degree of baseline hypoxemia related to limited pulmonary diffusion, which further limits the right-to-left shunt volume that can be tolerated, without leading to catastrophic hypoxemia. Therefore, such a risky approach is only justifiable because a small shunt can have a major beneficial effect.

There are two primary options available for creating a right-to-left shunt in adults with PAH who do not have a shunt: atrial septostomy or a Potts shunt. Atrial septostomy is better established, and there is greater experience with this approach. Because of the high peri-procedural risk, limited control over shunt size and compulsory cerebral hypoxemia, investigators have explored an alternative approach, i.e. the creation of a communication between the left pulmonary artery and the descending aorta (Potts shunt).

17.2.1.2 Atrial Septostomy

Atrial septostomy refers to the creation of a defect in the atrial septum. This is generally done percutaneously for adults with PAH. Balloon atrial septostomy was pioneered in the 1960s, aimed at creating an atrial communication to allow systemic and pulmonary venous mixing, thus allowing oxygenated blood to perfuse systemic tissues in patients with D-looped transposition of the great arteries and other patients with CHD [2]. The technique used for this population involves

tearing a large, uncontrolled rent in the atrial septum. An uncontrolled, large volume shunt can be catastrophic for adults with PAH, since it would be associated with acute, severe hypoxemia. Since the aim in these patients is to create as large a defect as possible with a tolerable degree of hypoxemia, a graded approach is preferred.

Atrial septostomy has been explored for adults with PAH since the 1980s and 1990s [3–5]. The technique involves creation of a small hole in the atrial septum with either a Park blade or Brockenbrough needle (occasionally with radiofrequency energy). The small defect is sequentially enlarged by dilatation with progressively larger balloons, with intervening pauses to assess the haemodynamic effects of the defect prior to further dilatation. Depending on final defect size and provider preference, some may opt to place a stent across the atrial septal defect [6]. The aim of stenting is to increase the likelihood that patency of the defect is maintained, an especially important consideration with small defects. Placement of a stent also allows more specific manipulation of defect size and geometry.

Immediate haemodynamic effects include decreased right atrial volume and pressure, increased left atrial volume (and, typically, concomitant increase in pressure), increased systemic cardiac index and hypoxemia; there is no important effect on the RV or pulmonary artery pressure. Since systemic cardiac index increases to a greater degree than arterial oxygen saturation falls, systemic arterial oxygen delivery tends to increase, albeit modestly. These effects are strongly related to baseline right atrial (RA) pressure. Those with higher RA pressure demonstrate more impressive immediate haemodynamic changes. Unfortunately, while those with extremely high RA pressure tend to have a dramatic improvement in systemic cardiac index, this is associated with a high risk of uncontrolled hypoxemia and death. As a consequence, patients with RA pressure >20 mmHg are usually not considered to be candidates for atrial septostomy; other strong predictors of adverse outcome include markedly elevated PVR (>55 WU m^2), low resting oxygen saturation (≤90%), markedly elevated left heart filling pressure and otherwise very poor prognosis without intervention [7, 8]. Patient selection is critical.

Clinical improvement correlates with the immediate haemodynamic response. Those who improve clinically tend to be those who have greater acute improvements in systemic cardiac index and oxygen delivery [9]. The effect of atrial septostomy on the haemodynamic response to physical work (activity or exercise) is not well studied, however. It seems likely that the benefit of an atrial-level shunt would be more pronounced during periods of increased demand, a hypothesis supported by an animal model of atrial shunt in PAH [10]. In addition, chronic hypoxemia causes secondary erythrocytosis. This effect is likely beneficial, since the higher haemoglobin concentration increases arterial oxygen carrying capacity.

17.2.1.3 Potts Shunt

Potts described an alternative to the classic Blalock–Taussig–Thomas shunt, with surgical creation of a side-to-side anastomosis between the descending aorta and left pulmonary artery, in 1946 [11]. In cyanotic CHD, the goal of systemic-to-pulmonary arterial shunts is to increase pulmonary blood flow (left-to-right shunt)

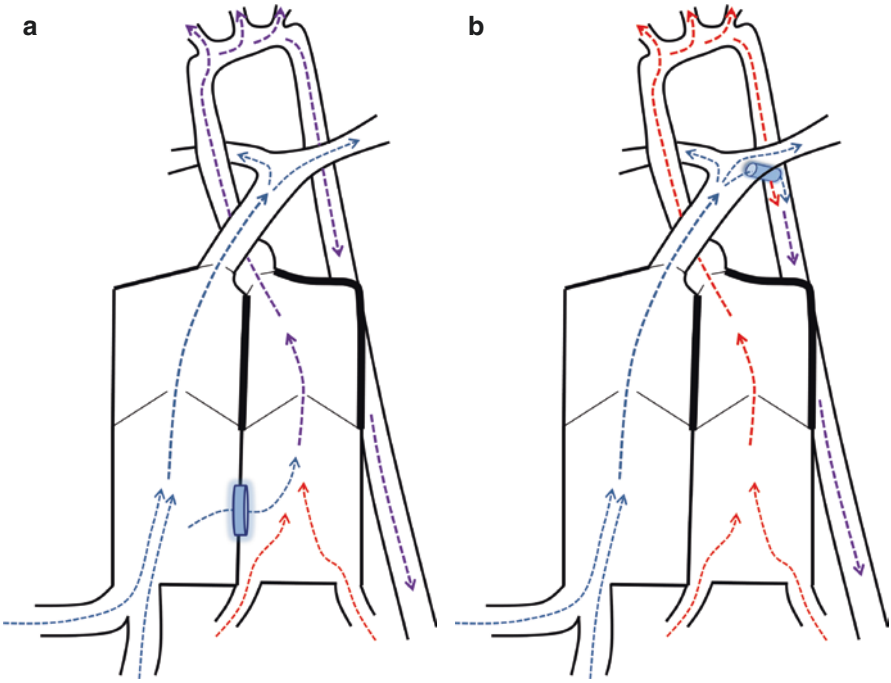

Fig. 17.1 (**a**) An atrial septostomy permits right-to-left shunting at the atrial level. This off-loads the right ventricle and augments systemic cardiac output, but at the expense of hypoxemia to the entire systemic circulation, including the head and neck. (**b**) A Potts shunt provides a connection between the left pulmonary artery and descending aorta. This permits right-to-left shunting at the arterial level distal to the take-off of the head and neck blood supply. As with the atrial septostomy, systemic cardiac output is increased and right ventricular load is reduced, but in this case, blood perfusing the head and neck is not hypoxemic. *Blue arrows*, systemic venous blood, most hypoxemic; *red arrows*, oxygenated pulmonary venous blood; *purple arrows*, mixed systemic and pulmonary venous blood with intermediate hypoxemia

and thereby increase systemic oxygen saturation. This is not the result in adults with PAH, as described in more detail below. The intended effect is, rather, equivalent to the aim of atrial septostomy: off-loading the failing right heart.

A small series first explored the role of surgical Potts shunt creation in children with PAH [12]. The benefit of this approach appears to be sustained over the medium to long term [13]. The physiology is akin to preserving or enlarging an otherwise insignificant patent ductus arteriosus in a young child, an uncommon but accepted approach in that age range [14]. Theoretical advantages of a Potts shunt compared with atrial septostomy are several. First, shunt size can be more precisely controlled. Second, because the right-to-left shunt is distal to the head and neck vessels, the carotid chemoreceptors and brain are perfused with near normoxic blood, unless there is an alternative reason for hypoxemia (Fig. 17.1). This might be expected to be associated with fewer symptoms related to hypoxemia, an observation made in the 1950s when comparing effort intolerance in patients with Eisenmenger

syndrome who had a shunt distal to the head and neck vessels (i.e. patent ductus arteriosus) with those at atrial or ventricular level [15]. Third, for similar reasons, coronary perfusion is also spared hypoxemia. The kidneys are still perfused with hypoxemic blood, so secondary erythrocytosis will result.

Thoracic surgery is fraught with risk in adults with severe PAH. Because of this, catheter-based options for Potts shunt creation have been explored. One group explored anatomical relationships to describe a potential new device approach to creating a Potts shunt percutaneously [16]. Another group, in 2013, reported the first series of patients undergoing this procedure; four patients 18–47 years old with PAH and intractable, severe symptoms despite maximal medical therapy were included [17]. The procedure involved positioning a vascular snare at the target site in the left PA and then advancing a shaped Brockenbrough transseptal needle to the aortic intima/media with contrast injection to confirm position; the sharpened back end of a wire was then advanced through the needle across the aortic wall, between the aorta and left PA, and into the left PA. A coronary balloon catheter was then threaded over the sharpened wire, allowing replacement by a soft-tipped wire as a primary rail within the PA. This wire was captured with the snare, and a long sheath was then advanced across the wire from the aorta into the PA, using the balloon catheter as a functional dilator. The aim of this approach was to maintain pressure (tamponade) across the rents created in the aorta and high pressure PA throughout the procedure. After this, the balloon catheter was removed, and a 7 × 22 mm covered stent was placed to span the distance between the two great vessels [17].

There was impressive symptomatic and functional improvement in two of the four patients. One of the patients was hospitalized critically ill and died of his underlying disease, including ventilator-associated pneumonia, after, but seemingly unrelated to the procedure. The fourth died of peri-procedural complications due to uncontrolled bleeding into the mediastinum. Three other patients were considered for the procedure, but all died prior to the procedure being performed, providing a perspective on the clinical status of those included in the series [17].

This experience confirms the potential benefits of creating a shunt between the left PA and descending aorta, but also highlights that further progress is needed in patient selection and technique, to identify patients most likely to benefit and improve acute outcomes [18]. Given the small number of patients treated with this therapy, it is unknown how the risk and clinical benefit of this procedure will compare with atrial septostomy, or developing new techniques.

17.2.2 Other Interventional Approaches

There are a number of other interventional approaches available or under study for the management of severe, drug refractory PAH. For example, patients may benefit from extracorporeal membrane oxygenation or ventilation (e.g. Novalung) while awaiting transplant. Others have been exploring the role for percutaneous pulmonary denervation. The biological basis for this therapy is not entirely established. There seems to be a reflex vasoconstrictive response, whereby stretch in the proximal PAs causes distal vasoconstriction. A group in China reported on 21 patients,

13 who underwent a simple procedure to denervate the PA and eight who refused the procedure [19]. After 3 months, those who underwent the procedure had remarkable improvement: mean PAP was lower (from 55 to 36 mmHg) and 6-min walk distance improved (324–491 m). A study including a larger number of more heterogeneous patients (not only PAH) with 1-year follow-up from the same group again reported benefit, though the magnitude was notably smaller (e.g. mPAP from 53.1 to 44.6 mmHg). The Kaplan–Meier 1-year estimate of mortality was just over 15%. There were no issues reported in short- to medium-term safety [20]. While exciting, a number of fundamental questions remain about this procedure in terms of safety and efficacy and its place in contemporary practice with an array of somewhat effective medications [21]. There has, however, been some research with animal models suggesting that pulmonary denervation may have beneficial effects [22]. As it stands, the applicability of the findings to patients with severe PAH remains in question, and the results have yet to be replicated or studied with a more scientifically rigorous study design. There are planned and ongoing studies to test this in patients with PAH and in those with PH related to other disease (e.g. NCT02525926, NCT02403908, NCT02220335).

Creation of a ventricular septal defect to off-load the RV [23], banding of the proximal main pulmonary artery to off-load the pulmonary vasculature [24–26] and banding of the aorta to alter the nature of the RV response to increased load [27] have been described: while there may be specific situations where these interventions may be considered, they are rarely considered as evidence is lacking and each has important recognized limitations.

17.3 The Concept of Treat-and-Repair: Eliminating a Shunt

While prevention is impossible for most types of PAH, timely intervention to repair congenital shunt lesions may avert PAH. In patients with a sizable shunt and normal pulmonary vascular physiology, interventional repair is clearly indicated. Effort tolerance improves and long-term outcomes are better, especially with early repair [28, 29]. Conversely, repair of cardiac shunt defects in the presence of severe pulmonary vascular disease is contraindicated; while there are a wide array of adverse consequences of PAH and right-to-left shunting [30, 31], the presence of a "relief outlet" appears to provide clinical benefit for the reasons discussed above for the creation of shunt in patients with severe PAH without a shunt. Indeed, those patients who have persistent, or new and progressive PAH after defect repair, have worse outcomes compared to patients who are left unrepaired [32].

The challenge is defining what constitutes important irreversible pulmonary vascular disease in the middle ground, between normal and severe PAH [33–36]. Most adults with such intermediate pulmonary haemodynamics have a pre-tricuspid lesion (e.g. atrial septal defect), since sizable post-tricuspid shunts (e.g. patent ductus arteriosus and ventricular septal defect) are usually associated with development of PAH during childhood. Different expert guideline documents vary widely in their recommendations (Table 17.1), underlining the lack of rigorous, prospective, long-term outcomes data. While low Q_p:Q_s and higher PVR are often present in patients

Table 17.1 Recommendations for atrial septal defect closure from three recent consensus documents

	Repair indicated	Repair possibly indicated	Repair contraindicated
ESC GUCH Guidelines, 2010 [37]	PVR < 5 WU with significant shunt regardless of symptoms (class I)	PVR ≥ 5 WU but <2/3rd SVR or PAP < 2/3rd systemic blood pressure (baseline or with vasodilator) and net L-to-R shunt (Q_p:Q_s > 1.5) (class IIb)	Eisenmenger physiology (class III)
AHA/ACC ACHD Guidelines, 2008 [38]	RA or RV enlargement, irrespective of symptoms (class I)	Net L-to-R shunt, PAP < 2/3rd systemic, PVR < 2/3rd SVR or when responsive to either pulmonary vasodilator therapy or test occlusion of the defect (class IIb)	Severe irreversible PAH and no evidence of a left-to-right shunt (class III)
Updated Clinical PH Classification, 2013 [39]	PVR < 2.3 WU (<4 WU m^2)	PVR 2.3–4.6 WU (4–8 WU m^2)	PVR > 4.6 WU (>8 WU m^2)

Classes I, IIb and III refer to the level of recommendation noted and defined in the respective documents

ESC European Society of Cardiology, *ACHD/GUCH* adult/grown-up congenital heart disease, *AHA/ACC* American Heart Association/American College of Cardiology, *PH* pulmonary hypertension, *PVR* pulmonary vascular resistance, *WU* Wood units, *RA* right atrial, *RV* right ventricular, *SVR* systemic vascular resistance, *PAP* pulmonary artery pressure, *L-to-R* left-to-right, Q_p:Q_s ratio of pulmonary-to-systemic flow, *PAH* pulmonary arterial hypertension

who have progressive PAH after defect repair [40], a subset of patients with entirely normal or borderline resting pulmonary haemodynamics at catheterization prior to repair later develop progressive disease. Furthermore, the presence of pulmonary vascular disease is often considered in a dichotomous way: present/progressive or absent. There is growing evidence, however, that underlying pulmonary vascular physiology and right heart function are abnormal even in some asymptomatic patients with normal resting haemodynamics after defect repair [41–43].

Given the likely substantial benefit of defect closure for many of these patients and, possibly, the innate desire to fix a defect, there has been increasing interest in using available medical therapy to facilitate defect closure. This is often referred to as a "treat-and-repair" approach. PAH medical therapy should not be viewed in this context as a bridge to safer perioperative management: while these medications may indeed be helpful in preventing acute RHF in patients with modestly elevated PVR, such outcomes are uncommon in mild PAH [40], and preventing them is not the goal of therapy. Rather, there are two possible aims of such neoadjuvant PAH medical therapy. First, an empiric trial of medication may help define a subset of patients who are strongly responsive to medical therapy. While there is no evidence to support the claim, such patients may be less likely to develop severe, progressive, medically refractory PAH after closure. Assessment of the response to medical treatment includes evaluation of functional

status, exercise capacity, cardiac function and haemodynamics (including pulmonary vasoreactivity). Some have also proposed lung biopsy to help guide patient selection [44], though this is not currently standard at most centres. Since many patients are asymptomatic, with reasonably preserved functional capacity, it is challenging to appreciate improvement with medications with short-term administration; there is some evidence that PAH medications may not only produce acute vasodilation but also facilitate long-term beneficial remodelling of the pulmonary vasculature.

Early reports suggest some promise for such the "treat-and-repair" approach [34, 45–47], but follow-up has been largely short term and limited to few centres, and generalized reproducibility has not been demonstrated [34]. Since the vast majority of such patients would be expected to do well for months to years in the absence of medical therapy, it is difficult to comment on whether the medication has any benefit or whether long-term outcomes would have been similarly positive [34]. Indeed, some reports include patients who would generally be considered reasonable candidates for repair without therapy, in whom PVR is not the only reason for markedly elevated pulmonary pressure [48, 49]. Of interest, patients with clear-cut PAH prior to repair often feel better after repair, but neither PAH nor the need for PAH medical therapy resolves. The anecdotal evidence is intriguing, yet does not allow much insight into chronic pulmonary vascular and right heart remodelling after repair. While one may hope for improvement, these PAH patients may, as is generally the case, have progressive disease; the concern is that their long-term prognosis may be worsened in the absence of a patent shunt.

Some have advocated defect closure with a fenestrated or valved patch/device to allow smaller volume right-to-left shunting if a patient develops RHF [50]. This may be useful in the uncommon context of acute RHF fenestrations must be relatively small in order for the procedure to provide the expected benefit for defect closure, and such small defects often spontaneously close over time. Furthermore, it is technically feasible to create an atrial septal defect or other shunt, as outlined in the prior section, for a patient who does develop progressive PAH and RHF. It is, therefore, unclear if there is benefit to this approach beyond the immediate postoperative period and in rare circumstances.

As outlined above, decisions regarding treatment and repair for patients with intermediate levels of pulmonary vascular disease are fraught with lack of dependable markers of future disease progression or reversibility. Individualized, thoughtful care should be provided by experts in both PAH and CHD, with dynamic (e.g. exercise or medication response), repeated evaluation of cardiopulmonary testing, imaging and invasive haemodynamics.

References

1. Marcus JT, Gan CT, Zwanenburg JJ, Boonstra A, Allaart CP, Gotte MJ et al (2008) Interventricular mechanical asynchrony in pulmonary arterial hypertension: left-to-right delay in peak shortening is related to right ventricular overload and left ventricular underfilling. J Am Coll Cardiol 51(7):750–757
2. Rashkind WJ, Miller WW (1966) Creation of an atrial septal defect without thoracotomy. A palliative approach to complete transposition of the great arteries. JAMA 196(11):991–992

3. Rich S, Lam W (1983) Atrial septostomy as palliative therapy for refractory primary pulmonary hypertension. Am J Cardiol 51(9):1560–1561
4. Nihill MR, O'Laughlin MP, Mullins CE (1991) Effects of atrial septostomy in patients with terminal cor pulmonale due to pulmonary vascular disease. Catheter Cardiovasc Diagn 24(3):166–172
5. Rothman A, Beltran D, Kriett JM, Smith C, Wolf P, Jamieson SW (1993) Graded balloon dilation atrial septostomy as a bridge to lung transplantation in pulmonary hypertension. Am Heart J 125(6):1763–1766
6. Prieto LR, Latson LA, Jennings C (2006) Atrial septostomy using a butterfly stent in a patient with severe pulmonary arterial hypertension. Catheter Cardiovasc Interv 68(4):642–647
7. Keogh AM, Mayer E, Benza RL, Corris P, Dartevelle PG, Frost AE et al (2009) Interventional and surgical modalities of treatment in pulmonary hypertension. J Am Coll Cardiol 54(1 Suppl):S67–S77
8. Al Maluli H, DeStephan CM, Alvarez RJ Jr, Sandoval J (2015) Atrial septostomy: a contemporary review. Clin Cardiol 38(6):395–400
9. Rothman A, Sklansky MS, Lucas VW, Kashani IA, Shaughnessy RD, Channick RN et al (1999) Atrial septostomy as a bridge to lung transplantation in patients with severe pulmonary hypertension. Am J Cardiol 84(6):682–686
10. Austen WG, Morrow AG, Berry WB (1964) Experimental studies of the surgical treatment of primary pulmonary hypertension. J Thorac Cardiovasc Surg 48:448–455
11. Potts WJ, Smith S, Gibson S (1946) Anastomosis of the aorta to a pulmonary artery; certain types in congenital heart disease. J Am Med Assoc 132(11):627–631
12. Blanc J, Vouhe P, Bonnet D (2004) Potts shunt in patients with pulmonary hypertension. N Engl J Med 350(6):623
13. Baruteau AE, Belli E, Boudjemline Y, Laux D, Levy M, Simonneau G et al (2015) Palliative Potts shunt for the treatment of children with drug-refractory pulmonary arterial hypertension: updated data from the first 24 patients. Eur J Cardiothorac Surg 47(3):e105–e110
14. Boudjemline Y, Patel M, Malekzadeh-Milani S, Szezepanski I, Levy M, Bonnet D (2013) Patent ductus arteriosus stenting (transcatheter Potts shunt) for palliation of suprasystemic pulmonary arterial hypertension: a case series. Circ Cardiovasc Interv 6(2):e18–e20
15. Wood P (1958) The Eisenmenger syndrome or pulmonary hypertension with reversed central shunt. Br Med J 2(5098):701–709
16. Guo K, Langleben D, Afilalo J, Shimony A, Leask R, Marelli A et al (2013) Anatomical considerations for the development of a new transcatheter aortopulmonary shunt device in patients with severe pulmonary arterial hypertension. Pulm Circ 3(3):639–646
17. Esch JJ, Shah PB, Cockrill BA, Farber HW, Landzberg MJ, Mehra MR et al (2013) Transcatheter Potts shunt creation in patients with severe pulmonary arterial hypertension: initial clinical experience. J Heart Lung Transplant 32(4):381–387
18. Zanjani KS (2013) Radiofrequency perforation may increase the safety of transcatheter Potts shunt creation. J Heart Lung Transplant 32(9):938
19. Chen SL, Zhang FF, Xu J, Xie DJ, Zhou L, Nguyen T et al (2013) Pulmonary artery denervation to treat pulmonary arterial hypertension: the single-center, prospective, first-in-man PADN-1 study (first-in-man pulmonary artery denervation for treatment of pulmonary artery hypertension). J Am Coll Cardiol 62(12):1092–1100
20. Chen SL, Zhang H, Xie DJ, Zhang J, Zhou L, Rothman AM et al (2015) Hemodynamic, functional, and clinical responses to pulmonary artery denervation in patients with pulmonary arterial hypertension of different causes: phase II results from the pulmonary artery denervation-1 study. Circ Cardiovasc Interv 8(11):e002837
21. Galie N, Manes A (2013) New treatment strategies for pulmonary arterial hypertension: hopes or hypes? J Am Coll Cardiol 62(12):1101–1102
22. Rothman AM, Arnold ND, Chang W, Watson O, Swift AJ, Condliffe R et al (2015) Pulmonary artery denervation reduces pulmonary artery pressure and induces histological changes in an acute porcine model of pulmonary hypertension. Circ Cardiovasc Interv 8(11):e002569

23. Meadows J, Pigula F, Lock J, Marshall A (2007) Transcatheter creation and enlargement of ventricular septal defects for relief of ventricular hypertension. J Thorac Cardiovasc Surg 133(4):912–918
24. Mocellin R, Buhlmeyer K (1975) Late banding operation in children with ventricular septal defect and pulmonary arterial hypertension. Eur J Cardiol 3(3):205–211
25. Khan SA, Gelb BD, Nguyen KH (2006) Evaluation of pulmonary artery banding in the setting of ventricular septal defects and severely elevated pulmonary vascular resistance. Congenit Heart Dis 1(5):244–250
26. Batista RJ, Santos JL, Takeshita N, Eocchino L, Lima PN, Goehr M et al (1997) Successful reversal of pulmonary hypertension in Eisenmenger complex. Arq Bras Cardiol 68(4): 279–280
27. Apitz C, Honjo O, Humpl T, Li J, Assad RS, Cho MY et al (2012) Biventricular structural and functional responses to aortic constriction in a rabbit model of chronic right ventricular pressure overload. J Thorac Cardiovasc Surg 144(6):1494–1501
28. Murphy JG, Gersh BJ, McGoon MD, Mair DD, Porter CJ, Ilstrup DM et al (1990) Long-term outcome after surgical repair of isolated atrial septal defect. Follow-up at 27 to 32 years. N Engl J Med 323(24):1645–1650
29. Attie F, Rosas M, Granados N, Zabal C, Buendia A, Calderon J (2001) Surgical treatment for secundum atrial septal defects in patients >40 years old. A randomized clinical trial. J Am Coll Cardiol 38(7):2035–2042
30. Diller GP, Gatzoulis MA (2007) Pulmonary vascular disease in adults with congenital heart disease. Circulation 115(8):1039–1050
31. Opotowsky AR, Landzberg MJ, Beghetti M (2014) The exceptional and far-flung manifestations of heart failure in Eisenmenger syndrome. Heart Fail Clin 10(1):91–104
32. Manes A, Palazzini M, Leci E, Bacchi Reggiani ML, Branzi A, Galie N (2014) Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: a comparison between clinical subgroups. Eur Heart J 35(11):716–724
33. Dimopoulos K, Peset A, Gatzoulis MA (2008) Evaluating operability in adults with congenital heart disease and the role of pretreatment with targeted pulmonary arterial hypertension therapy. Int J Cardiol 129(2):163–171
34. Beghetti M, Galie N, Bonnet D (2012) Can "inoperable" congenital heart defects become operable in patients with pulmonary arterial hypertension? Dream or reality? Congenit Heart Dis 7(1):3–11
35. Rosenzweig EB, Barst RJ (2012) Congenital heart disease and pulmonary hypertension: pharmacology and feasibility of late surgery. Prog Cardiovasc Dis 55(2):128–133
36. Krieger EV, Leary PJ, Opotowsky AR (2015) Pulmonary hypertension in congenital heart disease: beyond Eisenmenger syndrome. Cardiol Clin 33(4):599–609
37. Baumgartner H, Bonhoeffer P, De Groot NM, de Haan F, Deanfield JE, Galie N et al (2010) ESC guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J 31(23):2915–2957
38. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA et al (2008) ACC/AHA 2008 guidelines for the Management of Adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). Circulation 118(23):e714–e833
39. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A et al (2013) Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 62(25 Suppl):D34–D41
40. D'Alto M, Romeo E, Argiento P, Correra A, Santoro G, Gaio G et al (2013) Hemodynamics of patients developing pulmonary arterial hypertension after shunt closure. Int J Cardiol 168(4):3797–3801
41. Van De Bruaene A, La Gerche A, Prior DL, Voigt JU, Delcroix M, Budts W (2011) Pulmonary vascular resistance as assessed by bicycle stress echocardiography in patients with atrial septal defect type secundum. Circ Cardiovasc Imaging 4(3):237–245

42. Santos M, Systrom D, Epstein SE, John A, Ruiz G, Landzberg MJ et al (2014) Impaired exercise capacity following atrial septal defect closure: an invasive study of the right heart and pulmonary circulation. Pulm Circ 4(4):630–637
43. Van De Bruaene A, De Meester P, Buys R, Vanhees L, Delcroix M, Voigt JU et al (2013) Right ventricular load and function during exercise in patients with open and closed atrial septal defect type secundum. Eur J Prev Cardiol 20(4):597–604
44. Huang JB, Liu YL, Yu CT, Lv XD, Du M, Wang Q et al (2011) Lung biopsy findings in previously inoperable patients with severe pulmonary hypertension associated with congenital heart disease. Int J Cardiol 151(1):76–83
45. Schwerzmann M, Zafar M, McLaughlin PR, Chamberlain DW, Webb G, Granton J (2006) Atrial septal defect closure in a patient with "irreversible" pulmonary hypertensive arteriopathy. Int J Cardiol 110(1):104–107
46. Frost AE, Quinones MA, Zoghbi WA, Noon GP (2005) Reversal of pulmonary hypertension and subsequent repair of atrial septal defect after treatment with continuous intravenous epoprostenol. J Heart Lung Transplant 24(4):501–503
47. Huang ZW, Fan ZX, Sun JT, Li WM, Gao YQ, Quan YH et al (2012) The short- and medium-term results of transcatheter closure of atrial septal defect with severe pulmonary arterial hypertension. Heart Vessel 27(6):603–609
48. Hoetzenecker K, Ankersmit HJ, Bonderman D, Hoetzenecker W, Seitelberger R, Klepetko W et al (2009) Atrial septal defect repair after a 10-month treatment with bosentan in a patient with severe pulmonary arterial hypertension: a case report. J Thorac Cardiovasc Surg 137(3):760–761
49. Opotowsky AR (2015) Clinical evaluation and management of pulmonary hypertension in the adult with congenital heart disease. Circulation 131(2):200–210
50. Bruch L, Winkelmann A, Sonntag S, Scherf F, Rux S, Grad MO et al (2008) Fenestrated occluders for treatment of ASD in elderly patients with pulmonary hypertension and/or right heart failure. J Interv Cardiol 21(1):44–49

Eisenmenger Syndrome in Patients with Down Syndrome

18

Michele D'Alto and Giovanni Maria Di Marco

Abbreviations

AVSD	atrioventricular septal defect
CHD	congenital heart disease
DS	Down syndrome
ERA	endothelin receptor antagonist
PAH	pulmonary arterial hypertension
PH	pulmonary hypertension
RHC	right heart catheterization
VSD	ventricular septal defect
6MWD	six minute walk distance
6MWT	six minute walk test

18.1 Down Syndrome: Definition and Epidemiology

Down syndrome (DS) is the most common autosomal chromosome abnormality, with an estimated incidence of approximately 1.1 per 1000 live births [1], without significant differences according to race [2]. DS was first described by the French scientist Seguin in 1846 [3], but it was the ophthalmologist Haydon Down who described the most important clinical features of this syndrome in 1866 [4]. The genetic origin of the disease was discovered in 1959 [5], and the term "Down syndrome" was officially confirmed by the World Health Organization in 1965.

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The epidemiology of DS has remained unchanged over the years. On one hand, advanced maternal age has caused an increase in the number of live births with DS; on the other hand, improvements in antenatal diagnosis have led to an increase in terminations of DS pregnancies [1]. In most cases, the disease is caused by chromosome 21 trisomy, less frequently by Robertsonian translocations, isochromosomes or ring chromosomes. It has been hypothesized that a specific cluster of genes on chromosome 21 are involved in determining the DS phenotype, including craniofacial abnormalities, congenital heart defects and mental retardation [6–8]. However, several studies on humans and DS mouse models have shown that many critical chromosomal regions are involved, hence, making the identification of a subset of genes responsible for the DS phenotype impossible [9, 10].

DS has a strong impact on social and medical costs, relating to the intellectual disability and wide spectrum of comorbidities: congenital heart defects, systemic arterial hypertension, pulmonary hypertension (PH), craniofacial and physical abnormalities, gastrointestinal problems, leukaemia, cancer, Hirschsprung's disease and Alzheimer's disease.

18.2 Causes of Pulmonary Hypertension in Down Syndrome

PH significantly affects the prognosis and quality of life of DS patients. It is defined as a mean pulmonary artery pressure ≥25 mmHg at rest measured during right heart catheterization (RHC). Several complications or comorbidities associated with DS can cause or worsen PH (Table 18.1) [11, 12]. In patients with DS, the most important cause of PH is congenital heart disease (CHD)/Eisenmenger syndrome (group 1 PH or PAH, according to the 5th World Meeting on Pulmonary Hypertension, Nice 2013) [13]. CHD occurs in about 43% of DS patients [14–16]. According to the most recent medical literature [17], 43% of DS patients with CHD have an atrioventricular septal defect (AVSD), 31% a ventricular septal defect (VSD), 15% an atrial septal defect, 5% tetralogy of Fallot, 4% a patent ductus arteriosus and about 2% multiple abnormalities (including coarctation of the aorta, pulmonary valve

Table 18.1 Factors contributing to the development of pulmonary hypertension in patients with Down syndrome

- Congenital heart disease
- Endothelial dysfunction
- Respiratory disease
  - Obesity, macroglossia and neck conformation inducing sleep apnoea syndrome
  - Respiratory syncytial virus infection
  - Emphysema
  - Lower respiratory tract infection
  - Restrictive pathophysiology due to scoliosis or chest malformations
- Low birth weight
- Transient abnormal myelopoiesis

Modified from Saji [12]

stenosis or a vascular ring). The mechanism underlying the pathogenesis of an AVSD, so common in DS patients, is related to abnormalities in the CRELD1 (cysteine-rich with epidermal growth factor-like domains 1) and GATA4 genes [17].

Several congenital heart defects, such as AVSDs and VSDs, result in significant left-to-right shunting, which, if not timely corrected, can lead to PH. The risk of developing pulmonary vascular disease is related to shunt size and location, being lower in pre-tricuspid than in post-tricuspid shunts because of the different pathophysiology (pure volume vs. pressure and volume overload). Eisenmenger syndrome represents the extreme end of the spectrum of pulmonary arterial hypertension (PAH) in the setting of CHD. It is a complex, multisystemic syndrome caused by significant prolonged left-to-right shunting, leading to pulmonary vascular disease with a marked increase in pulmonary artery pressure that equals or exceeds systemic arterial pressure. This haemodynamic condition ultimately causes a bidirectional or right-to-left shunt and is responsible for the most important features of this syndrome, including cyanosis, erythrocytosis and chronic right heart failure.

In general, among individuals with uncorrected intra- or extracardiac shunts, those with DS develop PAH earlier and demonstrate more severe damage to the pulmonary vascular bed [18–20]. These findings have been reported since the 1970s [21], when Chi and Krovetz began investigating the relationship between DS and the pulmonary vascular bed. The tendency of DS patients to develop an earlier and more severe form of pulmonary vascular disease compared with non-Down subjects is likely due to endothelial dysfunction. Recent studies [22] have shown that an impaired endothelial homeostasis may play a role in the pathogenesis of PAH. DS patients with CHD-related PAH (PAH-CHD) and Eisenmenger syndrome have a reduced number of endothelial progenitor cells [23], which may contribute to vascular homeostasis. In addition, higher levels of inflammatory mediators, including tumour necrosis factor-α, interleukin-6 and C-reactive protein, indexes of nitric oxide synthesis and asymmetric dimethylarginine (ADMA), known to affect circulating endothelial progenitor cell numbers, have also been described in DS.

Yamaki [24] evaluated the indication for surgery in CHD patients, based on RHC data and lung biopsy findings. He observed that DS patients, different from non-DS subjects, do not develop medial thickening even in the presence of high pulmonary artery pressures, but rather show significant intimal thickening. These histopathological features may play a role in the development of PAH in DS patients. DS is associated with small-calibre blood vessels in both the pulmonary and systemic circulation, and this phenomenon seems to be more pronounced with increasing age [12].

Another cause for the development or worsening of PH in DS is respiratory (airways) disease. In many DS patients, pulmonary hypoplasia [25, 26] and a reduced number of alveoli mean that the alveolar surface area to be covered by capillaries is limited, which favours the development of PH. The cause of these structural lung abnormalities may be related to the presence of specific toxic substances in the amniotic fluid, absorbed by the lungs during fetal life. DS patients are also prone to upper respiratory tract obstruction due to enlarged adenoids, macroglossia and glossoptosis, associated with low muscle tone and hypoventilation, all factors contributing to the development of PH.

Individuals with DS and symptoms or risk factors for sleep apnoea or hypoventilation should undergo overnight polysomnographic evaluation, as sleep apnoea syndrome may account for the development of PH in some DS individuals. Special attention is warranted in patients with little improvement after surgical removal of adenoids and patients with other risk factors such as obesity or marked midfacial hypoplasia or if complications involving neurologic disorders are present [27].

Finally, persistent pulmonary hypertension of the newborn is not uncommon in DS, reaching an incidence as high as 1.2–5.2% [20–30]. It is, therefore, very important to consider all possible causes of PH, beyond CHD/Eisenmenger syndrome, in DS patients given that the management depends heavily on the type of PH.

18.3 Treatment Modalities for Eisenmenger Syndrome in Patients with Down Syndrome

Surgical management of cardiovascular anomalies has changed considerably over the past two decades, with improved results and reduced mortality, especially in the perinatal period.

A recent study from the regional paediatric cardiology database in Newcastle upon Tyne (UK) [22] has shown that, between 1985 and 1995, 62% infants with DS had surgery for CHD, with a 30% mortality. Conversely, in the period 1996–2006, 72% of DS infants had surgery for CHD with a 5% mortality. One-year survival for DS individuals with a cardiovascular anomaly improved from 82% in 1985–1995 to 94% in 1996–2006. Despite these advances, some patients still develop pulmonary vascular disease before they can be operated, and many patients with CHD and DS are currently reaching adulthood without having undergone surgical treatment. In fact, DS patients currently comprise one third of adults with Eisenmenger syndrome followed in tertiary centres.

In the last two decades, new treatment strategies targeting PAH have greatly improved the clinical status of patients with PAH-CHD. In particular, a large randomized controlled clinical trial [31, 32] and several single-centre, open-label studies [33–36] have shown that bosentan, an oral dual endothelin receptor antagonist (ERA), is effective at improving exercise and functional capacity at short and probably longer-term follow-up in patients with PAH-CHD and Eisenmenger syndrome.

Increasing evidence is also emerging on the beneficial effects of phosphodiesterase-5 inhibitors alone or in combination with ERAs in Eisenmenger syndrome patients [37–40]. Moreover, earlier initiation of targeted therapies is likely to be beneficial in patients with Eisenmenger syndrome, as it is in those with idiopathic PAH [41]. The ongoing MAESTRO trial, using a novel ERA (macitentan) in patients with Eisenmenger syndrome, has also included patients in NYHA class II and patients with DS and may provide further evidence on the efficacy of medical therapy in this setting [42].

Notwithstanding this, the majority of studies excluded DS patients, and, as a result, the treatment effect of PAH-targeted therapies in this population remains largely unknown. Owing to the lack of efficacy data on PAH-targeted drugs in this population, a recent registry study demonstrated that these patients are significantly less likely to receive PAH-specific treatment compared to non-DS patients, despite the fact that DS patients with PAH-CHD are more prone to develop PAH earlier and have a worse functional capacity, both established markers of poor prognosis [43–45].

Although there are, as yet, no randomized controlled clinical data in DS patients with PAH-CHD, data from open-label studies have become available in recent years. Two recent studies from the same group [46, 47] suggested that oral bosentan therapy is safe and well tolerated in adult patients with PAH-CHD and DS, but with no changes in quality of life during treatment and conflicting results on 6-min walk test (6MWT) distance. In the first study [48], an increase in the 6-min walk distance (6MWD) after 11.5 months of bosentan therapy was reported in 24 Down patients with PAH-CHD. In the second study [49], despite an increase in 6MWD in 30 patients with PAH-CHD without DS at 22 months of follow-up, the 6MWD remained stable after treatment in 28 patients with DS. No invasive measurements of pulmonary haemodynamics are available for these two studies. Indeed, the 6MWT tends to be unreliable in patients with DS [48] and significant learning difficulties due to poor compliance (see following paragraph). In the absence of a reliable test to evaluate exercise capacity, and the poor description of symptoms by patients, the functional assessment of DS patients remains extremely challenging.

More recently, D'Alto et al. [49] assessed the safety and long-term efficacy of oral bosentan in adult patients with PAH-CHD, with and without DS, evaluating both clinical features and invasive parameters. After 12 months of treatment, oral bosentan at standard doses was found to be safe and improved clinical status, exercise tolerance and pulmonary haemodynamics, regardless of the presence of DS. In particular, clinical and haemodynamic variables, expressed as percent change from baseline to the end of follow-up, did not differ between patients with and without DS (Table 18.2). This suggests a similar favourable effect of bosentan on the pulmonary circulation in patients with PAH-CHD, regardless of the presence of DS.

In terms of anticoagulation therapy, in general, PAH-CHD and Eisenmenger syndrome patients are felt to be at increased risk for bleeding complications [50]. Recent data from the COMPERA registry have shown that the use of anticoagulants is not associated with a survival benefit in patients with forms of PAH other than idiopathic PAH [51], such as connective tissue disease-related PAH and PAH-CHD. With this information, and considering the difficulties in monitoring INR in DS patients, there is a tendency nowadays not to initiate anticoagulation in these patients (see Chap. 15 for more information on anticoagulation).

Table 18.2 Clinical and haemodynamic features at baseline and after oral bosentan therapy in patients with and without Down syndrome

	Down syndrome (n = 18)			Non-Down syndrome (n = 56)		
	Baseline	Follow-up	p	Baseline	Follow-up	p
Clinical status						
SpO_2 (%)	83 ± 9	84 ± 9	0.07	84 ± 9	85 ± 8	0.2
HR (bpm)	90 ± 11	85 ± 8	0.0001	91 ± 14	84 ± 11	0.0003
WHO functional class	2.9 ± 0.6	2.5 ± 0.5	0.005	2.9 ± 0.5	2.5 ± 0.5	0.000002
Exercise tolerance (6MWT)						
Travelled distance (m)	239 ± 74	288 ± 71	0.0007	343 ± 86	389 ± 80	0.00003
HR at end exercise (bpm)	117 ± 19	109 ± 9	0.03	117 ± 19	111 ± 20	0.04
SpO_2 at end exercise (%)	72 ± 10	74 ± 10	0.011	69 ± 13	73 ± 12	0.005
Borg index	5.7 ± 2.6	3.5 ± 1.6	0.0003	5.0 ± 2.1	4.3 ± 1.9	0.001
Heart catheterization						
RAP (mmHg)	13 ± 5	12 ± 6	0.14	11 ± 4	11 ± 4	0.6
mPAP (mmHg)	66 ± 21	60 ± 17	0.06	74 ± 18	73 ± 21	0.6
mCWP (mmHg)	11 ± 3	12 ± 3	0.16	11 ± 3	12 ± 3	0.9
Qp (L/min/m^2)	3.5 ± 1.4	4.0 ± 1.6	0.006	2.8 ± 1.0	3.5 ± 1.4	0.0005
Qs (L/min/m^2)	3.6 ± 1.3	3.4 ± 1.7	0.37	3.3 ± 1.3	3.7 ± 1.9	0.064
Qp/Qs	1.0 ± 0.4	1.4 ± 0.7	0.003	0.9 ± 0.3	1.1 ± 0.7	0.012
PVRi (WUm^2)	20 ± 13	15 ± 9	0.007	26 ± 15	20 ± 10	0.002

6MWT 6-min walk test, *bpm* beats per minute, *HR* heart rate, *mCWP* mean capillary wedge pressure, *mPAP* mean pulmonary artery pressure, *PVRi* pulmonary vascular resistance index, *Qp* pulmonary flow, *Qs* systemic flow, *Qp/Qs* pulmonary-to-systemic flow ratio, *RAP* right atrial pressure, *SpO_2* transcutaneous oxygen saturation, *WHO* World Health Organization, *WU* Wood units
Modified from D'Alto et al. [50]

Table 18.3 6-min walk test and Down syndrome: problems and possible solutions

Problems	Possible solutions
Poor patient compliance	Optimize environment (calm environment, familiar site, familiar people)
Poor reproducibility	Extra training (consider only patients reaching acceptable reproducibility)
	Consider only patients with a minimum level of intellectual ability
	Repeat the test to assess reproducibility
Specific DS problems: loss of concentration/interest in the test	Examiner (or caregiver) walking behind the patient, avoiding body contact (i.e. holding hands) or encouragement
Interaction with the patient	Specific training for personnel working with DS patients
Specific arrangements for patients unable or unwilling to have a 6MWT	Schedule an extra test or visit

DS Down syndrome, *6MWT* 6-min walk test

18.4 Challenges and Limitations in Down Syndrome Patients with CHD-Related PAH

DS patients with PAH-CHD can pose major challenges and limitations in both their diagnostic and prognostic assessment. The tools commonly used in the diagnostic algorithm of PH, such as lung function tests, high-resolution computed tomography and ventilation/perfusion scanning, are often not easy to apply in Down patients due to poor compliance to instructions. In addition, RHC, which plays a key role in the diagnostic workup of patients with PH, is not devoid of ethical and safety issues. Informed consent depends on local legislation on mental capacity and is not an obvious process. General anaesthesia may also be required when performing RHC, and this carries risks in patients with established PH or other anaesthetic risk factors (e.g. obesity). If intubation is necessary, macroglossia and neck conformation may increase the risks.

The lack of randomized controlled or other prospective trials in DS patients with PAH–CHD and the paucity of haemodynamic data (just one study [49]) do not allow for the development of a DS-specific evidence-based workup protocol and risk assessment algorithm. Moreover, as stated above, PH in this population is often multifactorial, with a high prevalence of complex cardiac defects, upper airway obstruction, PH of the neonate, restrictive lung disease due to severe scoliosis, etc. For this reason, a complete workup is mandatory for an appropriate diagnosis before considering PAH-specific treatment.

Standard functional and prognostic markers are often difficult to apply in DS, starting with the assessment of the functional class. In general, PAH-CHD patients have been living with their symptoms for years, often since birth, and have, thus, adapted their daily activities to a lower intensity. As a result, they tend to underestimate and hence underreport the severity of their symptoms during everyday activities. In addition, in DS patients it is often the caregivers who provide information on the patient's functional limitations, casting further doubts on the validity of functional classification in this population. Quality of life questionnaires are even more difficult to apply in DS. None have been developed specifically for, or validated in DS.

Objective measures of exercise capacity are also difficult to apply across the DS population. The validity of the 6MWT, the standard means of assessment of exercise capacity in PAH, is at least questionable. Vis et al. [48] observed that the 6MWD in DS patients does not reflect the severity of cardiac disease, but is inversely correlated with the level of intellectual disability. It is recommended that, during the 6MWT, patients should walk alone and as fast as they can without running, and without any encouragement. Any deviation from this procedure may dramatically alter the results of the test [52, 53], and this is likely to account for the poor reliability of the 6MWT in DS. Possible ways to overcome this problem and improve the reliability of the 6MWT include the following: (1) perform a training session and only perform 6MWTs in patients who can clearly follow the protocol, (2) exclude patients with severe intellectual disability, (3) allow the examiner (or caregiver) to walk with the patient (avoiding contact and encouragement), (4) provide a

specific training to the personnel performing the 6MWT on how to best interact with DS patients, (5) schedule an extra test or visit to assess reproducibility and (6) optimize the environment (calm environment, familial site, familial people, etc.) (Table 18.3). Obviously, these solutions are not universally accepted or recommended by international guidelines, and some may even introduce bias.

Conclusion

The presence of PH adversely affects the quality of life of DS patients and is associated with significant morbidity and mortality. PAH-CHD accounts for most cases of PH in DS, but other causes of PH should be assessed for and treated. A multidisciplinary management is recommended for all DS patients, given the multitude to comorbidities and complications associated with PH in DS.

References

1. Morris JK, Alberman E (2009) Trends in Down's syndrome live births and antenatal diagnoses in England and Wales from 1989 to 2008: analysis of data from the National Down Syndrome Cytogenetic Register. BMJ 339:b3794
2. Wiseman FK, Alford KA, Tybulewic VL, Fisher EM (2009) Down syndrome—recent progress and future prospects. Hum Mol Genet 18(R1):R75–R83
3. Seguin E (1846) Traitement moral, hygiène et éducation des idiots et des autres enfants arriérés. Baillière, Paris
4. Down JL (1866) Observations on an ethnic classification of idiots. Clinical Lecture Reports: London Hospital 3:259–262
5. Lejeune J, Gauthier M, Turpin R (1959) Les chromosomes humains en culture de tissus. C R Hebd Seances Acad Sci 248:602–603
6. Delabar JM, Theophile D, Rahmani Z, Chettouh Z, Blouin JL, Prieur M et al (1993) Molecular mapping of twenty-four features of Down syndrome on chromosome 21. Eur J Hum Genet 1:114–124
7. Ohira M, Ichikawa H, Suzuki E, Iwaki M, Suzuki K, Saito-Ohara F et al (1996) A 1.6-Mb P1-based physical map of the Down syndrome region on chromosome 21. Genomics 33:65–74
8. Korbel JO, Tirosh-Wagner T, Urban AE, Chen XN, Kasowski M, Dai L et al (2009) The genetic architecture of Down syndrome phenotypes revealed by high-resolution analysis of human segmental trisomies. Proc Natl Acad Sci U S A 106:12031–12036
9. Shapiro BL (1999) The Down syndrome critical region. J Neural Transm Suppl 57:41–60
10. Asim A, Kumar A, Muthuswamy S, Jain S, Agarwal S (2015) Down syndrome: an insight of the disease. J Biomed Sci 22:41
11. Neill CA, Zuckerberg AL (1995) Syndromes and congenital heart defects. In: Nichols DG, Cameron DE, Greeley WJ et al (eds) Critical heart disease in infants and children. Mosby, St Louis, pp 987–1012
12. Saji T (2014) Clinical characteristics of pulmonary arterial hypertension associated with Down syndrome. Pediatr Int 56:297–303
13. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A et al (2013) Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 62(25 Suppl):D34–D41
14. Jaiyesimi O, Baichoo V (2007) Cardiovascular malformations in Omani Arab children with Down's syndrome. Cardiol Young 17:166–171

15. Vida VL, Barnoya J, Larrazabal LA, Gaitan G, de Maria GF, Castaneda AR (2005) Congenital cardiac disease in children with Down's syndrome in Guatemala. Cardiol Young 15:286–290
16. Lin AE, Basson CT, Goldmuntz E, Magoulas PL, McDermott DA, McDonald-McGinn DM et al (2008) Adults with genetic syndromes and cardiovascular abnormalities: clinical history and management. Genet Med 10:469–494
17. Sarkozy A, Esposito G, Conti E, Digilio MC, Marino B, Calabrò R et al (2005) CRELD1 and GATA4 gene analysis in patients with nonsyndromic atrioventricular canal defects. Am J Med Genet 139:236–238
18. Thieren M, Stijns-Cailteux M, Trémouroux-Wattiez M, Jaumin P, Kestens-Servaye Y, Moulin D et al (1988) Congenital heart diseases and obstructive pulmonary vascular diseases in Down's syndrome. A propos of 142 children with trisomy 21. Arch Mal Coeur Vaiss 81:655–661
19. Hasegawa N, Oshima M, Kawakami H, Hirano H (1990) Changes in pulmonary tissue of patients with congenital heart disease and Down syndrome: a morphological and histological study. Acta Paediatr Jpn 32:60–66
20. Greenwood RD, Nadas AS (1976) The clinical course of cardiac disease in Down's syndrome. Pediatrics 58:893–897
21. Chi TP, Krovetz J (1975) The pulmonary vascular bed in children with Down syndrome. J Pediatr 86:533–538
22. Irving CA, Chaudhari MP (2012) Cardiovascular abnormalities in Down's syndrome: spectrum, management and survival over 22 years. Arch Dis Child 97:326–330
23. Diller GP, van Eijl S, Okonko DO, Howard LS, Ali O, Thum T et al (2008) Circulating endothelial progenitor cells in patients with Eisenmenger syndrome and idiopathic pulmonary arterial hypertension. Circulation 117:3020–3030
24. Yamaki S (2000) The diagnosis in biopsied samples from patients with VSD and PDA. The diagnosis of pulmonary vasculopathy in lung biopsy samples for clinicians, 1st edn. Medical Reviews, Osaka
25. Cooney TP, Thurlbeck WM (1982) Pulmonary hypoplasia in Down's syndrome. N Engl J Med 307:1170–1173
26. Yamaki S, Horiuchi T, Takahashi T (1985) Pulmonary changes in congenital heart disease with Down's syndrome: their significance as a cause of postoperative respiratory failure. Thorax 40:380–386
27. Aurora RN, Zak RS, Karippot A, Lamm CI, Morgenthaler TI, Auerbach SH, American Academy of Sleep Medicine et al (2011) Practice parameters for the respiratory indications for polysomnography in children. Sleep 34:379–388
28. Weijerman ME, van Furth AM, van der Mooren MD, van Weissenbruch MM, Rammeloo L, Broers CJ et al (2010) Prevalence of congenital heart defects and persistent pulmonary hypertension of the neonate with Down syndrome. Eur J Pediatr 169:1195–1199
29. Cua CL, Blankenship A, North AL, Hayes J, Nelin LD (2007) Increased incidence of idiopathic persistent pulmonary hypertension in Down syndrome neonates. Pediatr Cardiol 28:250–254
30. Shah PS, Hellmann J, Adatia I (2004) Clinical characteristics and follow up of Down syndrome infants without congenital heart disease who presented with persistent pulmonary hypertension of newborn. J Perinat Med 32:168–170
31. Galiè N, Beghetti M, Gatzoulis MA, Granton J, Berger RM, Lauer A, Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) Investigators et al (2006) Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. Circulation 114:48–54
32. Gatzoulis MA, Beghetti M, Galiè N, Granton J, Berger RM, Lauer A, BREATHE-5 Investigators et al (2008) Longer-term bosentan therapy improves functional capacity in Eisenmenger syndrome: results of the BREATHE-5 open-label extension study. Int J Cardiol 127:27–32
33. Sitbon O, Beghetti M, Petit J, Iserin L, Humbert M, Gressin V et al (2006) Bosentan for the treatment of pulmonary arterial hypertension associated with congenital heart defects. Eur J Clin Investig 36(Suppl 3):25–31

34. Benza RL, Rayburn BK, Tallaj JA, Coffey GS, Pinderski LJ, Pamoukian SV et al (2006) Efficacy of bosentan in a small cohort of adult patients with pulmonary arterial hypertension related to congenital heart disease. Chest 129:1009–1015
35. Apostolopoulou SC, Manginas A, Cokkinos DV, Rammos S (2007) Long-term oral bosentan treatment in patients with pulmonary arterial hypertension related to congenital heart disease: a 2-year study. Heart 93:350–354
36. D'Alto M, Vizza CD, Romeo E, Badagliacca R, Santoro G, Poscia R et al (2007) Long term effects of bosentan treatment in adult patients with pulmonary arterial hypertension related to congenital heart disease (Eisenmenger physiology): safety, tolerability, clinical, and haemodynamic effect. Heart 93:621–625
37. Zhang ZN, Jiang X, Zhang R, Li XL, Wu BX, Zhao QH et al (2011) Oral sildenafil treatment for Eisenmenger syndrome: a prospective, open-label, multicentre study. Heart 97:1876–1881
38. Mukhopadhyay S, Sharma M, Ramakrishnan S, Yusuf J, Gupta MD, Bhamri N et al (2006) Phosphodiesterase-5 inhibitor in Eisenmenger syndrome: a preliminary observational study. Circulation 114:1807–1810
39. Iversen K, Jensen AS, Jensen TV, Vejlstrup NG, Sondergaard L (2010) Combination therapy with bosentan and sildenafil in Eisenmenger syndrome: a randomized, placebo-controlled, double-blinded trial. Eur Heart J 31:1124–1131
40. D'Alto M, Romeo E, Argiento P, Sarubbi B, Santoro G, Grimaldi N et al (2012) Bosentan-sildenafil association in patients with congenital heart disease-related pulmonary arterial hypertension and Eisenmenger physiology. Int J Cardiol 155:378–382
41. Galiè N, Rubin LJ, Hoeper M, Jansa P, Al-Hiti H, Meyer G et al (2008) Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. Lancet 371:2093–2100
42. MAESTRO (Macitentan in Eisenmenger Syndrome to Restore Exercise Capacity). ClinicalTrials.gov identifier: NCT01743001. https://clinicaltrials.gov/ct2/show/NCT01743001?term=NCT01743001&rank=1. Accessed 28 Aug 2015
43. Dimopoulos K, Inuzuka R, Goletto S, Giannakoulas G, Swan L, Wort SJ et al (2010) Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension. Circulation 121:20–25
44. Suzuki K, Yamaki S, Mimori S, Murakami Y, Mori K, Takahashi Y et al (2000) Pulmonary vascular disease in Down's syndrome with complete atrioventricular septal defect. Am J Cardiol 86:434–437
45. Van de Bruaene A, Delcroix M, Pasquet A, De Backer J, De Pauw M, Naeije R et al (2009) The Belgian Eisenmenger syndrome registry: implications for treatment strategies? Acta Cardiol 64:447–453
46. Duffels MG, Vis JC, van Loon RL, Berger RM, Hoendermis ES, van Dijk AP et al (2009) Down patients with Eisenmenger syndrome: is bosentan treatment an option? Int J Cardiol 134:378–383
47. Duffels MG, Vis JC, van Loon RL, Nieuwkerk PT, van Dijk AP, Hoendermis ES et al (2009) Effect of bosentan on exercise capacity and quality of life in adults with pulmonary arterial hypertension associated with congenital heart disease with and without Down's syndrome. Am J Cardiol 103:1309–1315
48. Vis JC, Thoonsen H, Duffels MG, de Bruin-Bon RA, Huisman SA, van Dijk AP et al (2009) Six-minute walk test in patients with Down syndrome: validity and reproducibility. Arch Phys Med Rehabil 90:1423–1427
49. D'Alto M, Romeo E, Argiento P, D'Andrea A, Sarubbi B, Correra A et al (2013) Therapy for pulmonary arterial hypertension due to congenital heart disease and Down's syndrome. Int J Cardiol 164:323–326
50. D'Alto M, Diller GP (2014) Pulmonary hypertension in adults with congenital heart disease and Eisenmenger syndrome: current advanced management strategies. Heart 100:1322–1328

51. Olsson KM, Delcroix M, Ghofrani HA, Tiede H, Huscher D, Speich R et al (2014) Response to letters regarding article "Anticoagulation and survival in pulmonary arterial hypertension: results from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA)". Circulation 130:e110–e112
52. Enright PL, Sherrill DL (1998) Reference equations for the six-minute walk in healthy adults. Am J Respir Crit Care Med 158(5 Pt 1):1384–1387
53. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW et al (1985) The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. Can Med Assoc J 132:919–923

Pregnancy and Contraception

19

Lorna Swan

Abbreviations

ACHD	Adult congenital heart disease
BNP	Brain natriuretic peptide
CHD	Congenital heart disease
CI	Cardiac index
LMW	Low molecular weight
PAH	Pulmonary arterial hypertension
PAP	Pulmonary artery pressure
PH	Pulmonary hypertension
RA	Right atrial
RV	Right ventricle
TAPSE	Tricuspid annular plane systolic excursion
6 MWT	6 minute walk test

19.1 Incidence

The management of a pregnant patient with pulmonary hypertension (PH) is challenging. The association with a possible poor outcome is well recognized, but there is limited data to provide robust evidence-based risk stratification or to guide treatment. When pregnancy does occur, miscarriage and medical termination are common. It is, therefore, difficult to estimate how frequently pregnancy occurs in patients with PH. Case reports can be informative, but there is publication bias with

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cases often reflecting those with the best outcomes. Data from the USA regarding idiopathic pulmonary arterial hypertension (PAH) can be used to provide an estimate of the number of pregnancies that progressed towards delivery [1]. This number is very small and in the region of 1 continuing pregnancy per 5 million population. This figure will vary significantly across countries, depending on access to PH care and comprehensive family planning services. Other UK authors have suggested that PH is present in 0.6 per 100,000 maternities [2]. In the Confidential Enquiries into maternal death in the UK, PH accounted for only five deaths over a period of 6 years. PH was a much more rare cause of maternal death than aortic dissection, heart failure or ischaemic heart disease [3].

19.2 Investigation

Patients can present with a pregnancy during any part of their PH "journey", and it is not uncommon for the first diagnosis of PH to be made during pregnancy or immediately postdelivery. A very important factor in determining outcome is timely and accurate diagnosis. If a patient presents with possible PH during pregnancy, then the same comprehensive diagnostic workup should be performed as for the non-pregnant patient. This is likely to include invasive haemodynamic assessment, which can be performed with minimal or no radiation exposure when needed [4]. Cardiac catheterization may need to be repeated during pregnancy if there is an ongoing concern about the diagnosis or failure to respond to treatment. Pregnancy should not be viewed as a reason to withhold care, but rather a reason for escalating care in view of the high mortality risk.

Progress during pregnancy should be monitored in the usual way with:

- Clinical examination including oxygen saturations
- Brain natriuretic peptide (BNP) levels
- Echo assessment of right ventricular (RV) function and pulmonary artery (PA) pressures
- Six-minute walk tests
- Cardiac catheterization (if needed)
- Fetal growth parameters

19.3 Haemodynamics of Pregnancy

The changes in the cardiovascular system related to pregnancy are well described [5, 6]. With specific references to the patient with PH, there are several features that may have an adverse impact. These include an increase in heart rate, volume loading and an increased tendency towards arrhythmia. For patients with septal defects or a patent foramen ovale, the reduction in systemic vascular resistance seen in pregnancy may lead to an increased right-to-left shunt and progressive cyanosis (Fig. 19.1).

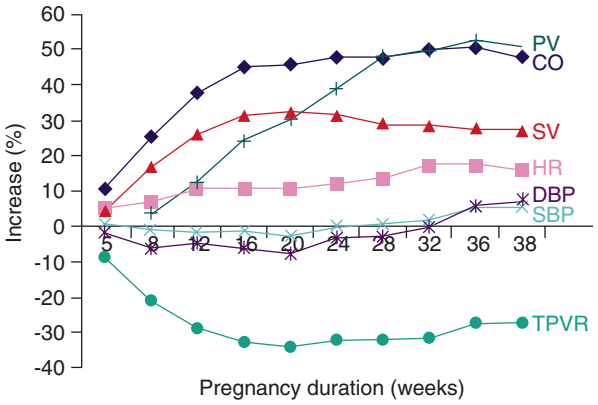

Fig. 19.1 Haemodynamic changes in normal pregnancy. *CO* cardiac output, *SBP/DBP* systolic/diastolic blood pressure, *HR* heart rate, *PV* plasma volume, *SV* stroke volume, *TPVR* total peripheral vascular resistance (Reprinted from Pregnancy and delivery in cardiac disease, P.E. Ruys,Jérôme Cornette,Jolien W. Roos-Hesselink, Journal of Cardiology, Vol 61, Issue 2 107-112, 2013 With Permission from Elsevier)

A general principle is that pregnant women need to have the ability to significantly increase their cardiac output during pregnancy and particularly during delivery. In healthy women, this increase in cardiac output is accommodated by a degree of pulmonary vasodilatation. In patients with pulmonary vascular disease, this mechanism is blunted, and increased flow may lead to increased pulmonary pressures and pressure loading of the RV. Detailed knowledge regarding the direct impact of pregnancy on the pulmonary vascular tree is lacking. Pregnancy is also known to be a hypercoagulable state, with a significantly increased risk of thrombosis, especially peri-delivery.

19.4 Risk Stratification

When the patient presents either in early pregnancy or contemplating pregnancy, it is essential to have a frank discussion about likely maternal and fetal outcomes. The pregnancy and heart disease literature is only partly helpful in this setting. The largest pregnancy outcome studies and cardiac scoring systems contained few PH patients and are, therefore, of limited utility [7, 8]. The modified WHO risk scoring groups place PH in group IV where pregnancy is categorized as "Extremely high risk of maternal mortality or severe morbidity; pregnancy contraindicated. If pregnancy occurs termination should be discussed. If pregnancy continues, care as for class III…(in a High-Risk Specialist Multi-Disciplinary Environment)" [9]. All such guidelines are of course generalizations encompassing various aetiologies and severities of PH. As such, the different types of PH cannot all be treated as being of equal risk.

Table 19.1 Possible factors impacting on maternal outcome in PH (modified from [10])

Better outcome	Determinant of outcome	Worse outcome
No	*Evidence of RV failure*	Yes
Slow	*Rate of symptom progression*	Rapid
No	*Syncope*	Yes
I, II	*WHO-FC*	IV
Longer (>500 m)	*6MWT*	Shorted (<300 m)
Peak O2 consumption >15 mL/min/kg	*Exercise test*	Peak O2 consumption <12 mL/min/kg
Normal or near normal	*BNP levels*	Very elevated/rising
No pericardial effusion	*Echocardiogram*	Pericardial effusion
TAPSE > 20 mm		TAPSE < 15 mm
RA pressure < 8 mmHg	*Haemodynamics*	RA pressure > 15 mmHg
CI > 2.5 L/min/m^2		CI < 2.0 L/min/m^2
Previous pregnancy	*Obstetric history*	Primigravida
<1000 dynes.s^{-1} cm^{-5}	*Pulmonary vascular resistance*	>1000 dynes.s^{-1} cm^{-5}
? Regional	*Type of delivery*	? General anaesthetic
? Responders	*Aetiology of PH*	? Eisenmenger

19.4.1 Can We Stratify Risk Further?

Outwith pregnancy, there are several well-recognized risk factors associated with a poor PH outcome. These include progressive symptoms, including syncope, evidence of right heart failure, impaired exercise capacity, elevated BNP, high right atrial pressure and reduced cardiac output [10]. There is no evidence that these factors are also relevant in pregnancy, but it would not be surprising if these factors were important in determining outcome also in this setting. The additional risk factors that have been studied during pregnancy are the aetiology of the PH, pulmonary vascular resistance, obstetric history and the type of delivery [11]. Some of these factors are self-explanatory—for example, maternal age is associated with an increased risk of morbidity and mortality—and not unexpected in a progressive disease [12]. Others, such as anaesthetic regimen at the time of delivery, are affected by patients' multiple confounding factors (Table 19.1).

19.4.2 Idiopathic PAH Patients Who Are Calcium Channel Blocker Responders

A question that is frequently asked is regarding the risk of pregnancy for patients who have had a significant reduction in their pulmonary vascular resistances on calcium channel clockers (or other agents). These patients may have had normalization of their PA pressures and RV function on catheter and echo. There is anecdotal evidence that these patients tolerate pregnancy better than more limited patients, but the impact of pregnancy on PH progression and long-term prognosis is unclear [13].

Table 19.2 Case series of pregnancies in patients with pulmonary hypertension

First author	Era and setting	No. of pregnancies	Outcomes	Comments
Jaix [13]	2007–2010 (European Registry)	26 (includes 6 terminations)	3 maternal deaths (15%)	
Kiely DG [17]	2002–2009 (Sheffield)	9	1 maternal death (11%)	
Curry RA [18]	1995–2010 (London)	12	2 maternal deaths (16%)	Deaths occurred in earlier cohort Mainly ACHD aetiology
Katsuragi S [14]	1982–2007 (Japan)	42 (included 18 terminations)	1 maternal death (4%)—check	Mainly ACHD aetiology
Subbaiah M [16]	2006–2012 (India)	30 (all >28 weeks)	1 maternal death	Severe PH defined if echo systolic PA pressure > 50 mmHg
Li B [19]	2007–2011 (Beijing)	103 (included 36 terminations)	9 maternal deaths (8.7%)	Echo definition of PAH (possibly included patients with left heart disease)
Ma L. [15]	1999–2008 (Beijing)	30	5 maternal deaths (16.7%) Fetal/neonatal death 13%	
Monagle J [20]	1994–2009 (Australia)	19	1 maternal death	Mixed population including patients with left heart disease

19.4.3 Has Risk Changed?

Institutional experience and the available literature would suggest that maternal mortality from PH is reducing. Bedard et al. reviewed the literature from two time windows (1978–1996 and 1997–2007). Mortality dropped for all groups including those with idiopathic PAH (from 30 to 17%) and for those with congenital heart disease-related PAH (PAH–CHD, 36–28%). This was thought to be reflection of the impact of advanced pulmonary vasodilator therapies—approximately 70% of idiopathic patients were on treatment in the second time window [11]. However, more recent studies have shown a similar reduction in mortality even in the absence of advanced therapies [14]. General improvements in diagnosis and antenatal care—especially elective early delivery—may be important.

One of the more recent studies was a multicentre study of 26 pregnancies. In this group, overall maternal mortality (or the need for urgent transplantation) was 15%. However, this paper included eight pregnancies that ended in either spontaneous or iatrogenic abortion and a high proportion of patients who were responders to calcium channel blockers [13]. The overall maternal mortality was very similar to a large Chinese study reported in 2012 [15]. In a recent series, there is a strong suggestion that patients with the most severe forms of PH are more likely to suffer from cardiac complications [16] (Table 19.2).

19.5 Causes of Maternal Death

When women with PH do die during or following pregnancy, the most common cause is refractory RV failure [11]. The majority of these deaths occur early in the postnatal period. Thromboembolic events and PH crisis are other recognized causes of maternal death. To date, the available literature has focused on maternal mortality, and little is known about maternal morbidity related to pregnancy. Even less is known regarding the impact of pregnancy on PH progression and long-term outcome. When counselling a PH patient contemplating pregnancy, all of these uncertainties need to be discussed.

19.6 Fetal Outcomes

There is only limited data on fetal outcomes in this population. The main fetal risks are associated with maternal cyanosis, fetal growth restriction and premature delivery. Cyanosis is particularly hazardous to the developing fetus. If the maternal saturations are below 85%, then the likelihood of a live birth is less than 15%. A very high maternal haemoglobin, as is seen in Eisenmenger syndrome, is also associated with a poor fetal outcome [21]. Whether maternal oxygen supplementation improves fetal outcome is unclear, although anecdotally this has been the case in our group's experience. In pregnancies that progress to a live birth, maternal cyanosis is associated with an increased risk of growth restriction and low birth weight [22]. When maternal cyanosis is combined with low maternal cardiac output, the risk to the fetus is particularly high.

19.7 Treatment Algorithms

The advent of pulmonary vasodilators has revolutionized the care of patients with PAH. Of the agents available, several have been used in pregnancy with no documented teratogenic effects. The exceptions to this are bosentan and other endothelin receptor antagonists (ERA), which are known to be teratogenic and are, therefore, contraindicated in pregnancy. Both prostaglandins and the phosphodiesterase type 5 inhibitor sildenafil have been used in PAH pregnancies. There is no data to support the use of riociguat or selexipag in pregnancy and should, thus, be avoided.

19.7.1 When Should Treatment Start in a Patient Naive to Treatment?

Practice varies between centres on the optimal medical care of pregnant patients with PAH, with little consensus regarding treatment strategies. Several units have published their own therapeutic algorithm based on experience and "common sense". One of the most widely accepted is the protocol described by the Sheffield

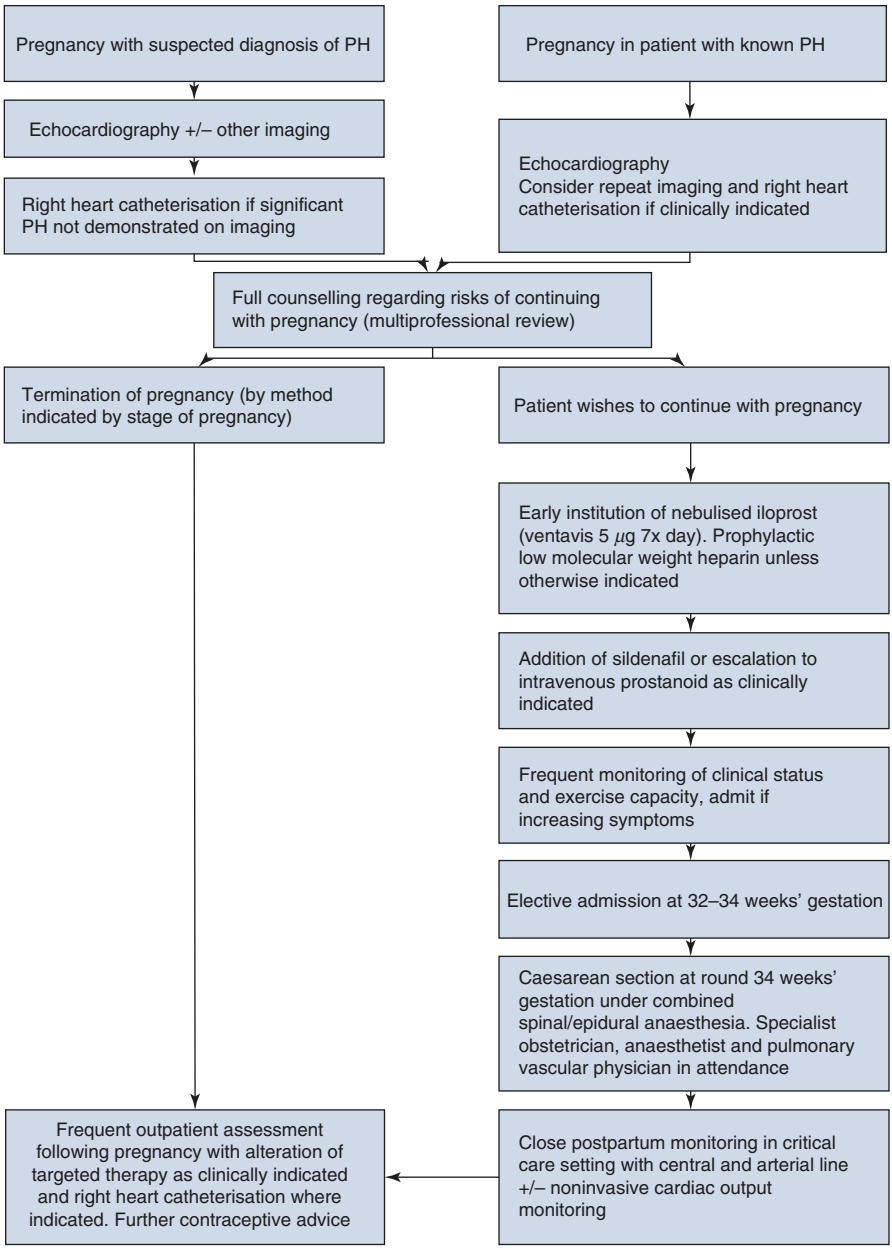

Fig. 19.2 Sheffield Antenatal Care Algorithm

(UK) group (Fig. 19.2) [17]. In other centres, IV prostanoids are commenced from the outset, with the attempt to proactively establish patients on the most efficacious combination of therapies. Combination therapy (sildenafil plus a prostanoid) is common in this scenario [23].

19.7.2 Anticoagulation

Pregnancy is a pro-thrombotic state with a particular risk of thrombotic events post-delivery. Many of these patients, with the possible exception of the Eisenmenger patients, are anticoagulated, either before or during pregnancy. Again, the risks of any therapy need to be carefully balanced with the expected benefits. Warfarin is both teratogenic and also systemically anticoagulates the fetus. Many units convert patients to low molecular weight heparin, but, again, this will depend on the nature of the PAH, the gestation and other risk factors.

19.8 Antenatal Care

Antenatal care must be delivered by a specialist multidisciplinary team. This needs to include obstetrician, PH specialist, anaesthetist, fetal medicine and neonatal specialists. Haematologists, midwives and pharmacists may also play a role. Most units advocate a monthly review in the first trimester and then fortnightly assessment. In the third trimester, the patient will need to be reviewed weekly. All the usual anaesthetist complications will need to be looked for and treated promptly. Even a minor cardiac or obstetric complication, such as an atrial arrhythmia, could lead to haemodynamic instability. Patients may require to be hospitalized for a period during their antenatal care, particularly if they are symptomatic or are undergoing escalation of their treatment regimen.

In the third trimester, or earlier if unstable, delivery planning should occur in agreement with all members of the multidisciplinary team. This planning should also include plans for a preterm labour and other common obstetric complications. A detailed plan should be made, anticipating the postdelivery care required for both the mother and the fetus (Table 19.3).

19.9 Delivery

Delivery and the immediate post-partum period are the time of greatest risk. Mode of delivery will depend on gestation, obstetric factors, logistics of care and patients' haemodynamic status. Vaginal delivery has many advantages, especially less impact on haemodynamics; elective caesarean section is a viable alternative, although the mother may be at increased risk of bleeding or thrombosis. In reality, the mode of delivery is often determined by the gestation, with the majority of PH patients being

Table 19.3 Example of a delivery plan

Delivery plan for high-risk patient			
If admitted to labour ward	*Please inform*	*Grade*	*Tick*
	Obstetrician on call	Senior consultant/junior	
	Anaesthetist on call	Senior consultant/junior	
	Cardiologist	Senior consultant/junior	
Antenatal admission	From _____ weeks		
Delivery	Elective LSCS/trial of vaginal delivery		
LSCS	*3rd stage Mx*: prophylactic compression suture/syntocinon 5 units over 10–20 min/syntocinon low-dose infusion (8–12 milliunits/min)		
	Anaesthetic technique: Epid/Spin/CSE/GA		
	Comments: _____		
	Maternal monitoring: ECG/SaO_2/non-invasive BP/invasive BP/CVP/_____		
	Other instructions/warnings: _____		
	Inform team if admitted in labour before scheduled LSCS date		
Vaginal delivery	HDU chart/TEDS in labour/medication to be continued _____		
First stage Mx	*Prophylactic antibiotics*: elective/if operative delivery		
	Epidural for analgesia: none/when requested/as soon as in established labour		
	Comments re anaesthetic _____		
	Maternal monitoring: ECG/SaO_2/non-invasive BP/invasive BP/CVP/_____		
Vaginal delivery	Normal second stage/short second stage (then assist if not del max _____		
Second stage Mx	_____ min pushing)/elective assisted delivery only		
Vaginal delivery	Normal active Mx (oxytocin and CCT)/syntocinon infusion 8–12 milliunits/min		
Third stage Mx	Continue syntocinon infusion _____ h		
Post delivery	High dependency unit (min stay _____h)/LMW heparin (duration _____) Other drugs post-partum _____		

delivered by caesarean section. Delivery must be performed in an expert multidisciplinary environment, with access to a full cardiac intensive care team, including ECMO and ventricular assist support. When planning a delivery, multiple components need to be considered. Delivery will often occur preterm, with the need for pre-delivery steroids for lung maturation and postdelivery admission to the Special Care Baby Unit for the neonate.

During delivery, careful maternal monitoring is key. This should include, but not be limited to, ECG monitoring, invasive blood pressure measurement, urinary catheterization, right atrial or central venous pressure line and repeat blood gas analysis.

The choice of anaesthetic regimen will be depend on the expertise of the team and other factors mentioned above. Regional anaesthesia, when performed slowly and in expert hands, can provide excellent pain relief with minimal disruption to haemodynamics. General anaesthesia has the advantage of allowing administration

Table 19.4 Obstetric drugs and their cardiovascular effects

Drug	Possible effects
Oxytocin	Use: *induction of labour; prevention or treatment of PPH*
	Caution: bolus administration associated with hypotension, chest pain, ECG changes, reflex tachycardia, fluid overload
Prostaglandins	
Misoprostol	Use: *cervical ripening; termination; uterotonic*
	Caution: minimal impact on blood pressure but less effective than oxytocin and ergometrine
Carboprost (Hemabate) (15-methyl prostaglandin F2α)	Use: *life-threatening haemorrhage (second line only)*
	Caution: severe bronchospasm, elevation of PA pressures, increased V/Q mismatch
Ergometrine	Use: *post-partum haemorrhage*
	Caution: hypertension, elevation of PA pressures, chest pain
Ritodrine/salbutamol (beta-agonists)	Use: *premature labour; tocolytic*
	Caution: tachycardia; fluid overload
Atosiban (oxytocic receptor antagonist)	Use: *premature labour*; *tocolytic*
	Minimal impact on heart rate and blood pressure

of nitric oxide, if needed, and the use of trans-oesophageal echocardiography to continuously monitor RV function. All of these components of care should be discussed several weeks prior to delivery in a multidisciplinary meeting and documented fully in a care plan.

If a vaginal delivery is planned, the second stage (active pushing) should be limited, with passive descent of the fetus and elective lift out using ventouse or forceps. Post-partum bleeding is common in these patients and should be managed proactively. If a caesarean section has been performed, then a compression suture may be placed to prevent uterine atony. Several of the normal obstetric drugs given at the time of delivery can destabilize the PH patient and should be avoided when possible (Table 19.4).

19.9.1 Peri-delivery Haemodynamics

One of the main challenges at the time of delivery is the sudden rise in circulating volume when the placenta is removed and the uterus contracts. RV function is often dependent on a narrow window of filling pressures. If underfilled or overfilled, the RV function can deteriorate. The optimal RA pressure is usually 8–12 mmHg. To achieve this, in the absence of significant bleeding, the patient should be diuresed aggressively postdelivery. Several groups suggest diuresis to the point of losing 10% of body weight or until the serum creatinine starts to rise. Diuretics should be continued for several weeks postdelivery and are often needed on discharge.

Postdelivery fluid balance and active management of bleeding are vital. In the critically unwell patient, ventilation, IV therapies, inotropes and even ECMO may be required. Elective admission to intensive care is mandatory, even in a stable patient, as the postdelivery period is of particular high risk.

19.10 Contraception

19.10.1 Emergency Contraception

An old-fashioned copper intrauterine coil can be used as emergency contraception for up to 5 days after unprotected sex. It is highly effective and will prevent 99% of pregnancies from progressing. Insertion of a coil can be associated with vasovagal syncope, and caution should be exercised when treating women with important PH: several groups have suggested that intrauterine devices are contraindicated in PH patients; however, in the correct environment, the benefits may outweigh the risks.

There are several varieties of morning after pill. The most frequently used is levonorgestrel (Levonelle). This is effective up to 72 h after sex. Levonorgestrel interacts strongly with warfarin. Its effectiveness is inhibited by bosentan, and some authors suggest the dose required is double the usual baseline dose (2.5–3 mg when on bosentan). Double contraception, adding barrier methods, is recommended in patients on ERAs.

19.11 Termination of Pregnancy

If a patient with PH does become pregnant, termination of pregnancy should be discussed. If less than 14 weeks' pregnant, a surgical procedure with dilatation and suction evacuation can be performed either under general anaesthesia, regional block or sedation. After 14 weeks, a more complex procedure is required, often using prostaglandins. Medical termination can be attempted at any stage with mifepristone, followed by misoprostol. A medical termination is a slower process than a surgical procedure and will be incomplete in approximately 15% of cases, requiring surgical evacuation. Any surgical procedure carries risks in PH patients, relating to the type of anaesthesia and the risk of bleeding, thrombosis and infection.

19.12 Contraception

Table 19.5 demonstrates the WHO classification for various contraceptive options for a PH patient. In this classification, WHO class 1 means that there is no limitation to use and class 4 is a strong contraindication.

Table 19.5 Contraceptive options in patients with pulmonary hypertension

	WHO class	Specific benefits	Specific risks
Combine oral contraceptive pill	4		Unacceptable risk of thrombosis/ disease exacerbation
Progesterone only pill "minipill"	1b	Reduced thrombotic risk compared with combined pill	Must be taken in tight time window
			Difficulties with compliance
Cerazette or equivalent	1	Reduced thrombotic risk compared with combined pill	Relies on maternal compliance
		Longer time window improves compliance	Interacts with bosentan (and other ERAs?)
DEPO Provera	1	High reliability	Occasionally causes fluid retention
IM injection			Bruising when anticoagulated
			Interacts with bosentan (and other ERAs?)
Implant (Nexplanon)	1	High reliability	Interacts with bosentan (and other ERAs?)
Mirena Coil	2	High reliability	Interacts with bosentan (and other ERAs?)
			Risk of vasovagal collapse (insertion/removal)
Copper coil	3	Reliability	Risk of pelvic infection
			Risk of vasovagal collapse (insertion/removal)
Sterilization	3	High reliability	Surgical procedure requiring sedation/anaesthesia
		Permanent contraception	

WHO eligibility criteria
1 = No limitation of use/contraindication
2 = Advantages generally outweigh the risks
3 = Risks usually outweigh the advantages
4 = Unacceptable health risk/contraindicated

Conclusion

Overall, pregnancy is contraindicated in patients with PH, despite a significant improvement in outcome in recent years. Interruption of pregnancy also carries significant risks and, hence, adequate contraception is important. Patients who choose to continue with a pregnancy despite adequate counselling should be managed in a multidisciplinary environment, with advanced planning and close monitoring around and especially in the days and weeks after delivery.

References

1. Chakravarty EF, Khanna D, Chung L (2008) Pregnancy outcomes in systemic sclerosis, primary pulmonary hypertension, and sickle cell disease. Obstet Gynecol 111(4):927–934
2. UK Obstetric Surveillance Study. Seventh Annual Report 2013. https://www.npeu.ox.ac.uk/downloads/files/ukoss/annual-reports/UKOSS-Annual-Report-2013.pdf

3. Lewis G (ed) Saving mothers' lives: reviewing maternal deaths to make motherhood safer—2006–08. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom
4. Tuzcu V, Gul EE, Erdem A, Kamali H, Saritas T, Karadeniz C, Akdeniz C (2015) Cardiac interventions in pregnant patients without fluoroscopy. Pediatr Cardiol 36(6):1304–1307
5. Gelson E et al Cardiovascular changes in normal pregnancy. In: Heart Disease and Pregnancy. Pub RCOG Press
6. Hunter S, Robson SC (1992) Adaptation of the maternal heart in pregnancy. Br Heart J 86:540–543
7. Siu SC, Sermer M et al (1997) Risk and predictors for pregnancy-related complications in women with heart disease. Circulation 96:2789–2794
8. Drenthen W, Boersma E, Balci A, Moons P, Roos-Hesselink JW, Mulder BJ, Vliegen HW, van Dijk AP, Voors AA, Yap SC, van Veldhuisen DJ, Pieper PG (2010) Predictors of pregnancy complications in women with congenital heart disease. Eur Heart J 31:2124–2132
9. Thorne S, MacGregor A, Nelson-Piercy C (2006) Risks of contraception and pregnancy in heart disease. Heart 92:1520–1525
10. McLaughlin VV, McGoon MD (2006) Pulmonary arterial hypertension. Circulation 114(13):1417–1431
11. Bedard E, Dimopoulos K, Gatzoulis MA (2009) Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? Eur Heart J 30:256–265
12. Weiss BM, Zemp L, Seifert B, Hess OM (1998) Outcome of pulmonary vascular disease in pregnancy: a systematic overview from 1978 through 1996. J Am Coll Cardiol 31:1650–1657
13. Jaïs X, Olsson KM, Barbera JA, Blanco I, Torbicki A, Peacock A, Vizza CD, Macdonald P, Humbert M, Hoeper MM (2012) Pregnancy outcomes in pulmonary arterial hypertension in the modern management era. Eur Respir J 40:881–885
14. Katsuragi S, Yamanaka K, Neki R, Kamiya C, Sasaki Y, Osato K et al (2012) Maternal outcome in pregnancy complicated with pulmonary arterial hypertension. Circ J 76:2249–2254
15. Ma L, Liu W, Huang Y (2012) Perioperative management for parturients with pulmonary hypertension: experience with 30 consecutive cases. Front Med 6:307–310
16. Subbaiah M, Kumar S, Roy KK, Sharma JB, Singh N (2013) Pregnancy outcome in women with pulmonary arterial hypertension: single-center experience from India. Arch Gynecol Obstet 288:305–309
17. Kiely DG, Condliffe R, Webster V, Mills GH, Wrench I, Gandhi SV, Selby K, Armstrong IJ, Martin L, Howarth ES, Bu'Lock FA, Stewart P, Elliot CA (2010) Improved survival in pregnancy and pulmonary hypertension using a multiprofessional approach. BJOG 117:565–574
18. Curry RA, Fletcher C, Gelson E, Gatzoulis MA, Woolnough M, Richards N, Swan L, Steer PJ, Johnson MR (2012) Pulmonary hypertension and pregnancy-a review of 12 pregnancies in nine women. BJOG 119:752–761
19. Li B, Sun X-Y, Wang K-F (2013) Pregnancy outcomes of 103 women with pulmonary arterial hypertension. Zhonghua Fu Chan Ke Za Zhi 48:659–662
20. Monagle J, Manikappa S, Ingram B, Malkoutzis V (2015) Pulmonary hypertension and pregnancy: the experience of a tertiary institution over 15 years. Ann Card Anaesth 18:153–160
21. Presbitero P, Somerville J, Stone S, Aruta E, Spiegalhalter D, Rabajoli F (1994) Pregnancy in cyanotic heart disease. Circulation 89:2673–2676
22. Gelson E, Curry R, Gatzoulis MA, Swan L, Lupton M, Steer P, Johnson M (2011) Effect of maternal heart disease on fetal growth. Obstet Gynecol 117:886–891
23. Pieper PG, Lameijer H, Hoendermis ES (2014) Pregnancy and pulmonary hypertension. Best Pract Res Clin Obstet Gynaecol 28:579–591

Training and Recommendations for Exercise

20

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Abbreviations

CHD	Congenital heart disease
CPET	Cardiopulmonary exercise test
HR	Heart rate
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
V̇E/V̇CO2	Ventilation per unit of carbon dioxide production

20.1 Introduction

Exercise capacity and quality of life are significantly reduced in patients with pulmonary arterial hypertension (PAH) secondary to congenital heart disease (PAH–CHD) [1, 2]. Physical performance is most severely impaired in the Eisenmenger syndrome [2]. In patients with idiopathic pulmonary hypertension, exercise training as add-on to medical treatment seems to improve exercise capacity, quality of life and functional class [3–5]. Data on the effect of exercise training in patients with PAH–CHD is limited; however, if exercise training is performed in a safe manner [6], a global beneficial effect can be expected.

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20.2 Exercise Capacity in Patients with PAH–CHD

Eisenmenger syndrome represents the most severe form of PAH–CHD. In these patients, a long-standing left-to-right shunt across a large defect leads to a progressive rise in pulmonary vascular resistance and pulmonary artery pressures, eventually leading to shunt reversal. This causes systemic desaturation and induces haematological and biochemical alterations: the red cell count and haemoglobin concentration increase, leading to secondary erythrocytosis and an increase in blood viscosity [7]. During physical exercise, the inability of the pulmonary circulation to accommodate a significant increase in pulmonary blood flow results in further right-to-left shunting and systemic oxygen desaturation. As a consequence, the exercise capacity of these patients, expressed as peak oxygen consumption on cardiopulmonary exercise testing [8, 9] or 6-min walk distance [10], is markedly depressed.

In noncongenital heart disease, myocardial performance is often the main determinant of exercise capacity. No definitive data are currently available on the exact mechanisms behind exercise intolerance and the onset of symptoms in patients with Eisenmenger syndrome. A high physiological dead space due to reduced pulmonary blood flow and right-to-left shunting, as well as stimulation of chemoreceptors in the systemic circulation of cyanotic patients [11, 12], is most likely responsible for the greatly enhanced ventilatory response to exercise, expressed as ventilation per unit of carbon dioxide production ($\dot{V}E/\dot{V}CO2$ slope) [13, 14]. Eisenmenger patients tend to ventilate excessively during exercise and may exhaust their breathing reserve quite early. Moreover, Broberg et al. found that more than 40% of Eisenmenger patients suffered from obstructive lung disease and 50% have a diffusion transfer coefficient lower than 80%. The latter was associated with a lower exercise duration [15].

Higher haemoglobin concentration and haematocrit are associated with a better exercise capacity in cyanotic CHD, at the expense of a higher blood viscosity. As severe hyperviscosity symptoms are relatively rare, this suggests that even significant erythrocytosis and the associated increase in functional capacity may be worth the cost of increased viscosity [16]. Although several reports suggest that skeletal muscle function is negatively influenced by chronic hypoxia [17–19], the effect of chronic cyanosis has never been investigated in patients with cyanotic CHD. Decreased peak oxygen consumption [8, 20] and a shorter 6-min walk distance [10] seem to be related to outcome in cyanotic patients with PAH.

PAH also occurs in patients who still have increased pulmonary artery pressures despite shunt closure [21]. In addition, Gabriels et al. recently reported that pulmonary artery pressures tend to increase in older patients after shunt repair even when normal pressures were present preoperatively [22]. PAH is also found in patients with a small shunt, which probably suggests the coincidental presence of PAH and the haemodynamically "insignificant" shunt lesion [23]. In these patients, an abnormal ventilatory response during exercise due to PAH and right ventricular dysfunction secondary to pressure overload may lead to impaired exercise tolerance [24].

Moreover, skeletal muscle myopathy is not uncommon in patients with PAH and contributes to decreased functional capacity [24]. Diller et al. showed that PAH, independent from cyanosis, correlates with peak oxygen consumption [8]. Peak oxygen consumption seems to be associated with late clinical outcome in these patients [8].

Another group of PAH–CHD patients are those with normal pulmonary artery pressures at rest and significantly increased pressures at maximal exercise, although not fulfilling the criteria of PAH as defined by international guidelines [23, 25]. Van de Bruaene et al. showed that pulmonary vascular resistance during exercise in patients who underwent late atrial septal defect repair was higher when compared to controls or those who underwent early repair [26]. Exercise echocardiography allows for the identification of *minimal pulmonary vascular disease*, defined as an increased slope of pulmonary artery pressure–flow during exercise (dynamic pulmonary vascular resistance). Remarkably, the pressure–flow slope correlated significantly with peak oxygen consumption in atrial septal defect patients. The prognostic value in CHD of this dynamic increase in pulmonary vascular resistance remains to be determined and could be correlated with morphometric changes in the right heart over time [22, 27].

20.3 Exercise Capacity and Quality of Life in PAH–CHD

There seems to be a close relationship between symptoms of pulmonary hypertension (including reduced exercise capacity) and health-related quality of life [28–30]. Increasingly, in recent years, studies that test the efficacy of disease-targeting therapy for PAH also include quality of life as a secondary endpoint. Indeed, recent data suggest that disease-targeting therapy not only improves exercise capacity but also quality of life [31, 32]. Moreover, improvement of quality of life seems to be related to better clinical outcome [32, 33]. Indirectly, quality of life is also related to the number of hospitalizations for PAH. Quality of life relates to functional capacity, which, in turn, is related to the number of hospital admissions [34].

In patients with PAH, a low health-related quality of life is associated with impaired exercise capacity [35]. This association is most pronounced in cyanotic patients [35]. Likewise disease-targeting therapy seems to improve exercise capacity and quality of life in CHD patients with PAH [36–39]. However, some studies showed an increase in exercise capacity without an effect on quality of life [40]. Finally, Blok et al. recently reported that quality of life predicts mortality in patients with PAH–CHD [41].

In summary, quality of life seems to be related to exercise capacity in PAH–CHD. It appears, therefore, reasonable to use all means possible to increase exercise capacity in these patients, as this is likely to result in a better quality of life and possibly clinical outcome. Unfortunately, specific studies on changes in exercise capacity and their effect on mortality have not yet been performed in PAH–CHD.

20.4 Data on Exercise Training in PAH–CHD Patients

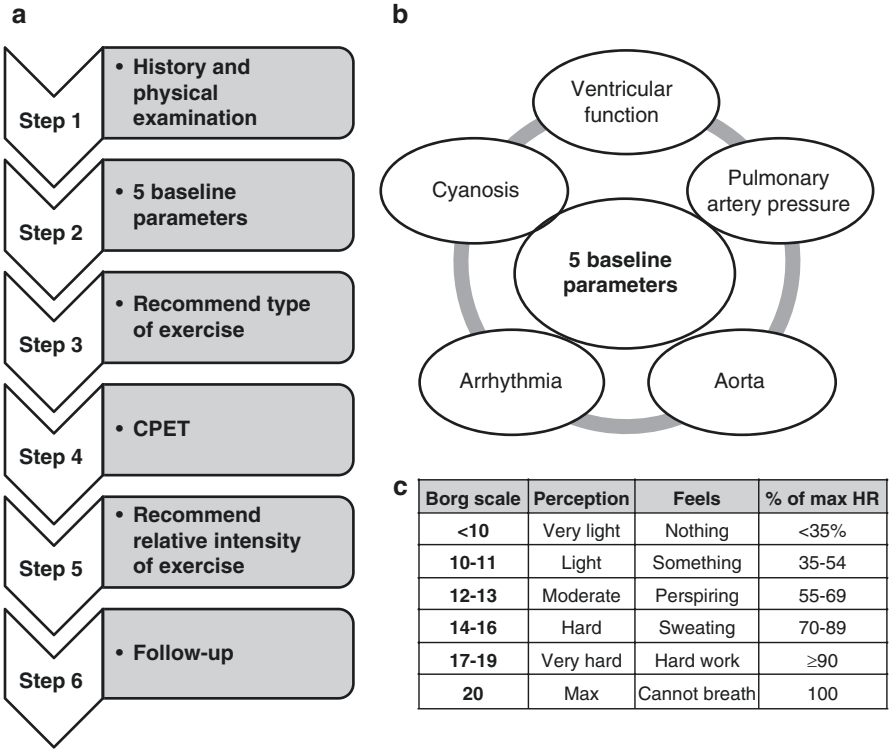
In coronary artery disease and chronic heart failure, exercise causes a decrease of pulmonary vascular resistance and improves endothelial function, exercise capacity and quality of life parameters [42, 43]. Supervised exercise training has also been shown to be safe and improves walking distance, exercise capacity, quality of life and NYHA functional class in patients with pulmonary hypertension of different aetiologies [44, 45]. The mechanisms responsible for the beneficial effects of exercise training are likely to be both central (pulmonary and cardiovascular) and peripheral (muscle).

Martínez-Quintana et al. were the first to perform a prospective randomized study of cardiac rehabilitation on patients with PAH-CHD [46]. Patients in the training group participated in an exercise program 2 days a week for 3 months. Training consisted of 10 min of warming up with stretching of long muscles, a brief period of resistance exercises and lifting 1–2 kg weights, followed by interval training on a bicycle ergometer for 24 min with a baseline of 10–25 W and 30-s peaks of 20–50 W. Modified Borg scale symptoms and heart rate defined the intensity of the exercise. While the authors reported no significant changes in analytical data, hand and leg strength or quality of life between the active and control group, the rehabilitation group improved their 6-min walk test distance, oxygen saturations at peak exercise and functional class. There were no adverse events reported.

Several years later, Becker-Grünig et al. prospectively studied the effect of exercise training in a nonrandomized cohort of patients with invasively confirmed PAH–CHD [47]. Exercise training was started in-hospital for 3 weeks. The program included at least 1.5 h of exercise training per day (in intervals distributed over the day) consisting of interval bicycle ergometer training at low workloads (10–60 W), 7 days a week. Furthermore, walking, dumbbell training of single muscle groups using low weights (500–1000 g) and respiratory training were performed 5 days per week. The target maximum heart rate during training corresponded to 60–80% of the peak heart rate reached during incremental cardiopulmonary exercise testing. Patients who were on oxygen therapy remained on supplemental oxygen throughout the whole training program. The exercise training was continued at home for 12 weeks and comprised of training at least 30 min per day at 5 days a week on a bicycle ergometer. Patients were also offered psychological support. At the end of the study, 6-min walk distance, peak oxygen consumption and maximal workload had improved significantly. Quality of life did not improve significantly, with the exception of the “bodily pain” subscale. Oxygen saturation and functional class did not change. All patients tolerated exercise training well without severe adverse events, and no syncope or pre-syncope occurred. The authors concluded that exercise training as add-on to medical therapy may be effective in PAH-CHD patients, improving work capacity, quality of life and further prognostically relevant parameters. To date, no further studies have been published on the effect of exercise training in PAH–CHD.

20.5 Recommendations for Exercise Training in PAH–CHD

Recently, a position paper was published by the European Society of Cardiology Working Group of Grown-Up Congenital Heart Disease and the Section of Sports Cardiology of the European Association for Cardiovascular Prevention and Rehabilitation on physical activity in adolescents and adults with congenital heart defects. In this paper, a stepwise approach is recommended, which includes the assessment of five fundamental parameters relating to ventricular morphology and function and the presence of aortic dilatation, arrhythmias, pulmonary hypertension and cyanosis (Fig. 20.1). Once these parameters are assessed and cardiopulmonary exercise testing is performed to objectively assess exercise capacity and the response



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Borg scale	Perception	Feels	% of max HR
<10	Very light	Nothing	<35%
10-11	Light	Something	35-54
12-13	Moderate	Perspiring	55-69
14-16	Hard	Sweating	70-89
17-19	Very hard	Hard work	≥90
20	Max	Cannot breath	100

Fig. 20.1 Recommendations for individualized (recreational) exercise prescription for adolescents and adults with congenital heart disease [48]. The recommended steps for the evaluation of ACHD patients with regard to exercise prescription are listed in (**a**). The five pillars on which patient evaluation and exercise recommendations are made are shown in (**b**). Based on these five parameters, recommendations on the level of static exercise and intensity of exercise are formulated (see Fig. 20.2). The intensity of the sport is defined based on the Borg scale (**c**), perception of effort and heart rate (as a percentage of the maximum heart rate achieved on incremental cardiopulmonary exercise testing). *CPET* cardiopulmonary exercise test, *HR* heart rate

1. Ventricles					
Systolic dysfunction	**n**	**n**	**+**	**++**	**+++**
Hypertrophy	**n**	**n**	**+**	**++**	**+++**
Pressure load	**n**	**+**		**++**	**+++**
Volume load	**n**	**+**			**++/+++**
Single ventricle/ Systemic RV			**y**		
2. PH	**n**	**n**	**+**		**++/+++**
3. Aortic dilation	**n/+**	**++**	**+++**	**+++/ due repair**	
4. Arrhythmia					
Burden	n	n	+		+++
Malignant	n	n	n		y
5. Cyanosis at rest or exercise	**n**	**n**	**n**	**y**	
	All apply	**≥1 applies**			**≥1 applies**
Sport					
Static component	↑↑↑	↑↑	↑↑	↑↑	↑
Intensity	↑↑↑	↑↑↑	↑↑	↑	↑
Intensity if highly static sport	↑↑↑	↑↑	↑	↑	↑

Fig. 20.2 Recommendations for individualized (recreational) exercise prescription for adolescents and adults with congenital heart disease [48]. Recommendations are based on five baseline parameters (see Fig. 20.1), including pulmonary hypertension (PH) and cyanosis at rest or exercise. Emphasis is put on static component of exercise, which should be reduced in PH and cyanotic patients. *RV* right ventricle, *n*/+/++/+++ none/mild/moderate/severe, ↑/↑↑/↑↑↑ low/moderate/high

to physical exertion, recommendations for exercise can be formulated. These focus on the intensity of the "static" or isometric component of the activity and its intensity (Fig. 20.2). The intensity of the sport is defined as low (rate of perceived exertion Borg scale 11–12, HR < 60% of max HR on CPET), moderate (Borg 13–14, HR 60–75% of max HR on CPET) or high (Borg 15–17, HR 75–90% of max HR on CPET). Patients should be followed up and recommendations adjusted appropriately.

This position paper encourages PAH–CHD patients to exercise [48]. Regular physical exercise is not only likely to improve exercise capacity (subjective and objective) and quality of life but also prevents the development of obesity [49] and ischaemic heart disease [50]. Patients exercising regularly are also likely to maintain a healthier lifestyle. As long as regular physical exercise is safe for the patient, he/she can benefit from it. Patients with mildly elevated pulmonary artery pressures

and no central cyanosis are advised to avoid physical activities with a high static component and should exercise at moderate intensity (Borg scale 13–14, heart rate 60–75% of maximal heart rate achieved during exercise test). Patients with mildly elevated pulmonary artery pressures and central cyanosis are also advised to avoid highly static physical activities but are advised to exercise at a low dynamic exercise intensity (Borg scale 11–12, heart rate < 60% of maximal heart rate achieved during exercise test). In patients with moderately/severely elevated pulmonary artery pressures, with or without cyanosis, physical activity with a low static component and at low dynamic intensity is recommended. With regard to the frequency and duration of each exercise session, a combined minimum of 3–4.5 h per week is recommended, with a minimum 30 min per session. These recommendations are, of course, arbitrary and validation is required.

Given the, often significant, symptoms experienced by PAH patient while exercising, an interval-type training program, combining dynamic aerobic and resistance exercises, is preferred. Moreover, respiratory muscle training seems to be a useful add-on to the training program. However, data on the effects of respiratory muscle training in PAH–CHD patients are lacking.

Conclusions

Data on the safety and efficacy of exercise training in patients with PAH–CHD are scarce. However, the information from a small number of available studies, as well as expert consensus, encourages PAH–CHD patients to remain physically active. Physicians should provide individualized recommendations based on detailed clinical assessment while monitoring the safety and efficacy of the recommended activity. Exercise training is believed to produce an improvement in physical capacity, quality of life and outcome of PAH–CHD patients, both directly and indirectly, through changes in lifestyle and health behaviour. More research is needed to establish the role of exercise training in this population.

References

1. Engelfriet PM, Duffels MG, Möller T, Boersma E, Tijssen JG, Thaulow E, Gatzoulis MA, Mulder BJ (2007) Pulmonary arterial hypertension in adults born with a heart septal defect: the euro heart survey on adult congenital heart disease. Heart 93:682–687
2. Müller J, Hess J, Hager A (2011) Exercise performance and quality of life is more impaired in eisenmenger syndrome than in complex cyanotic congenital heart disease with pulmonary stenosis. Int J Cardiol 150:177–181
3. Mereles D, Ehlken N, Kreuscher S, Ghofrani S, Hoeper MM, Halank M, Meyer FJ, Karger G, Buss J, Juenger J, Holzapfel N, Opitz C, Winkler J, Herth FF, Wilkens H, Katus HA, Olschewski H, Grünig E (2006) Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. Circulation 114:1482–1489
4. de Man FS, Handoko ML, Groepenhoff H, van 't Hul AJ, Abbink J, Koppers RJ, Grotjohan HP, Twisk JW, Bogaard HJ, Boonstra A, Postmus PE, Westerhof N, van der Laarse WJ, Vonk-Noordegraaf A (2009) Effects of exercise training in patients with idiopathic pulmonary arterial hypertension. Eur Respir J 34:669–675

5. Grünig E, Ehlken N, Ghofrani A, Staehler G, Meyer FJ, Juenger J, Opitz CF, Klose H, Wilkens H, Rosenkranz S, Olschewski H, Halank M (2011) Effect of exercise and respiratory training on clinical progression and survival in patients with severe chronic pulmonary hypertension. Respiration 81:394–401
6. Grünig E, Lichtblau M, Ehlken N, Ghofrani HA, Reichenberger F, Staehler G, Halank M, Fischer C, Seyfarth HJ, Klose H, Meyer A, Sorichter S, Wilkens H, Rosenkranz S, Opitz C, Leuchte H, Karger G, Speich R, Nagel C (2012) Safety and efficacy of exercise training in various forms of pulmonary hypertension. Eur Respir J 40:84–92
7. Budts W (2005) Eisenmenger syndrome: medical prevention and management strategies. Expert Opin Pharmacother 6:2047–2060
8. Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, Johansson B, Bouzas B, Mullen MJ, Poole-Wilson PA, Francis DP, Gatzoulis MA (2005) Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. Circulation 112:828–835
9. Kempny A, Dimopoulos K, Uebing A, Moceri P, Swan L, Gatzoulis MA, Diller GP (2012) Reference values for exercise limitations among adults with congenital heart disease. Relation to activities of daily life—single centre experience and review of published data. Eur Heart J 33:1386–1396
10. Kempny A, Dimopoulos K, Alonso-Gonzalez R, Alvarez-Barredo M, Tutarel O, Uebing A, Piatek P, Marino P, Swan L, Diller GP, Wort SJ, Gatzoulis MA (2013) Six-minute walk test distance and resting oxygen saturations but not functional class predict outcome in adult patients with eisenmenger syndrome. Int J Cardiol 168:4784–4789
11. Strieder DJ, Mesko ZG, Zaver AG, Gold WM (1973) Exercise tolerance in chronic hypoxemia due to right-to-left shunt. J Appl Physiol 34:853–858
12. Wensel R, Georgiadou P, Francis DP, Bayne S, Scott AC, Genth-Zotz S, Anker SD, Coats AJ, Piepoli MF (2004) Differential contribution of dead space ventilation and low arterial pco2 to exercise hyperpnea in patients with chronic heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 93:318–323
13. Sietsema KE, Cooper DM, Perloff JK, Rosove MH, Child JS, Canobbio MM, Whipp BJ, Wasserman K (1986) Dynamics of oxygen uptake during exercise in adults with cyanotic congenital heart disease. Circulation 73:1137–1144
14. Gläser S, Opitz CF, Bauer U, Wensel R, Ewert R, Lange PE, Kleber FX (2004) Assessment of symptoms and exercise capacity in cyanotic patients with congenital heart disease. Chest 125:368–376
15. Broberg CS, Van Woerkom RC, Swallow E, Dimopoulos K, Diller GP, Allada G, Gatzoulis MA (2014) Lung function and gas exchange in eisenmenger syndrome and their impact on exercise capacity and survival. Int J Cardiol 171:73–77
16. Broberg CS, Bax BE, Okonko DO, Rampling MW, Bayne S, Harries C, Davidson SJ, Uebing A, Khan AA, Thein S, Gibbs JS, Burman J, Gatzoulis MA (2006) Blood viscosity and its relationship to iron deficiency, symptoms, and exercise capacity in adults with cyanotic congenital heart disease. J Am Coll Cardiol 48:356–365
17. Horscroft JA, Murray AJ (2014) Skeletal muscle energy metabolism in environmental hypoxia: climbing towards consensus. Extrem Physiol Med 3:19
18. Gea J, Casadevall C, Pascual S, Orozco-Levi M, Barreiro E (2012) Respiratory diseases and muscle dysfunction. Expert Rev Respir Med 6:75–90
19. de Theije C, Costes F, Langen RC, Pison C, Gosker HR (2011) Hypoxia and muscle maintenance regulation: implications for chronic respiratory disease. Curr Opin Clin Nutr Metab Care 14:548–553
20. Dimopoulos K, Okonko DO, Diller GP, Broberg CS, Salukhe TV, Babu-Narayan SV, Li W, Uebing A, Bayne S, Wensel R, Piepoli MF, Poole-Wilson PA, Francis DP, Gatzoulis MA (2006) Abnormal ventilatory response to exercise in adults with congenital heart disease relates to cyanosis and predicts survival. Circulation 113:2796–2802
21. van Riel AC, Schuuring MJ, van Hessen ID, Zwinderman AH, Cozijnsen L, Reichert CL, Hoorntje JC, Wagenaar LJ, Post MC, van Dijk AP, Hoendermis ES, Mulder BJ, Bouma BJ

(2014) Contemporary prevalence of pulmonary arterial hypertension in adult congenital heart disease following the updated clinical classification. Int J Cardiol 174:299–305
22. Gabriels C, De Meester P, Pasquet A, De Backer J, Paelinck BP, Morissens M, Van De Bruaene A, Delcroix M, Budts W (2014) A different view on predictors of pulmonary hypertension in secundum atrial septal defect. Int J Cardiol 176:833–840
23. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M et al (2016) 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 37(1):67–119
24. Fowler RM, Gain KR, Gabbay E (2012) Exercise intolerance in pulmonary arterial hypertension. Pulm Med 2012:359204
25. Van De Bruaene A, La Gerche A, Prior DL, Voigt JU, Delcroix M, Budts W (2011) Pulmonary vascular resistance as assessed by bicycle stress echocardiography in patients with atrial septal defect type secundum. Circ Cardiovasc Imaging 4:237–245
26. Van De Bruaene A, Delcroix M, Pasquet A, De Backer J, De Pauw M, Naeije R, Vachiéry JL, Paelinck B, Morissens M, Budts W (2011) Iron deficiency is associated with adverse outcome in eisenmenger patients. Eur Heart J 32:2790–2799
27. De Meester P, Van De Bruaene A, Herijgers P, Voigt JU, Vanhees L, Budts W (2013) Increased pulmonary artery pressures during exercise are related to persistent tricuspid regurgitation after atrial septal defect closure. Acta Cardiol 68:365–372
28. Matura LA, McDonough A, Hanlon AL, Carroll DL, Riegel B (2015) Sleep disturbance, symptoms, psychological distress, and health-related quality of life in pulmonary arterial hypertension. Eur J Cardiovasc Nurs 14:423–430
29. Harzheim D, Klose H, Pinado FP, Ehlken N, Nagel C, Fischer C, Ghofrani A, Rosenkranz S, Seyfarth HJ, Halank M, Mayer E, Grünig E, Guth S (2013) Anxiety and depression disorders in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. Respir Res 14:104
30. Halank M, Einsle F, Lehman S, Bremer H, Ewert R, Wilkens H, Meyer FJ, Grünig E, Seyfarth HJ, Kolditz M, Wieder G, Höffken G, Köllner V (2013) Exercise capacity affects quality of life in patients with pulmonary hypertension. Lung 191:337–343
31. Rival G, Lacasse Y, Martin S, Bonnet S, Provencher S (2014) Effect of pulmonary arterial hypertension-specific therapies on health-related quality of life: a systematic review. Chest 146:686–708
32. Ghofrani HA, Galiè N, Grimminger F, Grünig E, Humbert M, Jing ZC, Keogh AM, Langleben D, Kilama MO, Fritsch A, Neuser D, Rubin LJ, Group P-S (2013) Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med 369:330–340
33. Fernandes CJ, Martins BC, Jardim CV, Ciconelli RM, Morinaga LK, Breda AP, Hoette S, Souza R (2014) Quality of life as a prognostic marker in pulmonary arterial hypertension. Health Qual Life Outcomes 12:130
34. Burger CD, Long PK, Shah MR, McGoon MD, Miller DP, Romero AJ, Benton WW, Safford RE (2014) Characterization of first-time hospitalizations in patients with newly diagnosed pulmonary arterial hypertension in the reveal registry. Chest 146:1263–1273
35. Bruto VC, Harrison DA, Fedak PW, Rockert W, Siu SC (2007) Determinants of health-related quality of life in adults with congenital heart disease. Congenit Heart Dis 2:301–313
36. Cha KS, Cho KI, Seo JS, Choi JH, Park YH, Yang DH, Hong GR, Kim DS (2013) Effects of inhaled iloprost on exercise capacity, quality of life, and cardiac function in patients with pulmonary arterial hypertension secondary to congenital heart disease (the eisenmenger syndrome) (from the eiger study). Am J Cardiol 112:1834–1839
37. Tay EL, Papaphylactou M, Diller GP, Alonso-Gonzalez R, Inuzuka R, Giannakoulas G, Harries C, Wort SJ, Swan L, Dimopoulos K, Gatzoulis MA (2011) Quality of life and

functional capacity can be improved in patients with eisenmenger syndrome with oral sildenafil therapy. Int J Cardiol 149:372–376
38. Duffels MG, Vis JC, van Loon RL, Nieuwkerk PT, van Dijk AP, Hoendermis ES, de Bruin-Bon RH, Bouma BJ, Bresser P, Berger RM, Mulder BJ (2009) Effect of bosentan on exercise capacity and quality of life in adults with pulmonary arterial hypertension associated with congenital heart disease with and without down's syndrome. Am J Cardiol 103:1309–1315
39. Rosenzweig EB, Kerstein D, Barst RJ (1999) Long-term prostacyclin for pulmonary hypertension with associated congenital heart defects. Circulation 99:1858–1865
40. Vis JC, Duffels MG, Mulder P, de Bruin-Bon RH, Bouma BJ, Berger RM, Hoendermis ES, van Dijk AP, Mulder BJ (2013) Prolonged beneficial effect of bosentan treatment and 4-year survival rates in adult patients with pulmonary arterial hypertension associated with congenital heart disease. Int J Cardiol 164:64–69
41. Blok IM, van Riel AC, Schuuring MJ, Duffels MG, Vis JC, van Dijk AP, Hoendermis ES, Mulder BJ, Bouma BJ (2015) Decrease in quality of life predicts mortality in adult patients with pulmonary arterial hypertension due to congenital heart disease. Neth Heart J 23:278–284
42. Belardinelli R, Paolini I, Cianci G, Piva R, Georgiou D, Purcaro A (2001) Exercise training intervention after coronary angioplasty: the ETICA trial. J Am Coll Cardiol 37:1891–1900
43. Zafrir B (2013) Exercise training and rehabilitation in pulmonary arterial hypertension: rationale and current data evaluation. J Cardiopulm Rehabil Prev 33:263–273
44. Buys R, Avila A, Cornelissen VA (2015) Exercise training improves physical fitness in patients with pulmonary arterial hypertension: a systematic review and meta-analysis of controlled trials. BMC Pulm Med 15:40
45. Martínez-Quintana E, Miranda-Calderín G, Ugarte-Lopetegui A, Rodríguez-González F (2010) Rehabilitation program in adult congenital heart disease patients with pulmonary hypertension. Congenit Heart Dis 5:44–50
46. Budts W, Borjesson M, Chessa M, van Buuren F, Trigo Trindade P, Corrado D, Heidbuchel H, Webb G, Holm J, Papadakis M (2013) Physical activity in adolescents and adults with congenital heart defects: individualized exercise prescription. Eur Heart J 34:3669–3674
47. Pinto NM, Marino BS, Wernovsky G, de Ferranti SD, Walsh AZ, Laronde M, Hyland K, Dunn SO, Cohen MS (2007) Obesity is a common comorbidity in children with congenital and acquired heart disease. Pediatrics 120:e1157–e1164
48. Chow CK, Redfern J, Hillis GS, Thakkar J, Santo K, Hackett ML, Jan S, Graves N, de Keizer L, Barry T, Bompoint S, Stepien S, Whittaker R, Rodgers A, Thiagalingam A (2015) Effect of lifestyle-focused text messaging on risk factor modification in patients with coronary heart disease: a randomized clinical trial. JAMA 314:1255–1263
49. Apostolopoulou SC, Manginas A, Cokkinos DV, Rammos S (2007) Long-term oral bosentan treatment in patients with pulmonary arterial hypertension related to congenital heart disease: a 2-year study. Heart 93:350–354
50. Martini J, Cabrales P, Tsai AG, Intaglietta M (2006) Mechanotransduction and the homeostatic significance of maintaining blood viscosity in hypotension, hypertension and haemorrhage. J Intern Med 259:364–372

Prognostication in PAH–CHD

21

Aleksander Kempny

Abbreviations

ACHD	Adult congenital heart disease
ASD	Atrial septal defect
AVSD	Atrioventricular septal defect
CHD	Congenital heart disease
ES	Eisenmenger syndrome
PAH	Pulmonary arterial hypertension
RV	Right ventricle
SMR	Standardized mortality ratio
VSD	Ventricular septal defect

21.1 Introduction

Approximately 5–10% of patients with congenital heart disease develop pulmonary arterial hypertension (PAH–CHD), which impacts on their quality of life and long-term outcome [1–3]. Eisenmenger syndrome (ES) represents the extreme manifestation of PAH in this setting. Patients with PAH–CHD, particularly those with ES, are significantly impaired in their exercise capacity and have a relatively high mortality compared to other groups of CHD patients [4–6] (Fig. 21.1).

Optimal clinical management of PAH–CHD patients requires validated morbidity and mortality risk stratification algorithms. In fact, in other areas of cardiology such as heart failure, coronary artery disease or atrial fibrillation, risk scores are

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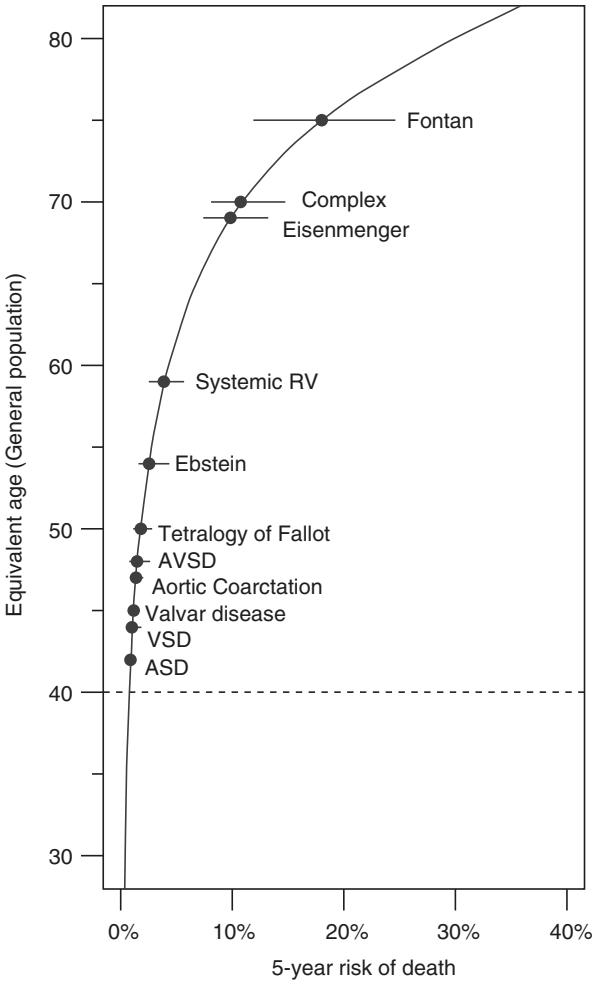

Fig. 21.1 Five-year risk of death for 40-year-old patients. Projected 5-year mortality rates for 40-year-old ACHD patients compared with that expected for the general UK population, based on the results of the standardized mortality ratio (SMR) analysis. Points present the estimated mortality within 5 years (on the *x* axis) and also indicate the equivalent age – expressed as the age of subgroup of UK population with the most similar 5-year mortality (*y* axis). *Horizontal lines* represent 95% confidence intervals for the 5-year mortality. The *black curve* presents 5-year mortality for the UK population based on life table data. *ASD* indicates atrial septal defect, *AVSD* atrioventricular septal defect, *RV* right ventricle, *VSD* ventricular septal defect [5]

widely used for guiding therapy [7–12] and improving patient outcome [13, 14]. Risk stratification algorithms have also been developed for patients with idiopathic PAH (iPAH), based on US, UK and French registries [15–18]. As the pathophysiology and natural history of PAH–CHD differs significantly to that of iPAH, scores developed for the latter may not be accurate for risk stratification in PAH–CHD patients. Due to the heterogeneity of CHD lesions, wide spectrum of comorbidities, gender differences and lack of validated risk stratification algorithms, mortality risk

stratification in PAH–CHD remains challenging. This chapter focuses on parameters used in clinical practice with documented significant association to mortality in patients with significant PAH.

21.1.1 Underlying CHD Anatomy

The underlying CHD anatomy seems to be one of the most important parameters influencing PAH–CHD prognostication. This refers to the size of defect, its location, as well as the shunt direction.

Viktor Eisenmenger described in 1897 a case of patient with progressive heart failure, cyanosis and postmortem diagnosed with a large ventricular septal defect (VSD). It was later recognized that the cyanosis in this setting results from pulmonary hypertension and, accordingly, ES became synonymous with PAH with bidirectional or reversed shunt through a large VSD. As the clinical picture of heart failure and cyanosis resulting from right-to-left shunt emerges in patients regardless of shunt location, also patients with pre-tricuspid or complex shunts have been included into the ES diagnosis [19, 20]. Recent studies demonstrated, however, significant differences in morbidity, mortality and exercise performance depending on the underlying lesion.

CHD lesions associated with PAH may be classified into four categories based on the location of the defect: pre-tricuspid (atrial septal defect or anomalous pulmonary venous drainage), post-tricuspid (ventricular septal defect or patent ductus arteriosus in the absence of a pre-tricuspid shunt), complex anatomy (other shunt lesions including AVSD, univentricular physiology, transposition of the great arteries, aortopulmonary window and common arterial trunk) and operated lesions [21–23].

The majority of patients with pre-tricuspid defects tend to tolerate increased pulmonary blood flow well and do not develop pulmonary vascular disease [24]. Nevertheless, a fraction of patients with pre-tricuspid shunt presents with PAH, usually in adulthood. The development of PAH in this setting seems to be the result of a reaction of the pulmonary vascular tree to increased pulmonary blood flow: these patients seem to be predisposed to adverse pulmonary vascular remodelling with its negative impact on survival. In clinical practice, it is often not possible to define whether the pre-tricuspid lesion, particularly if only of moderate size, significantly contributed to the development of PAH or if the shunt is rather a bystander, while other underlying processes contribute to the development of pulmonary vascular disease. The prognosis in patients with pre-tricuspid lesions, compared to both post-tricuspid and complex shunts, is significantly worse [25]. The reason for this appears multifactorial and possibly includes the predisposition for progressive adverse pulmonary vascular remodelling and also adverse cardiac remodelling in response to increased pulmonary vascular resistance. In patients with pre-tricuspid shunts, in contrary to patients with post-tricuspid or complex lesions, pressure load on the right ventricle increases later on in life. Therefore, right ventricular adaptation may be unfavourable, with progressive right ventricular dilatation, excessive ventricular wall stress, right ventricular dysfunction and failure [26].

Mortality is also higher in patients with repaired lesions and severe PAH compared to Eisenmenger patients. Occasionally, patients may have normal pulmonary vascular resistance at the time of repair and increase their PVR later on in life, presumably due to underlying predisposition of the pulmonary vascular tree. More often, however, there is already significant PAH at the time of surgical or percutaneous repair, which may be not recognized or may not be deemed a contraindication to repair of the defect. Closing defects in severe PAH, particularly in patients with reversed shunt at rest or on exercise, can have an immediate and long-term negative impact, both on haemodynamics and on tissue oxygenation, which may explain the higher mortality in this group compared to all other forms of PAH–CHD [6, 27].

While some anatomical or clinical features may be significantly associated with survival, the absolute survival estimation remains challenging. This is particularly so in patients with left-to-right shunts. While there is consensus that PAH in these patients has a negative impact of prognosis, absolute survival prospects may vary considerably in patients with PAH-CHD and still left-to-right shunting. The presence of cyanosis due to reversed shunt in the presence of PAH, on the other hand, enables an unambiguous diagnosis of ES. The diagnosis of ES can often be made without invasive testing, based on the presence of a nonrestrictive lesion, and reversed or bidirectional shunting resulting in cyanosis. There are, to date, several publications reporting survival in Eisenmenger patients [28]. Based on recent studies, the 1, 5 and 10 years survival is 94%, 80% and 69%, respectively (Table 21.1). These estimates are, however, based on cohorts of patients, many of whom were not treated with advanced therapies (ATs) for PAH, which are now known to be associated with improved survival in Eisenmenger patients [23]. Thanks to recent evidence of a positive impact of AT on survival, exercise performance and quality of life, the majority of contemporary Eisenmenger patients in developed countries are put on AT. There is also increasing awareness of conservative

Table 21.1 Overview on survival prospects in AT naïve Eisenmenger syndrome patients

Study size (n)	Average age (years)	Follow-up time			Reference
		1y	5y	10y	
201	19	97%	87%	80%	Saha A, Int J Cardiol, 1994
188	33	–	–	–	Daliento L, Eur Heart J, 1998
161	34	91%	76%	–	Dimopoulos K, Circulation/own data, 2010
109	29	–	–	–	Cantor WJ, Am J Cardiol, 1999
106	34	98%	77%	58%	Oya H, Am Heart J, 2002
92	38	–	83%	66%	Sandoval J, Cong Heart Dis, 2012
68	29	91%	–	–	Sun YJ, J Clin Pharmacol, 2013
62	–	–	–	56%	Cerone S, Arch Mal Coeur Vaiss, 1992
57	21	–	–	–	Young D, Am J Cardiol, 1971
47	–	–	–	–	Callegari G, Monaldi Arch Chest Dis, 2004
23	32	80%	–	–	Sandoval J, Am J Resp Crit Care, 2001
17	34	88%	51%	–	Adriaenssens T, Eur Heart J, 2006
∑ = 1131	**Mean = 30.3y**	**94%**	**80%**	**69%**	**–**

Caption: Average survival calculated as weighed mean. Based on Diller G-P, et al. *Heart 2014* [28]

management guidelines, avoidance of pitfalls and outdated practices and tertiary care for all Eisenmenger patients, survival has improved significantly [14]. For this reason, the above-mentioned survival estimates are likely to underestimate the survival of contemporary Eisenmenger patients. Published survival estimates and models may be interesting from a statistical perspective, due to the significant association of multiple variables with mortality, but, in their current form, are less suited for individual patient counselling.

21.1.2 Functional Class, 6-Min Walk Test and Survival

Patients with PAH–CHD, and particularly ES patients, are significantly impaired in their exercise capacity [4]. The New York Heart Association functional class, on which the WHO functional classification used in pulmonary hypertension is based, is widely used both clinically and in studies. Patients with significant symptoms (i.e. WHO ≥ 3) are at significantly higher risk of death compared to those being oligosymptomatic. Most patients, however, are classified as functional class II or III. The low discriminative power and also significant interobserver variability do not allow to appreciate subtle changes in functional capacity, which may precede death or clinical decompensation [29]. Extending the functional classification by adding, for example, class II subgroups (i.e. IIa, IIb) seems promising, but data on the prognostic and discriminative ability of such a modified scale are lacking at present [29, 30].

Moreover, patients may deny significant limitations and may be, thus, classified as functional class II, while objective assessment with 6-min walk test (6MWT) or cardiopulmonary exercise testing (CPET) confirms severe exercise intolerance [31, 32]. In fact, in many patients PAH is present already early in life and progresses gradually over the years, allowing adaptation of daily activities [33], "masking" symptoms and contributing to the disparity between subjective and objective measures of functional capacity.

Assessment of exercise capacity with CPET is considered the golden standard in CHD. As the majority of patients with PAH–CHD are, however, significantly impaired in their exercise capacity, certain standard CPET protocols may be not suitable. Some patients do not tolerate breathing through a mask and some may struggle keeping up with a treadmill. Dizziness on exercise is not uncommon in this cohort and is associated with a risk of fall and injury. Testing on a bike (cycloergometer), is more safe and allows easy adjustment of the protocol to an intensity appropriate for even the most impaired patients. It is, however, considered less physiological and not all patients may be familiar with this type of effort. Despite the above, CPET should be the exercise test of choice, in all cardiovascular disease, including PAH-CHD, both for diagnostic and follow-up purposes.

In the majority of PAH–CHD, it may however be more feasible to quantify exercise performance with simpler tests designed for patients with significantly impaired exercise performance, such as the shuttle walk test or 6MWT [34]. The 6MWT is the most popular test in PAH practice, and is also an endpoint in clinical studies on pulmonary hypertension, including PAH–CHD [32, 35, 36]. The relationship of 6MWT distance and baseline oxygen saturation to survival is particularly well documented in Eisenmenger patients (Fig. 21.2), while oxygen saturation at peak effort

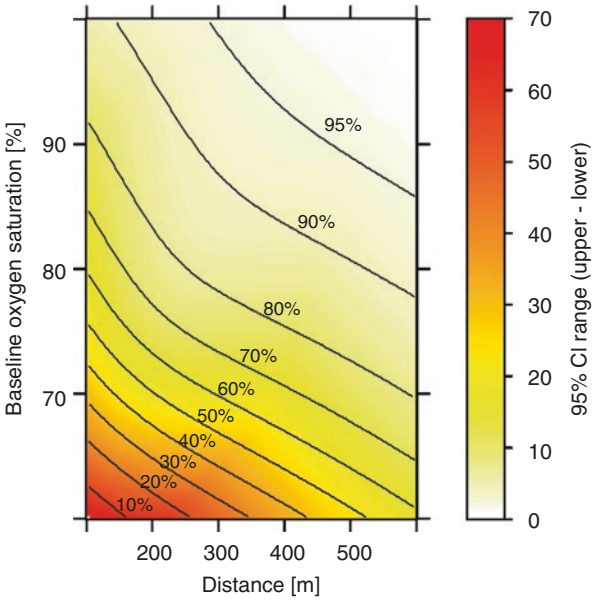

Fig. 21.2 Six-minute walk test distance, oxygen saturation at rest and survival in patients with Eisenmenger syndrome. The figure presents predicted survival at 3 years in adult patients with Eisenmenger syndrome. *Colour* represents the range of 95% CI, i.e., the difference between the *upper* and *lower* 95% CI values [32]

and the Borg scale, used for the assessment of dyspnoea and overall fatigue, seem not to significantly contribute to mortality risk stratification, but may be useful for clinical monitoring in serial testing over time [32, 37].

21.1.3 Imaging

Imaging is an essential part of baseline assessment and follow-up in all PAH–CHD patients. It enables guiding clinical management, and numerous studies have also documented significant association of various measures of cardiac size, function and also the presence or absence of pericardial collection with survival in PAH patients.

Most CHD patients with significant PAH, particularly ES patients, present with cardiomegaly. The cardiothoracic ratio (CTR), derived from plain postero-anterior chest radiographs, is a robust and reproducible measure of heart size, suitable both for baseline assessment and for monitoring changes during follow-up in adult CHD, with confirmed positive association with increased mortality risk [38].

Yet, transthoracic echocardiography (TTE) and increasingly cardiac magnetic resonance (CMR) imaging are performed in all patients for baseline assessment and during follow-up, both to confirm diagnosis and to monitor the progression of disease and response to therapy. Particularly TTE has an established role in the clinical management of various forms of PAH with demonstrated strong association of various parameters with survival. These include indices of right heart dilatation and

dysfunction, for example impaired tricuspid annular plane systolic excursion (TAPSE), right ventricular (RV) fractional area change, presence of significant tricuspid regurgitation, right atrial dilatation and presence of pericardial effusion [39, 40]. Echocardiographic parameters have been demonstrated to be significantly associated with mortality in ES patients (see also Chapter 11). A composite echocardiographic score outperformed resting oxygen saturation and brain natriuretic peptide (BNP) in mortality risk stratification over a follow-up period of 1.5 years in this cohort. The score included reduced TAPSE (<15 mm), increased RV systolic to diastolic duration ratio (≥1.5), right atrial area (≥25.0 cm^2) and right-to-left atrial area ratio (≥1.5) [41].

21.1.4 Blood Tests

Blood testing is obligatory for both baseline assessment and follow-up, particularly in patients on ATs for PAH and those deteriorating over time. As advanced PAH results in multi-organ dysfunction, many blood test parameters have been demonstrated to be significantly associated with outcome in various forms of PAH, including PAH–CHD patients.

21.1.4.1 Full Blood Count and Haematinics

Patients with advanced PAH–CHD may present with heart failure, which may, in turn, be associated with anaemia and iron deficiency. Anemia in PAH-CHD is typically but not always the result of iron deficiency (see Chapter 15): B12 or folic acid deficiency may also be present, as well as coexisting renal dysfunction with reduced erythropoietin synthesis or increased synthesis with resistance to erythropoietin, due to bone marrow dysfunction and chronic inflammation [42]. As a consequence, in adult CHD excluding cyanotic patients, anaemia is a strong predictor of mortality. The potential association of haemoglobin level to mortality in PAH–CHD patients is, however, more complex, due to the right-to-left shunt with resulting cyanosis at rest or on effort. In patients with normal oxygen saturation at rest, increased haemoglobin concentration is a sensitive indicator of shunt reversal and cyanosis on effort and may indicate significantly increased pulmonary vascular resistance, associated with an increased mortality.

In cyanotic PAH–CHD, higher haemoglobin levels result from more profound cyanosis in iron-replete patients. Both haemoglobin levels and haematocrit seem not to be significantly associated with survival in cyanotic PAH–CHD patients. Relative anaemia, i.e. a lower than expected haemoglobin concentration in cyanotic patients, confounds further the relationship of haemoglobin and haematocrit to survival [4, 43]. Iron supplementation in iron-deficient patients has been shown to have a positive impact on symptoms in randomized studies in non-CHD heart failure, in a pilot study in patients with iPAH and in a small cohort of cyanotic CHD/Eisenmenger patients [44–47].

21.1.4.2 Creatinine and Sodium

Both renal dysfunction and hyponatraemia are common in CHD, PAH and ES patients, and are markers of more advanced disease, associated with an increased mortality [48, 49]. The pathogenesis of renal dysfunction and hyponatraemia appear multifactorial. As in acquired heart failure, low cardiac output in PAH-CHD results in reduced renal perfusion and leads to arterial vasoconstriction and activation of the renin–angiotensin–aldosterone system (RAAS). Patients presenting with pulmonary congestion or fluid overload may require intense diuretic therapy, which may, in turn, negatively impact on renal function and contribute to sodium loss.

21.1.4.3 Brain Natriuretic Peptide

BNP is often increased in symptomatic CHD patients, patients with various forms of PAH and ES patients; it is also associated with higher mortality. The reason behind the increased BNP in ES is likely multifactorial and includes increased stretch of the ventricular myocardium and activation of RAAS system. Assessment of BNP may be clinically useful in monitoring of patients, particularly those in whom subjective and objective measures of functional capacity and the effect of ATs are not available (e.g. patients with Down syndrome or other comorbidity).

21.1.4.4 High-Sensitivity Troponin

In a study by Schuuring et al., an elevated concentration (>99th percentile of normal, >0.014 μg/L) of high-sensitivity cardiac troponin T (hsTnT) was present in 26% of patients with significant PAH–CHD and was associated with an over 7-fold higher risk of death, compared to patients with normal hsTnT [50]. It has been suggested that an increased right ventricular pressure load results in higher myocardial oxygen demand but reduced myocardial perfusion, resulting in ischemic injury. Also standard TnT is elevated in a significant proportion of patients: in a study of 56 clinically stable PAH patients, including PAH–CHD patients, increased TnT was present in 14% of patients and was associated with 5-fold higher mortality, also in a multivariable model [51].

21.1.4.5 C-Reactive Protein

C-reactive protein (CRP) is commonly raised (>10 mg/mL) in adult patients with PAH–CHD. In a retrospective study in ES patients, 26% had elevated CRP at baseline, after exclusion of patients with infection, recent transfusions or procedures. Mortality was four times higher in patients with increased CRP (>10 mg/dL), compared to those with normal CRP concentration [52]. The strong association of increased CRP with higher mortality has also been demonstrated in other forms of pulmonary hypertension, including iPAH and thromboembolic pulmonary hypertension. High CRP levels were associated with more advanced disease, both in terms of NYHA functional class and 6MWT distance [53]. The association of CRP with survival and clinical status in PAH–CHD patients supports the role of inflammation in

cardiovascular remodelling. For example, CRP inhibits the production of nitric oxide in the endothelium and attenuates angiogenesis [54]. Future studies with high-sensitivity CRP and other inflammatory markers may provide further insight into the role of inflammation in the pathogenesis and progression of PAH-CHD and its role in influencing mortality.

21.1.4.6 Serum Proteins

In patients with acquired heart failure, including CHD patients, hypoproteinaemia and particularly hypoalbuminaemia are common and are associated with significantly increased mortality and more advanced disease [55–58]. While in the general CHD population hypoalbuminaemia (<35 g/L) was present in 13.3% patients, in ES patients it was twice as common. Hypoalbuminaemia was associated with a 3-fold increased risk of death, even after adjustment for age, renal function and serum sodium. The reasons for the strong predictive value of serum albumins are likely multifactorial and include venous congestion, with increased transcapillary albumin escape rate [59], amplified by chronic systemic inflammation and endothelial dysfunction with resulting increased vascular permeability and extravascular albumin catabolism [52, 60].

21.1.5 Multivariable Mortality Risk Stratification

Although there are multiple published parameters related to mortality in PAH–CHD, in the clinical setting risk stratification remains challenging. As the maximal number of parameters to be tested in a statistical multivariable model is limited by the number of events, most studies are powered to test only a very limited number of parameters. As PAH–CHD, and particularly ES, is a multiorgan disease with multiple factors contributing to premature death, a prognostication model must be a multivariable one. In a recent, multinational study including 1098 ES patients, many of the above-mentioned parameters were tested for their significance in mortality risk stratification [25, 61]. Fig. 21.3 shows the predicted 5-year mortality of contemporary patients with ES based on multivariable Cox regression model using data from the paper by Kempny et al. On multivariable Cox regression analysis, age (HR 1.35/10 years, 95% CI 1.14–1.61, $P < 0.001$), pre-tricuspid shunt (HR 1.97, 95% CI 1.12–3.46, $P = 0.019$), oxygen saturation at rest (HR 0.61/10%, 95% CI 0.46–0.82, $P < 0.001$), 6 MWT distance (HR 0.67/100 m, 95% CI 0.54–0.82, $P < 0.001$) and presence of pericardial effusion (HR 2.35, 95% CI 1.33–4.13, $P = 0.003$) remained significant predictors of death. Absolute mortality risk stratification appears feasible (Figure 21.3), although further studies are needed to validate the model. As mortality after heart and lung transplantation remains high, approaching 55% at five years, Eisenmenger patients with an estimated 5-year mortality above 55% may be appropriate candidates for heart and lung transplantation.

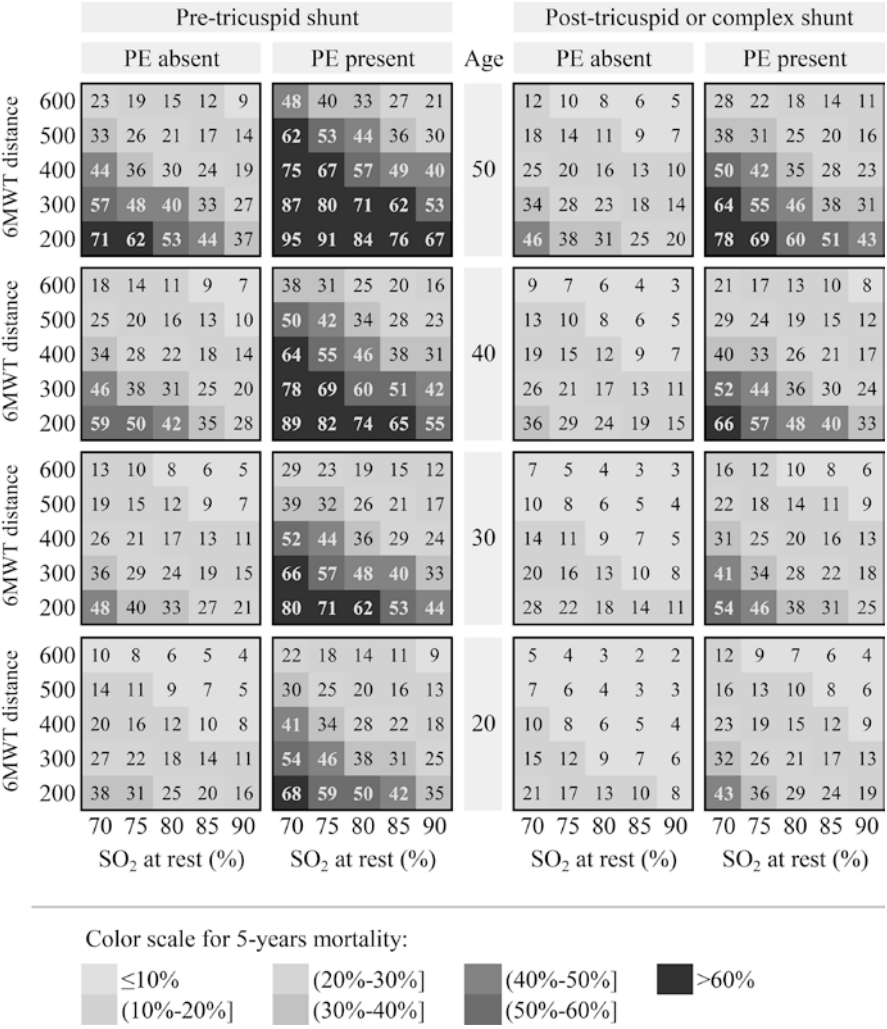

Fig. 21.3 Predicted 5-years mortality in adult patients with Eisenmenger syndrome based on a multivariable Cox regression model using age (in years), underlying shunt type, presence of pericardial effusion (PE), six minute walk test (6MWT) distance and oxygen saturation (SO2) at rest (on room air). This model is based on the data published by: Kempny A et al, Predictors of death in contemporary adult patients with Eisenmenger syndrome: A multicentre study, Circulation, 2016

Conclusions

There is significant ongoing mortality among contemporary adult PAH–CHD patients, especially ES patients, those with repaired defects and patients with small lesions. There is, however, also a large group of CHD patients with moderate PAH, on whom information is scarce.

As PAH in CHD patients often results in multi-organ failure, markers reflecting ventricular pressure or volume overload (BNP), myocardial injury (troponin), renal dysfunction and inflammation are associated with increased mortality. Moreover, the type and direction of the shunt and the degree of cyanosis are significantly associated with mortality. A recent study, based on data from a large cohort of patients provides estimates of 5-year survival in ES patients and may facilitate risk stratification and referral for heart and lung transplantation, as well as identify patients who are most likely to benefit from aggressive AT therapy [25]. Future studies are needed to improve and externally validate prognostication models in PAH–CHD patients and prospectively investigate the impact of ATs, iron supplementation and, potentially, anti-inflammatory agents on survival in this high-risk population.

References

1. Steele PM, Fuster V, Cohen M, Ritter DG, McGoon DC (1987) Isolated atrial septal defect with pulmonary vascular obstructive disease—long-term follow-up and prediction of outcome after surgical correction. Circulation 76(5):1037–1042. Epub 1987/11/01
2. Kidd L, Driscoll DJ, Gersony WM, Hayes CJ, Keane JF, O'Fallon WM et al (1993) Second natural history study of congenital heart defects. Results of treatment of patients with ventricular septal defects. Circulation 87(2 Suppl):I38–I51. Epub 1993/02/01
3. Engelfriet PM, Duffels MG, Moller T, Boersma E, Tijssen JG, Thaulow E et al (2007) Pulmonary arterial hypertension in adults born with a heart septal defect: the Euro Heart Survey on adult congenital heart disease. Heart 93(6):682–687. Epub 2006/12/14
4. Diller GP, Dimopoulos K, Broberg CS, Kaya MG, Naghotra US, Uebing A et al (2006) Presentation, survival prospects, and predictors of death in Eisenmenger syndrome: a combined retrospective and case-control study. Eur Heart J 27(14):1737–1742. Epub 2006/06/24
5. Diller GP, Kempny A, Alonso-Gonzalez R, Swan L, Uebing A, Li W et al (2015) Survival prospects and circumstances of death in contemporary adult congenital heart disease patients under follow-up at a large tertiary centre. Circulation 132(22):2118–2125. Epub 2015/09/16
6. Manes A, Palazzini M, Leci E, Bacchi Reggiani ML, Branzi A, Galiè N (2014) Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: a comparison between clinical subgroups. Eur Heart J 35(11):716–724
7. Cowie MR, Sarkar S, Koehler J, Whellan DJ, Crossley GH, Tang WH et al (2013) Development and validation of an integrated diagnostic algorithm derived from parameters monitored in implantable devices for identifying patients at risk for heart failure hospitalization in an ambulatory setting. Eur Heart J 34(31):2472–2480. Epub 2013/03/21
8. Fonarow GC, Adams KF Jr, Abraham WT, Yancy CW, Boscardin WJ (2005) Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. JAMA 293(5):572–580. Epub 2005/02/03
9. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV (2003) Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. JAMA 290(19):2581–2587. Epub 2003/11/20
10. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB et al (2006) The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation 113(11):1424–1433. Epub 2006/03/15
11. Wu C, Camacho FT, Wechsler AS, Lahey S, Culliford AT, Jordan D et al (2012) Risk score for predicting long-term mortality after coronary artery bypass graft surgery. Circulation 125(20):2423–2430. Epub 2012/05/02

12. O'Boyle F, Mediratta N, Fabri B, Pullan M, Chalmers J, McShane J et al (2012) Long-term survival after coronary artery bypass surgery stratified by EuroSCORE. Eur J Cardiothorac Surg 42(1):101–106. discussion 6–7. Epub 2012/01/06
13. Fonarow GC, Albert NM, Curtis AB, Gheorghiade M, Heywood JT, Liu Y et al (2011) Associations between outpatient heart failure process-of-care measures and mortality. Circulation 123(15):1601–1610. Epub 2011/04/06
14. Mylotte D, Pilote L, Ionescu-Ittu R, Abrahamowicz M, Khairy P, Therrien J et al (2014) Specialized adult congenital heart disease care: the impact of policy on mortality. Circulation 129(18):1804–1812
15. Benza RL, Gomberg-Maitland M, Miller DP, Frost A, Frantz RP, Foreman AJ et al (2012) The REVEAL Registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension. Chest 141(2):354–362. Epub 2011/06/18
16. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V et al (2010) Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. Circulation 122(2):156–163. Epub 2010/06/30
17. Lee WT, Ling Y, Sheares KK, Pepke-Zaba J, Peacock AJ, Johnson MK (2012) Predicting survival in pulmonary arterial hypertension in the UK. Eur Respir J 40(3):604–611. Epub 2012/05/05
18. Thenappan T, Shah SJ, Rich S, Tian L, Archer SL, Gomberg-Maitland M (2010) Survival in pulmonary arterial hypertension: a reappraisal of the NIH risk stratification equation. Eur Respir J 35(5):1079–1087. Epub 2009/12/25
19. Partin C (2003) The evolution of Eisenmenger's eponymic enshrinement. Am J Cardiol 92(10):1187–1191. Epub 2003/12/12
20. Wood P (1958) The Eisenmenger syndrome or pulmonary hypertension with reversed central shunt. Br Med J 2(5099):755–762. Epub 1958/09/27
21. Hopkins WE, Waggoner AD (2002) Severe pulmonary hypertension without right ventricular failure: the unique hearts of patients with Eisenmenger syndrome. Am J Cardiol 89(1):34–38. Epub 2002/01/10
22. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA et al (2009) Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 30(20):2493–2537. Epub 2009/08/29
23. Dimopoulos K, Inuzuka R, Goletto S, Giannakoulas G, Swan L, Wort SJ et al (2010) Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension. Circulation 121(1):20–25. Epub 2009/12/23
24. Webb G, Gatzoulis MA (2006) Atrial septal defects in the adult: recent progress and overview. Circulation 114(15):1645–1653
25. Kempny A, Sørensen Hjortshøj C, Hong G, Li W, Opotowsky A, Landzberg M, et al. (2016) Predictors of death in adult patients with Eisenmenger syndrome. In: 10th National Heart and Lung Institute Annual Postgraduate Research Day, Imperial College, London
26. Moceri P, Kempny A, Liodakis E, Alonso Gonzales R, Germanakis I, Diller G-P et al (2015) Physiological differences between various types of Eisenmenger syndrome and relation to outcome. Int J Cardiol 179:455–460
27. Diller GP, Lammers AE, Haworth SG, Dimopoulos K, Derrick G, Bonhoeffer P et al (2010) A modelling study of atrial septostomy for pulmonary arterial hypertension, and its effect on the state of tissue oxygenation and systemic blood flow. Cardiol Young 20(1):25–32. Epub 2010/02/11
28. Diller G-P, Kempny A, Inuzuka R, Radke R, Wort SJ, Baumgartner H et al (2014) Survival prospects of treatment naïve patients with Eisenmenger: a systematic review of the literature and report of own experience. Heart 100(17):1366–1372
29. Raphael C, Briscoe C, Davies J, Ian Whinnett Z, Manisty C, Sutton R et al (2007) Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. Heart 93(4):476–482. Epub 2006/09/29

30. Spoladore R, Fragasso G, Montanaro C, D'Amato R, Palloshi A, Salerno A et al (2010) NYHA Class II subgrouping: correlation with left ventricular dysfunction questionnaire (LVD-36) and ejection fraction. Minerva Cardioangiol 58(4):441–448. Epub 2010/10/13
31. Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS et al (2005) Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. Circulation 112(6):828–835. Epub 2005/08/03
32. Kempny A, Dimopoulos K, Alonso-Gonzalez R, Alvarez-Barredo M, Tutarel O, Uebing A et al (2013) Six-minute walk test distance and resting oxygen saturations but not functional class predict outcome in adult patients with Eisenmenger syndrome. Int J Cardiol 168(5):4784–4789. Epub 2013/08/22
33. Dimopoulos K, Giannakoulas G, Wort SJ, Gatzoulis MA (2008) Pulmonary arterial hypertension in adults with congenital heart disease: distinct differences from other causes of pulmonary arterial hypertension and management implications. Curr Opin Cardiol 23(6):545–554. Epub 2008/10/03
34. Irisawa H, Takeuchi K, Inui N, Miyakawa S, Morishima Y, Mizushima T et al (2014) Incremental shuttle walk test as a valuable assessment of exercise performance in patients with pulmonary arterial hypertension. Circ J 78(1):215–221
35. Galiè N, Beghetti M, Gatzoulis MA, Granton J, Berger RMF, Lauer A et al (2006) Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. Circulation 114(1):48–54
36. Hoeper MM, Schwarze M, Ehlerding S, Adler-Schuermeyer A, Spiekerkoetter E, Niedermeyer J et al (2000) Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. N Engl J Med 342(25):1866–1870
37. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories (2002) ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 166(1):111–117
38. Dimopoulos K, Giannakoulas G, Bendayan I, Liodakis E, Petraco R, Diller GP et al (2013) Cardiothoracic ratio from postero-anterior chest radiographs: a simple, reproducible and independent marker of disease severity and outcome in adults with congenital heart disease. Int J Cardiol 166(2):453–457. Epub 2011/12/06
39. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A et al (2016) 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 37(1):67–119. Epub 2015/09/01
40. Grapsa J, Pereira Nunes MC, Tan TC, Cabrita IZ, Coulter T, Smith BC, et al. (2015) Echocardiographic and hemodynamic predictors of survival in precapillary pulmonary hypertension: seven-year follow-up. Circ Cardiovasc Imaging 8(6). Epub 2015/06/13
41. Moceri P, Dimopoulos K, Liodakis E, Germanakis I, Kempny A, Diller GP et al (2012) Echocardiographic predictors of outcome in eisenmenger syndrome. Circulation 126(12):1461–1468. Epub 2012/08/18
42. van Veldhuisen DJ, Anker SD, Ponikowski P, Macdougall IC (2011) Anemia and iron deficiency in heart failure: mechanisms and therapeutic approaches. Nat Rev Cardiol 8(9):485–493. Epub 2011/06/02
43. Van De Bruaene A, Delcroix M, Pasquet A, De Backer J, De Pauw M, Naeije R et al (2011) Iron deficiency is associated with adverse outcome in Eisenmenger patients. Eur Heart J 32(22):2790–2799. Epub 2011/05/25
44. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H et al (2009) Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med 361(25):2436–2448. Epub 2009/11/19
45. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V et al (2015) Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiencydagger. Eur Heart J 36(11):657–668. Epub 2014/09/02

46. Viethen T, Gerhardt F, Dumitrescu D, Knoop-Busch S, ten Freyhaus H, Rudolph TK et al (2014) Ferric carboxymaltose improves exercise capacity and quality of life in patients with pulmonary arterial hypertension and iron deficiency: a pilot study. Int J Cardiol 175(2):233–239. Epub 2014/06/02
47. Tay EL, Peset A, Papaphylactou M, Inuzuka R, Alonso-Gonzalez R, Giannakoulas G et al (2011) Replacement therapy for iron deficiency improves exercise capacity and quality of life in patients with cyanotic congenital heart disease and/or the Eisenmenger syndrome. Int J Cardiol 151(3):307–312. Epub 2010/06/29
48. Dimopoulos K, Diller GP, Koltsida E, Pijuan-Domenech A, Papadopoulou SA, Babu-Narayan SV et al (2008) Prevalence, predictors, and prognostic value of renal dysfunction in adults with congenital heart disease. Circulation 117(18):2320–2328. Epub 2008/04/30
49. Dimopoulos K, Diller GP, Petraco R, Koltsida E, Giannakoulas G, Tay EL et al (2010) Hyponatraemia: a strong predictor of mortality in adults with congenital heart disease. Eur Heart J 31(5):595–601. Epub 2009/11/26
50. Schuuring MJ, van Riel AC, Vis JC, Duffels MG, van Straalen JP, Boekholdt SM et al (2013) High-sensitivity troponin T is associated with poor outcome in adults with pulmonary arterial hypertension due to congenital heart disease. Congenit Heart Dis 8(6):520–526. Epub 2012/12/18
51. Torbicki A, Kurzyna M, Kuca P, Fijalkowska A, Sikora J, Florczyk M et al (2003) Detectable serum cardiac troponin T as a marker of poor prognosis among patients with chronic precapillary pulmonary hypertension. Circulation 108(7):844–848. Epub 2003/08/06
52. Scognamiglio G, Kempny A, Price LC, Alonso-Gonzalez R, Marino P, Swan L et al (2014) C-reactive protein in adults with pulmonary arterial hypertension associated with congenital heart disease and its prognostic value. Heart 100(17):1335–1341
53. Quarck R, Nawrot T, Meyns B, Delcroix M (2009) C-reactive protein: a new predictor of adverse outcome in pulmonary arterial hypertension. J Am Coll Cardiol 53(14):1211–1218. Epub 2009/04/04
54. Verma S, Wang CH, Li SH, Dumont AS, Fedak PW, Badiwala MV et al (2002) A self-fulfilling prophecy: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis. Circulation 106(8):913–919. Epub 2002/08/21
55. Arquès S, Ambrosi P, Gélisse R, Luccioni R, Habib G (2003) Hypoalbuminemia in elderly patients with acute diastolic heart failure. J Am Coll Cardiol 42(4):712–716
56. Cowger J, Sundareswaran K, Rogers JG, Park SJ, Pagani FD, Bhat G et al (2013) Predicting survival in patients receiving continuous flow left ventricular assist devices: the HeartMate II risk score. J Am Coll Cardiol 61(3):313–321
57. Uthamalingam S, Kandala J, Daley M, Patvardhan E, Capodilupo R, Moore SA et al (2010) Serum albumin and mortality in acutely decompensated heart failure. Am Heart J 160(6):1149–1155
58. Kempny A, Diller GP, Alonso-Gonzalez R, Uebing A, Rafiq I, Li W et al (2015) Hypoalbuminemia predicts outcome in adult patients with congenital heart disease. Heart 101(9):699–705. Epub 2015/03/05
59. Hesse B, Parving HH, Lund-Jacobsen H, Noer I (1976) Transcapillary escape rate of albumin and right atrial pressure in chronic congestive heart failure before and after treatment. Circ Res 39(3):358–362
60. Diller GP, van Eijl S, Okonko DO, Howard LS, Ali O, Thum T et al (2008) Circulating endothelial progenitor cells in patients with Eisenmenger syndrome and idiopathic pulmonary arterial hypertension. Circulation 117(23):3020–3030. Epub 2008/06/04
61. Yusen RD et al (2015) The Registry of the International Society for Heart and Lung Transplantation: Thirtysecond Official Adult Lung and Heart-Lung Transplantation Report-2015; Focus Theme: Early Graft Failure. J Heart Lung Transplant 34(10):1264–1277

Management of Fontan Patients

22

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Abbreviations

ACE-I	Angiotensin-converting enzyme inhibitors
BDG	Bidirectional Glenn
CI	Cardiac Index
EDVi	End-diastolic volume index
ESVi	End-systolic volume index
INR	International normalized ratio
NO	Nitric oxide
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
PLE	Protein-losing enteropathy
PVR	Pulmonary vascular resistance
SVC	Superior vena cava
UVH	Univentricular heart

A univentricular heart (UVH) and single ventricle physiology are common terms used to describe a heterogeneous group of congenital heart disease patients characterized by only one functional ventricle. Examples of these heart defects are tricuspid or mitral atresia, hypoplastic left heart syndrome, double-inlet left ventricle, pulmonary atresia with intact ventricle septum, severe Ebstein's anomaly, unbalanced atrioventricular defect and large ventricle septal defect with straddling

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atrioventricular valve. The prevalence of UVH is approximately 350 per 1,000,000 live born or 3–5% of all congenital heart defects.

The natural history of UVH is dismal with a survival rate of less than 50% at 1 year and 10% at 10 years [1]. However, the introduction of Fontan-type circulation in 1971 and its later modifications has dramatically changed the prognosis of patients with UVH [2]. Today UVH children completing the Fontan procedure have a 10-year post-operative survival rate above 90% [3, 4]. Despite improved survival, patients with Fontan-type circulation face a number of complications including exercise impairment, arrhythmia, thromboembolic events and secondary organ complications such as protein-losing enteropathy (PLE), plastic bronchitis and liver disease [5, 6].

The impaired exercise capacity may—among other factors—be due to the absence of a sub-pulmonary ventricle, elevated pulmonary vascular resistance (PVR) and diastolic dysfunction of the systemic ventricle. The Fontan-type circulation and the staging of the surgical palliation may partly explain all three factors. The pulmonary and systemic circulations are in parallel and not serial in a UVH (before Fontan palliation). This causes volume overload of the ventricle, cyanosis and—in case of no pulmonary stenosis—pulmonary hyper-perfusion. Within the neonatal period, the first stage is performed aiming to regulate the pulmonary blood flow by banding the pulmonary artery or by disconnecting the pulmonary artery from the heart and securing the pulmonary blood flow through a shunt. After the first stage, the patient is still cyanotic and the ventricle volume overloaded. The second stage is performed at age 6–18 months and involves an anastomosis between the superior vena cava (SVC) and the pulmonary arteries, the so-called Glenn anastomosis, which reduces the volume overload and cyanosis. The third and final stage is currently done at age 3–4 years, when a connection from inferior vena cava to the pulmonary arteries is created, either as a lateral or an extra-cardiac tunnel. At this point in-series circulation is established, the ventricle is volume unloaded and the patient fully oxygen saturated. However, exceptions exist, e.g. in case of fenestration or veno-venous collaterals.

22.1 Absence of a Sub-pulmonary Ventricle

The single ventricle in a Fontan-type circulation needs to generate energy to pump the blood through not only the systemic but also the pulmonary circulation. This leads to a “Fontan portal system”, where one capillary bed pools blood into another capillary bed without passing through the heart. A consequence of this is a chronic state of systemic venous congestion and decreased cardiac output with decreased exercise tolerance [5]. Thus, the pulmonary blood flow is mainly passive, non-pulsatile or severely attenuated pulsatile and dependent of elevated systemic venous pressure and negative intrathoracic pressure during inspiration as the driving force.

22.2 Elevated Pulmonary Vascular Resistance

An important criterion for successful palliation with a Fontan-type circulation is low PVR. Due to the absence of a sub-pulmonary ventricle, even a modest increase in PVR is likely to have a negative impact on the longevity of a Fontan-type circulation. Mitchell and colleagues have shown that failing Fontan-type patients, who undergo heart transplantation, often have mild-to-moderate pulmonary vascular disease [7]. Hyper-perfusion of the pulmonary vascular bed, as well as cyanosis in UVH prior to palliation and Fontan completion, may both introduce vascular changes leading to elevated PVR. Another possible explanation of the development of pulmonary vascular disease in Fontan patients is the non-pulsatile blood flow. Experimental studies have shown that lack of pulsatility results in endothelial dysfunction and increased PVR [8, 9]. Furthermore, exogenous nitric oxide (NO) late after Fontan operation has been shown to reduce PVR [10].

22.3 Ventricular Diastolic Dysfunction

The ventricular volume overload prior to completion of the Fontan circulation induces myocardial hypertrophy. At the time of the Glenn anastomosis and again at Fontan completion, volume deprivation of the ventricle leads to a reduced ventricular volume with myocardial hypertrophy. Although often presenting with normal systolic function, the less compliant single ventricle has diastolic impairment and requires a high preload to maintain normal cardiac output, particularly during exercise. In the absence of a sub-pulmonary ventricle and elevated PVR, an adequate rise in preload in Fontan-type circulations is not possible and, thereby, limits exercise capacity.

22.4 Secondary Complications of the Fontan Circulation

The chronic systemic venous congestion and low cardiac output due to the Fontan circulation may result in end-organ complications, such as liver cirrhosis or malignancy, PLE and plastic bronchitis [11].

22.4.1 Hepatic Dysfunction, Liver Cirrhosis and Hepatocellular Carcinoma

Hepatic dysfunction and cirrhotic changes are common in patients with UVH palliated with a Fontan-type circulation. Observed changes are fibrosis, cirrhosis, focal nodular hyperplasia and portal hypertension [12]. Baek et al. described a prevalence of hepatic pathology of 57% in Fontan-palliated patients and that hepatic complications are correlated with the duration of Fontan circulation [13]. A feared

complication to cirrhosis, which in itself is a potential precursor of carcinoma, is the development of hepatocellular carcinoma in these young patients. Despite the known risk of hepatic complications, it may be difficult to monitor the Fontan patients regularly with traditional hepatic blood test, such as INR, albumin and alpha-fetoprotein tumour marker, since some patients may be on oral anticoagulation or have subclinical or clinical PLE. Furthermore, 10–20% of patients do not produce the alpha-fetoprotein tumour marker. Imaging may be used, but there is currently no consensus on which modality to use and how frequently the patients should be screened. Besides improving haemodynamics, there is currently no treatment to prevent the development of cirrhosis. If the patient develops hepatocellular carcinoma, surgical resection may be limited by portal hypertension and regional therapy by extrahepatic shunts (radioembolization) and abnormal vasculature (chemoembolization). Other options are liver or liver and heart transplantation [12].

22.4.2 Protein-Losing Enteropathy

PLE is a well-known and severe complication after the Fontan-type palliation. Although it only occurs in about 5% of the post-Fontan patients, it is associated with high morbidity and mortality within 5 years of diagnosis. PLE is defined as an abnormal loss of proteins such as albumin, immunoglobulin and clotting factors through the gastrointestinal tract. As a result of low serum proteins, intravascular oncotic pressure is reduced, and fluid leaks from the vascular space into the interstitium, resulting in peripheral oedema, ascites or pleural effusion [14, 15]. The pathophysiology remains unclear; however, it is thought to be mediated by chronically elevated central venous pressure causing intestinal lymphangiectasia, and low cardiac output leading to reduced intestinal perfusion and chronic inflammation [16, 17]. Consequently, multiple therapeutic approaches have been suggested with varying success. These include dietary modifications with high-protein and high medium-chain triglycerides, afterload-reducing agents, inotropic agents, pulmonary vasodilators, low molecular weight heparin, corticosteroids, octreotide, albumin infusions, creation of a fenestration, Fontan revision or conversion and heart transplant [18]. Heart transplant is the most effective therapy, but may not always resolve PLE.

22.4.3 Plastic Bronchitis

Plastic bronchitis is a rare complication after Fontan palliation, most often seen in paediatric patients but occasionally also in adults. Plastic bronchitis is occlusion of major bronchial airways by a firm, gelatinous mucoid cast. It is a life-threatening complication that can result in airway obstruction and asphyxiation. The pathophysiology is not well understood, but is believed to be associated with high central venous pressure. Treatment options are limited, but a favourable response to aerosolized urokinase and tissue plasminogen activator has been described [19].

Furthermore, sildenafil has been effective in selected patients affected by plastic bronchitis and PLE [20, 21].

22.5 Management of Fontan Patients

Exercise capacity is known to be reduced in the Fontan circulation. Through childhood and early puberty, the average maximal exercise capacity (peak oxygen consumption) for patients with a Fontan circulation is in the range of 65% of normal [22]. This initially only limits more strenuous activities, but as the patients get older, the exercise impairment becomes more pronounced. The time course for this development is uncertain, but Giardini et al. have described that exercise capacity declines over time, approximately 2.6% predicted per year [23]. This, in combination with diminished efficiency of the Fontan circuit, may lead to hospitalization, need for transplantation and death [6]. Nevertheless some patients remain stable for several years before declining, and it seems that underlying morphology, operation type and timing of operation matter [6, 23].

Standard heart failure therapies, which target the ventricular function through remodelling and afterload reduction and improve cardiac output, seem to have limited effects in Fontan patients, probably because the problem is often not systolic dysfunction, but diastolic ventricular failure due to chronic preload deprivation and ventricular hypertrophy [24]. Angiotensin-converting enzyme inhibitors (ACE-I) dilate both the arteriolar (afterload reduction) and venous circuits, as well as inhibit ventricular remodelling, but also have beneficial effects on left ventricular diastolic dysfunction [25, 26]. However, 10 weeks of enalapril treatment neither altered systemic vascular resistance, resting cardiac index and diastolic function, nor exercise capacity in stable Fontan patients compared to placebo [27]. Enalapril was also tested in patients with single ventricle physiology administered prior to the bidirectional Glenn (BDG) operation [28]. Although treatment improved the inappropriate degree of ventricular hypertrophy secondary to a volume-overloaded ventricle, this anti-hypertrophic effect was abolished 9 months post-BDG, and no difference in ventricular function was found.

The chronic low preload state results in remodelling, reduced compliance with increasing end-diastolic pressure, impaired ventricular filling and, eventually, progressively declining cardiac output, which may partly explain the increasing exercise impairment and increased hospitalization rate. One potential way to improve the Fontan-type circulation is to target the preload, which may be possible by maximizing the efficiency of the portal system. An elevation of the systemic venous pressure will lead to a chronic elevation in venous pressures with side effects such as vascular congestion, oedema, ascites and lymphatic failure. Diuretics can partially control these complications of congestion, but may further increase the problems related to low cardiac output. Modulation of resistance of the neo-portal system may have a major influence on the haemodynamics. Therefore, it is important to look for and address, if possible, focal areas of stenosis, hypoplasia, distortion or abundant collateral flow in the Fontan circuit.

Another effective way of increasing cardiac output is to create a bypass around the congested pulmonary circuit, in the form of a small fenestration between the

conduit and the atrium. Whereas a fenestration at the time of Fontan completion often reduces post-operative complications and length of hospital stay, the creation of a fenestration in later years may not be as well-tolerated. These patients are referred for fenestration because of the failure of their Fontan circuit, often characterized by elevated PVR and high transpulmonary pressure gradient. In this setting, achieving the proper balance in the creation of a fenestration is difficult and may not be possible. A small fenestration will not allow the degree of decompression necessary to alleviate symptoms, and a larger fenestration might alleviate congestion and augment cardiac output, but may result in an unacceptable desaturation. Nevertheless, this is a potential treatment in failing Fontan patients, as bridge to transplantation.

22.5.1 Pulmonary Vasodilators in Fontan Patients

In Fontan patients, pulmonary blood flow is passive due to the lack of a sub-pulmonary pump and depends on the gradient between the central venous pressure and ventricular end-diastolic pressure, as well as the resistance to flow across the pulmonary vascular bed. The modulation of the pressure gradient across the pulmonary vasculature is limited, especially during exercise, since it is dependent on the skeletal muscle pump and respiration, which are inferior to a sub-pulmonary pump [29]. Instead pharmacological ways to improve pulmonary blood flow and perhaps prevent or delay Fontan-related complications are intriguing. There has been an increasing interest towards a decrease in the ventricular end-diastolic pressure and directly modulating the PVR, both of which are theoretically relevant. Khambadkone et al. showed that PVR was elevated late after the Fontan operation and could be reduced by 25% with inhaled nitric oxide (NO), indicating pulmonary endothelial dysfunction and reactivity [10].

Endogenous NO is an important mediator of vascular smooth muscle tone and cell proliferation. Exogenous NO is a potent pulmonary vasodilator, but not practical for long-term therapy due to a very short half-life and need for administration via a ventilator. Phosphodiesterase-5 enzyme inhibitors augment and prolong the effect of endogenous NO in the pulmonary vascular bed and are, therefore, attractive for lowering PVR. Sildenafil and tadalafil are commercially available phosphodiesterase-5 enzyme inhibitors for oral administration. In 2008 Giardini et al. demonstrated an acute increase in exercise performance in Fontan patients after a single dose of the pulmonary vasodilator sildenafil [30]. Two further studies have examined the effect of phosphodiesterase type 5 inhibitors in Fontan patients. Goldberg et al. did not find any beneficial effect after 6 weeks of sildenafil 20 mg bid on peak VO_2 in 28 Fontan children/young adults, but found a significantly improved ventilatory efficiency during peak and submaximal exercise [31]. Van de Bruaene et al. examined ten adult Fontan patients with cardiac magnetic resonance imaging at rest and during supine bicycle exercise before and after a single dose of sildenafil [32]. Sildenafil improved cardiac index (CI) during exercise, mostly during high-intensity exercise. The increase in CI may be attributed to a relative increase in heart rate, an unchanged end-diastolic volume index (EDVi) and

a decrease in both PVR and end-systolic volume index (ESVi). PVR was lower throughout the exercise after sildenafil administration, but the most significant difference was again observed during high-intensity exercise, when PVR remained unchanged in contrast to the increase observed during exercise before sildenafil. EDVi did not increase after sildenafil administration. This may in part be explained by the fact that the heart rate was consistently higher after sildenafil administration. When compared with the baseline, sildenafil enhanced the ventricular filling rate, as evidenced by the greater increase from ESVi to EDVi (i.e. higher filling volume) within a shorter diastolic period. Recently, a small study examined the effect of 6 weeks of tadalafil treatment and found a significant improvement in myocardial function, exercise performance and NYHA functional class [33].

Prostacyclin is an endogenous pulmonary and systemic vasodilator with inhibitory effects on vascular smooth muscle cell proliferation. Synthetic prostacyclins are available (epoprostenol, treprostinil and iloprost), but due to short plasma half-lives, clinically relevant pulmonary vasodilatation requires drug administration to be either continuous infusion or frequent inhalations. Prostanoids have also been tested in a single study in Fontan patients. Rhodes et al. investigated the effect of a single dose of inhaled iloprost on exercise capacity in 15 stable children and adult Fontan patients and showed a significant improvement in peak oxygen pulse (a surrogate for stroke volume) and peak VO_2 [34]. The treatment appeared to be particularly beneficial among patients with substantially impaired exercise capacity.

Endothelin-1 is one of the most potent vasoconstrictive molecules, and also has mitogenic properties. Endothelin-1 is elevated in patients with various types of pulmonary arterial hypertension (PAH) and is also elevated following the Fontan operation [35]. A correlation was also shown between the endothelin-1 levels and PVR [35, 36]. Ishida et al. reported that there is an overexpression of endothelin-1 and its receptors in the pulmonary arteries, which can cause pulmonary vasoconstriction and vascular remodelling, possibly leading to failing Fontan circulation [37]. Furthermore, endothelin-1 plasma levels have been shown to correlate with increased PVR, Fontan failure and death [35, 37, 38].

The endothelin receptor antagonist bosentan has been examined in Fontan patients with the longest follow-up and largest randomized study. Bosentan is an endothelin receptor antagonist with vasodilation and possible antiproliferative effects on the pulmonary vascular smooth muscle. A concern when using endothelin receptor antagonists in Fontan patients was drug-induced hepatic toxicity, since the Fontan circulation itself may affect the liver [12]. An uncontrolled study on eight adult Fontan patients reported that 6 months of bosentan was safe and resulted in improvements in NYHA class and systolic ventricular function [39]. However, the initial open-label study with bosentan treatment in 42 adult Fontan patients did not show any significant improvement in peak VO_2 after 6 months of treatment. It is noteworthy that almost 25% of patients did not complete the study [40]. Hebert et al. tested the exercise capacity and safety in 75 adolescents and adult Fontan patients treated with bosentan for 14 weeks in a randomized placebo-controlled, double-blinded study. They found that bosentan improved peak VO_2, exercise time and functional class, without serious adverse events or hepatotoxicity (Figs. 22.1, 22.2 and 22.3 [41]).

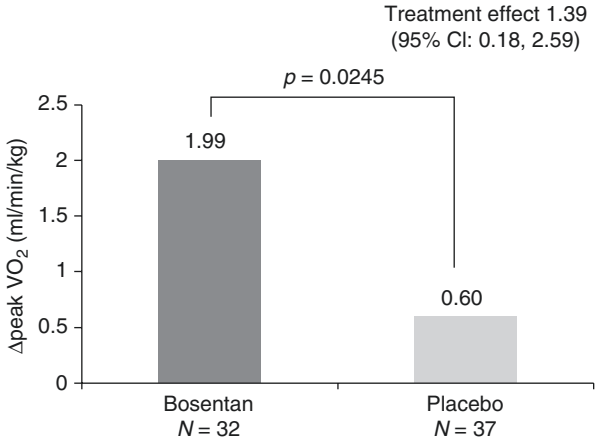

Fig. 22.1 A significant improvement in peak oxygen consumption (peak VO_2) was observed in Fontan patients after 14 weeks of treatment with bosentan compared to placebo. CI indicates confidence interval. From: Hebert A et al. Circulation 2014; 130:2021–30

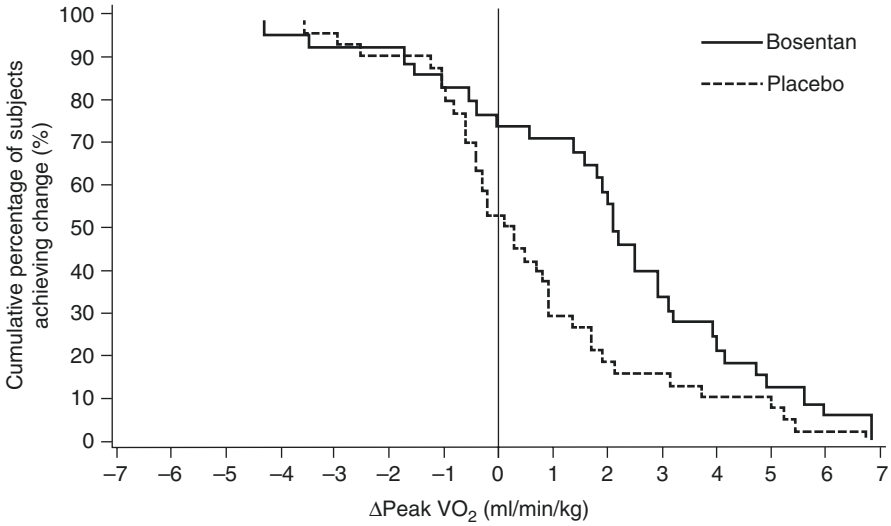

Fig. 22.2 Cumulative percentages of subjects achieving improvement in the study by Herbert et al. Each point represents the percentage of patients achieving any particular change or better from baseline. The vertical distance between the two curves marks the difference in percentage of patients with a specific change between the two groups. The area between the curves can be interpreted as the treatment effect. A positive change was achieved by 75% of subjects in the bosentan group vs. 54% of subjects in the placebo group, and a change of ≥2 was achieved by 56% of subjects in the bosentan group vs. 19% of subjects in the placebo group. Δ Peak VO_2 indicates change in peak oxygen consumption from baseline to end of treatment. From: Hebert A et al. Circulation 2014; 130:2021–30

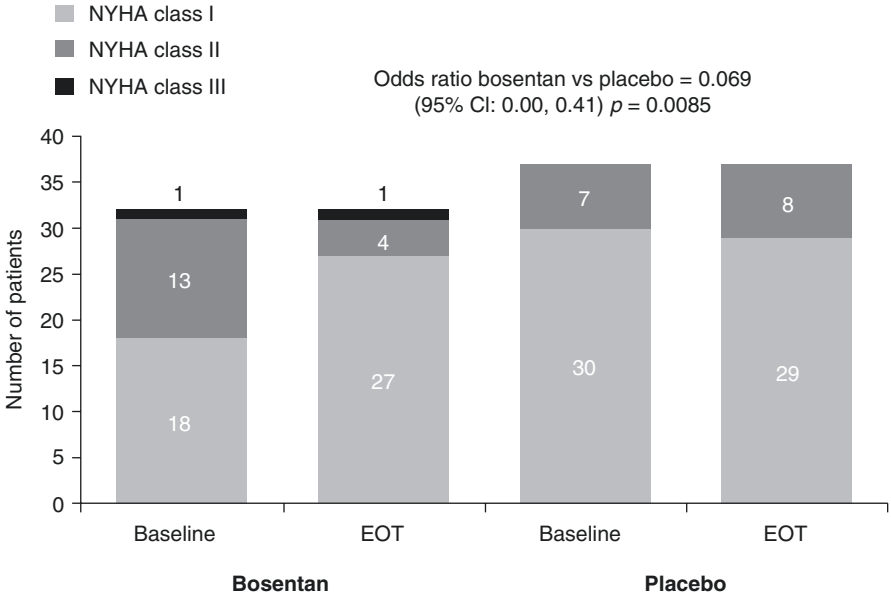

Fig. 22.3 Changes in New York Heart Association (NYHA) class on bosentan or placebo in the study by Herbert et al. CI indicates confidence interval and EOT end of treatment. From: Hebert A et al. Circulation 2014; 130:2021–30

Despite promising results regarding pulmonary vasodilator therapy in Fontan patients, there are still unanswered questions. Thus, it is debatable whether this therapy should be targeting only symptomatic or also asymptomatic patients. Moreover, since the longest treatment duration in reported studies was 6 months, the long-term efficacy and safety still remains unknown. Currently there is no consensus regarding routine use of bosentan or other vasodilators in Fontan patients, beyond cases presenting with serious complication, such as PLE or plastic bronchitis, where case reports have shown improvement of these conditions [21, 42–44].

22.5.2 Anticoagulation in Fontan Patients

Patients with (especially idiopathic) PAH are in general treated with oral anticoagulation, since retrospective studies have shown a high prevalence of vascular thrombotic lesions, as well as possible abnormalities in coagulation and fibrinolytic pathways [45]. These recommendations do not include patients with congenital heart disease.

Fontan patients are known to have a high prevalence of thromboembolic events, and the haemodynamic consequences of pulmonary emboli may be devastating and

a cause of mortality in Fontan patients. Despite this, no consensus has been reached regarding anticoagulation in Fontan patients [46]. The only existing randomized study of antithrombotic treatment in Fontan patients did not show a significant difference in thromboembolic events between patients treated with anti-platelet and well-regulated anticoagulation therapy during the first 2 years after Fontan completion [47]. The general recommendation is, therefore, for anti-platelet therapy, especially for newer version of the Fontan operation (total cavopulmonary connection, TCPC), unless patients present with arrhythmias, atrial thrombus or previous thromboembolic events, when anticoagulation is recommended [48, 49]. The American ACHD guidelines also recommend anticoagulation if patients have a classic Fontan palliation a with dilated right atrium, fenestrated tunnel or veno-venous collaterals.

References

1. Ghanayem NS, Berger S, Tweddell JS (2007) Medical management of the failing Fontan. Pediatr Cardiol 28:465–471
2. Fontan F, Baudet E (1971) Surgical repair of tricuspid atresia. Thorax 26:240–248
3. d'Udekem Y, Iyengar AJ, Cochrane AD, Grigg LE, Ramsay JM, Wheaton GR et al (2007) The Fontan procedure: contemporary techniques have improved long-term outcomes. Circulation 116:I157–I164
4. Idorn L, Olsen M, Jensen AS, Juul K, Reimers JI, Sorensen K, Johnsen SP, Sondergaard L (2013) Univentricular hearts in Denmark 1977 to 2009: incidence and survival. Int J Cardiol 167:1311–1316
5. Idorn L, Juul K, Jensen AS, Hanel B, Nielsen KG, Andersen H et al (2013) Arrhythmia and exercise intolerance in Fontan patients: current status and future burden. Int J Cardiol 168:1458–1465
6. Gewillig M, Goldberg DJ (2014) Failure of the fontan circulation. Heart Fail Clin 10:105–116
7. Mitchell MB, Campbell DN, Ivy D, Boucek MM, Sondheimer HM, Pietra B et al (2004) Evidence of pulmonary vascular disease after heart transplantation for Fontan circulation failure. J Thorac Cardiovasc Surg 128:693–702
8. Henaine R, Vergnat M, Bacha EA, Baudet B, Lambert V, Belli E et al (2013) Effects of lack of pulsatility on pulmonary endothelial function in the Fontan circulation. J Thorac Cardiovasc Surg 146:522–529
9. Zongtao Y, Huishan W, Zengwei W, Hongyu Z, Minhua F, Xinmin L et al (2010) Experimental study of nonpulsatile flow perfusion and structural remodeling of pulmonary microcirculation vessels. Thorac Cardiovasc Surg 58:468–472
10. Khambadkone S, Li J, de Leval MR, Cullen S, Deanfield JE, Redington AN (2003) Basal pulmonary vascular resistance and nitric oxide responsiveness late after Fontan-type operation. Circulation 107:3204–3208
11. Rychik J, Goldberg D, Rand E, Semeao E, Russo P, Dori Y et al (2013) End-organ consequences of the Fontan operation: liver fibrosis, protein-losing enteropathy and plastic bronchitis. Cardiol Young 23:831–840
12. Rychik J, Veldtman G, Rand E, Russo P, Rome JJ, Krok K et al (2012) The precarious state of the liver after a Fontan operation: summary of a multidisciplinary symposium. Pediatr Cardiol 33:1001–1012
13. Baek JS, Bae EJ, Ko JS, Kim GB, Kwon BS, Lee SY et al (2010) Late hepatic complications after Fontan operation; non-invasive markers of hepatic fibrosis and risk factors. Heart 96:1750–1755
14. Mertens L, Hagler DJ, Sauer U, Somerville J, Gewillig M (1998) Protein-losing enteropathy after the Fontan operation: an international multicenter study. PLE study group. J Thorac Cardiovasc Surg 115:1063–1073

15. John AS, Johnson JA, Khan M, Driscoll DJ, Warnes CA, Cetta F (2014) Clinical outcomes and improved survival in patients with protein-losing enteropathy after the Fontan operation. J Am Coll Cardiol 64:54–62
16. Rychik J (2007) Protein-losing enteropathy after Fontan operation. Congenit Heart Dis 2:288–300
17. Ostrow AM, Freeze H, Rychik J (2006) Protein-losing enteropathy after fontan operation: investigations into possible pathophysiologic mechanisms. Ann Thorac Surg 82:695–700
18. Johnson JN, Driscoll DJ, O'Leary PW (2012) Protein-losing enteropathy and the Fontan operation. Nutr Clin Pract 27:375–384
19. Do TB, Chu JM, Berdjis F, Anas NG (2009) Fontan patient with plastic bronchitis treated successfully using aerosolized tissue plasminogen activator: a case report and review of the literature. Pediatr Cardiol 30:352–355
20. Haseyama K, Satomi G, Yasukochi S, Matsui H, Harada Y, Uchita S (2006) Pulmonary vasodilation therapy with sildenafil citrate in a patient with plastic bronchitis after the Fontan procedure for hypoplastic left heart syndrome. J Thorac Cardiovasc Surg 132:1232–1233
21. Uzun O, Wong JK, Bhole V, Stumper O (2006) Resolution of protein-losing enteropathy and normalization of mesenteric Doppler flow with sildenafil after Fontan. Ann Thorac Surg 82:e39–e40
22. Paridon SM, Mitchell PD, Colan SD, Williams RV, Blaufox A, Li JS et al (2008) A cross-sectional study of exercise performance during the first 2 decades of life after the Fontan operation. J Am Coll Cardiol 52:99–107
23. Giardini A, Hager A, Pace Napoleone C, Picchio FM (2008) Natural history of exercise capacity after the Fontan operation: a longitudinal study. Ann Thorac Surg 85:818–821
24. Gewillig M, Brown SC, Eyskens B, Heying R, Ganame J, Budts W et al (2010) The Fontan circulation: who controls cardiac output? Interact Cardiovasc Thorac Surg 10:428–433
25. Gonzalez-Fernandez RA, Altieri PI, Diaz LM, Rodriguez PJ, Fernandez J, Miranda JG, Baez J, Cantellops D, Lugo JE (1992) Effects of enalapril on heart failure in hypertensive patients with diastolic dysfunction. Am J Hypertens 5:480–483
26. Pouleur H, Rousseau MF, van Eyll C, Stoleru L, Hayashida W, Udelson JA, Dolan N, Kinan D, Gallagher P, Ahn S (1993) Effects of long-term enalapril therapy on left ventricular diastolic properties in patients with depressed ejection fraction. SOLVD Investigators. Circulation 88:481–491
27. Kouatli AA, Garcia JA, Zellers TM, Weinstein EM, Mahony L (1997) Enalapril does not enhance exercise capacity in patients after Fontan procedure. Circulation 96:1507–1512
28. Hsu DT, Zak V, Mahony L, Sleeper LA, Atz AM, Levine JC, Barker PC, Ravishankar C, McCrindle BW, Williams RV, Altmann K, Ghanayem NS, Margossian R, Chung WK, Border WL, Pearson GD, Stylianou MP, Mital S (2010) Enalapril in infants with single ventricle: results of a multicenter randomized trial. Circulation 122:333–340
29. Shafer KM, Garcia JA, Babb TG, Fixler DE, Ayers CR, Levine BD (2012) The importance of the muscle and ventilatory blood pumps during exercise in patients without a subpulmonary ventricle (Fontan operation). J Am Coll Cardiol 60:2115–2121
30. Giardini A, Balducci A, Specchia S, Gargiulo G, Bonvicini M, Picchio FM (2008) Effect of sildenafil on haemodynamic response to exercise and exercise capacity in Fontan patients. Eur Heart J 29:1681–1687
31. Goldberg DJ, French B, McBride MG, Marino BS, Mirarchi N, Hanna BD et al (2011) Impact of oral sildenafil on exercise performance in children and young adults after the Fontan operation: a randomized, double-blind, placebo-controlled, crossover trial. Circulation 123:1185–1193
32. Van De Bruaene A, La Gerche A, Claessen G, De Meester P, Devroe S, Gillijns H et al (2014) Sildenafil improves exercise hemodynamics in Fontan patients. Circ Cardiovasc Imaging 7:265–273
33. Sabri MR, Zolfi-Gol A, Ahmadi A, Haghjooy-Javanmard S (2016) Effect of Tadalafil on myocardial and endothelial function and exercise performance after modified Fontan operation. Pediatr Cardiol 37(1):55–61

34. Rhodes J, Ubeda-Tikkanen A, Clair M, Fernandes SM, Graham DA, Milliren CE et al (2013) Effect of inhaled iloprost on the exercise function of Fontan patients: a demonstration of concept. Int J Cardiol 168:2435–2440
35. Yamagishi M, Kurosawa H, Hashimoto K, Nomura K, Kitamura N (2002) The role of plasma endothelin in the Fontan circulation. J Cardiovasc Surg 43:793–797
36. Hiramatsu T, Imai Y, Takanashi Y, Seo K, Terada M, Aoki M et al (1999) Time course of endothelin-1 and adrenomedullin after the Fontan procedure. Ann Thorac Surg 68:169–172
37. Ishida H, Kogaki S, Ichimori H, Narita J, Nawa N, Ueno T et al (2012) Overexpression of endothelin-1 and endothelin receptors in the pulmonary arteries of failed Fontan patients. Int J Cardiol 159:34–39
38. d'Udekem Y, Cheung MM, Setyapranata S, Iyengar AJ, Kelly P, Buckland N, Grigg LE, Weintraub RG, Vance A, Brizard CP, Penny DJ (2009) How good is a good Fontan? Quality of life and exercise capacity of Fontans without arrhythmias. Ann Thorac Surg 88:1961–1969
39. Bowater SE, Weaver RA, Thorne SA, Clift PF (2012) The safety and effects of bosentan in patients with a Fontan circulation. Congenit Heart Dis 7:243–249
40. Schuuring MJ, Vis JC, van Dijk APJ, van Melle JP, Vliegen HW, Pieper PG et al (2013) Impact of bosentan on exercise capacity in adults after the Fontan procedure: a randomized controlled trial. Eur J Heart Fail 15:690–698
41. Hebert A, Mikkelsen UR, Thilen U, Idorn L, Jensen AS, Nagy E et al (2014) Bosentan improves exercise capacity in adolescents and adults after Fontan operation: the TEMPO (Treatment With Endothelin Receptor Antagonist in Fontan Patients, a Randomized, Placebo-Controlled, Double-Blind Study Measuring Peak Oxygen Consumption) study. Circulation 130:2021–2030
42. Goldberg DJ, Paridon SM (2014) Fontan circulation: the search for targeted therapy. Circulation 130:1999–2001
43. Apostolopoulou SC, Papagiannis J, Rammos S (2005) Bosentan induces clinical, exercise and hemodynamic improvement in a pre-transplant patient with plastic bronchitis after Fontan operation. J Heart Lung Transplant 24:1174–1176
44. Do P, Randhawa I, Chin T, Parsapour K, Nussbaum E (2012) Successful management of plastic bronchitis in a child post Fontan: case report and literature review. Lung 190:463–468
45. Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery J-L, Barbera JA et al (2009) Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 30:2493–2537
46. Khairy P, Fernandes SM, Mayer JE, Triedman JK, Walsh EP, Lock JE et al (2008) Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. Circulation 117:85–92
47. Monagle P, Cochrane A, Roberts R, Manlhiot C, Weintraub R, Szechtman B et al (2011) A multicenter, randomized trial comparing heparin/warfarin and acetylsalicylic acid as primary thromboprophylaxis for 2 years after the Fontan procedure in children. J Am Coll Cardiol 58:645–651
48. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA et al (2008) ACC/AHA 2008 Guidelines for the Management of Adults with Congenital Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). Circulation 118:e714–e833
49. Baumgartner H, Bonhoeffer P, De Groot NMS, de Haan F, Deanfield JE, Galie N et al (2010) ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J 31:2915–2957

Palliative Care and End-of-Life Considerations in Patients with PAH–CHD

23

Laura C. Price, Edith Ubogagu, Laura Bernstein, Jenny Wright, and Konstantinos Dimopoulos

Abbreviations

ACP	Advance care planning
AICD	Automatic implantable cardioverter-defibrillator
BNP	Brain natriuretic peptide
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CCGs	Clinical commissioning groups
CHD	Congenital heart disease
CI	Cardiac index
CMR	Cardiac magnetic resonance
CPR	Cardiopulmonary resuscitation
DNACPR	Do not attempt cardiopulmonary resuscitation
EP	Electrophysiology
EpaCCS	Electronic Palliative Care Coordination System
ESC	European Society of Cardiology
GMC	General Medical Council
GP	General practitioner
HF	Heart failure
IV	Intravenous
LASA	Linear Analogue Self-Assessment
LTOT	Long-term oxygen therapy
NHS	National Health System
NSAID	Non-steroidal anti-inflammatory drug
PAH	Pulmonary arterial hypertension

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PAH-CHD	Pulmonary arterial hypertension related to congenital heart disease
PH	Pulmonary hypertension
RA	Right atrium
RAP	Right atrial pressure
RCT	Randomized controlled trial
RV	Right ventricle
SOB	Shortness of breath
VCO_2	Carbon dioxide production
VE	Ventilation
VO_2	Oxygen consumption
VT	Ventricular tachycardia
WHO	World Health Organization

23.1 Introduction: The Disease Trajectory of PAH–CHD

Pulmonary arterial hypertension related to congenital heart disease (PAH–CHD) in most of its forms is a progressive condition with high morbidity and mortality [1]. Despite huge leaps in managing this condition over the last three decades, there remains no cure, and significant morbidity and mortality persist. The disease trajectory of PAH–CHD varies significantly in this heterogeneous population and does not necessarily follow the severity of pulmonary vascular disease. Adult patients with Eisenmenger syndrome, the extreme end of the spectrum of PAH–CHD, are expected to live for several years or even decades, while patients with previously repaired defects and persistent (or newly developed) PAH appear to have a far worse outcome [2]. Right ventricular (RV) maladaptation, comorbidities relating to the congenital heart defect and pulmonary arterial hypertension (PAH), other congenital abnormalities and complications relating to chronic cyanosis or previous surgery impact on both the outcome and quality of life of patients with PAH–CHD. Clinical problems encountered include arrhythmias, endocarditis, cerebral abscess, renal dysfunction, restrictive ventilatory defects, obstructive or central sleep apnoea, need for long-term oxygen therapy (LTOT) and osteopathy. Ultimately, these lead to detraining, pain, discomfort, cardiac cachexia and a negative impact on prognosis.

While sudden death is not uncommon and usually attributable to events such as ventricular or fast supraventricular tachycardias or massive haemoptysis, more commonly death is the result of progressive right ventricular failure. This leads to a gradual decline in exercise capacity and repeat hospitalizations for off-loading of congestive heart failure (HF), uptitration of PAH therapies and treatment of chest infections, arrhythmias and other precipitants or comorbidities. All of the above impact on patients' quality of life but also impart a burden, both psychological and financial, upon patients and their families.

Currently available PAH therapies are able to improve symptoms and possibly prolong life, but none are, as yet, curative [3–5]. Lung transplantation is considered

Table 23.1 Definition of the candidates for end-of-life care, according to the General Medical Council, UK [7]

Patients are "approaching the end of life" when they are likely to die within the next 12 months. This includes patients whose death is imminent (expected within a few hours or days) and those with:
(a) Advanced, progressive, incurable conditions
(b) General frailty and coexisting conditions that mean they are expected to die within 12 months
(c) Existing conditions if they are at risk of dying from a sudden acute crisis in their condition
(d) Life-threatening acute conditions caused by sudden catastrophic events

the only curative treatment for PAH–CHD. However, few patients are listed, and even fewer undergo successful transplantation, often requiring heart–lung transplant or lung transplant plus repair of the cardiac defect in few centres with transplant and congenital surgical expertise. Moreover, the appropriate timing of referral of PAH–CHD patients for transplantation remains unknown. Survival rates for recipients of heart–lung transplants are still suboptimal, with a reported 60% survival at 5 years in transplant survivors. As the expected survival of stable PAH–CHD patients is often much longer, transplant referral is usually delayed until deterioration occurs. At this point, however, multi-organ failure has often occurred, precluding transplantation. Therefore, a focus on relieving symptoms and improving quality of life is important.

23.1.1 Definition of Palliative Care (WHO) and End-of-Life Care (General Medical Council UK)

"Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" [6]. Palliative care should be offered to any patient with a chronic life-limiting condition. This includes both patients early in their disease trajectory and those in whom death is imminent. The General Medical Council's (GMC) definition of patients who should be eligible to end-of-life care is summarized in Table 23.1 [7].

23.2 What Palliative Care Can Offer to PAH–CHD Patients

23.2.1 The Aims and Delivery of Palliative Care to PAH Patients

While formal palliative care services may not be ubiquitously available in all countries worldwide, the issues addressed by palliative care are universal, and measures

should be taken to address these uniformly across all PAH services. In a life-limiting condition like PAH, for which no cure is yet available, management aims should include both prolongation of life and preservation or improvement of the quality of life of patients and their families. The latter can be achieved by preventing and managing suffering: physical, psychosocial or spiritual. Palliative care can have multiple benefits and it is not just targeted to patients who are dying. This should be emphasized when palliative care discussions with the patient and family are initiated. Beyond improving patients' quality of life and supporting patients and their families, palliative care aids in establishing goals and coordination of care and psychosocial, spiritual and bereavement support.

Palliative care should be provided within a multidisciplinary environment and should involve PAH physicians and nurses, palliative care physicians, nurses and pharmacists, general physicians, occupational therapists, physiotherapists and, if appropriate, the chronic pain team. The first step should be assessing the patients' understanding of their condition, the cause of their symptoms and their prognosis. Thereafter, all symptoms, especially those spontaneously described, should be explored, with a focus on provoking and related factors or symptoms, severity, temporality and the response to therapies. Rating instruments are at times used to assess symptom severity, such as the Borg and modified Borg scales (Table 23.4). Patients should be followed up and reassessed to document the effectiveness of treatment or changes in symptoms relating to disease progression.

In end-stage PAH–CHD, attempts to improve symptoms and if possible reverse the process should be made. Medications should be reviewed for compliance and uptitration, using stronger HF and PAH therapies and iron supplementation, when needed; options such as atrial septostomy and transplantation should also be considered. Patients should be assessed with particular focus on ongoing haemodynamic lesions and other factors that can aggravate symptoms such as sleep apnoea, loss of muscle mass and detraining. Structured rehabilitation programmes can address skeletal myopathy and improve these symptoms.

Palliative care should facilitate advance care planning (ACP), taking into account the patient's preferences on place of care and place of death and whether cardiopulmonary resuscitation (CPR) should be performed in the event of cardiac arrest. The latter is particularly important, as patients with PAH who experience a cardiac arrest rarely survive. In a retrospective study of more than 3000 patients with PAH who received CPR, only 6% survived at 90 days [8].

In England, service specifications for tertiary PAH centres dictate that patients and their carers must receive a palliative approach, involving symptom control and psychological, social and spiritual support throughout the course of the illness, "regardless of whether they wish to receive active treatment". Moreover, they recommend that patients with exceptional palliative care needs should, in agreement with their general practitioner, be referred to specialists in palliative care and should be managed in accordance with the National End of Life Care Strategy. Unfortunately, many patients with chronic diseases, including PAH patients, are referred to palliative care late in life or not at all [9, 10]. This results in a larger number dying in

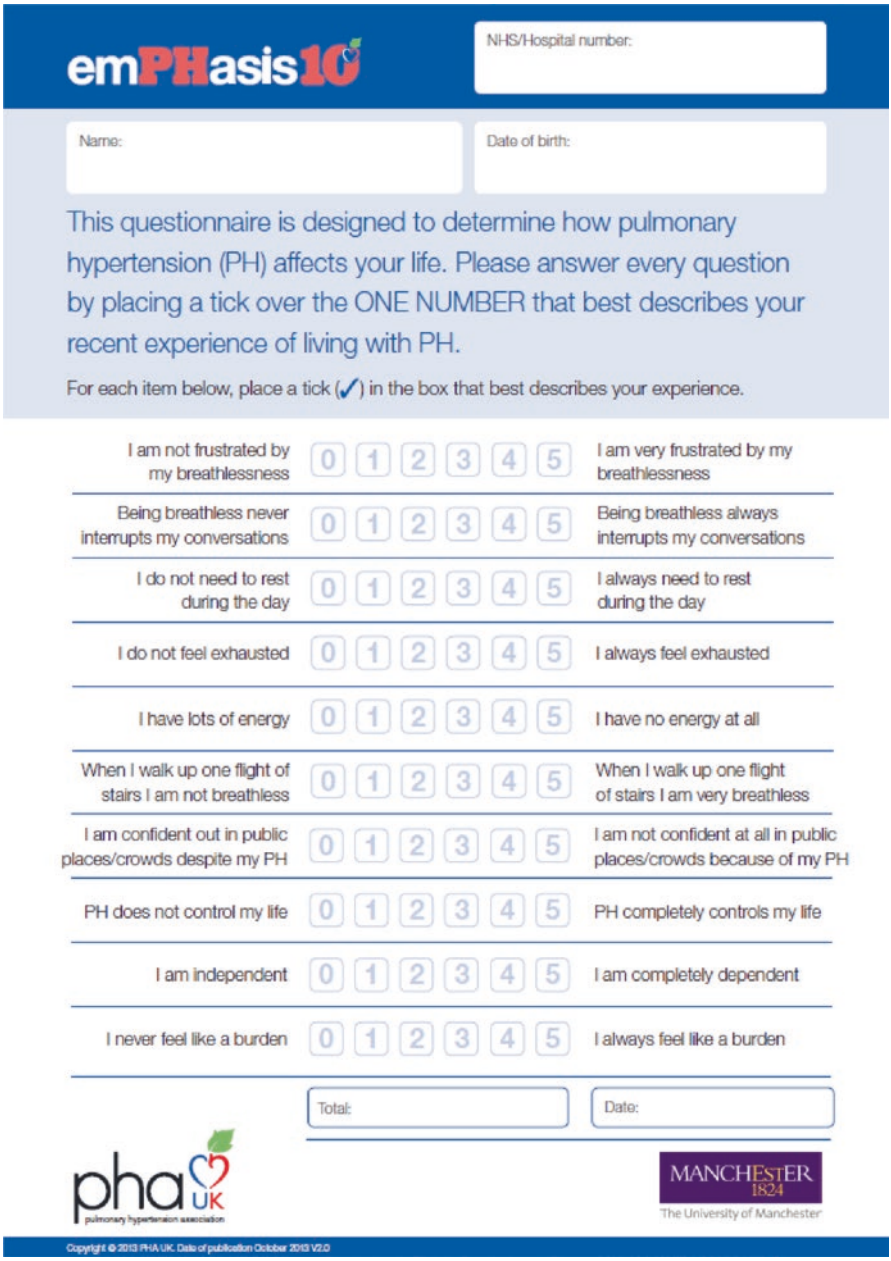
hospital rather than at home with their family, after numerous hospitalizations, and often in an intensive care setting [11].

Effective communication between patients and clinicians is important. Clinicians are known to underrate the severity of symptoms and may also consider tolerable, symptoms that patients find intolerable. Patients, on the other hand, may downplay symptoms when they consider these to be an inevitable component of their condition. Communication barriers may exist, e.g. cultural or language factors or cognitive impairment. Patient-centred achievable goals should be agreed with the patients and their families, including appropriate ACP. Psychosocial and spiritual support for both patients and their families is important, as is assistance in bereavement.

23.2.2 Timing of Referral to Palliative Care and the Challenges of Prognostication in PAH–CHD

Palliative care becomes essential in patients who are severely limited in their activities and symptomatic at rest or minimal effort. In these patients, palliative care should be established early on, in order to help patients and relatives cope with disease and its impact on everyday life. Discussions regarding palliative care and end-of-life care should certainly be initiated while the patient is still capable of participating in decision-making. Timing of referral to palliative care should also incorporate measures of quality of life and other patient-reported outcomes. Disease-specific quality of life (QoL) scores appear more appropriate than generic or HF ones, assessing domains affected specifically by PAH and validated in this population (Fig. 23.1). When assessing physical limitation and its impact on QoL, physicians should remember that many patients with congenital heart disease will underestimate their level of limitation, especially those in whom PAH developed early in life leading to adaptation of ordinary activities.

Risk stratification and validated predictors of outcome are important in aiding physicians to formulate an opinion on prognosis and deciding whether to refer a patient to palliative care (see chapters 15 and 21, and Tables 15.5 and 23.2). The great variability in the natural history of PAH–CHD and the response to therapies make prognostication and timing of palliative care referral even more difficult [14]. It has been recommended that physicians should use the "surprise" question to identify people appropriate for referral to palliative care: "Would you be surprised if this patient had died by next year?" [15, 16] However, physicians are known to overestimate the life expectancy of patients with chronic conditions, perhaps in part due to the close relationship established over time between the pulmonary hypertension (PH) team and the patients and their families. PH clinicians may tend to focus on positive aspects, encouraging patients to adhere to PAH medication despite important side effects, in an effort to prolong life and alleviate symptoms. This optimistic approach should not become an obstacle to open discussions with the patients with regard to their prognosis and wishes [17].



emPHasis10

NHS/Hospital number:

Name:

Date of birth:

This questionnaire is designed to determine how pulmonary hypertension (PH) affects your life. Please answer every question by placing a tick over the ONE NUMBER that best describes your recent experience of living with PH.

For each item below, place a tick (✓) in the box that best describes your experience.

I am not frustrated by my breathlessness	0 1 2 3 4 5	I am very frustrated by my breathlessness
Being breathless never interrupts my conversations	0 1 2 3 4 5	Being breathless always interrupts my conversations
I do not need to rest during the day	0 1 2 3 4 5	I always need to rest during the day
I do not feel exhausted	0 1 2 3 4 5	I always feel exhausted
I have lots of energy	0 1 2 3 4 5	I have no energy at all
When I walk up one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up one flight of stairs I am very breathless
I am confident out in public places/crowds despite my PH	0 1 2 3 4 5	I am not confident at all in public places/crowds because of my PH
PH does not control my life	0 1 2 3 4 5	PH completely controls my life
I am independent	0 1 2 3 4 5	I am completely dependent
I never feel like a burden	0 1 2 3 4 5	I always feel like a burden

Total:

Date:

pha UK pulmonary hypertension association

MANCHESTER 1824 The University of Manchester

Fig. 23.1 The emPHasis-10 questionnaire [12]

Table 23.2 Risk assessment in pulmonary arterial hypertension [13]

Determinants of prognosis (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[a]	Repeated syncope[b]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 > 15 mL/min/kg (>65% pred.)	Peak VO_2 11–15 mL/min/kg (35–65% pred.)	Peak VO_2 < 11 mL/min/kg (<35% pred.)
	VE/VCO_2 slope <36	VE/VCO_2 slope 36–44.9	VE/VCO_2 slope ≥ 45
NT-proBNP plasma levels	BNP <50 ng/L	BNP 50–300 ng	BNP > 300 ng/L
	NT-proBNP <300 ng/L	NT-proBNP 300–1400 ng/L	NT-proBNP > 1400 ng/L
Imaging	RA area < 18 cm^2	RA area 18–26 cm^2	RA area > 26 cm^2
(echocardiography, CMR imaging)	No pericardial effusion	No or minimal pericardial effusion	Pericardial effusion
Haemodynamics	RAP < 8 mmHg	RAP 8–14 mmHg,	RAP > 14 mmHg
	CI ≥ 2.5 L/min/m^2	CI 2.0–2.4 L/min/m^2	CI <2.0 L/min/m^2
	SvO_2 > 65%	SvO_2 60–65%	SvO_2 < 60%

Proposed variables and cut-off values are based on expert opinion. The proposed variables and cut-offs apply to idiopathic PAH, but may not apply to PAH–CHD

[a]Occasional syncope during brisk or heavy exercise or occasional orthostatic syncope in an otherwise stable patient

[b]Repeated episodes of syncope, even with little or regular physical activity

23.3 Approach to Palliative Care in PAH–CHD: Overlap Between Heart Failure, Chronic Lung Disease and Palliative Care for the Young

In other chronic diseases, there is increasing evidence of the positive impact of early palliative care consultation on patients' quality of life and even their survival [18, 19]. Unfortunately, there are very few data in PAH–CHD on the ideal mode of delivery and benefits of palliative care [20]. Hence, much of the data presented here are extrapolated from HF and chronic lung disease. HF guidelines by the European Society of Cardiology recommend that palliative care should certainly be offered to patients with frequent admissions to the hospital due to decompensation or patients

in functional class IV with poor quality of life, especially those with treatment-refractory disease when heart transplantation and mechanical circulatory support are not an option [21]. The guidelines recommend frequent assessment of the physical, psychological and spiritual needs of the patient, with a focus on relief of symptoms relating to the primary disease or comorbidities. A "needs assessment" tool to help physicians assess palliative care needs of patients with irreversible interstitial lung disease is currently undergoing validation and could potentially be adapted for the PAH–CHD population in the future (Table 23.3) [22–24].

23.3.1 Physical Symptoms in PAH–CHD

PAH carries a high symptom burden relating to the disease itself but also to the effects of the medication. A high prevalence of severe dyspnoea, tiredness, anxiety, lack of well-being and depression is reported by PAH patients and their families, and, when compared to published data, the symptoms appear to be more prevalent than in cancer patients. Both oral and parenteral therapies can cause side effects, which include mild or cosmetic to debilitating: common side effects range from gastrointestinal problems, "red eyes", headaches and peripheral oedema in oral therapies, and severe pain, nausea and diarrhoea with prostanoids. Moreover, parenteral therapies are often difficult to manage, are time-consuming and may add to the background anxiety and discomfort relating to the disease. Measures to minimize symptoms and improve the quality of life should be an integral part of the management of PAH–CHD patients.

The most frequent reported symptoms in patients with end-stage PAH were assessed in a recent survey of physicians caring for PAH patients, including those with PAH–CHD (Fig. 23.2) [25]. Dyspnoea on exertion, fatigue and oedema were the most frequent symptoms, followed closely by depression and anxiety. Anorexia and pain are also extremely common.

Table 23.3 The indications for palliative care

Who needs palliative care?	Why?
High symptom burden or refractory symptoms	Can improve symptom control and quality of life
Significant psychological distress	Reduces psychological distress
Difficulty coping with their illness	Enhances patients' coping strategies
Complex family and social needs	Helps family caregivers and addresses patients' social needs
Significant and/or persistent misperceptions about their illness trajectory and overall prognosis	Enhances patients' prognostic understanding
May have a poor prognosis and limited life expectancy (i.e. you would not be surprised if they die within 1 year)	Upstream advance care planning, preparing for any adverse event, not just the end of life

Adapted from [22, 23]

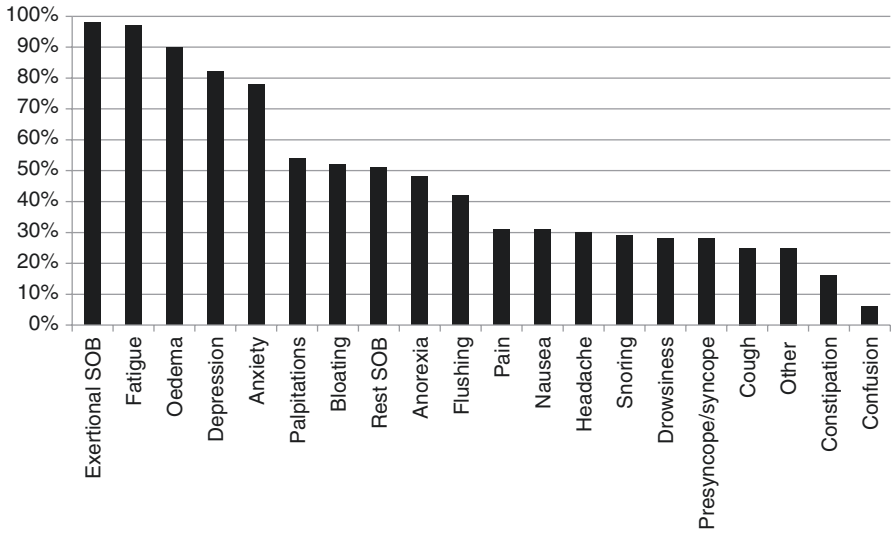


Fig. 23.2 Symptoms encountered in patients with pulmonary arterial hypertension–from [25]. Y-axis shows percentage of respondents. SOB, shortness of breath

Table 23.4 The shortness of breath modified Borg dyspnoea scale

Score	Description of breathlessness
0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

23.3.2 Dyspnoea

Dyspnoea is the most common symptom in PAH–CHD and a primary target for all therapies in PAH. It is a subjective symptom, and objective parameters, such as respiratory rate or oxygen saturations, often do not directly correlate with the severity of dyspnoea. The patient's ability to perform everyday tasks is a good indicator of the severity of dyspnoea, while scales (e.g. the modified Borg scale, Table 23.4) may be utilized to quantify the severity of the dyspnoea.

Dyspnoea (and fatigue or oedema) can be improved by initiation or escalation of PAH therapy or by the use of diuretics, aimed at a reduction in RV filling pressures and improvement in RV function. Recent PAH guidelines acknowledge that there are no randomized controlled trials (RCTs) on the use of diuretics in PAH, but clinical experience shows a clear symptomatic benefit in fluid-overloaded patients treated. The choice and dose of diuretic therapy is left to the physician [13]. In patients with severe PAH and RV dysfunction, optimizing RV filling is particularly important, avoiding very high or very low RV filling pressures that may compromise cardiac output. Patients with severe congestion and RV dysfunction who are refractory to intravenous diuretics may benefit from dobutamine infusion [26].

Exercise training can also be considered in patients who are in World Health Organization functional class (WHO FC) 2 or 3, improving their dyspnoea and quality of life, even though evidence for this remains limited. In more advanced disease, with dyspnoea refractory to medication, opioids could be attempted, as they reduce the hypoxic ventilatory drive and may help with off-loading of fluid. When renal function is impaired, morphine should be used with caution, and other opioids, which are more appropriate in renal impairment, such as fentanyl and alfentanil, or perhaps even oxycodone should be considered. Evidence for the use of opioids in non-malignant diseases comes from studies in patients with chronic obstructive pulmonary disease [27]. There is little evidence on the use of opioids in relieving dyspnoea in HF [28–30]. Local guidelines on the use of opioids should be consulted.

Nondrug options, including the use of a handheld fan directed to the face, can help reduce the sensation of breathlessness, although this has not formally been tested in PAH [31].

23.3.3 Pain

Pain is common in advanced chronic HF, most commonly affecting the lower legs, but also the chest, back and major joints. It is important to routinely ask patients about pain and manage this appropriately. Physical therapy or heat/cold therapy should be considered. In HF (PAIN-HF study), only opioids appear to be effective in reducing pain [32], and it is recommended that opioids are considered at low doses in patients with advanced HF refractory to other treatments, adjusting for renal function: compounds with renal-excreted metabolites (e.g. morphine and oxycodone) should be used with caution, and other opioids, which are more appropriate in renal impairment, such as fentanyl, alfentanil or transdermal buprenorphine, should be considered. Nonsteroidal anti-inflammatory drugs (NSAIDs) should also be avoided, as they can affect renal function and may result in sodium and fluid retention.

23.3.4 Cachexia, Anorexia and Nausea

Neurohormonal and cytokine activation are known to occur in patients with advanced HF of different causes and can result in anorexia, weight loss (cachexia) and skeletal myopathy [33, 34]. Anorexia may also result from congestion of the gut

and liver. Optimization of the PAH and HF medication should be pursued, always remembering to adjust doses to the current lean mass as muscle wasting occurs. Dietary advice should aim at optimizing calorie intake, with small frequent meals in patients with advanced disease.

Nausea is a common feature in patients with advanced HF, due to medication, gut oedema, and renal and liver dysfunction. Current medication should be reviewed for causes of nausea, volume status optimized and a proton pump inhibitor considered. Local guidelines on the usage of anti-emetics should be consulted when determining which anti-emetic to prescribe, as some anti-emetics (e.g. haloperidol, ondansetron and domperidone) may prolong the QT interval.

23.3.5 Psychological, Spiritual and Social Support

PAH, like HF, has a significant impact on the patients and their families. Physical and social function is often affected, including work, sexual relations, family and social life and financial uncertainty. Recurrent hospitalizations and cumbersome therapies with a high side effect burden add to the psychological stress of a life-threatening condition. Depression is more prominent in patients with advanced disease and a high symptom burden, who should be screened regularly and offered counselling [35, 36]. In HF, paroxetine resulted in a reduction in depression and an improvement in the psychological aspects of their quality of life [37]. Other medication may be considered, ensuring that the QT interval is monitored in patients receiving tricyclic antidepressants and sodium levels in patients on serotonin reuptake inhibitors. Spiritual support is also important.

23.3.6 Management of Patients Likely to Be in the Last Weeks to Days of Life (End-of-Life Care)

In patients with severe, advanced disease, clear and honest communication with individuals and their families of the approach to care is essential [38]. While medical management is being optimized in this context and ideally before all life-prolonging interventions have been exhausted, attempts should be made for referral and involvement of palliative care teams in order to continue with an integrated focus on the optimization of symptom control, quality of life and well-being.

Even when prognosis is short, many patients will request invasive or burdensome treatments, so not to lose the hope of improvement. A “hope for the best, plan for the worst” approach can then be followed, for example, even while working with the patient to prolong life, gentle conversations about the end of life can be framed to identify preferences for place of care and place of death if things do not go as hoped. Discussions with patients and their loved ones at the end of life must be honest but communicated sensitively. Table 23.5 provides a rough guide to approaching these discussions and should be adapted to each individual’s information needs, level of acceptance of their condition and level of distress that might be caused.

Table 23.5 Framework for end-of-life discussions in PAH (Adapted from [38, 39])

Steps to end-of-life discussion	
Step 1: Discussions with patients and their loved ones	As cognition worsens, discussions regarding patient expectations should be held promptly, with important topics including:
	• Wishes relating to the place of care
	• Wishes relating to the place of death
	• Being connected to a machine or power source and its likely implications, including needing assistance with all basic functions and loss of the ability to talk with friends or family
	• Cardiopulmonary resuscitation (CPR) in the event that the heart or lungs stop working
	• Ceilings of care, including:
	– Step-by-step plan for symptom management, especially in the event of discharge to home for end-of-life care (avoid unnecessary readmission to hospital)
	– General values and resources for spiritual and emotional support for patient and family
	If patients decide to spend their last weeks or months of life at home, clear instructions should be provided to local healthcare teams and the family with regard to medication
Step 2: Rationalization of life-prolonging management	Withdrawal of treatments is a difficult topic: few patients are likely to accept being taken completely off PAH medication. There are complex ethical issues in withdrawing essential medication, which can accelerate death
	Medical treatment may need to be adjusted towards the end of life as patients may not be able to tolerate certain drugs as well.
	Patients with advanced heart failure may not tolerate large doses of medication due to hypotension, and treatment should be adjusted accordingly. Withdrawal of evidenced-based therapies may be appropriate for some patients. When treatments are discontinued, a plan to manage symptoms should be enacted. Life-prolonging therapies that are also likely to improve symptoms should be continued as long as possible

When patients with capacity have made a decision not to be informed that they are approaching the end of their life, this should be documented and respected. In the absence of this, all patients entering the last few days of life should be made aware, alongside their loved ones, and offered discussions on their needs (*shared decision-making*), preferences and how their end-of-life care will be managed on an individualized basis (*individualized care plan*):

- Begin by establishing *what the patient wants to know* about the current changes in their condition, their deterioration and the likelihood that they are entering the last few days of life.
- Establish their understanding about their *prognosis*.
- Establish *who they would like to involve in their end-of-life care* including their loved ones – family, relatives, carers, faith-based support, allied health professions and specialist teams including the palliative care team.

- Establish their *preferences culturally*, *spiritually* and *emotionally* and preferences with regard to management in the days preceding, during and after death.
- Establish their *concerns and anxieties* about their current and future management now, through and beyond their death.
- Explore the preferences of the patient and their loved ones on *where they wish to receive end-of-life care*, i.e. hospice, home, hospital, etc.
- Establish *a management plan for anticipated symptoms* in the last few days of life including the management of pain, breathlessness, nausea/vomiting, respiratory secretions and terminal agitation, considering specialist symptoms such as bleeding.
- Explain the need to manage these symptoms with subcutaneous injections of anticipatory medications and a *continuous infusion via a syringe driver* when indicated to continue symptom management when they are no longer able to swallow.
- Explore the risks and benefits of *clinically assisted nutrition and hydration* at the end of life including the importance of maintaining good mouth care, oral intake of fluids and food and other appropriate means of nutrition and hydration, i.e. the limitations of subcutaneous fluid and enteral and parenteral nutrition.
- Establish the management of *body fluid and waste* considering catheterization when indicated and a suitable bowel management at the end of life.
- Lastly explain the *practical support for the patient and their loved ones* including visiting hours, accommodation and parking for their love ones.

Having explored, established and communicated these preferences alongside the patient, their loved ones and those involved in their care, document this carefully as the patient's individualized care plan.

23.4 Communication with Patients and Their Families

Misconceptions on the purpose of palliative care can make its introduction to the patients and their families difficult [40, 41]. Discussion of palliative care issues will differ depending on stage of disease, age and comorbidities. While an estimate of life expectancy may be difficult to provide, it is important that patients and their families are made aware of the effect that PAH may have on life expectancy early in their care, ideally around the time of diagnosis, with the formulation of a long-term management plan (ACP). Such plans should be reviewed and updated periodically. Misperceptions by the patient or family can be clarified, and statements of estimated prognosis should be offered if appropriate.

Palliative care is best introduced as a form of support (or supportive care) for patients and their families, in addition to other therapies, focusing on symptom management and improved communication with the healthcare team [40]. It is best if family members are present, especially if ACPs are discussed, and it is preferable that this occurs when the patient is stable and can participate in the discussion [42, 43]. Patients may be surprised by the information on their prognosis, and the

uncertainty on predicting length of life should be acknowledged [44]. At the same time, a commitment by the physician to keep providing care in parallel to palliative care is helpful. An "ask-tell-ask" and "hope for the best and prepare for the worst" approach to the conversation may be taken, and the conversation should end by explaining the management plan [41, 45–47]. Discussions with the patients and their families should be repeated when there are changes in the patient's status or patient's preferences [48]. Topics to be covered should include the patient's values and beliefs, in a patient-centred approach, balancing reality to sensitivity [49].

PAH is a severe condition, thus, discussions on prognosis, the goals of care and ACP should ideally occur around the time of diagnosis. However, many PAH–CHD patients are diagnosed in childhood, and hence other opportunities in the patient's disease trajectory should prompt initial or repeat discussions [1, 42, 49]. Examples include when a new therapy is started because of a functional decline or when life-prolonging therapeutic options have been exhausted. Moreover, repeated hospitalizations for exacerbations, initiation of intravenous therapies or referral to transplantation should trigger such discussions. Focus on uncontrolled dyspnoea or other symptoms and the levels of dependence on others for ordinary activities may facilitate discussion of referral to palliative care.

The discussion of end-of-life issues is, anecdotally, variable in clinical practice, and we believe it should be discussed more openly. PH physicians are likely to have a long-standing relationship with patients and their families, and the trigger for such discussions is not universally agreed. In the PAH setting, and specifically in PAH–CHD, there are no patient surveys to question opinion regarding timing and whether such open discussions are useful in practice. Clinical experience in our unit is that early discussions may be difficult but are best tailored to the individual patient. For some, the setting for such discussions may be the outpatient setting, while for others initiation of these conversations may be more appropriate during an inpatient admission. Time must be given to the patient and their families to reflect on the issues raised and on the contents of the conversation. If decisions have not been made in this setting, the decision regarding resuscitation (do not attempt cardiopulmonary resuscitation (DNACPR)) should be made at the time of hospital admission, during the day, ideally with the PH physician and specialist PH nurse known to the patient and family. We believe that this should be a basic standard of care for our patients. It is important that once an ACP is agreed upon, it is shared, with the patient's permission, with other relevant professionals, i.e. their GP, community palliative care services and out-of-hour services in order to facilitate the preferences of the patient. The Electronic Palliative Care Coordination System (EPaCCS) provides a tool in the UK for sharing ACPs once agreed.

23.5 Barriers to the Use of Palliative Care to Improve Quality of Life (QoL) in Patients with PAH

Provider knowledge and misperception about palliative care appear to be a major barrier to its use in the setting of PH. Fenstad et al. surveyed PH physicians with high levels of confidence in medically managing PAH, including medical therapy

and end-of-life care [25]. Relatively few used palliative care on regular basis throughout the trajectory of PAH. Fears that palliative care would be seen as if the physician was “giving up hope” or that the name “palliative care” has a negative connotation were commonly raised. Moreover, physicians often felt that patients were not end of life and expressed the opinion that it was hard to aggressively treat PAH and provide palliative care at the same time. Many physicians felt that they were comfortable in dealing with end-of-life care; hence, palliative care referral was unnecessary. As a result of the above misconceptions about palliative care and the way in which it is presented to the patients and their relatives, the most common barrier to palliative care referral remains patient or family refusal to engage.

Grinnan et al. surveyed relatives of patients with PAH who had died, with the scope of understanding the end-of-life experience of patients with PAH [11]. This survey included demographic information and the Edmonton Symptoms Assessment Scale. A 36% response rate was achieved, and the vast majority of patient deaths (90%) were related to PAH. Two thirds of patients died in hospital (67%), the vast majority (83%) in intensive care. Palliative care was infrequently involved in patient care, and many surrogates were unaware of the palliative care and hospice services available. A high symptom burden was reported, especially dyspnoea, tiredness, lack of appetite, anxiety, lack of well-being and depression, which may be the reason why most patients were in the hospital at the time of death. When compared to published data, PAH patients appear to have a higher burden of all of the above symptoms, suggesting a greater potential benefit from palliative care involvement. Despite this, in few cases were palliative care services involved, and the high rate of death in an intensive care environment suggests that more work is needed to promote the concept of advanced planning and ceiling of care. In this study, there was no significant difference in symptom scores between patients dying at home or in hospital. Moreover, educating local teams in managing patients on PAH therapies, especially those on intravenous prostanoids, may lead to less need for patients being admitted to intensive care.

Swetz et al. examined the QoL in PAH patients and assessed the use of palliative care for addressing QoL issues and the barriers hindering its early implementation in this population [50]. This was an Internet-based survey distributed through the US Pulmonary Hypertension Association. Symptom burden was assessed using the Linear Analogue Self-Assessment (LASA), while QoL was assessed by the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) score [51]. There was 41% overall response rate with 88% analysable responses. Mean age was 48.9 years, 86% were female (86%), and 42% had idiopathic PAH. Profound deficiency in overall QoL (40%), fatigue (57%), physical well-being (56%), social activity (49%), emotional well-being (49%) and pain (38%) was reported. Most patients believed that their PAH physician had excellent understanding of PAH progression/plan of care (92%) but less were satisfied with care regarding QoL management (77%). Few patients considered palliative care (8%) or had pain management (4%) or palliative care involved (1%). Most common reasons were belief that patients were doing well/"not sick" (63%) or that palliative care had not been suggested (22%). Less than one half of patients expressed wishes with regard

to life support, resuscitation and end-of-life care. Even fewer had engaged in any type of ACP, such as discussion with a loved one (38.4%), or completed a living will (33.7%) or a durable healthcare power of attorney (25.4%). Very few (13.8%) had completed a discussion with their PH physician with regard to ACP.

Reasons why patients had not pursued palliative care consultation included the misconception that it equated to hospice and end of life, the fact that many patients felt they were too well to need palliative care despite its supportive role, or that they would need to stop their PAH medication once they received palliative care, while others had not heard of it. Unfortunately, palliative care awareness by PH patients and providers remains low. This study emphasizes the need to integrate palliative care early into the care for PH patients [50].

23.6 Delivery and Funding for Palliative Care in the UK

Funding models vary between different services, with funding provided by charitable donations and state funding methods, resulting in most hospices being able to provide free palliative care for all. There are 32 clinical commissioning groups (CCGs) across London that commission differing amounts of specialist palliative care, often from multiple providers. All the multi-speciality hospitals serving London have palliative care teams which, in all but one case, are funded directly by the National Health System (NHS) trust concerned. Eleven out of 15 inpatient units in London are owned by charities and are mainly charitably funded; four are NHS-run [52].

23.7 Sudden Death and the Role of Implantable Defibrillators in PAH–CHD

While sudden death is not uncommon in PH, current PH guidelines do not provide any guidance on which patients should receive an automated implantable converter defibrillator (AICD). AICDs are implanted in other cohorts for either primary or secondary prevention of sudden cardiac death. Secondary prevention with an AICD is recommended when a patient has survived sudden cardiac death or a malignant, haemodynamically significant tachycardia. The decision to implant an AICD should be balanced against life expectancy and the expected mode of death. The American Heart Association adult congenital heart disease guidelines make a generic comment on this topic: “it is reasonable to recommend the use of an implantable cardioverter defibrillator for any patient who has had a cardiac arrest or experienced an episode of haemodynamically significant or sustained VT” [53]. The European Society of Cardiology guidelines identify the five congenital defects with the greatest known risk of late sudden cardiac death (tetralogy of Fallot, transposition of the great arteries, congenitally corrected transposition, aortic stenosis and univentricular hearts) and provide recommendations for individual conditions and the overall CHD population (Table 23.6), without, however, taking into account the functional status and

Table 23.6 European Society of Cardiology guidelines on the use of automated implantable converter defibrillators (AICDs) in adults with congenital heart disease [54]

Indications for an AICD in adults with congenital heart disease
• ICD implantation is indicated in survivors of cardiac arrest after exclusion of reversible causes
• Patients with spontaneous sustained ventricular tachycardia (VT) should undergo invasive haemodynamic and EP evaluation. Recommended therapy includes catheter ablation or surgical resection to eliminate VT. If that is not successful, ICD implantation is recommended
• Invasive haemodynamic and electrophysiology (EP) evaluation is reasonable in patients with unexplained syncope and impaired ventricular function. In the absence of a defined and reversible cause, ICD implantation is reasonable
• EP testing may be considered for patients with ventricular couplets or nonsustained VT to determine the risk of sustained VT
• Prophylactic antiarrhythmic therapy is not indicated for asymptomatic patients with isolated premature ventricular beats

overall prognosis of the patients [54]. The ESC HF guidelines, on the other hand, recommend that AICDs should be implanted in patients with good functional status and a life expectancy of over 1 year, in whom the intent is to increase survival. Moreover, they state that ACP is important and should take account of preferences for place of death and resuscitation, and may include deactivating of the AICD [21]. Indeed, the same guidelines do not recommend AICDs for patients in New York Health Association (NYHA) class IV with severe, drug-refractory, symptoms who are not transplantation candidates, as such patients have a very limited life expectancy and are more likely to die from pump failure rather than an arrhythmia. It is reasonable to apply similar recommendations to patients with advanced PAH–CHD, who are likely to die of congestive HF rather than arrhythmia. Moreover, implantation of the device and the use of sedation to test its efficacy can carry significant risks in PAH. For these reasons, currently few patients with PAH–CHD receive an AICD.

If an AICD is recommended, patients should be counselled on the purpose of the device and possible complications relating to implantation and function, including the risk of inappropriate shocks. In very advanced disease, deactivation of a patient's AICD (shock therapies) may be considered with the scope of preserving quality of life during the dying process, after appropriate discussion with the patients and family. An AICD deactivation policy has been proposed for patients with HF, which takes into account ethical considerations and informed consent.

Conclusions

PAH remains a life-threatening condition, despite advances in management. Palliative care has an important role in patients with advanced disease, aiding the PH clinicians to support the patients and their families and maintain an acceptable quality of life both in and out of the hospital. It is increasingly recognized that best care for PAH patients can only be provided through a collaborative, person-centred, multidisciplinary, partnership approach, and palliative care is an integral part.

Early and timely referral is the key to the successful integration of palliative care services in the delivery of care to patients with severe, advanced, deteriorating PAH. This aims to optimize the patient's QoL, while the PAH team continues with ongoing management of a challenging condition for which a cure has yet to be established. This symbiotic relationship between PAH and palliative care services, introduced in a timely manner during disease progression, will help to dispel myths and establish joint working between expert teams to maximize the patients' quality of life.

References

1. Dimopoulos K, Wort SJ, Gatzoulis MA (2014) Pulmonary hypertension related to congenital heart disease: a call for action. Eur Heart J 35:691–700
2. Manes A, Palazzini M, Leci E, Bacchi Reggiani ML, Branzi A, Galiè N (2013) Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: a comparison between clinical subgroups. Eur Heart J 35(11):716–724
3. Galiè N, Beghetti M, Gatzoulis MA, Granton J, Berger RMF, Lauer A, Chiossi E, Landzberg M, Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) Investigators (2006) Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. Circulation 114:48–54
4. Dimopoulos K, Inuzuka R, Goletto S, Giannakoulas G, Swan L, Wort SJ, Gatzoulis MA (2010) Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension. Circulation 121:20–25
5. Diller G-P, Alonso-Gonzalez R, Dimopoulos K, Alvarez-Barredo M, Koo C, Kempny A, Harries C, Parfitt L, Uebing AS, Swan L, Marino PS, Wort SJ, Gatzoulis MA (2013) Disease targeting therapies in patients with Eisenmenger syndrome: response to treatment and long-term efficiency. Int J Cardiol 167:840–847
6. World Health Organization. WHO definition of palliative care [Internet]. [cited 2016 Jun 26]. about:reader?url=http%3A%2F%2Fwww.who.int%2Fcancer%2Fpalliative%2Fdefinition%2Fen%2F
7. General Medical Council. Treatment and care towards the end of life: good practice in decision making [Internet]. [cited 2016 Jun 26]. http://www.gmc-uk.org/guidance/ethical_guidance/end_of_life_care.asp
8. Hoeper MM, Granton J (2011) Intensive care unit management of patients with severe pulmonary hypertension and right heart failure. Am J Respir Crit Care Med 184:1114–1124
9. Lindell KO, Liang Z, Hoffman LA, Rosenzweig MQ, Saul MI, Pilewski JM, Gibson KF, Kaminski N (2015) Palliative care and location of death in decedents with idiopathic pulmonary fibrosis. Chest 147:423–429
10. Elkington H, White P, Addington-Hall J, Higgs R, Edmonds P (2005) The healthcare needs of chronic obstructive pulmonary disease patients in the last year of life. Palliat Med 19:485–491
11. Grinnan DC, Swetz KM, Pinson J, Fairman P, Lyckholm LJ, Smith T (2012) The end-of-life experience for a cohort of patients with pulmonary arterial hypertension. J Palliat Med 15:1065–1070
12. PHA UK. emPHasis-10—Pulmonary hypertension professionals [Internet]. [cited 2016 Jun 26]. http://www.phprofessionals.org.uk/emphasis-10/
13. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M (2015) 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 37(1):67–119

14. The Gold Standards Framework Centre In End of Life Care CIC. Prognostic Indicator Guidance October 2011.pdf [Internet]. [cited 2016 Jun 26]. http://www.goldstandardsframework.org.uk/cd-content/uploads/files/General%20Files/Prognostic%20Indicator%20Guidance%20October%202011.pdf
15. Pattison M, Romer AL (2001) Improving care through the end of life: launching a primary care clinic-based program. J Palliat Med 4:249–254
16. Murray S, Boyd K (2011) Using the "surprise question" can identify people with advanced heart failure and COPD who would benefit from a palliative care approach. Palliat Med 25:382
17. Goggin J CTS Inspirations | Summer 2012 California Thoracic Society 2 End-of-Life Care Challenges in Chronic Lung Disease [Internet]. [cited 2015 Oct 31]. https://www.calthoracic.org/sites/default/files/pdfs/End-of-LifeCareChallenges_Goggin.pdf
18. Zimmermann C, Swami N, Krzyzanowska M, Hannon B, Leighl N, Oza A, Moore M, Rydall A, Rodin G, Tannock I, Donner A, Lo C (2014) Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. Lancet 383:1721–1730
19. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, Dahlin CM, Blinderman CD, Jacobsen J, Pirl WF, Billings JA, Lynch TJ (2010) Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 363:733–742
20. Tobler D, de Stoutz N, Greutmann M (2011) Supportive and palliative care for adults dying from congenital heart defect. Curr Opin Support Palliat Care 5:291–296
21. McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GYH, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, ESC Committee for Practice Guidelines (2012) ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 33:1787–1847
22. Leblanc JG (2009) Creating a global climate for pediatric cardiac care. World J Pediatr 5:89–92
23. McIlvennan CK, Allen LA (2016) Palliative care in patients with heart failure. BMJ 353:i1010
24. Boland JW, Reigada C, Yorke J, Hart SP, Bajwah S, Ross J, Wells A, Papadopoulos A, Currow DC, Grande G, Macleod U, Johnson MJ (2016) The adaptation, face, and content validation of a needs assessment tool: progressive disease for people with interstitial lung disease. J Palliat Med 19:549–555
25. Fenstad ER, Shanafelt TD, Sloan JA, Novotny PJ, Durst LA, Frantz RP, McGoon MD, Swetz KM (2014) Physician attitudes toward palliative care for patients with pulmonary arterial hypertension: results of a cross-sectional survey. Pulm Circ 4:504–510
26. Naeije R, Manes A (2014) The right ventricle in pulmonary arterial hypertension. Eur Respir Rev 23:476–487
27. Smallwood N, Le B, Currow D, Irving L, Philip J (2015) Management of refractory breathlessness with morphine in patients with chronic obstructive pulmonary disease. Intern Med J 45:898–904
28. Jennings AL, Davies AN, Higgins JP, Broadley K (2001) Opioids for the palliation of breathlessness in terminal illness. Cochrane Database Syst Rev 4:CD002066
29. Oxberry SG, Torgerson DJ, Bland JM, Clark AL, Cleland JGF, Johnson MJ (2011) Short-term opioids for breathlessness in stable chronic heart failure: a randomized controlled trial. Eur J Heart Fail 13:1006–1012
30. Johnson MJ, McDonagh TA, Harkness A, McKay SE, Dargie HJ (2002) Morphine for the relief of breathlessness in patients with chronic heart failure--a pilot study. Eur J Heart Fail 4:753–756
31. Galbraith S, Fagan P, Perkins P, Lynch A, Booth S (2010) Does the use of a handheld fan improve chronic dyspnea? A randomized, controlled, crossover trial. J Pain Symptom Manag 39:831–838
32. Goodlin SJ, Wingate S, Albert NM, Pressler SJ, Houser J, Kwon J, Chiong J, Storey CP, Quill T, Teerlink JR, PAIN-HF Investigators (2012) Investigating pain in heart failure patients: the pain assessment, incidence, and nature in heart failure (PAIN-HF) study. J Card Fail 18:776–783

33. Doehner W, Frenneaux M, Anker SD (2014) Metabolic impairment in heart failure: the myocardial and systemic perspective. J Am Coll Cardiol 64:1388–1400
34. Piepoli MF, Crisafulli A (2014) Pathophysiology of human heart failure: importance of skeletal muscle myopathy and reflexes. Exp Physiol 99:609–615
35. Freedland KE, Carney RM, Rich MW, Steinmeyer BC, Rubin EH (2015) Cognitive behavior therapy for depression and self-care in heart failure patients: a randomized clinical trial. JAMA Intern Med 175:1773–1782
36. Sullivan M, Levy WC, Russo JE, Spertus JA (2004) Depression and health status in patients with advanced heart failure: a prospective study in tertiary care. J Card Fail 10:390–396
37. Gottlieb SS, Kop WJ, Thomas SA, Katzen S, Vesely MR, Greenberg N, Marshall J, Cines M, Minshall S (2007) A double-blind placebo-controlled pilot study of controlled-release paroxetine on depression and quality of life in chronic heart failure. Am Heart J 153:868–873
38. Leadership Alliance for the Care of Dying, People (LACDP). One chance to get it right [Internet]. [cited 2016 Jun 26]. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/323188/One_chance_to_get_it_right.pdf
39. The National Institute for Health and Care Excellence (NICE). Care of dying adults in the last days of life | Guidance and guidelines | NICE [Internet]. [cited 2016 Jun 26]. https://www.nice.org.uk/guidance/ng31
40. Maciasz RM, Arnold RM, Chu E, Park SY, White DB, Vater LB, Schenker Y (2013) Does it matter what you call it? A randomized trial of language used to describe palliative care services. Support Care Cancer 21:3411–3419
41. Goodlin S. Palliative care for patients with advanced heart failure [Internet]. [cited 2016 Jun 26]. http://www.uptodate.com/contents/palliative-care-for-patients-with-advanced-heart-failure
42. Bernacki RE, Block SD, American College of Physicians High Value Care Task Force (2014) Communication about serious illness care goals: a review and synthesis of best practices. JAMA Intern Med 174:1994–2003
43. Fried TR, O'Leary JR (2008) Using the experiences of bereaved caregivers to inform patient- and caregiver-centered advance care planning. J Gen Intern Med 23:1602–1607
44. Heffner JE, Fahy B, Hilling L, Barbieri C (1996) Attitudes regarding advance directives among patients in pulmonary rehabilitation. Am J Respir Crit Care Med 154:1735–1740
45. Shannon SE, Long-Sutehall T, Coombs M (2011) Conversations in end-of-life care: communication tools for critical care practitioners. Nurs Crit Care 16:124–130
46. Back AL, Arnold RM, Quill TE (2003) Hope for the best, and prepare for the worst. Ann Intern Med 138:439–443
47. Goodlin SJ (2009) Palliative care in congestive heart failure. J Am Coll Cardiol 54:386–396
48. Janssen DJA, Spruit MA, Schols JMGA, Cox B, Nawrot TS, Curtis JR, Wouters EFM (2012) Predicting changes in preferences for life-sustaining treatment among patients with advanced chronic organ failure. Chest 141:1251–1259
49. Reinke LF, Engelberg RA, Shannon SE, Wenrich MD, Vig EK, Back AL, Curtis JR (2008) Transitions regarding palliative and end-of-life care in severe chronic obstructive pulmonary disease or advanced cancer: themes identified by patients, families, and clinicians. J Palliat Med 11:601–609
50. Swetz KM, Shanafelt TD, Drozdowicz LB, Sloan JA, Novotny PJ, Durst LA, Frantz RP, McGoon MD (2012) Symptom burden, quality of life, and attitudes toward palliative care in patients with pulmonary arterial hypertension: results from a cross-sectional patient survey. J Heart Lung Transplant 31:1102–1108
51. McKenna SP, Ratcliffe J, Meads DM, Brazier JE (2008) Development and validation of a preference based measure derived from the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) for use in cost utility analyses. Health Qual Life Outcomes 6:65
52. London Cancer Alliance, PAllE8, Marie Curie. A review of specialist palliative care provision and access across London—london-spc-provision-report.pdf [Internet]. [cited 2016 Jun 26]. https://www.mariecurie.org.uk/globalassets/media/documents/research/london-spc-provision-report.pdf

53. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, del Nido P, Fasules JW, Graham TP Jr, Hijazi ZM, Hunt SA, King ME, Landzberg MJ, Miner PD, Radford MJ, Walsh EP, Webb GD, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Buller CE, Creager MA, Ettinger SM, Halperin JL, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Page RL, Riegel B, Tarkington LG, Yancy CW, American College of Cardiology, American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease), American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons (2008) ACC/AHA 2008 guidelines for the management of adults with congenital heart disease. J Am Coll Cardiol 52:e143–e263
54. Baumgartner H, Bonhoeffer P, De Groot NMS, de Haan F, Deanfield JE, Galie N, Gatzoulis MA, Gohlke-Baerwolf C, Kaemmerer H, Kilner P, Meijboom F, Mulder BJM, Oechslin E, Oliver JM, Serraf A, Szatmari A, Thaulow E, Vouhe PR, Walma E (2010) ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J 31:2915–2957

PAH in ACHD: Research, Global Perspective and Future Prospects. An Epilogue

24

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Abbreviations

ACHD	Adult congenital heart disease
CHD	Congenital heart disease
PAH	Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) has received incremental attention over the past two decades from the medical profession, health administrators, patient associations and pharmaceutical industry. The design and completion of numerous multicentre randomized controlled trials and the development of new compounds have led to enhanced survival prospects and improved quality of life for patients with PAH. However, the majority of these randomized controlled studies have excluded patients with Eisenmenger syndrome, namely, those with severe PAH related to bidirectional or right-to-left congenital heart shunts. Due to similarities with idiopathic PAH, PAH in patients with congenital heart disease (PAH–CHD) and previous reparative surgery were the only adult congenital heart disease (ACHD) subgroup to be included in major PAH trials. This subgroup, however, represents a small proportion

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of patients in large PAH studies (typically less than 10% of the total population enrolled). Despite some progress in recent years, it is necessary to invest further in clinical research and collaboration between expert ACHD centres and address areas of controversy and lack of evidence in PAH-CHD.

Significant advances in our understanding and management of PAH-CHD have occurred since 1897, when Viktor Eisenmenger first described a typical example of the syndrome that would later bear his name: a detailed anatomical and clinical account of a man with cyanosis and a ventricular septal defect presenting with heart failure and dying of hemoptysis. However, there are still numerous questions to be addressed [1, 2]. Firstly, we need robust data on the epidemiology of PAH-CHD. For instance, the exact number of patients with Eisenmenger syndrome worldwide remains unknown [3]. Previous studies have based the diagnosis on echocardiography and included patients from previous eras, when early reparative or palliative surgery of congenital cardiac disease was not always available. This may still be applicable in some parts of the developing world, but it is not the case in most developed countries. Moreover, little is known about the natural history and appropriate management of paediatric patients with PAH–CHD, who have been reported to have a far worse outcome compared to their adult counterparts [4]. Research is also required into understanding how best to functionally assess patients with Down syndrome, who at present, constitute a significant proportion of the Eisenmenger syndrome cohort (up to a third is some series) [5].

Although current guidelines and recommendations have defined criteria for shunt closure in patients with net left-to-right shunting and PAH, a significant grey area of uncertainty remains [6]. There are unresolved issues, such as the management of patients with borderline pulmonary vascular resistance at rest, the long-term implications and prognostic relevance of reversibility studies using pulmonary vasodilators for the purpose of assessing operability, and the use of a staged treatment approach, e.g. partial defect closure with one-way flaps or a small fenestration to act as a "pop-off" valve. Critically, the decision for intervening and closing a defect should not be based solely on procedural feasibility or other technical aspects, as such a decision may compromise the long-term prospects for these patients by converting the disease into a more aggressive and malignant form of PAH. We submit that patients with PAH and left-to-right shunts need to be followed in tertiary academic centres, with experience the use of PAH therapies and the management of borderline cases, and where patients can be included in long-term follow-up clinical studies or international registries. Patients with PAH–CHD and left-to-right shunts should only undergo defect repair, if a clear and long-standing benefit from such intervention can be expected. The exact circumstances in which this can be sufficiently guaranteed are currently uncertain, and both surgical and catheter therapies may have long-term detrimental effects. Moreover, indications for a "treat-and-repair" approach in this population (i.e. to treat patients with PAH-specific therapy and, if they respond well, consider defect closure) are based on expert opinion, and there is no substantive evidence to support this approach at present [7].

The response of the pulmonary vascular bed to similar haemodynamic stimuli varies between patients, which implies a different underlying predisposition to pulmonary vascular disease relating to, as yet, unknown genetic factors [5]. This is also

supported by the different phenotype and natural history of PAH in patients with Down syndrome and those with PAH–CHD in the presence of an atrial septal defect [8]. Some patients develop PAH later on in life, even after timely early childhood repair of a defect and the absence of significant residual haemodynamic lesions (e.g. PAH in the setting of repaired transposition of the great arteries). Much work is needed to understand the genetic and molecular mechanisms underlying the development of PAH, both in CHD and other types of disease, leading to a common endpoint of histologically deranged pulmonary vascular bed. Therefore, there is a need for closer collaboration between CHD and PAH physicians and geneticists/epidemiologists towards this end, with inclusion of PAH–CHD patients in national and international registries and detailed genotypic/phenotypic characterization.

The traditional belief that survival prospects are far superior in PAH-CHD compared to other PAH aetiologies has not been supported by recent studies [9, 10]. There is now evidence that, at least patients at the extreme end of the spectrum of PAH–CHD, namely patients with Eisenmenger syndrome, respond well and safely to PAH-specific therapy and improve their haemodynamics, 6-min walking test distance, functional class and survival prospects [11]. It is, therefore, appropriate to treat these patients proactively, similar to patients with idiopathic PAH. Although the positive impact of disease-targeting therapies in PAH–CHD is now widely recognized, there are areas of uncertainty, such as the timing of initiation of medical therapy, the indications and optimal use of combination medical therapy (upfront versus sequential), the administration of parenteral prostanoids and the potential use of novel treatments based on alternative pathophysiology pathways, known to be prominent in PAH-CHD (e.g. inflammation). Furthermore, the efficacy of disease-targeting therapies in PAH–CHD with a net left-to-right shunt remains unclear: administration of targeted PAH therapies with the scope of increasing pulmonary blood flow in patients in whom this is already high due to the shunt may appear counterintuitive and may even accelerate the progression of pulmonary vascular disease. Hence, physicians remain somewhat hesitant to treat such patients, although data from the Bologna pulmonary hypertension (PH) group suggest that they do respond well to PAH-specific therapy, in an intention-to-treat protocol. Other unexplored areas are the administration of targeting therapies in patients with complex disease, such as those with univentricular heart and PAH, and in patients with segmental PH, as these patients have been excluded from major trials thus far [12].

It is unclear to date whether PAH–CHD patients should be treated with a goal-oriented strategy (as has been proposed for idiopathic PAH) and what these treatment targets should be. The optimal use of antiplatelet and oral anticoagulation therapy in Eisenmenger patients, who are prone to both thrombosis and bleeding, also remains unknown [13]. Further data are needed to establish the role of physical rehabilitation and exercise prescription, iron supplementation, long-term oxygen therapy, etc. [14] Finally, it remains unclear which clinical endpoints should be used in trials on PAH–CHD and especially in adult patients with Eisenmenger syndrome [15]. In fact, the relative stability of adults with Eisenmenger syndrome, who may live for several decades after diagnosis, makes hard endpoints, such as mortality or morbidity, difficult to implement in such an uncommon disease. There is, therefore, a need for closer collaboration between PAH–CHD centres to

establish multicentre collaborations and facilitate randomized trials, overcoming limitations in sample size. All efforts should be made to obtain adequate funding from national and international bodies to support such endeavours. Finally, in line with the idiopathic PAH paradigm, additional endpoints, beyond exercise capacity, that reflect clinical changes should be agreed and validated, such as quality of life and overall prognosis [16].

Lately, the utilization of PAH-specific therapies in populations beyond the Eisenmenger complex has gained increased interest. Indeed, a large patient group, which remains untreated, is the Fontan population. These patients, strictly speaking, do not meet criteria for PAH. However, recent evidence has suggested an abnormal vascular bed in the Fontan circulation, with low cardiac output and increased pulmonary vascular resistance, which in theory could be modulated by PAH-specific therapy. Although recent randomized controlled trials have shown that bosentan or other pulmonary vasodilators have small but significant beneficial effects on important cardiopulmonary measures [17], there is still uncertainty, and future research is needed in order to identify which Fontan patients are true responders and whether earlier than later treatment may maximize efficacy.

There are inherent difficulties in performing randomized controlled trials in the field of PAH-CHD in order to overcome areas of controversy and lack of evidence. Blinding can be difficult, and it is not clear how such trials can be funded, unless a strong case for greater cost-effectiveness against the standard treatment can be made or industry develops an interest. Therefore, a need arises to perform collaborative clinical research between specialist centres, organize international registries and strengthen expert opinion and consensus.

It is paramount for PAH-CHD patients to be followed in tertiary centres and benefit from a multidisciplinary approach, including areas such as complex electrophysiology, anaesthesia, gynaecology, haematology, high-risk obstetrics, dentistry, etc. [18]. The improvement in referral patterns will lead to diminishing numbers of patients who are lost to follow-up or present late with advanced disease, while closer collaboration between CHD and PAH centres can improve the clinical outcome of this population. Patients who are lost to follow-up globally should be brought back to tertiary care and offered PAH-specific therapy, when in functional class III or greater. Inappropriate practices of the past, such as routine venesections and absolute exercise restriction, should be abandoned. Education in ACHD and specifically in the field of PAH is a key task [19]. There is, clearly, a need for wider engagement, including education on PAH–CHD for a broader healthcare professional audience, with direct links to tertiary centres to achieve optimal patient care in this complex area, minimizing risks through safety mechanisms and avoidance of pitfalls.

One of the future aims for PAH–CHD physicians and policymakers should be a coordinated effort in support of developing countries. This can be achieved through greater allocation of resources and the collaboration and support of international bodies and the PAH–CHD community worldwide, aiming at better awareness and improved diagnosis, followed by wider availability and affordability of PAH therapies.

Medical and scientific research in this field in the past few years has gradually become globalized, inclusive and collaborative. Looking ahead, national and

Table 24.1 Future global prospects in the field of PAH associated with CHD

Provide early diagnosis and timely repair of congenital heart lesions that are prone to PAH development, especially in developing countries (thus, preventing the development of PAH)
Improve transition patterns in tertiary centres from paediatric care
Patients lost to follow-up should be brought back into expert care and offered PAH-specific therapy, when in functional class III or greater
Develop registries/genetic databases in order to elucidate the pathophysiologic mechanisms (e.g. patients who develop PAH late despite early intervention)
Organize multicentre collaboration between centres of excellence in developed countries and improve infrastructure in developing countries
Organize collaboration and alliance between research organizations and scientific societies that share common interests
Support the development of national/international registries (e.g. on anticoagulation and haemoptysis in Eisenmenger patients, parenteral prostanoids in PAH–CHD, etc.)
Study pathophysiology pathways (e.g. inflammation) with the view to develop novel therapeutic modules
Encourage the design of multicentre randomized trials with novel hypotheses/targets (e.g. early treatment of Eisenmenger syndrome, the potential role of supplemental oxygen, targeted PAH therapy in the Fontan population)

international registries should provide a better understanding of the epidemiology, genetics, natural history and therapeutic outcomes of what is a very heterogeneous PAH population (Table 24.1). Registries should focus on areas, such as safety and efficacy of anticoagulation, pregnancy, management of patients with shunts and mild or moderately elevated pulmonary vascular resistance and long-term assessment of the "treat-and-repair" approach in carefully selected subgroups. Finally, we urge that randomized controlled trials assessing the benefits of PAH-specific therapy should now be extended to less symptomatic Eisenmenger patients, to those with "pre-Eisenmenger physiology" (i.e. PAH–CHD patients with a large communication, severe PAH but no cyanosis) and those with a Fontan circulation. A standardized assessment approach for PAH-CHD and Eisenmenger syndrome, as presented herewith and in international guidelines, should be applied widely and validated prospectively, so that more patients may benefit and reach their full life potential.

References

1. Kempny A, Fernández-Jiménez R, Tutarel O, Dimopoulos K, Uebing A, Shiina Y et al (2013) Meeting the challenge: the evolving global landscape of adult congenital heart disease. Int J Cardiol 168(6):5182–5189
2. Gatzoulis MA, Beghetti M, Landzberg MJ, Galiè N (2014) Pulmonary arterial hypertension associated with congenital heart disease: recent advances and future directions. Int J Cardiol 177(2):340–347

3. Gatzoulis MA, Alonso-Gonzalez R, Beghetti M (2009) Pulmonary arterial hypertension in paediatric and adult patients with congenital heart disease. Eur Respir Rev 18(113):154–161
4. Ivy DD, Abman SH, Barst RJ, Berger RM, Bonnet D, Fleming TR et al (2013) Pediatric pulmonary hypertension. J Am Coll Cardiol 62(25 Suppl):D117–D126
5. Dimopoulos K, Wort SJ, Gatzoulis MA (2014) Pulmonary hypertension related to congenital heart disease: a call for action. Eur Heart J 35(11):691–700
6. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A et al (2013) Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 62(25 Suppl):D34–D41
7. Dimopoulos K, Peset A, Gatzoulis MA (2008) Evaluating operability in adults with congenital heart disease and the role of pretreatment with targeted pulmonary arterial hypertension therapy. Int J Cardiol 129(2):163–171
8. Dimopoulos K, Giannakoulas G, Wort SJ, Gatzoulis MA (2008) Pulmonary arterial hypertension in adults with congenital heart disease: distinct differences from other causes of pulmonary arterial hypertension and management implications. Curr Opin Cardiol 23(6):545–554
9. Diller GP, Kempny A, Inuzuka R, Radke R, Wort SJ, Baumgartner H et al (2014) Survival prospects of treatment naïve patients with Eisenmenger: a systematic review of the literature and report of own experience. Heart 100(17):1366–1372
10. Manes A, Palazzini M, Leci E, Bacchi Reggiani ML, Branzi A, Galiè N (2014) Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: a comparison between clinical subgroups. Eur Heart J 35(11):716–724
11. Dimopoulos K, Inuzuka R, Goletto S, Giannakoulas G, Swan L, Wort SJ et al (2010) Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension. Circulation 121(1):20–25
12. Schuuring MJ, Bouma BJ, Cordina R, Gatzoulis MA, Budts W, Mullen MP et al (2013) Treatment of segmental pulmonary artery hypertension in adults with congenital heart disease. Int J Cardiol 164(1):106–110
13. Giannakoulas G, Boutsikou M (2015) The Gordian knot of thromboembolism in congenital heart disease. Heart 101(19):1523–1524
14. Giannakoulas G, Dimopoulos K (2010) Exercise training in congenital heart disease: should we follow the heart failure paradigm? Int J Cardiol 138(2):109–111
15. Dimopoulos K (2008) Trials and tribulations in adult congenital heart disease. Int J Cardiol 129:160–162
16. Giannakoulas G, Mouratoglou SA, Gatzoulis MA, Karvounis H (2014) Blood biomarkers and their potential role in pulmonary arterial hypertension associated with congenital heart disease. A systematic review. Int J Cardiol 174(3):618–623
17. Hebert A, Mikkelsen UR, Thilen U, Idorn L, Jensen AS, Nagy E et al (2014) Bosentan improves exercise capacity in adolescents and adults after Fontan operation: the TEMPO (Treatment With Endothelin Receptor Antagonist in Fontan Patients, a Randomized, Placebo-Controlled, Double-Blind Study Measuring Peak Oxygen Consumption) study. Circulation 130(23):2021–2030
18. Diller GP, Kempny A, Piorkowski A, Grübler M, Swan L, Baumgartner H et al (2014) Choice and competition between adult congenital heart disease centers: evidence of considerable geographical disparities and association with clinical or academic results. Circ Cardiovasc Qual Outcomes 7(2):285–291
19. Gatzoulis MA (2006) Adult congenital heart disease: education, education, education. Nat Clin Pract Cardiovasc Med 3(1):2–3