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

Lorna Swan · Alexandra A. Frogoudaki
Editors

Heart Failure 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

Series Editors

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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.

More information about this series at http://www.springer.com/series/13454

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Heart Failure in Adult Congenital Heart Disease

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To our families, our teachers and our patients who show us the true values needed to practice good medicine and journey in life.

Lorna Swan
Alexandra A. Frogoudaki

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.

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Münster, Germany — Helmut Baumgartner
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Foreword

The care of children with congenital heart disease (CHD) has been one of the greatest success stories of cardiovascular medicine and surgery of the twentieth century. As a result, the number of adults with congenital heart disease has grown exponentially. In parallel, there are more patients with complex congenital heart disease, who with much improved care now survive to adulthood.

Although patients have benefited a great deal from these advances, many of them will require one or more re-interventions (catheter and or surgical) and late complications such as arrhythmias, heart failure and pulmonary hypertension are common. The spectrum of anatomic substrate, the range of cardiovascular physiology, and the dynamic and continuously evolving nature of catheter and surgical interventions both at presentation and thereafter means that adults with congenital heart disease represent a very heterogeneous patient population that clearly requires tertiary expertise and a multi-disciplinary environment. Furthermore, standard therapies for patients with heart failure due to ischemic or dilated cardiomyopathy are not directly applicable to adult patients with CHD. Further research and better understanding are, therefore, paramount in these areas of late complications.

The textbook *Heart Failure in Adult Congenital Heart Disease* edited by Lorna Swan and Alexandra A. Frogoudaki addresses this topical subject. The two editors, from London and Athens, have brought together authorities and leaders in their respective fields to contribute to this effort. The definition, pathophysiology and diagnosis are firstly discussed. There are chapters on risk stratification and prognosis, co-morbidities and in specific ACHD conditions such as single ventricle physiology, systemic right ventricle and pulmonary arterial hypertension. Chapters regarding treatment including catheter intervention, surgery, drug therapy, device management and transplantation are included. Last but not least, there are chapters on holistic care and palliation for ACHD and on future research directions.

The book by Drs. Swan and Frogoudaki will serve as an important aid to all involved in the care of ACHD patients. Furthermore, knowledge gaps identified herewith should stimulate and lead to future research. Clearly we have more work to do before every single patient with CHD born anywhere in the world can reach their full life potential.

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Preface

The field of adult congenital heart disease (ACHD) stands on the edge of a new era. The journey before this point has been focused on optimising neonatal and childhood surgery, understanding haemodynamics and benefiting from new technologies particularly in the realm of cardiac imaging.

This next era will be dominated by heart failure and arrhythmia—the two most common long-term complications and an inevitable outcome for many ageing ACHD patients.

Unfortunately, the ACHD clinician has few tools, in terms of evidence-based therapies, to meet this new challenge. There are, however, a vast number of opportunities to gain fresh insight into ACHD HF and in turn acquired HF. Patients with ACHD demonstrate unique models of extreme physiology—be that chronic volume loading, abnormal intravascular pressures or chronic cyanosis. Careful investigation of these models will bring fresh understanding to the wider fields of acute and chronic HF management.

This book aims to summarise our current understanding of ACHD HF and explore the unknowns in this field. It focuses in detail on the multiple causes of HF and their pathophysiology. It also underlines the significance of prognostic assessment and of co-morbidities, as every ACHD patient is unique and should be addressed individually. Particular reference is made to those areas where extreme physiology presents unique causes of HF such as the failing Fontan and the systemic right ventricle. The later section discusses the many potential treatment options for these patients. Finally the emphasis is placed on the key future research avenues that should be investigated over the next decade.

ACHD clinicians and ACHD patients have the opportunity to form innovative clinical partnerships to explore this new era—embracing all its challenges and further journeying along this exciting path of congenital heart disease.

London, UK — Lorna Swan
Athens, Greece — Alexandra A. Frogoudaki

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Part I

Heart Failure in ACHD

1 Incidence and Prevalence of Heart Failure in Adults with Congenital Heart Disease

Gerhard-Paul Diller

1.1 Introduction

The population of adults with congenital heart disease (ACHD) is constantly growing in developed countries. This is a testimony to past and current advances in the fields of cardiac surgery and cardiology. In the current era, it is estimated that well over 85–90% of children born with various forms of congenital heart disease will survive childhood and reach adulthood [1]. Even today, the number of adults with congenital heart disease outnumbers children with the condition in Western countries. Moreover, it has been suggested that the number of ACHD patients will further increase by approximately 60% per decade [2]. This leads to a constant growth of the ACHD population at risk for complications, including HF. Unfortunately, despite all progress, ACHD patients are—by and large—not cured and continue to be afflicted by lifelong complications. Leading long-term medical problems are arrhythmias, need for interventions and reoperations, pulmonary hypertension, extracardiac complications, and especially HF. This chapter focuses on epidemiology of HF in ACHD patients, highlighting subgroups of patients at particular risk of HF and attempting to prognosticate future challenges.

1.2 Definition of Heart Failure, Prevalence, and Incidence

As HF represents the end-stage condition in most diseases of the cardiac system, it is not surprising that it is also a major complication in ACHD patients. However, delineating the exact prevalence/incidence is dependent on the exact definition of

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HF used. Over time, numerous **definitions of HF** have been suggested. For the scope of this overview, the definition proposed by Poole-Wilson (1985) is favored. Accordingly, HF is defined as a "clinical syndrome caused by an abnormality of the heart and recognized by a characteristic pattern of haemodynamic, renal, neural and hormonal responses" [3]. This definition accounts for the fact that HF may be multifactorial and not necessarily linked to low cardiac output or depressed systolic ventricular function in isolation.

The **prevalence** of HF describes the number of patients with the condition at any given point in time or across the entire life-span. Estimates of the point prevalence are normally straightforward to obtain as cross-sectional studies suffice to describe the proportion of subjects with the condition at the time of data acquisition. Estimating lifetime prevalence of HF is more challenging as a complete temporal overview of the patient's medical history is usually not available. In the setting of ACHD-related HF, it is reasonable to assume that documentation of a diagnosis of HF late in life or at death can serve as a useful surrogate for HF across lifetime. This is due to the fact that HF risk increases steadily throughout life in ACHD patients and HF represents a chronically progressive disease not usually cured by interventions (although symptoms may resolve) [4].

Incidence of HF relates to the number of new cases in a given period of time. It normally requires access to longitudinal data and is therefore more difficult to calculate compared to estimates of point prevalence. While prevalence provides important insights into the current burden of disease and can guide resource allocation, knowledge of HF incidence across the spectrum of congenital heart disease, stratified by age, gives important clues for future planning of service provision.

1.3 Scope of the Problem

The general prevalence of HF in European countries (associated with the European Society of Cardiology—total population of approx. 900 million) is estimated at 15 million cases [5]. For the United States, it is suspected that approximately six million people suffer from HF [6]. In acquired heart disease, the prevalence of the condition increases sharply with age. Overall, 6–8% of persons over the age of 80 years are expected to present with HF [7]. A recent report suggests that the incidence of HF among the elderly is decreasing, while an increasing number of younger persons develop the condition [8]. This shift in the age at onset is most likely related to increasing numbers of patients with cardiovascular risk factors (such as diabetes mellitus, obesity) as well as congenital heart disease in the current era. Interestingly, the number of patients with incident HF below 50 years of age increased from 3% in 1995 to 6% in 2012 [8]. In contrast to acquired heart disease, the number of ACHD patients with HF is much lower, but it is growing rapidly both in numbers and complexity.

By definition, almost all ACHD patients present with an underlying cardiac abnormality. Signs and symptoms of HF are also common in this population. Piran and co-workers, for example, have reported that the lifetime prevalence of signs and

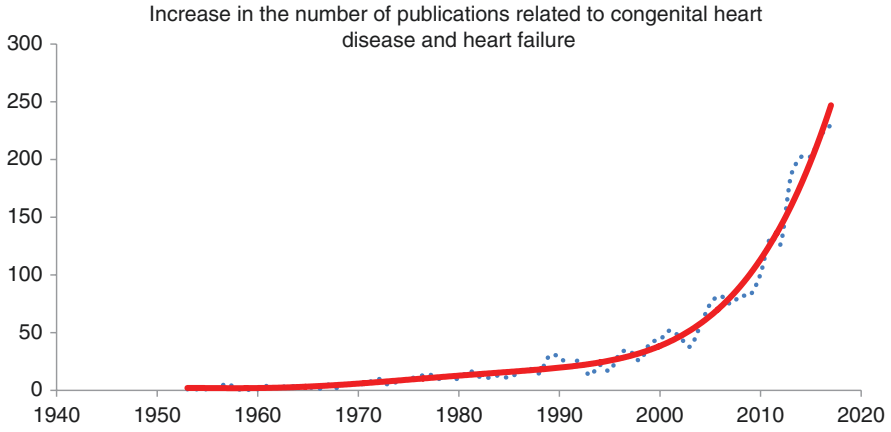

Fig. 1.1 Publications referring to "congenital heart disease" and "heart failure" based on PubMed database query

symptoms of HF is 22% in patients with complete transposition of the great arteries (TGA), 32% in congenitally corrected TGA patients, and up to 40% in patients with functionally univentricular hearts post-Fontan palliation [9]. Neurohormonal derangement and immune inflammatory patterns typical of HF are also commonly seen in ACHD patients [10, 11]. Many ACHD patients, thus, fulfill the conventional criteria for HF. Not surprisingly, HF is increasingly recognized as a major healthcare issue in ACHD patients. The number of publications investigating HF has increased exponentially over the last few decades (see Fig. 1.1, with a shift from pediatric to adult HF), and end-stage HF is rapidly becoming the leading cause of mortality in this vulnerable population [12].

Studies assessing causes of mortality in ACHD provide important insights into the prevalence of HF. As usually only the main or direct cause of death is recorded, these data likely underestimate the true HF burden in this population. However, the data provides useful minimal estimates of the expected HF prevalence. Based on a large nationwide Finnish dataset of 6024 patients who survived the corrective initial operation for congenital heart disease and were followed up to 45 years postoperatively, Nieminen and colleagues reported that 39.9% of the late deaths in ACHD patients were related to HF. As noted above, even this likely underestimated the true prevalence of the condition as some patients who died due to sudden cardiac death or perioperatively may in fact have had HF as an additional underlying condition [13]. HF was the leading cause of death in patients with transposition of the great arteries, univentricular hearts, ductus arteriosus, and atrial and ventricular septal defects. Similarly, Oechslin et al. investigated 2609 ACHD patients assessed at a specialty clinic. Of these, 199 patients deceased at a mean age of 37 years. HF accounted for 21% of deaths in this investigation [14]. In this study HF was the leading mechanism of death for patients with atrioventricular septal defect and complete transposition of the great arteries. Based on data from the Dutch CONCOR registry, 26% of ACHD patients died due to

chronic HF at an average age 51 years. Main predictors of HF-related mortality were a history of arrhythmias, endocarditis, myocardial infarction, as well as systemic and pulmonary hypertension. HF was identified as a particular problem in patients with univentricular hearts, systemic right ventricle, tetralogy of Fallot, and atrioventricular septal defect [15]. A recent study based on the German National Registry for congenital heart disease confirmed previous findings while also providing temporal insights into HF-related mortality in ACHD. Over the study period from 2001 to 2015, the prevalence of HF-related deaths increased from 23 to 30%. This increase is likely related to an aging population coupled with increasing complexity of disease. HF was identified as a major cause of mortality in patients with Eisenmenger syndrome, univentricular hearts, systemic right ventricles, and Ebstein's anomaly [16].

A study based on the patient population under follow-up at the Royal Brompton Hospital, London, included 6969 adult patients (mean age 30 years) under follow-up between 1991 and 2013. Causes of death were ascertained from official death certificates. Not unexpectedly, leading causes of death were chronic HF, sudden cardiac death, and extracardiac causes of mortality, while perioperative ACHD mortality was low. Mortality increased over time, and especially HF-related deaths increase dramatically as ACHD patients aged. The highest mortality rates were noted in patients with complex congenital heart disease, Fontan physiology, and Eisenmenger syndrome.

Figure 1.2 illustrates the dramatic increase in HF-related mortality in this population, while, for example, sudden cardiac death seems to be relatively unaffected by the aging patient group [12].

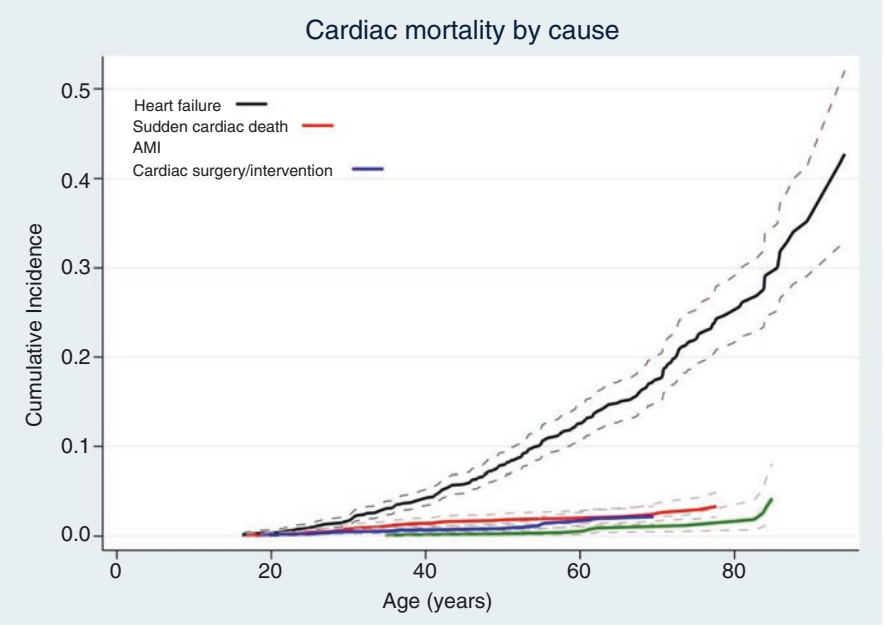

Fig. 1.2 Exponential increase in heart failure-related cardiac mortality by age compared to other modes of mortality

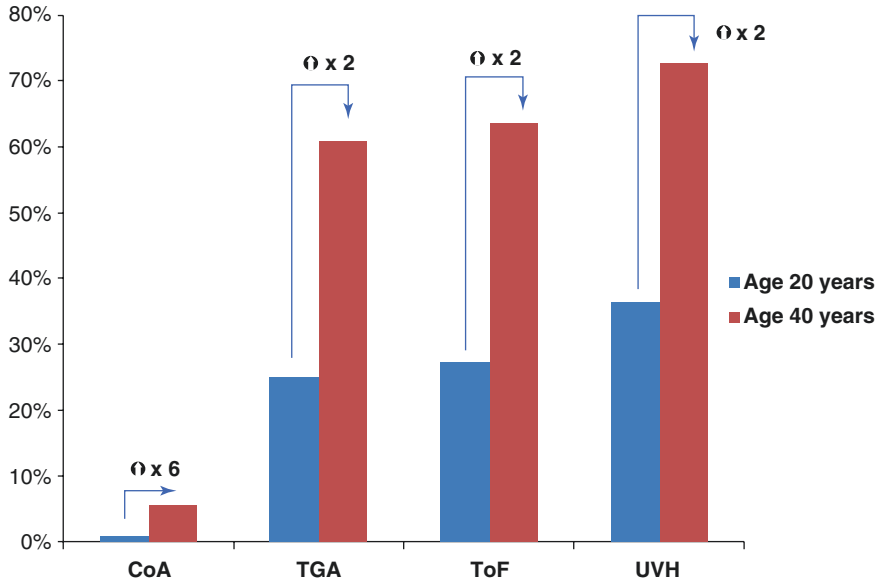

Fig. 1.3 Change in prevalence of heart failure in patients with aortic coarctation (CoA), transposition of the great arteries (TGA), tetralogy of Fallot (ToF), and univentricular hearts (UVH) between patient age 20 and 40. Data based on Norozi et al. 2006 (see text for details)

Limited data is available on the exact incidence of HF in different patient subgroups. Norozi and colleagues reported on 345 ACHD patients assessed between 2003 and 2004 (Fig. 1.3). The prevalence of HF increased with age in all studied diagnostic subgroups suggesting a high incidence of new-onset HF in this population [17]. The highest risk of developing HF was related to a diagnosis of a univentricular heart, transposition of the great arteries, and tetralogy of Fallot.

HF-related hospitalization data has been reported both from the Netherlands and the United States. While it may provide some indication on the approximate incidence of the condition, this type of data is biased by the fact that not all patients are admitted for the first time related to HF and not all HF episodes require inpatient therapy [18, 19]. Zomer et al. reported an incidence of first HF admission of 1.2 per 1000 patient-years. Risk factors for HF admissions were a diagnosis of a univentricular heart (odds ratio 11), transposition of the great arteries (odds ratio 5), atrioventricular septal defect (odds ratio 3), and tetralogy of Fallot (odds ratio 2). In addition to underlying cardiac diagnosis, the presence of multiple defects, previous surgery, and pacemaker implantation in childhood were linked to higher risk of HF. Furthermore, admissions for HF were significantly related to worse outcome in this population.

1.4 Summary and Outlook

Available data suggests that HF is common in ACHD with a life prevalence of at least 30% in most patients with complex underlying diagnoses, represents one of the two leading causes of death in this population, and continues to increase as

patients age. As more patients with complex heart disease survive to older age and there is a general increase in the ACHD population, HF is likely to become epidemic in this population. From an epidemiologic perspective, continued efforts are required to better delineate the incidence of HF in various age groups and across the spectrum of ACHD. In addition, existing—in part historic—data may not fully reflect the current needs of ACHD patients, particularly those who underwent surgical correction earlier in life or in the current era with better myocardial protection and improved surgical expertise. In addition, the advent of interventional techniques may allow for early hemodynamic correction, avoiding some of the reported long-term complications, including HF. As a consequence, joint efforts to collect data on HF incidence and prevalence in contemporary ACHD patients are required. This could be based on national or international registries or on large administrative datasets. Improved identification of patients at risk, early detection, and hopefully the advent of new therapeutic options are urgently required to avoid a catastrophic increase in HF-related morbidity and mortality in this population.

References

1. Moons P, Bovijn L, Budts W, Belmans A, Gewillig M. Temporal trends in survival to adulthood among patients born with congenital heart disease from 1970 to 1992 in Belgium. Circulation. 2010;122(22):2264–72.
2. Marelli AJ, Ionescu-Ittu R, Mackie AS, Guo L, Dendukuri N, Kaouache M. Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. Circulation. 2014;130(9):749–56.
3. Poole-Wilson PA, Buller NP. Causes of symptoms in chronic congestive heart failure and implications for treatment. Am J Cardiol. 1988;62(2):31A–4A.
4. Hunt SA, American College of Cardiology, American Heart Association Task Force on Practice Guidelines. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (writing committee to update the 2001 guidelines for the evaluation and Management of Heart Failure). J Am Coll Cardiol. 2005;46(6):e1–82.
5. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail. 2008;10(10):933–89.
6. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. Circulation. 2014;129(3):e28–e292.
7. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham study. J Am Coll Cardiol. 1993;22(4 Suppl A):6A–13A.
8. Christiansen MN, Kober L, Weeke P, Vasan RS, Jeppesen JL, Smith JG, et al. Age-specific trends in incidence, mortality, and comorbidities of heart failure in Denmark, 1995 to 2012. Circulation. 2017;135(13):1214–23.
9. Piran S, Veldtman G, Siu S, Webb GD, Liu PP. Heart failure and ventricular dysfunction in patients with single or systemic right ventricles. Circulation. 2002;105(10):1189–94.

10. Bolger AP, Sharma R, Li W, Leenarts M, Kalra PR, Kemp M, et al. Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease. Circulation. 2002;106(1):92–9.
11. Sharma R, Bolger AP, Li W, Davlouros PA, Volk HD, Poole-Wilson PA, et al. Elevated circulating levels of inflammatory cytokines and bacterial endotoxin in adults with congenital heart disease. Am J Cardiol. 2003;92(2):188–93.
12. Diller GP, Kempny A, Alonso-Gonzalez R, Swan L, Uebing A, Li W, et al. Survival prospects and circumstances of death in contemporary adult congenital heart disease patients under follow-up at a Large Tertiary Centre. Circulation. 2015;132(22):2118–25.
13. Nieminen HP, Jokinen EV, Sairanen HI. Causes of late deaths after pediatric cardiac surgery: a population-based study. J Am Coll Cardiol. 2007;50(13):1263–71.
14. Oechslin EN, Harrison DA, Connelly MS, Webb GD, Siu SC. Mode of death in adults with congenital heart disease. Am J Cardiol. 2000;86(10):1111–6.
15. Verheugt CL, Uiterwaal CS, van der Velde ET, Meijboom FJ, Pieper PG, van Dijk AP, et al. Mortality in adult congenital heart disease. Eur Heart J. 2010;31(10):1220–9.
16. Engelings CC, Helm PC, Abdul-Khaliq H, Asfour B, Bauer UM, Baumgartner H, et al. Cause of death in adults with congenital heart disease—an analysis of the German National Register for congenital heart defects. Int J Cardiol. 2016;211:31–6.
17. Norozi K, Wessel A, Alpers V, Arnhold JO, Geyer S, Zoege M, et al. Incidence and risk distribution of heart failure in adolescents and adults with congenital heart disease after cardiac surgery. Am J Cardiol. 2006;97(8):1238–43.
18. Rodriguez FH III, Moodie DS, Parekh DR, Franklin WJ, Morales DL, Zafar F, et al. Outcomes of heart failure-related hospitalization in adults with congenital heart disease in the United States. Congenit Heart Dis. 2013;8(6):513–9.
19. Zomer AC, Vaartjes I, van der Velde ET, de Jong HM, Konings TC, Wagenaar LJ, et al. Heart failure admissions in adults with congenital heart disease; risk factors and prognosis. Int J Cardiol. 2013;168(3):2487–93.

2 Pathophysiology and Causes of Heart Failure in Adult Congenital Heart Disease

Alexandra A. Frogoudaki

2.1 Introduction

Early diagnosis and improvements in cardiac surgery and interventional cardiology have resulted in unprecedented survival of patients with congenital heart disease (CHD), even those with the most complex lesions. Despite remarkable success in treatments, many interventions are palliative rather than curative, and patients often develop cardiac complications, including heart failure (HF) [1].

HF is a complex clinical syndrome resulting from diverse primary and secondary causes and shared pathways of disease progression, correlating with substantial mortality, morbidity, and cost [2]. Approximately one third of patients with CHD have disease that is categorized as severe (comprising univentricular hearts, heterotaxy, conotruncal defects, atrioventricular (AV) septal defects, total anomalous pulmonary venous return, left ventricular outflow tract (LVOT) obstruction, or right ventricular outflow tract (RVOT) obstruction) and require intervention in the first year of life [3]. Prevalence of HF in adults with CHD may exceed 20% of this specific population and is one of the leading causes of death [3].

There are numerous causes for a high prevalence of HF in adults with congenital heart disease, including genetic predisposition that may be the cause of myocardial dysfunction per se, cyanosis, prior surgical incisions and scars, inadequate myocardial protection during cardiopulmonary bypass, pressure and volume overload, arrhythmias as a consequence of abovementioned issues, and of course acquired heart disease.

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2.2 Pathophysiology of Heart Failure

Progressive deterioration of myocardial function leads to an inability of the heart to meet the body's requirements for oxygen and other key substrates and is, essentially, a mismatch of supply and demand. Energy starvation is proposed as a unifying mechanism underlying cardiac contractile failure. This is frequently the result of a downward spiral of events in which decreases in oxygen and substrate availability trigger adaptive mechanisms, including neuroendocrine overdrive, activation of signaling pathways, extracellular matrix remodeling, and alterations in mechanical load, among others. Although these adaptive mechanisms stabilize contractile function in the short term, over the long term, they may result in further compromise and worsening of the vicious cycle of demand outstripping supply.

Both LV and RV dysfunction may lead to heart failure. The molecular events that mark the transition from a stressed but compensated state, e.g., stable hypertrophy, to overt heart failure, defined by significant reduction in cardiac output, elevation of RV or LV filling pressure, and increased fibrosis, are still not completely understood [4, 5].

2.2.1 Left Ventricular Dysfunction

Much of the terminology used to describe HF is historical and is based on measurement of the LV ejection fraction (EF). HF comprises a wide range of patients, from those with normal LVEF [typically considered as ≥50%; HF with preserved EF (HFpEF)] to those with reduced LVEF [typically considered as <40%; HF with reduced EF (HFrEF)]. Patients with an LVEF in the range of 40–49% represent a "gray area," which since 2016 is defined as HFmrEF (midrange EF) [6].

Patients with HFpEF generally do not have a dilated LV but instead often have an increase in LV wall thickness and/or increased left atrial (LA) size as a sign of increased filling pressures. Most have additional "evidence" of impaired LV filling or suction capacity, also classified as diastolic dysfunction, which is generally accepted as the likely cause of HF in these patients (hence the term "diastolic HF"). However, most patients with HFrEF (previously referred to as "systolic HF") also have diastolic dysfunction, and subtle abnormalities of systolic function have been shown in patients with HFpEF, hence the preference for stating preserved or reduced LVEF over preserved or reduced "systolic function" [6, 7].

The adaptive mechanisms that may be adequate to maintain the overall contractile performance of the heart at relatively normal levels become maladaptive when trying to sustain adequate cardiac performance. The primary myocardial response to chronically increased wall stress is myocyte hypertrophy, cell death due to apoptosis, and regeneration. This process eventually leads to ventricular remodeling, usually the eccentric type, and reduced cardiac output, causing a cascade of the neurohormonal and vascular response mechanism.

Activation of natriuretic peptides and the sympathoadrenergic system, endothelin, and renin-angiotensin-aldosterone system (RAAS) can be driven by any of ischemia, abnormal cardiac distension from deranged pressure, or volume loading.

Decreased carotid baroreceptor stimulation and renal perfusion will activate the sympathetic nervous system and RAAS. Sympathetic nervous system activation will cause increased heart rate and inotropy, leading to myocardial toxicity. RAAS activation leads to vasoconstriction, increasing afterload (angiotensin II) and hemodynamic alterations, increasing preload (aldosterone). All of these mechanisms will cause adverse remodeling and worsen the left ventricular function, causing symptoms of heart failure.

It is likely that adverse remodeling, the process by which an initial injury or stressor to the ventricle leads to progressive and predictable structural changes of the ventricle such as dilatation or hypertrophy, is another result of the adverse loading and structural conditions driving subcellular signals and cellular changes. Regardless of initial insult, remodeling certainly occurs and in itself can lead to progressive ventricular failure and deterioration.

It seems that all types of CHD are associated with neurohormonal activation. Patients with CHD have marked activation of the natriuretic, endothelin, sympathoadrenergic, and renin-aldosterone systems. The magnitude of neurohormonal activation is equivalent to that found in HF caused by other causes, with good concordance between NYHA class in the two populations. The correlations found between neurohormones and clinical variables demonstrate that relatively simple and routine noninvasive cardiac investigations (chest X-ray, measurement of atrial volume by echocardiography, and cardiopulmonary exercise testing stand out) could help identify which patients with congenital heart disease are likely to have significant neurohormonal activation and be at risk of developing HF [8].

2.2.2 Right Ventricular Dysfunction

RV dysfunction is one of the leading causes of HF in CHD, as a large group of CHD patients may have either a systemic RV or important hemodynamic lesion in the subpulmonary RV. An RVEF less than 45% is considered abnormal [9]. Decreased cardiac performance arises from dysfunctional cardiomyocytes, and relative hypoxia of the myocardium might be one of the factors responsible for the documented fibrosis that develops in the hypertrophied RV. The changes in composition and reorientation of the collagen and the excessive degradation of extracellular matrix (ECM) that characterize the fibrotic process are common responses to the tissue hypoxia arising from ischemia and microcirculatory insufficiency [5].

Long-term survival studies show that patients who have single ventricle physiology with a systemic RV progress to heart failure sooner and more often than those with a systemic LV. Patients with congenitally corrected transposition of the great arteries (ccTGA), where the RV functions as the systemic ventricle, have an increased risk of RV failure as they age, even in the absence of atrioventricular valve

regurgitation or other lesions. Similarly, the systemic RV is at risk in patients who have undergone an atrial switch operation for d-transposition of the great arteries (TGA). These systemic RVs develop hypertrophy, usually at a very early age, and therefore increased wall stress alone cannot be the only factor predisposing these ventricles to failure.

There is little data on RV remodeling in response to hemodynamic stressors and the pathways leading to RV failure. In addition, there is minimal data on the volume-loaded LV and even less data on the volume-loaded RV. This is a critical issue for patients with CHD where the RV is uniquely at risk, e.g., in patients with right-sided obstructive lesions (such as tetralogy of Fallot, pulmonary atresia), in patients with systemic right ventricles (ccTGA, hypoplastic left heart syndrome, TGA after atrial switch), and also in patients with pulmonary hypertension (PHT).

In the past, differences in global structure and loading conditions were thought to represent the main differences between the right and left ventricles. We now recognize that these differences begin early in development, before afterload differences become important (the fetal right and left ventricles are both coupled to the systemic circulation and both function at high pressure) [10]. This divergence begins with the primary and secondary heart fields, leading to the differentiation of left or right ventricular cardiomyocytes during early development, and continues with chamber-specific differences in cell signaling and Ca2+ handling, all suggesting fundamental differences between the two ventricles also exist at the cellular level.

2.2.2.1 Metabolic Adaptations to Pressure Overload

The RV and LV differ in their workload and hence in their energy needs. Based on ventricular afterload alone, the LV workload is five times greater than the RV due to the higher systemic vascular resistance when compared to the low-resistance pulmonary vascular bed. Due to decreased workload on the resting RV, both oxygen consumption and metabolic stress (adenosine triphosphate (ATP) generation rate/maximum ATP generation rate) are lower than in the LV. Afterload stress induces alterations in the metabolic profile of both ventricles. Both the RV and LV myocardium utilize free fatty acids for biosynthesis and energy production in the normal fasting state. With the onset of hypertrophy, however, the myocardium shifts to a greater dependence on glucose for its energy source via increased glucose uptake and glycolysis, since there is less oxygen consumed per ATP generated compared to fatty acid metabolism. While this shift is beneficial during acute stress, chronic dependence on glycolysis for energy production is inadequate to meet the demands of the myocardium and to maintain normal function, leading to an energy-starved state and contributing to heart failure.

During the progression into the maladaptive hypertrophied RV, there is a rise in mitochondrial reactive oxygen species (ROS), which inhibits hypoxia-inducible factor-α (HIF1α) and activates pathways, both of which contribute to downregulation of pyruvate dehydrogenase kinase (PDK) and decreased glucose uptake [5]. Overall, elevated ROS levels can lead to cellular, molecular, and structural changes causing further remodeling leading to failure.

2.2.2.2 Metabolic Response to Chronic Volume Overload

During the early stages of RV volume overload, there is diastolic dysfunction and preserved systolic function, at which point there is downregulation of several metabolic pathway regulators, important for ATP production. There are also decreases in genes encoding transport of nutrients across the cell membrane such as ATP-binding transporters [11]. During the later stages of RV volume overload, there is worsening of diastolic dysfunction and the onset of fibrosis, but similar to the clinical situation, systolic function at this stage is largely preserved. There is a shift away from β-oxidation with downregulation of fatty acid-binding protein and upregulation of adenosine monophosphate (AMP) kinases and increased glycogenolysis with upregulation of GSK3β gene and glycogen phosphorylase. These adaptations are similar to those described during LV volume overload; however, additional research will be required to determine if more subtle differences exist.

2.2.2.3 Ischemia

The RV has a lower resting oxygen consumption and therefore lower resting coronary blood flow than the LV. In the normal RV, the majority of coronary flow occurs in systole, in contrast to the normal LV where coronary flow is mostly in diastole. During RV afterload stress, some have described increased right coronary artery flow and increased oxygen extraction to support the increased oxygen demand of the hypertrophied RV, whereas others have reported increased right coronary flow but impaired oxygen extraction [12, 13].

When stressed, the RV is more susceptible to ischemia. This RV susceptibility to ischemia is compounded by an impaired angiogenic response to pressure overload compared to the LV. Thus, reduced coronary perfusion, exacerbated by a failure of angiogenic upregulation in the setting of hypertrophy, may exacerbate RV ischemia, possibly one of the triggers for the metabolic shift from mitochondrial oxidative phosphorylation to glycolysis described earlier [4].

2.2.2.4 Neurohormonal Activation

Although β-adrenergic receptor signal regulation appears to be similar in the failing RV vs. the LV, the clinical response of the two ventricles to β-adrenergic blockers is quite different. In the normal RV, β-adrenergic receptor stimulation induces similar positive inotropic responses as in the normal LV. In RV failure, secondary to PHT or pulmonary arterial banding (PAB), there is downregulation of β1, α1, and DA1 receptors, decreased cyclic AMP levels, and increased G protein-coupled receptor kinase-2 (GRK2) activity, leading to an impaired inotropic response. This downregulation of adrenergic signaling is greater in PHT-induced than in PAB-induced RV hypertrophy [4].

Activation of the RAAS occurring in the setting of low LV cardiac output and/or low systemic vascular resistance causes vasoconstriction and increased renal tubular sodium reabsorption peripherally and also has direct effects on cardiomyocyte fibrosis. The RAAS has not been fully evaluated in RV failure. Whether the RAAS is stimulated with RV failure in the setting of CHD remains to be determined and is particularly important when considering the role of ACE inhibitors and angiotensin II receptor antagonists on right heart failure in patients with a systemic RV [14].

2.2.3 Mechanical and Functional Interdependence Between the RV and LV

Although it has been customary to consider LV function and RV function as separate entities, this approach is flawed. The ventricles share common injury mechanisms and anatomically share fibers that encircle both ventricles. They are intimately attached through a common septum and share the pericardial space. Consequently, the function of the two ventricles is inextricably linked in both the structurally normal and abnormal heart [10].

Changes in RV pressure resulting from changes in LV volume and from coronary occlusion correlated with the degree of septal bulging into the RV cavity during systole, suggesting that the septum plays an important role in mediating ventricular-ventricular interactions. From experiments, it was estimated that >50% of the normal RV mechanical work may be generated by LV contraction and that the LV free wall plays a pivotal role in RV function [15]. Similarly, LV isovolumetric contraction results in simultaneous increases in RV stroke volume and developed pressure for a constant RV volume.

Normally, LV electric activation and RV electric activation are temporally close enough that it is difficult to separate the peak dp/dt spike of one ventricle from the other. When LV activation is sufficiently separated from RV activation by a ventricular extrasystole or by left bundle branch block (LBBB), the contribution of LV contraction to RV dp/dt becomes apparent [16]. The RV also profoundly affects LV performance. Changes in RV volume lead to substantial changes in load-independent measures of LV function and a shift in the LV pressure-volume relation. These effects may be clinically relevant when the RV is volume unloaded by placement of a caval pulmonary shunt [17].

In PAH, in addition to decreased cardiac output that results directly from RV failure, leftward displacement of the interventricular septum impedes LV filling. This secondary LV geometric change is linearly related to cardiac output, whereas RV end-diastolic volume, in and of itself, is not related to cardiac output [18]. Similarly, in patients with tetralogy of Fallot and conduit stenosis, the prolonged septal shift induced by RV afterload and prolonged RV contraction leads to reduced LV filling as the septum bulges into the LV in diastole. Relief of conduit stenosis reverses septal curvature, shortens RV contraction, synchronizes LV and RV contraction and relaxation, improves LV filling, and improves exercise capacity [19].

RV hypertension, dilation, and septal displacement also create RV dyssynchronous motion and dyssynchronous RV-LV contraction. Interventricular dyssynchrony and intraventricular delay may affect both myocardial mechanics and ventricular filling/output [10].

2.2.4 Diastolic Dysfunction

Diastolic dysfunction is characteristic of many types of congenital heart disease from infancy through to the aging heart. Increased ventricular stiffness and a change in the microscopic structure of the myocardium are inevitable parts of

aging. This, coupled with changes in vascular stiffness, may lead to increased vulnerability in certain groups to developing symptomatic HF even when the ejection fraction remains within the normal range. Traditional assessment of systolic heart function will not identify these patients. The increased stiffness of the myocardium is thought to be due to changes in the collagen content of the ECM and increased fibrosis. There are other changes including reduced phosphorylation of sarcomeric proteins and changes in titin, which may be of importance at a cellular level [20].

Pressure overload lesions such as aortic stenosis and systemic hypertension cause a decrease in LV compliance due to hypertrophy. Volume overload leads to increased LV compliance up until a point, when hypertrophy or fibrosis occurs.

Mixed pressure and volume overload can combine to affect compliance of the RV, such as in repaired ToF with some pulmonary valve stenosis and incompetence.

TGA leads to a special situation in which the RV is faced with increased afterload and the LV with a much lower pressure than normal, both of which may cause decreased compliance [20]. In several studies diastolic function of systemic RV in ccTGA [21] or post Mustard or Senning repair [22] measured either by echocardiography [21] or MRI [22] was correlated with MVO2 consumption [21, 22] and brain natriuretic peptide [22].

In patients with rapid RV dilatation, restrictive RV physiology might be frequently noted at the initial MRI assessment [23]. Restrictive RV physiology was an independent risk factor for rapid RV enlargement in a cohort of tetralogy of Fallot patients.

In CHD, surgical patches and scars may contribute to diastolic as well systolic myocardial dysfunction.

2.3 Causes of Heart Failure in Congenital Heart Disease

Adult patients with CHD experience myocardial dysfunction that is caused by abnormal loading conditions, fibrosis, cyanosis, and hypoperfusion. Genetics may also play a pivotal role in myocardial cell dysfunction. Arrhythmias and acquired heart disease also contribute to HF development. In addition there is often the added insult of poor myocardial preservation during (multiple sometimes) cardiopulmonary bypass surgery. Causes of HF in ACHD are summarized in Fig. 2.1.

2.3.1 Genetics

The development of the heart is under genetic control, and CHD is highly influenced by genetic factors, although teratogens and maternal factors may also contribute to disease manifestation. The genetic causes of CHD include chromosome abnormalities, genomic disorders in which the clinical phenotype is a consequence of abnormal dosage of gene(s) located within the rearranged genomic fragments, and single-gene causes [2].

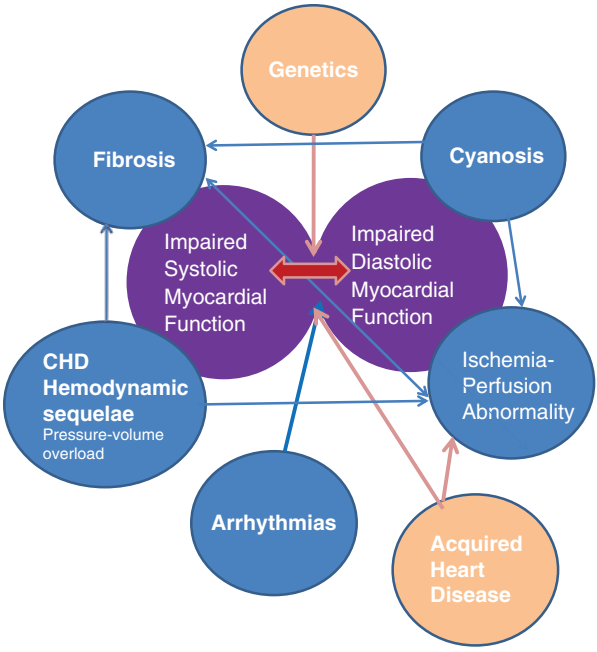

Fig. 2.1 Interdependence between multiple causes of myocardial dysfunction in patients with congenital heart disease

Familial dilated cardiomyopathy, for example, most often illustrates a Mendelian pattern of inheritance. CHD, in contrast, is most often multifactorial with a complex interplay of multiple genes and environment contributing a susceptibility to the development of a structural defect. The underlying causes of CHD remain relatively poorly understood, and although it has long been thought to have both genetic and environmental contributions, the epidemiology of CHD points to genetics contributing to the majority of CHD. The overall incidence of CHD has been stable at 0.8–1.1% of live births, with small changes in CHD incidence attributable to improved diagnostic methods. The risk of recurrence of related forms of CHD among siblings is elevated, ranging from 3.4 for atrial septal defects (ASDs) to 79.1 for heterotaxy in the Danish national cohort study [24].

Although the increased prevalence of HF in ACHD is primarily viewed as a result of a volume or pressure overload, when the starting point is an abnormal heart, an independent genetic component will also be present. This route depicted in Fig. 2.2 with permission from Fahed et al. [25] delineates a purely genetic component that causes both cardiac malformation and a cardiomyopathy that result in HF, unrelated to hemodynamic stress. Many of the pathways involved in cardiac development in utero are also involved in myocardial structure and stability. Therefore, it is not surprising that certain molecular perturbations can cause both a cardiac defect at birth and a cardiomyopathy that can present later in life, often in childhood [25].

Recent data indicate that mutations in sarcomeric genes are associated with CHD in addition to cardiomyopathy [26]. Mutations in specific protein domains of the *MYH7* gene cause Ebstein anomaly in addition to causing cardiomyopathy [27].

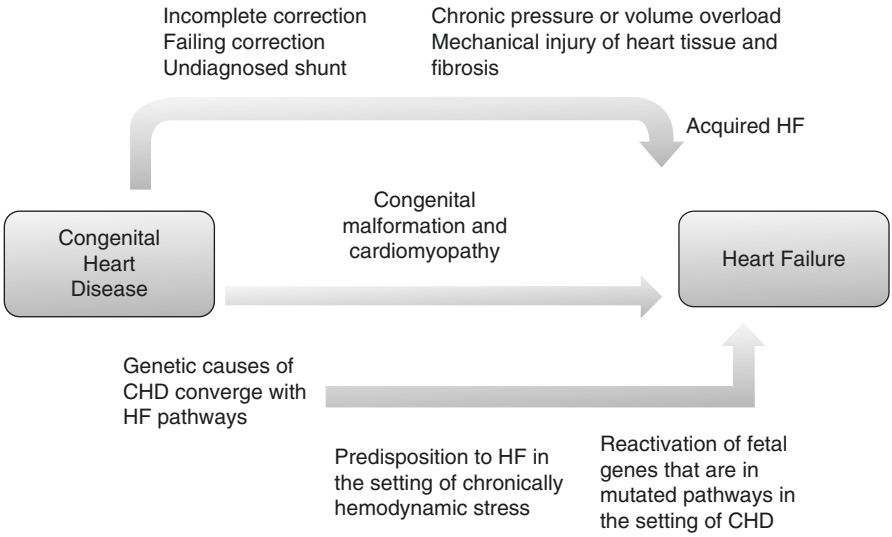

Fig. 2.2 Schematic of the hypothesized mechanisms linking congenital heart disease with heart failure. Three putative routes may lead to HF in ACHD: rare monogenic entities that cause both CHD and HF (middle arrow), severe CHD lesions in which acquired hemodynamic effects of CHD or surgery result in HF (top arrow), and most commonly a combined effect of complex genetics in overlapping pathways and acquired stressors caused by the lesion (bottom arrow). From [25] with permission. *HF* heart failure, *ACHD* adult congenital heart disease

Interestingly, in the original description, 6% of a cohort of patients with Ebstein anomaly, a defect of tricuspid valve formation and position, had *MYH7* mutations, of which 75% had left ventricular noncompaction cardiomyopathy [28].

The genetics underlying CHD have identified critical biological pathways involved in CHD, including chromatin remodeling, Notch signaling, cilia function, sarcomere structure and function, and RAS signaling. These pathways are anticipated to provide direct insights into the mechanism of heart development and to provide insights into potential CHD comorbidities, such as ventricular dysfunction observed in the setting of sarcomere and RAS pathway mutations [3]. It will take many years to establish how genetic factors play a specific role in myocardial cell function and how these factors interact to predispose the patient with CHD to myocardial dysfunction and HF.

2.3.2 Hemodynamic Sequelae of Congenital Heart Disease

LV and RV volume and pressure overload can cause myocardial dysfunction and HF through the mechanisms previously analyzed. Lesion type is a useful risk stratifier. HF in patients with CHD is typically attributed to concomitant pressure or volume overload (see Chap. 4). Therefore, patients with specific types of CHD will universally experience HF without surgical correction, while patients with surgical

Table 2.1 Main causes and mechanisms of heart failure in congenital heart disease

Causes	Mechanisms
Genetics	Sarcomere structure
CHD-related hemodynamic sequelae	Pressure and/or pressure-volume overload of systemic and/or subpulmonary ventricle, reduced cardiac output
Fibrosis	Hypertrophy, increased filling pressures, surgical scars
Cyanosis	Hypoxia
Impaired myocardial perfusion—ischemia	Congenital coronary artery abnormalities, postsurgical coronary artery abnormalities, demand-supply oxygen mismatch
Arrhythmias	Tachycardia-induced cardiomyopathy, dyssynchrony
Acquired heart disease	Coronary artery disease, diabetes mellitus, arterial hypertension

correction may or may not present with HF during their lifetime. Systemic to pulmonary shunts surgically created can also cause LV volume overload and in time PAH if the shunt is sizable (Table 2.1).

2.3.3 Myocardial Fibrosis

The normal myo-architecture of the heart differs between the LV and the RV. The LV has a thicker compact layer with its myocytes arrayed in varying orientations through its depth, while the more apical parts of the human RV are predominantly trabeculated, with only a thin outermost compact layer. The RV has a complex geometrical shape. It is wrapped around the LV, which allows it to shorten in systole as well as to benefit from ventricle-ventricle interdependence from the LV contraction due to its sharing of common fibers, septum, and pericardial space. The RV subendocardial fibers are shared with the LV subendocardial layer via the interventricular septum. Likewise, the RV subepicardial fibers are shared with the LV subepicardial layer [29].

The myo-architecture of a normal RV wall is not considered to contain a middle layer of circumferential fibers apart from that in the RVOT. However, in a diseased RV [tetralogy of Fallot (ToF)], a middle circumferential layer was identified. These changes in myo-architecture were not only found in adult ToF patients' post-repair but also in infants before surgery [30, 31].

The myocardial extracellular space is the interstitial tissue that contains the fibrocollagenous material, endomysium. The endomysium acts like a mesh that coordinates the conduction of impulses and transmission of forces and provides a supportive framework. In immediate proximity to cardiac myocytes is the perimysium, which is the thicker connective tissue that transmits shearing forces [29].

One downstream effect of neurohormonal and RAAS activation is alteration in collagen turnover by myofibroblasts, leading to detectable myocardial fibrosis. Myocardial fibrosis may be a final common pathophysiological pathway that links a wide spectrum of congenital heart conditions. There is great importance in detecting its various forms and understanding its prognostic significance for a more targeted treatment approach. Broadly, there are two forms of fibrotic processes that can occur:

replacement fibrosis and interstitial fibrosis. Replacement fibrosis is irreversible and occurs following an insult to myocytes, commonly ischemia. This focal type of fibrosis can be detected usually by LGE imaging, assuming there is a neighboring normal myocardium. Interstitial fibrosis is secondary to increased collagen deposition within ECM as a response to abnormal loading conditions on the myocardium such as typically occurs in CHD patients' myocardium. Abnormal accumulation and/or change in the quality of the connective tissue increases myocardial stiffness and reduces the compliance of the ventricle [1, 29].

There has been interest in the presence and impact of myocardial fibrosis in CHD as detected by delayed enhancement after gadolinium injection during cardiac magnetic resonance imaging (MRI), a phenomenon referred to as late gadolinium enhancement (LGE). Gadolinium increases signal intensity of extracellular material in myocardium late after injection, which correlates with fibrosis. This method has been used to demonstrate macroscopic areas of fibrosis in several different CHD subgroups, including TOF (53%), systemic RV (61%), Eisenmenger syndrome (73%), and Fontan palliation (26%) [1]. Interstitial fibrosis can be detected with T1 mapping and extracellular measurements and remains undetected by LGE imaging because it is more diffuse and widespread throughout the myocardium preventing identification by comparison to neighboring "normal" myocardium. Patients studied with methods that quantify diffuse fibrosis using T1 mapping to measure the extracellular volume fraction, a marker of fibrosis, demonstrated significantly more fibrosis than healthy control subjects and more than the amount detected by LGE; the increased diffuse fibrosis correlated with ventricular enlargement and decreased ventricular systolic function [32]. Fibrosis may be one of the causes of systolic and/or diastolic dysfunction in CHD that leads to clinical heart failure.

2.3.4 Cyanosis

Myocardial ischemia in cyanotic patients may not have a detectable impact on ventricular function in the short term but may jeopardize or preprogram the myocardium to more serious dysfunction later in life. In terms of coronary circulation, extramural coronary arteries in cyanotic CHD initially dilate in response to endothelial nitric oxide and prostaglandins which are increased because of the increased shear stress associated with the increased viscosity of the erythrocytotic perfusate. Aneurysmal dilatation (coronary ectasia) results from mural attenuation caused by coexisting abnormalities of the media. Basal coronary blood flow is substantially increased in the dilated extramural coronary arteries, but flow reserve and hyperemic flow remain normal because the coronary microcirculation is remodeled by vascular endothelial growth factor (vasculogenesis) and nitric oxide (angiogenesis). Dilated extramural coronary arteries are thought to be atheroma-free because of the antiatherogenic effects of hypocholesterolemia, hypoxemia, upregulation of nitric oxide, hyperbilirubinemia, and low platelet counts [33].

In ToF cyanotic patients, the high degree of right ventricular obstruction and the smaller size of the pulmonary annulus and main pulmonary artery are responsible for the preoperative chronic hypoxic state. In a recent analysis were identified several genes deregulated in the cyanotic heart that might be responsible for the susceptibility of cyanotic children to ischemia and reoxygenation injury during and after surgical intervention [34]. Cyanotic patients may have significant perioperative myocardial cell damage compared with acyanotic patients undergoing cardiac surgery. This susceptibility to ischemia and reperfusion damage can be explained by the impairment of factors crucial to cardiac function, induction of apoptotic pathways, and alteration of signal transduction pathways seen in cyanotic patients [35, 36].

2.3.5 Ischemia

Ischemia leads to myocardial dysfunction and HF in the long term. Besides cyanosis there are other causes of myocardial hypoperfusion in patients with CHD such as coronary artery anomalies and supply-demand ratio mismatch in patients with systemic RV supplied only by right coronary artery. Many studies demonstrated perfusion abnormalities in patients with a systemic RV in whom the typical coronary anatomy supplying the RV was insufficient for a hypertrophied, enlarged ventricle, although there are conflicting data on the frequency and clinical importance of these findings.

In a recent study, RV myocardial microvascular density of the septal wall in TGA and TOF patients with RV hypertrophy due to pressure and/or volume overload was reduced. This appeared to be related to a reduced myocardial perfusion reserve and impaired right ventricular systolic function [37].

Congenital coronary artery abnormalities (anomalous origin and/or course) have been described in a variety of congenital heart defects, for example, ccTGA. Another rare cause of angina and myocardial ischemia in patients with Eisenmenger syndrome is an extrinsic compression of the left coronary ostium by a dilated pulmonary artery. Furthermore, manipulation of the coronary arteries can be an unavoidable part of the surgical repair of the congenital heart defect, for example, reimplantation of the coronary arteries during the arterial switch procedure in transposition of the great arteries or during aortic root replacement.

Although few patients >40 years of age have undergone arterial switch operation, this surgery is now routinely performed, and an older population will be emerging. The great arteries are transected, and the coronary arteries are translocated to the opposite arterial root. This translocation involves injury of the sympathetic nerves that supply the coronary arteries, with attendant denervation. Abnormal vasoreactivity has been documented in these arteries, as well as increased intimal thickness and rare coronary events. Whether this seemingly increased risk would qualify as the “high-risk” category is unclear at this time.

2.3.6 Arrhythmia

As patients with complex congenital heart lesions age, arrhythmias have emerged as leading sources of morbidity and mortality. Heart failure and arrhythmias are intertwined, as one may herald, beget, or aggravate the other [38]. The relationship of heart failure to arrhythmogenesis and sudden cardiac death risk is increasingly appreciated. Hemodynamic and electrophysiologic conditions that lead to heart failure, clinical arrhythmias, and adverse outcomes in adults with CHD often extend over several decades. These include long-standing effects of prior atrial or ventricular volume loading, scarring, patches, baffles and surgical barriers, electromechanical dyssynchrony, ongoing deleterious effects on cell-cell electrical coupling, and underlying genetic aspects. Inevitably, the incidence of arrhythmias in the adult CHD population far exceeds that seen in younger patients. Several forms of CHD predispose to arrhythmias even in the absence of surgical intervention because of abnormalities of the conduction system and intrinsic structural malformations.

Surgical interventions might result in sinus node dysfunction and propensity for supraventricular and ventricular arrhythmias. Moreover, arrhythmias in adults with congenital heart disease and heart failure can be poorly tolerated or life-threatening. They are significant risk factors for sudden death in the CHD population [39]. Chronotropic incompetence may contribute in exercise intolerance in CHD patients [40].

Ventricular dyssynchrony due to intrinsic or pacing-induced ventricular conduction delay can likewise have deleterious effects on systemic ventricular function. In adults with CHD, RBBB is more common than LBBB, particularly in the setting of ToF, ventricular septal defects, double-outlet right ventricle variants, Rastelli surgery, AV septal defects, and Ebstein malformation of the tricuspid valve. In most cases, RBBB is a complication of surgical repair [40]. Device therapies directed at maintaining chronotropic competence, cardiac resynchronization, and preventing sudden death are increasingly used [38] (see Chap. 12).

2.3.7 Acquired Heart Disease

The CHD population has increased dramatically over the past few decades, with many patients now in middle age or the geriatric age range. The relationship between the risk factors of hypertension, hyperlipidemia, and diabetes mellitus with cardiovascular disease is well established. As the CHD patient ages, exposure to these risk factors may be considered no less problematic than with the non-CHD population.

The CHD individual may have abnormal myocardial substrate, abnormal cardiovascular physiology, abnormal anatomy, or any combination of the three. The adverse impact of superimposed cardiovascular risk factors may well be amplified in this group, who also may already be at risk for systemic ventricular dysfunction, rhythm disturbances, and heart failure. It has been reported that ≈80% of adults with CHD had at least 1 cardiovascular risk factor. Coronary artery disease (CAD)

in this population may be atherosclerotic or of other etiology as mentioned above [41, 42].

Hypertension is a leading risk factor for heart disease and stroke, the leading and third-leading causes of death in the United States, respectively. Appropriate treatment in any population is imperative. The CHD patient may be particularly vulnerable because many already have abnormal hemodynamics. Changes in aortic stiffness, diameter, and wave reflection that can occur with aging may lead to increased ventricular afterload, resulting in potential adverse effects in late systolic ejection and diastolic relaxation. The single or systemic ventricle, which may poorly tolerate increased afterload, may be particularly sensitive to these changes, resulting in detrimental effects.

Coarctation of the aorta is another group with increased cardiovascular risk [41].

After coarctation repair patients have increased muscle sympathetic nerve activity, dampened sympathetic baroreflex response, endothelial dysfunction, and increased ambulatory arterial stiffness index, all of which may contribute to the development of late hypertension [43]. As with systemic hypertension, diabetes mellitus may exacerbate diastolic dysfunction in CHD not only via coronary artery disease but because of microvascular disease. In a recent study, CHD patients had an increased risk of developing type 2 diabetes mellitus after age 30. Patients with cyanotic CHD were at particular risk. This population-based cohort study included Danish subjects with CHD who were born between 1963 and 1980 and were alive at age 30 years [44]. As diabetes mellitus and glucose intolerance are such potent risk factors for cardiovascular morbidity, appropriate screening and treatment strategies are increasingly an important part of the care of the ACHD patient [41].

2.4 Clinical Scenarios of Heart Failure in Congenital Heart Disease

HF due to CHD may be classified in seven categories [45]:

1. *Systemic LV dysfunction and/or elevated pulmonary wedge pressure caused by congenital lesions of the left circulation* (repaired or unrepaired) such as mitral stenotic lesions, aortic stenosis -subvalvar, valvar, supravalvar- and coarctation of the aorta (LV pressure overload, ischemia), ventricular septal defects, and patent ductus arteriosus unrepaired (LV volume overload). This type is similar to HF due to acquired heart disease.
2. *Post tetralogy of Fallot (ToF) repair*. Patients with repaired ToF constitute the largest group of ACHD survivors with surgically repaired cyanotic CHD. The presence of RV volume (i.e., pulmonary valve regurgitation) or pressure overload, myocardial fibrosis, or disorders of electrical conduction is universal in the population of adults late after ToF repair. There is along (possibly indefinite) preclinical phase where symptoms and signs of overt HF are absent despite important underlying right heart dilation and dysfunction. This reflects the tremendous adaptive capacity of the RV, as end-diastolic volume increases to

maintain stroke volume and mass augments to maintain wall stress [46]. Twenty percent of patients with repaired ToF have also impaired LV function. Number of years with a palliative shunt prior to full repair has emerged as an independent predictor of impaired LV function in later life [47]. These observations attest the fact that chronic cyanosis has a deleterious effect on myocardial architecture with long-term implications for the development of ventricular fibrosis, as demonstrated histologically and through advanced imaging.

3. *Systemic RV*. There are two situations with a biventricular physiology in which the morphologically RV is positioned to deliver systemic blood flow TGA after a Mustard or Senning procedure and ccTGA with or without associated cardiac abnormalities. Many patients have asymptomatic systemic ventricular dysfunction with depressed ejection fraction or chamber dilation in the absence of symptoms. Asymptomatic ventricular dysfunction may persist for prolonged time periods before the onset of symptoms. The morphological RV is perfused by a single right coronary artery. In such a situation, there may be limitations of myocardial perfusion and <functional> ischemia. Tricuspid regurgitation is a major cause of ventricular dysfunction, and there has been much debate about the cause of systemic ventricular failure. In addition to the morphological RV's inherent vulnerability to failure, it has a complex relationship with systemic atrioventricular valve regurgitation, and controversy exists as to which is the "chicken" and which is the "egg." It appears that primary RV failure, while uncommon, is a frequent sequel to systemic atrioventricular valve regurgitation [48–51].
4. *Single ventricle post Fontan-type operation*. Ventricular dysfunction can be caused by the congenital malformation itself, previous surgical interventions, or the very abnormal working conditions of the ventricle at the various stages of palliation, both before and after Fontan-type operation. During the first months after birth, the ventricle will usually be volume overloaded, either by a band or by an aorta-pulmonary shunt. This volume overload will lead to dilation and spherical reconfiguration, cardiac overgrowth, and eccentric hypertrophy. After unloading at the time of a Fontan-type operation, some regression to normalization will occur but will be frequently incomplete. The preload to the ventricle is, at the time of a Fontan-type operation, reduced to levels well below normal for body surface area (50–70%), and even more when expressed in relation to ventricular size (25–70%). The ventricle thus evolves from being volume overloaded and overstretched to overgrown and (severely) under loaded. It should therefore not be a surprise that the deprived ventricle in a Fontan circuit shows systolic and diastolic dysfunction. The ventricle may now enter a vicious cycle, whereby the low preload results in remodeling, reduced compliance, poor ventricular filling, and eventually continuously declining cardiac output. This phenomenon of progressive "disuse hypofunction" occurs at a chronic preload of less than 70% of the "due" preload [52]. Venous congestion may occur at any time due to elevated pulmonary artery pressures. Higher systemic venous pressures could not only indicate impaired systemic ventricular myocardial performance but also refer to obstructions in the systemic venous return or to an increased pulmonary vascular resistance. In case of the latter, too much preload reduction might compromise

the Fontan circulation and lower the systemic cardiac output. Unique manifestation of failing Fontan are protein-losing enteropathy and plastic bronchitis caused by elevated venous and pulmonary artery pressures, respectively [53].

5. *Cyanotic congenital heart disease with or without pulmonary hypertension*. There are hematologic, neurologic, renal, and rheumatic complications in patients with cyanotic congenital heart disease. There is chronic heart muscle hypoperfusion and severely reduced exercise capacity. In a CHD patients' cohort of 560, patients with cyanosis had a lower peak VO2 than those without. VE/VCO2 slope was 73% higher in patients with cyanosis than in those without. A significant inverse correlation was present between resting oxygen saturations and the VE/VCO2 slope in the cyanotic patients. Cyanosis is a powerful stimulus for this abnormal ventilatory response, irrespective of pulmonary arterial hypertension [54]. Both chronic cyanosis and pressure loading likely contribute to various signaling pathways leading to myofibroblast activity that causes fibrosis. Fibrosis is generally associated with arrhythmia and myocardial dysfunction, which is a common cause of HF and eventual death in these patients. In cyanotic patients there was a strong correlation between fibrosis and systemic end-diastolic volume [55]. In Eisenmenger syndrome there is severe pulmonary arterial hypertension due to increased pulmonary vascular resistance (PVR). There is RV pressure overload that precedes RV failure.
6. *Acquired heart disease in ACHD patients*. Acquired heart disease as mentioned above may have varying prevalence in the CHD population. Cyanotic patients rarely have coronary artery disease, but patients post coarctation repair may have systemic arterial hypertension, while patients post arterial switch surgery may be of high risk in developing CAD [41].

   Nonetheless, considering that risk factors for the development of heart failure in the general population like arterial hypertension, diabetes, and CAD, to name a few, are also present in CHD patients, it seems reasonable to assume that these risk factors could also play a role in the development of heart failure in this patient group. And indeed, it is reported that the association between CAD and systemic ventricular size and functional impairment suggested that CAD may contribute to ventricular dilatation and functional limitation [42, 56], in CHD patients.
7. *Tachycardia-induced cardiomyopathy*: Arrhythmia-induced cardiomyopathy (AIC) is a condition in which atrial or ventricular tachyarrhythmias or frequent ventricular ectopy results in LV dysfunction, leading to systolic HF. The hallmark of this condition is partial or complete reversibility once arrhythmia control is achieved. AIC can be classified into two categories: one where the arrhythmia is the sole reason for ventricular dysfunction (arrhythmia-induced) and another where the arrhythmia exacerbates ventricular dysfunction and/or worsens HF in a patient with concomitant heart disease (arrhythmia-mediated) [57]. Patients with CHD without pervious systemic ventricular dysfunction may present with arrhythmia-mediated HF. In animal models during the early phase (the first 3 to 7 days) of rapid pacing, LV dilation occurs with a decline in LVEF. This early remodeling phase is not accompanied by compromises in cardiac output or

systemic perfusion pressures [58]. By the second week, LV dilation, a fall in LVEF, and elevations in central venous and pulmonary capillary wedge pressures and systemic vascular resistance ensue. Eventually, HF develops. Rapid pacing in animals results in a predictable, time-dependent change in neurohormonal pathways and synthesis and release of bioactive peptides.

Plasma atrial natriuretic peptide and B-type natriuretic peptide (BNP) increase early, concomitant with LV dilation; eventually, natriuretic peptides plateau or decrease, likely due to suppression of synthesis and increased degradation by endopeptidases. Another hallmark is activation of sympathetic pathways, resulting in norepinephrine spillovver. Consistent with the phenotype of progressive LV failure, rapid pacing invariably causes activation of the renin-angiotensin-aldosterone system. Other bioactive molecules activated and released include endothelin and inflammatory cytokines, such as tumor necrosis factor alpha.

Atrial arrhythmias, the most common complication in adults with CHD, may have devastating outcomes when timely recognition is missed and treatment delayed [59]. Due to pathologic substrate, in most cases, sustained fast heart rate may be the cause of severe ventricular dysfunction in CHD patients.

Early recognition is critical, and aggressive treatment aimed at controlling or eliminating the inciting arrhythmia results in symptom resolution and recovery of ventricular function. However, cellular and extracellular ultrastructural changes can persist and can contribute to a rapid decline in cardiac function with arrhythmia recurrence, as well as confer a risk of sudden cardiac death [57].

References

1. Stout K, Broberg C, Book W, Cecchin F, Chen JM, Dimopoulos K, Everitt MD, Gatzoulis M, Harris L, Hsu D, Kuvin J, Law Y, Martin C, Murphy AM, Ross H, Singh G, Spray TL. Chronic heart failure in congenital heart disease: a scientific statement from the American Heart Association. Circulation. 2016;133(8):770–801.
2. Hinton R, Ware SM. Heart failure in pediatric patients with congenital heart disease. Circ Res. 2017;120:978–9942.
3. Zaidi S, Brueckner M. Genetics and genomics of congenital heart disease. Circ Res. 2017; 120(6):923–40.
4. Reddy S, Bernstein D. Molecular mechanisms of right ventricular failure. Circulation. 2015; 132(18):1734–42.
5. Iacobazzi D, M-S Suleiman MG, SJ George MC, Tulloh RM. Cellular and molecular basis of RV hypertrophy in congenital heart disease. Heart. 2016;102:12–7.
6. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-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, Authors/Task Force Members. 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. 2016;37(27):2129–200.
7. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA Focused Update of the

2013 ACCF/AHA Guideline for the Management of Heart Failure: a Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2017;70(6):776–803. https://doi.org/10.1016/j.jacc.2017.04.025. Epub 2017 Apr 28.
8. Bolger AP, Sharma R, Li W, Leenarts M, et al. Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease. Circulation. 2002;106(1):92–9.
9. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. 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. 2015;28(1):1–39.e14.
10. Friedberg MK, Redington AN. Right versus left ventricular failure: differences, similarities, and interactions. Circulation. 2014;129(9):1033–44.
11. Reddy S, Zhao M, Hu DQ, Fajardo G, Katznelson E, Punn R, Spin JM, Chan FP, Bernstein D. Physiologic and molecular characterization of a murine model of right ventricular volume overload. Am J Physiol Heart Circ Physiol. 2013;304:H1314–27.
12. Zong P, Tune JD, Downey HF. Mechanisms of oxygen demand/supply balance in the right ventricle. Exp Biol Med (Maywood). 2005;230:507–19.
13. Saito D, Tani H, Kusachi S, Uchida S, Ohbayashi N, Marutani M, Maekawa K, Tsuji T, Haraoka S. Oxygen metabolism of the hypertrophic right ventricle in open chest dogs. Cardiovasc Res. 1991;25:731–9.
14. van der Bom T, Winter MM, Bouma BJ, Groenink M, Vliegen HW, Pieper PG, van Dijk AP, Sieswerda GT, Roos-Hesselink JW, Zwinderman AH, Mulder BJ. Effect of valsartan on systemic right ventricular function: a double-blind, randomized, placebo-controlled pilot trial. Circulation. 2013;127:322–30.
15. Schertz C, Pinsky MR. Effect of the pericardium on systolic ventricular interdependence in the dog. J Crit Care. 1993;8:17–23.
16. Feneley MP, Gavaghan TP, Baron DW, Branson JA, Roy PR, Morgan JJ. Contribution of left ventricular contraction to the generation of right ventricular systolic pressure in the human heart. Circulation. 1985;71:473–80.
17. Danton MH, Byrne JG, Flores KQ, Hsin M, Martin JS, Laurence RG, Cohn LH, Aklog L. Modified Glenn connection for acutely ischemic right ventricular failure reverses secondary left ventricular dysfunction. J Thorac Cardiovasc Surg. 2001;122:80–91.
18. Gan C, Lankhaar JW, Marcus JT, Westerhof N, Marques KM, Bronzwaer JG, Boonstra A, Postmus PE, Vonk-Noordegraaf A. Impaired left ventricular filling due to right-to-left ventricular interaction in patients with pulmonary arterial hypertension. Am J Physiol Heart Circ Physiol. 2006;290(4):H1528–33.
19. Lurz P, Puranik R, Nordmeyer J, Muthurangu V, Hansen MS, Schievano S, Marek J, Bonhoeffer P, Taylor AM. Improvement in left ventricular filling properties after relief of right ventricle to pulmonary artery conduit obstruction: contribution of septal motion and interventricular mechanical delay. Eur Heart J. 2009;30:2266–74.
20. Panesar DK, Burch M. Assessment of diastolic function in congenital heart disease. Front Cardiovasc Med. 2017;4:5.
21. Tay EL, Frogoudaki A, Inuzuka R, Giannakoulas G, Prapa M, Li W, Pantely G, Dimopoulos K, Gatzoulis MA. Exercise intolerance in patients with congenitally corrected transposition of the great arteries relates to right ventricular filling pressures. Int J Cardiol. 2011;147(2):219–23.
22. Ladouceur M, Kachenoura N, Soulat G, Bollache E, Redheuil A, Azizi M, Delclaux C, Chatellier G, Boutouyrie P, Iserin L, Bonnet D, Mousseaux E. Impaired atrioventricular transport in patients with transposition of the great arteries palliated by atrial switch and preserved systolic right ventricular function: a magnetic resonance imaging study. Congenit Heart Dis. 2017. https://doi.org/10.1111/chd.12472. [Epub ahead of print].
23. Shin YR, Jung JW, Kim NK, Choi JY, Kim YJ, Shin HJ, Park YH, Park HK. Factors associated with progression of right ventricular enlargement and dysfunction after repair of tetralogy

of Fallot based on serial cardiac magnetic resonance imaging. Eur J Cardiothorac Surg. 2016;50(3):464–9.
24. Oyen N, Poulsen G, Boyd HA, Wohlfahrt J, Jensen PK, Melbye M. Recurrence of congenital heart defects in families. Circulation. 2009;120:295–301.
25. Fahed AC, Roberts AE, Mital S, Lakdawala NK. Heart failure in congenital heart disease: a confluence of acquired and congenital. Heart Fail Clin. 2014;10(1):219–27.
26. Wessels MW, Willems PJ. Mutations in sarcomeric protein genes not only lead to cardiomyopathy but also to congenital cardiovascular malformations. Clin Genet. 2008;74:16–9.
27. Kelle AM, Bentley SJ, Rohena LO, Cabalka AK, Olson TM. Ebstein anomaly, left ventricular non-compaction, and early onset heart failure associated with a de novo α-tropomyosin gene mutation. Am J Med Genet A. 2016;170(8):2186–90.
28. Arbustini E, Favalli V, Narula N, Serio A, Grasso M. Left ventricular noncompaction: a distinct genetic cardiomyopathy? J Am Coll Cardiol. 2016;68:949–66.
29. Ghonim S, Voges I, Gatehouse PD, Keegan J, Gatzoulis MA, Kilner PJ, Babu-Narayan S. Myocardial architecture, mechanics, and fibrosis in congenital heart disease. Front Cardiovasc Med. 2017;4:30. https://doi.org/10.3389/fcvm.2017.00030.
30. Sanchez-Quintana D, Anderson RH, Ho SY. Ventricular myoarchitecture in tetralogy of Fallot. Heart. 1996;76(3):280–6.
31. Redington A, Anderson R, Van Arsdell G. Congenital diseases in the right heart. London: Springer; 2009.
32. Broberg CS, Chugh SS, Conklin C, Sahn DJ, Jerosch-Herold M. Quantification of diffuse myocardial fibrosis and its association with myocardial dysfunction in congenital heart disease. Circ Cardiovasc Imaging. 2010;3:727–34.
33. Perloff JK. Cyanotic congenital heart disease: the coronary arterial circulation. Curr Cardiol Rev. 2012;8:1–5.
34. Ghorbel MT, Cherif M, Jenkins E, Mokhtari A, Kenny D, Angelini GD, Caputo M. Transcriptomic analysis of patients with tetralogy of Fallot reveals the effect of chronic hypoxia on myocardial gene expression. J Thorac Cardiovasc Surg. 2010;140(2):337–45.
35. Imura H, Caputo M, Parry A, Pawade A, Angelini GD, Suleiman MS. Age-dependent and hypoxia related differences in myocardial protection during pediatric open heart surgery. Circulation. 2001;103:1551–6.
36. Modi P, Imura H, Caputo M, Pawade A, Parry A, Angelini GD, et al. Cardiopulmonary bypass induced myocardial reoxygenation injury in pediatric patients with cyanosis. J Thorac Cardiovasc Surg. 2002;124:1035–6.
37. Rutz T, de Marchi SF, Schwerzmann M, Vogel R, Seiler C. Right ventricular absolute myocardial blood flow in complex congenital heart disease. Heart. 2010;96:1056–62.
38. Mondésert B, Dubin AM, Khairy P. Diagnostic tools for arrhythmia detection in adults with congenital heart disease and heart failure. Heart Fail Clin. 2014;10(1):57–67.
39. Escudero C, Khairy P, Sanatani S. Electrophysiologic considerations in congenital heart disease and their relationship to heart failure. Can J Cardiol. 2013;29:821–9.
40. Khairy P, Van Hare GF, Balaji S, Berul CI, Cecchin F, Cohen MI, Daniels C, Deal BJ, Dearani JA, de Groot N, Dubin AM, Harris L, Janousek J, Kanter RJ, Karpawich PP, Perry JC, Seslar SP, Shah MJ, Silka MJ, Triedman JK, Walsh EP, Warnes CA. PACES/HRS expert consensus statement on the recognition and management of arrhythmias in adult congenital heart disease. Developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the Governing Bodies of PACES, HRS, the American College of Cardiology (ACC), the American Heart Association (AHA), the European Heart Rhythm Association (EHRA), the Canadian Heart Rhythm Society (CHRS), and the International Society for Adult Congenital Heart Disease (ISACHD). Can J Cardiol. 2014;30:e1–e63.
41. Bhatt A, Foster E, Kuehl K, et al. Congenital heart disease in the older adult: a scientific statement from the American Heart Association. Circulation. 2015;131(21):1884–931.
42. Tutarel O. Acquired heart conditions in adults with congenital heart disease: a growing problem. Heart. 2014;100(17):1317–21.

43. Lee MGY, Hemmes RA, Mynard J, Lambert E, Head GA, Cheung MMH, Konstantinov IE, Brizard CP, Lambert G, d'Udekem Y. Elevated sympathetic activity, endothelial dysfunction, and late hypertension after repair of coarctation of the aorta. Int J Cardiol. 2017;243:185–90.
44. Madsen NL, Marino BS, Woo JG, Thomsen RW, Videbœk J, Laursen HB, Olsen M. Congenital heart disease with and without cyanotic potential and the long-term risk of diabetes mellitus: a population-based follow-up study. J Am Heart Assoc. 2016;5(7).
45. Budts W, Roos-Hesselink J, Rädle-Hurst T, Eicken A, McDonagh TA, Lambrinou E, Crespo-Leiro MG, Walker F, Frogoudaki AA. Treatment of heart failure in adult congenital heart disease: a position paper of the Working Group of Grown-Up Congenital Heart Disease and the Heart Failure Association of the European Society of Cardiology. Eur Heart J. 2016;37(18):1419–27.
46. Wald R, Valente AM, Marelli A. Heart failure in adult congenital heart disease: emerging concepts with a focus on tetralogy of Fallot. Trends Cardiovasc Med. 2015;25(5):422–32.
47. Broberg CS, Aboulhosn J, Mongeon FP. Prevalence of left ventricular systolic dysfunction in adults with repaired tetralogy of Fallot. Am J Cardiol. 2011;107(8):1215–20.
48. Cuypers J, Eindhoven J, Slager M, et al. The natural and unnatural history of the Mustard procedure: long-term outcome up to 40 years. Eur Heart J. 2014;35:1666–74.
49. Rydman R, Gatzoulis M, Yen Ho S, et al. Systemic right ventricular fibrosis detected by cardiovascular magnetic resonance is associated with clinical outcome, mainly new-onset atrial arrhythmia, in patients after atrial redirection surgery for transposition of the great arteries. Circ Cardiovasc Imaging. 2015;8:e002628.
50. Warnes C. Transposition of the great arteries. Circulation. 2006;114:2699–709.
51. Frogoudaki AA. Assessing the failing systemic right ventricle. Angiology. 2008;59(2 Suppl): 93S–6S.
52. Gewillig M. The Fontan circulation. Heart. 2005;91:839–46.
53. Deal B, Jacobs M. The failing Fontan circulation. Heart. 2012;98:1098e1104.
54. Dimopoulos K, Okonko D, Diller GP. Abnormal ventilatory response to exercise in adults with congenital heart disease relates to cyanosis and predicts survival. Circulation. 2006; 113:2796–802.
55. Broberg C, Prasad S, Carr C, et al. Myocardial fibrosis in Eisenmenger syndrome: a descriptive cohort study exploring associations of late gadolinium enhancement with clinical status and survival. J Cardiovasc Magn Res. 2014;16:32.
56. Giannakoulas G, Dimopoulos K, Engel R, et al. Burden of coronary artery disease in adults with congenital heart disease and its relation to congenital and traditional heart risk factors. Am J Cardiol. 2009;103:1445–50.
57. Gopinathannair R, Etheridge SP, Marchlinski FE, Spinale FG, Lakkireddy D, Olshansky B. Arrhythmia-induced cardiomyopathies: mechanisms, recognition, and management. Am Coll Cardiol. 2015;66(15):1714–28.
58. Armstrong PW, Stopps TP, Ford SE, et al. Rapid ventricular pacing in the dog: pathophysiologic studies of heart failure. Circulation. 1986;74:1075–84.
59. Stämpfli SF, Plass A, Müller A, Greutmann M. Complete recovery from severe tachycardia-induced cardiomyopathy in a patient with Ebstein's anomaly. World J Pediatr Congenit Heart Surg. 2014;5(3):484–7.

Definition and Diagnosis of Heart Failure in Adult Congenital Heart Disease

3

Craig S. Broberg

3.1 Introduction

The term heart failure (HF) is frequently applied to adults with congenital heart disease (ACHD) in several different settings. Population studies cite rising numbers of affected individuals. Providers respond to dyspnoea and oedema with standard HF treatment strategies. Patients themselves may ask, "Do I have heart failure?" or look to the Internet for treatment options. It has been stated that ACHD is the original HF syndrome [1], but what exactly this term connotes varies considerably.

This chapter will review definitions that have been used and the challenges of an accurate and uniform HF diagnosis. It will become apparent, as was observed decades ago, that "no definition of HF is universally accepted" [2].

A precise definition of HF is necessary to understand the natural history of various congenital defects, HF pathophysiology, and therefore its prevention and treatment [3]. It is necessary for defining population outcomes, since HF is typically associated with increased mortality [4–6]. A clear definition is also crucial for studying the role of so-called "advanced" HF therapies such as mechanical support. Varying definitions mean considerable variation in published disease prevalence and impact [7]. It is unlikely however that one universal set of diagnostic criteria will serve all potential purposes.

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3.2 General Definitions Considered

The most elementary definitions of HF state that "the heart cannot pump enough blood to meet the body's needs." Others add that the heart is unable to "pump blood at an adequate rate or in adequate volume" [8], for effective end-organ perfusion [9]. This can include someone with adequate resting perfusion but inadequate perfusion during exertion. Others state that the heart can pump adequately but "only (with) an elevated diastolic filling pressure" [10] hence the rationale for the additional term "congestive."

These terms have two limitations. First, they are too inclusive of all the components of the cardiovascular system that may be abnormal including valve disease, arrhythmia, shunts, or even noncardiac components such as the lungs, all of which may be impaired in ACHD. Second, they do not include situations where physiologic adaptations preserve "adequate" output even when myocardial dysfunction is present. A HF definition that requires evidence of inadequate systemic perfusion, particularly at rest, would only include individuals with end-stage conditions.

For example, an asymptomatic patient with a systemic RV with reduced systolic function and no evidence of poor perfusion would not meet this definition, whereas a patient with severe pulmonary valve stenosis and pre-syncope during activity would. However the physician may argue that the first patient had HF and the second did not.

Physicians will universally agree that HF is a *clinical* diagnosis. For example, the words "heart failure" are never included on an echocardiogram report, even when poor myocardial function is present. Importantly, the terms "heart failure," "systolic dysfunction," and "cardiomyopathy" are not synonymous [11, 12]. They each refer to distinct clinical imaging and pathophysiologic changes, respectively. Research criteria for HF published decades ago were based exclusively on clinical criteria such as elevated jugular venous pressure, third heart sound, and oedema [13]. These criteria did not consider the "myocardial factor" [14], a term used often in the day to denote myocardial dysfunction as an isolated cause of these symptoms apart from limitations due to valves, shunts, arrhythmia, etc.

Today the term HF now denotes a clinical syndrome that includes some form of fundamental myocardial abnormality [15]. For example, the ACC/AHA Task Force defines HF as "a complex *clinical* syndrome *that results from* any structural or functional impairment of ventricular filling or ejection of blood" (italics added) [11, 12]. The ESC definition is similar, describing clinical symptoms in the setting of "a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress" [16]. These Task Force definitions acknowledge the wide range of "structural" abnormalities possible and the many variations of myocardial alterations (such as systolic and diastolic impairment) and symptoms (such as during exertion) that may be relevant. Symptoms and signs that may be encountered include indications of elevated LV filling pressure (dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea) or RV filling pressure (ankle oedema, increased abdominal girth) and of low output (marked fatigue, pre-syncope, renal impairment, or gastrointestinal disturbance).

This coupling of clinical findings with functional changes is essentially what we now understand to be HF. Going further, in ACHD specifically, the HF definition should encompass the astute observation in ACHD from over 50 years ago that "the status of the myocardium is the final determinant of the clinical course and

prognosis" [17]. With this in mind, it seems that the designation of HF should indicate clinical manifestations of *myocardial* abnormalities rather than any other cardiac component.

When considering the physiologic right heart specifically, distinctions have been made between "right heart failure" and "right ventricular failure" [18]. For example, a patient with tetralogy of Fallot may have been labelled as having "right heart failure" by clinicians that fail to recognize and treat pulmonary valve regurgitation as the true cause of the clinical manifestations.

3.3 Diagnostic Criteria Used in Existing Publications

Common published diagnostic criteria include a range of clinical, functional, biochemical imaging and haemodynamic features either alone or in combination (Table 3.1). Arguably the most reliable of these metrics are those that have been shown to predict increased morbidity or mortality. Many of these prognostic

Table 3.1 Criteria for heart failure diagnosis used in published research

• Clinical
Jugular venous pulse elevation
Need for diuretic
Oedema
Shortness of breath
Ascites
Second heart sound
Symptom scores (Minnesota living with HF, Seattle HF, etc.)
"Coded" as such in administrative or billing codes
• Biochemical
B-type natriuretic peptide
Renin-angiotensin-aldosterone activation
Circulating byproducts of collagen metabolism (fibrosis markers)
• Functional
Subjective NYHA class
6-min walk distance
Peak VO2 or percent predicted peak VO2
• Imaging
Cardiothoracic ratio on chest radiography
Ventricular ejection fraction (or surrogates such as fractional shortening or fractional area shortening)
Ventricular diastolic dimension
Myocardial fibrosis (by late gadolinium enhancement or extracellular volume)
Myocardial strain
"Myocardial dysfunction" reported on imaging tests even if not specified
• Haemodynamic
Cardiac output or cardiac index
Right or left ventricular pressure elevation (including wedge pressure)
• Outcomes based
Inotrope dependent
Hospital admissions for diuretics
"CHF" recorded in chart notes or as defined by codes, diuretic need, or BNP
Listed for heart transplant
Cause of death noted on death record

markers are continuous variables, such as ejection fraction for which varying cut-off values have been inconsistently applied. Others are only semi-quantitative, such as the New York Heart Association (NYHA) class, and others are not quantifiable in practical use such as the presence of ascites or orthopnoea. Some may vary over time such as the need for diuretic use or exercise parameters. Billing codes are often used in large data sets. The specificity of these codes for HF diagnosis is high but at the expense of a low sensitivity [19].

3.4 Criteria Used in ACHD Studies

In ACHD research, many of these same diagnostic criteria have been used to define HF. They include those purely based on clinical findings such as the NYHA class [20], billing codes for hospital admissions [18], or clinical definitions used in non-ACHD HF guidelines [21]. Some studies incorporate a combination of clinical and functional parameters or risk models based on a number of different clinical and imaging metrics [22–24]. BNP and peak oxygen consumption (VO_2) during exercise have both been widely used and are associated with each other [25, 26]. Indeed, many of these HF markers are interrelated and interdependent [27–31]. Some authors have relied on clinicians' descriptions in clinical notes [32] or HF listed on death records [6, 33, 34]. Others use imaging findings, such as ejection fraction [6]. Each instance seems suited towards the data available at the time of study and the nature of the question being addressed.

Much research attention has shifted to preclinical indicators of myocardial dysfunction. These may include newer markers of neurohormonal activation [35–37], high-sensitivity troponin [38], and renin-angiotensin-aldosterone activity, including various genotypes that have been demonstrated to be associated with diastolic function and BNP [39]. Others include markers of collagen turnover and changes in the extracellular volume fraction of the myocardium, indicative of diffuse myocardial fibrosis [40–42]. Early signs of altered ventricular mechanics through novel imaging, such as strain metrics [43–45], may also be applicable in identifying HF patients. These could all play a role as preclinical indicators of early HF, prior to symptom manifestations. Although they are objectively quantifiable and gaining credibility in general cardiology, they have not yet been validated in ACHD.

3.5 Diagnostic Challenges in ACHD

Considering the two halves of the HF definition, the assessment of either can be problematic in ACHD. Symptoms may not be present or at least not recognized by the patient who has been accustomed to long-standing limitations [46]. NYHA classification is an important discriminator of poor exercise capacity that matches objectively measured function [47], though subjective and only loosely assessed. Formal symptom scores using established symptom survey instruments have had limited validation in ACHD [15, 48].

There is also the challenge of defining ventricular dysfunction in ACHD, either diastolic or systolic, at rest or with exercise, or in a geometrically altered ventricle. Functional measurements may be inconsistent either between patients or serially in the same patient. Despite numerous methodologies, there is a certain degree of subjectivity with almost each one. Even cardiac magnetic resonance, often considered the gold standard for volumetric quantification, has limitations [49]. Furthermore, normative values for ventricular diameter, volume, or ejection fraction may not be well established, particularly for a systemic right or single ventricle. It is impossible therefore to propose strict criteria for a HF diagnosis using these metrics.

There is a poor correlation between symptom severity and the degree of myocardial change [12], and there are a number of confounding factors regarding symptoms (such as diet or deconditioning) and measured myocardial performance (such as rhythm or loading conditions). The disconnection between symptoms and function has been shown to hold in ACHD conditions particularly in those with a systemic right ventricle [50].

Because exertional intolerance is central to the definition and diagnosis of HF [12], much has been written about the value of formal exercise testing in ACHD [47, 51]. Exercise capacity, quantified either by peak oxygen consumption (VO_2) or heart rate reserve, is associated with hospitalization and mortality risk [47, 51, 52]. The disadvantage is that exercise intolerance is often multifactorial, not simply related to myocardial dysfunction alone. Pulmonary vascular disease, valvular dysfunction, cyanosis, chronotropic incompetence, skeletal muscle abnormalities, lung disease, and anaemia may all be contributing factors, which partly explain the significant ranges of exercise capacity between various ACHD subtypes [47]. When considering therapeutic strategies for a patient based on exercise testing, the degree to which these other conditions are limiting exertion needs to be sorted out on an individual basis. However, it should be noted that any exercise-limiting condition may also trigger neurohormonal activation that can in turn contribute to myocardial alteration and eventual dysfunction.

Since HF definitions include the presence of high filling pressures or low cardiac output, the standard for such quantification is invasive haemodynamic assessment in the catheterization laboratory. Carefully measured haemodynamics are often called upon to distinguish ventricular dysfunction (diastolic or systolic) from other structural problems that would be addressed through different means. However haemodynamics vary in response to different metabolic states. For example, a patient with normal baseline filling pressures, while fasting and lying recumbent, may not have after saline administration or during upright exercise. Therefore haemodynamic data also needs careful interpretation in the context of the patient's condition.

3.6 The Heart Failure Continuum

HF is a long-standing process [14]. A simplified description of this complex progression may be stated as follows: it begins with some abnormal component of the cardiovascular system that leads to altered ventricular loading. This triggers

neurohormonal changes, altered myofibrillar function, and ventricular geometry, leading to declines in ventricular performance, then symptoms/signs of HF. The prevalence of HF will be dependent on how early or late in the progression one elects to define affected individuals. Often, precursors of HF may warrant just as much consideration and treatment [16].

The clinical trajectory of HF is not typically a gradual, uninterrupted decline, particularly in ACHD patients (Fig. 3.1). Fluctuations in the clinical course may include the need for repeat cardiac surgery and other acute triggers which are temporarily overcome. Exertional limitations may improve with intervention and/or training. BNP may increase with worsening systemic atrioventricular valve regurgitation [27, 53], then improve with diuresis or after valve intervention. Therefore, any one criterion that identifies an affected patient may not be present later under different circumstances.

While defining HF as any point on the continuum recognizes vulnerability across the ACHD spectrum, it does not help to identify which patients should be thought of as deserving different management considerations at certain time points. In consideration of this, HF guidelines now incorporate different stages of HF, spanning the range from asymptomatic preclinical HF to those with end-stage HF [12]. Stage A identifies those with risks only. Stage B denotes asymptomatic individuals with some structural heart problems, such as hypertrophy, valve disease, or reduced ventricular function. Stage C includes those with early symptoms (most importantly dyspnoea with effort) and stage D those with persistent symptoms despite treatment, which may also be termed "advanced" HF, thus meriting consideration for mechanical support or heart transplant. Therefore, different diagnostic criteria are utilized for different stages.

When applied to the ACHD population, virtually all ACHD patients from birth may be said to be Stage "B" inherently (Fig. 3.1), given the ubiquity of preclinical myocardial changes in the context of pressure or volume loading, etc. Reflecting this strengthens the appellation of ACHD as "the original heart failure syndrome" [1], in part because nearly all individuals start life somewhere on this continuum. It is also important to recognize ACHD-related HF as a final common pathway of a number of factors, rather than one entity, and the management approach to HF should vary according to underlying aetiologies. Tetralogy of Fallot, single ventricle/Fontan, and coarctation of the aorta, for example, each have very different pathogenic mechanisms for myocardial dysfunction and clinical deterioration. As much as possible, therapeutic pathways should not be "borrowed" using data on other HF treatment algorithms [46] but should reflect an understanding of the unique aetiology of HF, including whether ventricular dysfunction (and what kind) is present or whether other hemodynamic problems ought to be addressed through other means.

Reviewing the above, it seems that criteria for ACHD-related HF ought to (1) indicate the presence of myocardial dysfunction specifically, either with or without other "structural" abnormalities; (2) rely on more than one parameter recognizing their dynamic nature; (3) be lesion-specific, for example, criteria in Ebstein's anomaly should differ from Shone syndrome; (4) wherever possible use metrics that have

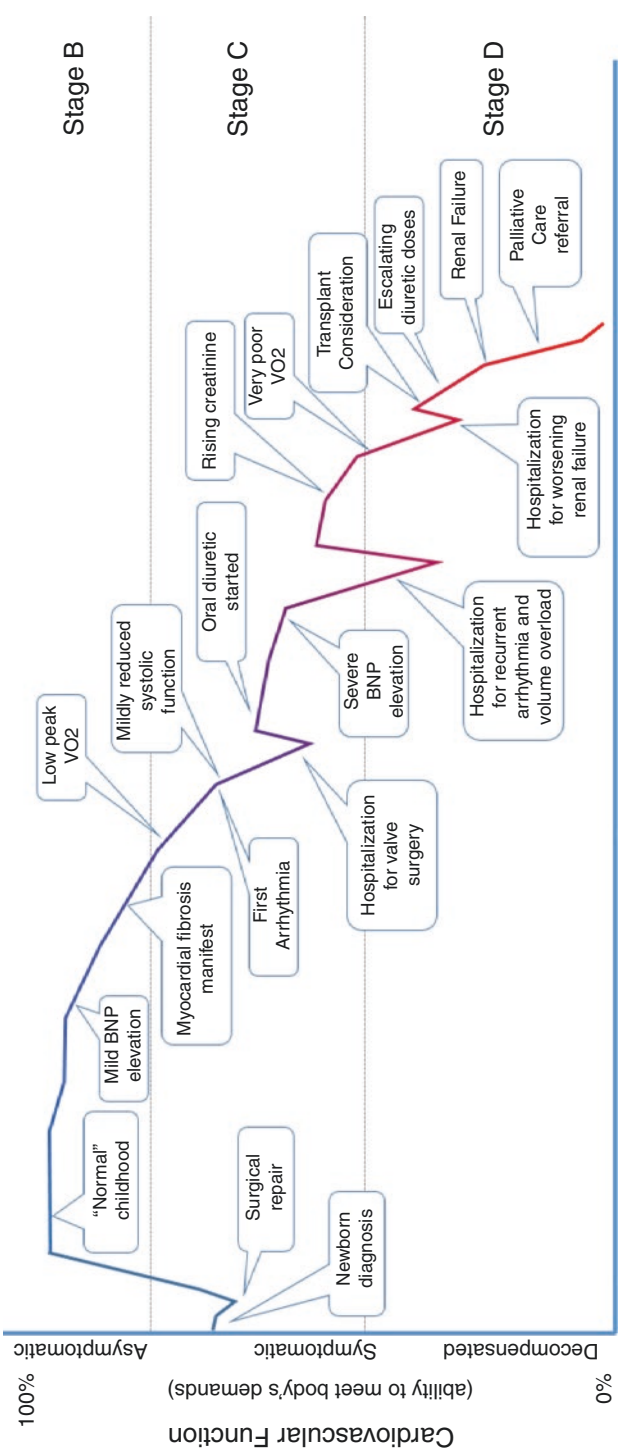

Fig. 3.1 Schematic representation of hypothetical HF manifestations and events over the course of a theoretic lifespan of an ACHD patient. The figure demonstrates the different stages of HF (Stage B asymptomatic, Stage C early symptoms, Stage D advanced symptoms or decompensation; Stage A, not shown, would include those without risks for HF, which arguably does not apply to most individuals with congenital heart disease). Almost any of the points indicated could be viewed as a criterion for diagnosing HF. Based on what criteria are used, prevalence, treatment, and prognosis will all differ accordingly. *BNP* B-type natriuretic peptide; *VO2* maximum oxygen consumption on cardiopulmonary exercise testing

been shown to have prognostic relevance; and (5) be relevant to the stage in the HF continuum being evaluated. For example, a study investigating an intervention to reduce myocardial fibrosis may need to define HF differently than a mechanical support intervention. In other words, definitions of HF may need to be as progressive and adaptable as the disease itself.

3.7 Additional Considerations

Arrhythmias are frequent in congenital heart disease [54–58], and may be both a cause of and manifestation of HF. Many patients become symptomatic when arrhythmias occur, and such symptoms mimic those of HF. But arrhythmia is also driven by myocardial dysfunction and is often associated with myocardial fibrosis [59, 60]. Ventricular arrhythmia has been linked to an elevated left ventricular end-diastolic pressure in the tetralogy of Fallot [57] and to abnormal diastolic dysfunction parameters by echocardiography [61]. Both findings demonstrate this important relationship between HF and arrhythmia. Hence, it seems appropriate to consider tachyarrhythmia as an apt criterion for a HF designation.

3.7.1 Fontan Failure

One variant of HF, "Fontan failure," deserves its own consideration. By definition all Fontan patients have myocardial dysfunction in the form of an absent sub-pulmonic ventricle, as well as symptoms of venous congestion that inevitably stem from Fontan physiology. However defining all of these patients as having HF does not aid the physicians planning optimal care. One study of single-ventricle Fontan patients defined HF as a combination of symptoms with systemic ventricular dysfunction and distinguished this from "Fontan failure" alone wherein systolic ventricular function was preserved [62]. Again, one challenge among many with this tactic is measuring ventricular function of the single ventricle, but there are important outcome differences in those with reported dysfunction (see Chap. 6).

3.7.2 Advanced Heart Failure

Finally, there are remaining questions regarding what should be considered by the term "advanced" HF. Often the term centres around the need for mechanical support. However ACHD patients are often not candidates for such therapies. When status on a transplant list is defined by the therapies in place (such as mechanical support or inotropes), ACHD HF patients may be disadvantaged [63]. Hence criteria may need to be more ACHD-specific (see Chap. 13).

3.8 Diagnostic Tools for Heart Failure in ACHD

The diagnostic tools used to diagnose ACHD-related heart failure are identical to those used in acquired heart disease. The emphasis is, of course, often on carefully identifying the specific anatomy and physiology of the patient and correctly interpreting the findings in the patient's unique context. The precise details of this will be key to understanding the aetiology of the HF and its optimal treatment strategy. The list below is not exhaustive but highlights an overview of some of the major areas. The specific prognostic, rather than diagnostic, significance of these variables are discussed in Chap. 4.

3.8.1 Symptoms

Although symptoms bring patients to medical attention, many of the symptoms of HF are non-specific and do not, therefore, help discriminate between HF and other cardiovascular problems. Symptoms that are more specific (i.e. orthopnoea and paroxysmal nocturnal dyspnoea) are less common, especially in patients with mild disease. Many of the signs of HF result from sodium and water retention. These are also not specific (such as peripheral oedema) and resolve quickly with diuretic therapy making it more difficult to assess patients already treated in this way. More specific signs, such as elevated jugular venous pressure and displacement of the apical impulse, are less reproducible in many congenital defects. Jugular venous pressure waveforms in a Fontan patient, for example, are inherently different. Symptoms and signs may be particularly difficult to identify and interpret in obese individuals, in the elderly, and in patients with chronic lung disease.

Syncope or atrial arrhythmias, as mentioned, may in a sense be considered signs of HF in patients with ACHD as they may relate to elevated filling pressures of the systemic or pulmonary ventricle. More unusual manifestations of HF in ACHD may include worsening cyanosis and, specific to the Fontan patient, plastic bronchitis or protein-losing enteropathy.

3.8.2 Electrocardiography

Most ACHD patients have abnormal ECGs. RBBB and signs of ventricular hypertrophy are common. Arrhythmias should be carefully excluded. An assessment of changes from previous ECGs is particularly important and should trigger detailed review.

3.8.3 Chest X-Ray

Chest X-ray is of particular value in assessing the bronchial situs, previous surgical scars, and the position of the heart. Signs of HF are as per acquired HF. In ACHD

patients a cardiothoracic ratio >55% was associated with an eightfold increased risk of death [64].

3.8.4 Echocardiogram

An echo forms the backbone of ACHD assessment. In the HF patient, the echo is particularly useful for:

- Establishing or confirming the segmental anatomical diagnosis
- Identify concomitant/residual lesions
- Assess ventricular function
- Assessing haemodynamics
- Detecting new lesions such as a new shunt or valve dysfunction
- Serially monitoring disease progression
- Guiding intervention

Guidelines are in place for many of the subsets of ACHD with specific protocols and echo risk scores (see Chap. 4). All of the varieties of echo techniques including stress, strain, and 3D can be utilized in this population [63, 65–68].

3.8.5 Magnetic Resonance Imaging and CT Scanning

Magnetic resonance imaging (MRI) is the gold standard for estimating RV and LV volumes and function. It enables excellent three-dimensional anatomical reconstruction and has rapidly improving spatial and temporal resolution. It is particularly useful for volumetric measurements, assessment of extra-cardiac vessels, and detection of myocardial fibrosis. ESC recommendations for the use of MRI in ACHD have been published [69]. Computed tomography provides excellent spatial resolution and is less hampered by metallic implants. It is particularly good for imaging epicardial coronary arteries, venous connections, collateral vessels, and the arterial tree [65] but provides less physiologic information that may be informative of HF.

3.8.6 Cardiac Catheterization

Cardiac catheterization, particularly haemodynamic assessment, as discussed above, is of paramount importance in detecting and treating HF. Yet because of its invasive nature, often it is reserved for resolution of specific anatomical and physiological questions or for intervention. Continuing indications include assessment of pulmonary vascular resistance (PVR), LV and RV diastolic function, pressure gradients, and shunt quantification when non-invasive evaluation leaves uncertainty. It

also has an important role in coronary artery assessment and the evaluation of extracardiac vessels such as aortopulmonary collaterals.

3.8.7 Cardiopulmonary Exercise Test

As mentioned earlier, cardiopulmonary exercise test is a valuable tool with prognostic implications (see Chap. 4). Exercise ability is reduced in ACHD patients, and relating exercise capacity to normal values obtained in healthy volunteers may not tell the whole story. For example, in an Eisenmenger patient, it may be more appropriate to interpret the achieved level of exercise capacity in comparison with what would be usual/expected given the underlying diagnosis or to the patient's previous results. Reference values for exercise limitations among adults with congenital heart disease have been published [52, 70].

3.8.8 Laboratory Testing

Useful lab testing includes full blood count, renal function tests, liver function tests, protein and albumin, and thyroid function. Laboratory testing may reveal treatable conditions which with adequate management may delay HF progression or diseases that masquerade as HF. The prognostic implications of anaemia, hypoalbuminemia [71], and renal dysfunction are discussed in Chap. 4. Other abnormalities seen in laboratory tests are not diagnostic of HF but may be secondary to overt HF. They can therefore be indicative of the degree to which HF is poorly controlled. For example, the deranged liver function tests may reflect cardiac dysfunction and therefore may improve by treating HF, either increasing cardiac output or decongestion. Hyponatraemia is common in ACHD especially in those with complex disease. Predictors of hyponatraemia are worse functional class, higher serum creatinine levels, and treatment with diuretics, and it is a strong predictor of death [72].

3.8.8.1 Thyroid Dysfunction

Thyroid dysfunction can be associated with various adverse cardiologic outcomes, including arrhythmias and ventricular dysfunction. Thyroid-stimulating hormone (TSH) should be measured in any new HF patient or in those with arrhythmia.

3.8.8.2 Natriuretic Peptides

B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) have both a diagnostic and prognostic role and are further discussed in Chap. 4.

3.8.8.3 Lung Function Tests

Lung disease may mimic heart failure, and restrictive lung defects are common in ACHD (see Chap. 5). Therefore symptoms of dyspnoea should always warrant a thorough pulmonary review.

3.9 Mortality Impact

Despite varied definitions of ACHD-related HF used in research, there is no doubt about its impact on morbidity and mortality. More and more studies now show a rising tide of HF, however defined, as a prominent concern in the ACHD patient population. Numerous studies consistently show HF as the leading cause of death among ACHD patients [4–6, 21, 33, 34, 73], and patients with HF have worse outcomes than those who do not [18, 22, 34]. Thus, regardless of the definition, it is imperative that we study the process and explore ways to prevent, diagnose, and treat it, in the interest of the long-term survival of this vulnerable population.

Conclusion

In summary, HF is a continual process on which nearly all ACHD patients can be said to be. Myocardial dysfunction and its clinical manifestations are a final common pathway in the natural history of many ACHD conditions with or without intervention. HF is diagnosed when clinical manifestations are present in the context of myocardial dysfunction. But the process of HF also requires recognition of preclinical stages of HF when myocardial changes are present but symptoms not yet manifest. There is no set of criteria for HF that will aptly identify each type of vulnerable patient. Instead, specific definitions in specific groups become useful for different situations along the HF continuum. The diagnostic testing regimen for ACHD HF is very similar to that for acquired disease but with a focus on determining each component of the segmental anatomy and its role on the aetiology of the HF syndrome.

References

1. Bolger AP, Coats AJ, Gatzoulis MA. Congenital heart disease: the original heart failure syndrome. Eur Heart J. 2003;24:970–6.
2. Denolin H, Kuhn H, Krayenbuehl HP, Loogen F, Reale A. The definition of heart failure. Eur Heart J. 1983;4:445–8.
3. Stout KK, Broberg CS, Book WM, Cecchin F, Chen JM, Dimopoulos K, Everitt MD, Gatzoulis M, Harris L, Hsu DT, Kuvin JT, Law Y, Martin CM, Murphy AM, Ross HJ, Singh G, Spray TL, American Heart Association Council on Clinical Cardiology CoFG, Translational Biology, Council on Cardiovascular Radiology and Imaging. Chronic heart failure in congenital heart disease: a scientific statement from the American Heart Association. Circulation. 2016;133:770–801.
4. Nieminen HP, Jokinen EV, Sairanen HI. Causes of late deaths after pediatric cardiac surgery: a population-based study. J Am Coll Cardiol. 2007;50:1263–71.
5. Oechslin EN, Harrison DA, Connelly MS, Webb GD, Siu SC. Mode of death in adults with congenital heart disease. Am J Cardiol. 2000;86:1111–6.
6. Verheugt CL, Uiterwaal CS, van der Velde ET, Meijboom FJ, Pieper PG, van Dijk AP, Vliegen HW, Grobbee DE, Mulder BJ. Mortality in adult congenital heart disease. Eur Heart J. 2010;31:1220–9.
7. Bjork JB, Alton KK, Georgiopoulou VV, Butler J, Kalogeropoulos AP. Defining advanced heart failure: a systematic review of criteria used in clinical trials. J Card Fail. 2016;22:569–77.
8. Merriam-Websters Dictionary. 2017.
9. Farlex Medical Dictionary. 2017.

10. Dorland's Illustrated Medical Dictionary. 28th ed. Philadelphia: WB Saunders; 1994.
11. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013;128:1810–52.
12. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW, Antman EM, Smith SC Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B, American College of Cardiology, American Heart Association Task Force on Practice Guidelines, American College of Chest Physicians, International Society for Heart and Lung Transplantation, Heart Rhythm Society. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation. 2005;112:e154–235.
13. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. N Engl J Med. 1971;285:1441–6.
14. Broberg CS, Burchill LJ. Myocardial factor revisited: the importance of myocardial fibrosis in adults with congenital heart disease. Int J Cardiol. 2015;189:204–10.
15. Bolger AP, Gatzoulis MA. Towards defining heart failure in adults with congenital heart disease. Int J Cardiol. 2004;97(Suppl 1):15–23.
16. 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, Authors/Task Force Members. 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. 2016;37:2129–200.
17. McIntosh HD, Cohen AI. Pulmonary stenosis; the importance of the myocardial factor in determining the clinical course and surgical results. Am Heart J. 1963;65:715–6.
18. Rodriguez FH III, Moodie DS, Parekh DR, Franklin WJ, Morales DL, Zafar F, Adams GJ, Friedman RA, Rossano JW. Outcomes of heart failure-related hospitalization in adults with congenital heart disease in the United States. Congenit Heart Dis. 2013;8:513–9.
19. McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA. Validity of heart failure diagnoses in administrative databases: a systematic review and meta-analysis. PLoS One. 2014;9:e104519.
20. Piran S, Veldtman G, Siu S, Webb GD, Liu PP. Heart failure and ventricular dysfunction in patients with single or systemic right ventricles. Circulation. 2002;105:1189–94.
21. Moussa NB, Karsenty C, Pontnau F, Malekzadeh-Milani S, Boudjemline Y, Legendre A, Bonnet D, Iserin L, Ladouceur M. Characteristics and outcomes of heart failure-related hospitalization in adults with congenital heart disease. Arch Cardiovasc Dis. 2017;110:283–91.
22. Stefanescu A, Macklin EA, Lin E, Dudzinski DM, Johnson J, Kennedy KF, Jacoby D, DeFaria Yeh D, Lewis GD, Yeh RW, Liberthson R, Lui G, Bhatt AB. Usefulness of the Seattle Heart Failure Model to identify adults with congenital heart disease at high risk of poor outcome. Am J Cardiol. 2014;113:865–70.
23. Lin EY, Cohen HW, Bhatt AB, Stefanescu A, Dudzinski D, DeFaria Yeh D, Johnson J, Lui GK. Predicting outcomes using the heart failure survival score in adults with moderate or complex congenital heart disease. Congenit Heart Dis. 2015;10:387–95.
24. Connolly D, Rutkowski M, Auslender M, Artman M. The New York University Pediatric Heart Failure Index: a new method of quantifying chronic heart failure severity in children. J Pediatr. 2001;138:644–8.

25. Norozi K, Wessel A, Alpers V, Arnhold JO, Geyer S, Zoege M, Buchhorn R. Incidence and risk distribution of heart failure in adolescents and adults with congenital heart disease after cardiac surgery. Am J Cardiol. 2006;97:1238–43.
26. Schoonbeek RC, Pieper PG, van Slooten YJ, Freling HG, Sieswerda GT, van Dijk AP, Jongbloed MR, Post MC, Bouma BJ, Berger RM, Ebels T, van Melle JP. NT-proBNP and exercise capacity in adult patients with congenital heart disease and a prosthetic valve: a multicentre PROSTAVA study. Neth Heart J. 2016;24:653–65.
27. Koch AM, Zink S, Singer H. B-type natriuretic peptide in patients with systemic right ventricle. Cardiology. 2008;110:1–7.
28. Garg R, Raman SV, Hoffman TM, Hayes J, Daniels CJ. Serum markers of systemic right ventricular function and exercise performance. Pediatr Cardiol. 2008;29:641–8.
29. Oosterhof T, Tulevski II, Vliegen HW, Spijkerboer AM, Mulder BJ. Effects of volume and/or pressure overload secondary to congenital heart disease (tetralogy of fallot or pulmonary stenosis) on right ventricular function using cardiovascular magnetic resonance and B-type natriuretic peptide levels. Am J Cardiol. 2006;97:1051–5.
30. Law YM, Keller BB, Feingold BM, Boyle GJ. Usefulness of plasma B-type natriuretic peptide to identify ventricular dysfunction in pediatric and adult patients with congenital heart disease. Am J Cardiol. 2005;95:474–8.
31. Tulevski II, Groenink M, van Der Wall EE, van Veldhuisen DJ, Boomsma F, Stoker J, Hirsch A, Lemkes JS, Mulder BJ. Increased brain and atrial natriuretic peptides in patients with chronic right ventricular pressure overload: correlation between plasma neurohormones and right ventricular dysfunction. Heart. 2001;86:27–30.
32. Schuuring MJ, van Gulik EC, Koolbergen DR, Hazekamp MG, Lagrand WK, Backx AP, Mulder BJ, Bouma BJ. Determinants of clinical right ventricular failure after congenital heart surgery in adults. J Cardiothorac Vasc Anesth. 2013;27:723–7.
33. Engelings CC, Helm PC, Abdul-Khaliq H, Asfour B, Bauer UM, Baumgartner H, Kececioglu D, Korten MA, Diller GP, Tutarel O. Cause of death in adults with congenital heart disease—an analysis of the German National Register for congenital heart defects. Int J Cardiol. 2016;211:31–6.
34. Zomer AC, Vaartjes I, van der Velde ET, de Jong HM, Konings TC, Wagenaar LJ, Heesen WF, Eerens F, Baur LH, Grobbee DE, Mulder BJ. Heart failure admissions in adults with congenital heart disease; risk factors and prognosis. Int J Cardiol. 2013;168:2487–93.
35. Miyamoto K, Takeuchi D, Inai K, Shinohara T, Nakanishi T. Prognostic value of multiple biomarkers for cardiovascular mortality in adult congenital heart disease: comparisons of single−/two-ventricle physiology, and systemic morphologically right/left ventricles. Heart Vessel. 2016;31:1834–47.
36. Lipczynska M, Szymanski P, Kumor M, Klisiewicz A, Hoffman P. Collagen turnover biomarkers and systemic right ventricle remodeling in adults with previous atrial switch procedure for transposition of the great arteries. PLoS One. 2017;12:e0180629.
37. Bolger AP, Sharma R, Li W, Leenarts M, Kalra PR, Kemp M, Coats AJ, Anker SD, Gatzoulis MA. Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease. Circulation. 2002;106:92–9.
38. Kowalik E, Klisiewicz A, Rybicka J, Biernacka EK, Hoffman P. High sensitivity cardiac troponin T and systemic right ventricular function in adults with congenitally corrected transposition of the great arteries. Int J Cardiol. 2017;241:168–72.
39. Burchill LJ, Redington AN, Silversides CK, Ross HJ, Jimenez-Juan L, Mital S, Oechslin EN, Dragulescu A, Slorach C, Mertens L, Wald RM. Renin-angiotensin-aldosterone system genotype and serum BNP in a contemporary cohort of adults late after Fontan palliation. Int J Cardiol. 2015;197:209–15.
40. Broberg CS, Chugh SS, Conklin C, Sahn DJ, Jerosch-Herold M. Quantification of diffuse myocardial fibrosis and its association with myocardial dysfunction in congenital heart disease. Circ Cardiovasc Imaging. 2010;3:727–34.
41. Chen CA, Dusenbery SM, Valente AM, Powell AJ, Geva T. Myocardial ECV fraction assessed by CMR is associated with type of hemodynamic load and arrhythmia in repaired tetralogy of Fallot. JACC Cardiovasc Imaging. 2016;9:1–10.

42. Kozak MF, Redington A, Yoo SJ, Seed M, Greiser A, Grosse-Wortmann L. Diffuse myocardial fibrosis following tetralogy of Fallot repair: a T1 mapping cardiac magnetic resonance study. Pediatr Radiol. 2014;44:403–9.
43. Auger DA, Bilchick KC, Gonzalez JA, Cui SX, Holmes JW, Kramer CM, Salerno M and Epstein FH. Imaging left-ventricular mechanical activation in heart failure patients using cine DENSE MRI: validation and implications for cardiac resynchronization therapy. J Magn Reson Imaging. 2017.
44. Tutarel O, Orwat S, Radke RM, Westhoff-Bleck M, Vossler C, Schulke C, Baumgartner H, Bauersachs J, Rontgen P, Diller GP. Assessment of myocardial function using MRI-based feature tracking in adults after atrial repair of transposition of the great arteries: reference values and clinical utility. Int J Cardiol. 2016;220:246–50.
45. Orwat S, Diller GP, Kempny A, Radke R, Peters B, Kuhne T, Boethig D, Gutberlet M, Dubowy KO, Beerbaum P, Sarikouch S, Baumgartner H. German Competence Network for Congenital Heart Defects I. Myocardial deformation parameters predict outcome in patients with repaired tetralogy of Fallot. Heart. 2016;102:209–15.
46. Krieger EV, Valente AM. Heart failure treatment in adults with congenital heart disease: where do we stand in 2014? Heart. 2014;100:1329–34.
47. 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. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. Circulation. 2005;112:828–35.
48. Cedars AM, Stefanescu Schmidt A, Broberg C, Zaidi A, Opotowsky A, Grewal J, Kay J, Bhatt AB, Novak E, Spertus J. Adult congenital heart disease patients experience similar symptoms of disease activity. Circ Cardiovasc Qual Outcomes. 2016;9:161–70.
49. Winter MM, Bernink FJ, Groenink M, Bouma BJ, van Dijk AP, Helbing WA, Tijssen JG, Mulder BJ. Evaluating the systemic right ventricle by CMR: the importance of consistent and reproducible delineation of the cavity. J Cardiovasc Magn Reson. 2008;10:40.
50. Book W, McConnell M, Oster M, Lyle T, Kogon B. Predicting functional capacity in patients with a systemic right ventricle: subjective patient self-assessment is better than B-type natriuretic peptide levels and right ventricular systolic function. Congenit Heart Dis. 2013;8:550–5.
51. Diller GP, Dimopoulos K, Okonko D, Uebing A, Broberg CS, Babu-Narayan S, Bayne S, Poole-Wilson PA, Sutton R, Francis DP, Gatzoulis MA. Heart rate response during exercise predicts survival in adults with congenital heart disease. J Am Coll Cardiol. 2006;48(6):1250.
52. Inuzuka R, Diller GP, Borgia F, Benson L, Tay EL, Alonso-Gonzalez R, Silva M, Charalambides M, Swan L, Dimopoulos K, Gatzoulis MA. Comprehensive use of cardiopulmonary exercise testing identifies adults with congenital heart disease at increased mortality risk in the medium term. Circulation. 2012;125:250–9.
53. Koch AM, Zink S, Singer H, Dittrich S. B-type natriuretic peptide levels in patients with functionally univentricular hearts after total cavopulmonary connection. Eur J Heart Fail. 2008;10:60–2.
54. Walsh EP, Cecchin F. Arrhythmias in adult patients with congenital heart disease. Circulation. 2007;115:534–45.
55. Khairy P, Harris L, Landzberg MJ, Fernandes SM, Barlow A, Mercier LA, Viswanathan S, Chetaille P, Gordon E, Dore A, Cecchin F. Sudden death and defibrillators in transposition of the great arteries with intra-atrial baffles: a multicenter study. Circ Arrhythm Electrophysiol. 2008;1:250–7.
56. Khairy P, Aboulhosn J, Gurvitz MZ, Opotowsky AR, Mongeon FP, Kay J, Valente AM, Earing MG, Lui G, Gersony DR, Cook S, Ting JG, Nickolaus MJ, Webb G, Landzberg MJ, Broberg CS. Alliance for Adult Research in Congenital C. Arrhythmia burden in adults with surgically repaired tetralogy of Fallot: a multi-institutional study. Circulation. 2010;122:868–75.
57. Khairy P, Harris L, Landzberg MJ, Viswanathan S, Barlow A, Gatzoulis MA, Fernandes SM, Beauchesne L, Therrien J, Chetaille P, Gordon E, Vonder Muhll I, Cecchin F. Implantable cardioverter-defibrillators in tetralogy of Fallot. Circulation. 2008;117:363–70.
58. Bouchardy J, Therrien J, Pilote L, Ionescu-Ittu R, Martucci G, Bottega N, Marelli AJ. Atrial arrhythmias in adults with congenital heart disease. Circulation. 2009;120:1679–86.

59. Babu-Narayan SV, Goktekin O, Moon JC, Broberg CS, Pantely GA, Pennell DJ, Gatzoulis MA, Kilner PJ. Late gadolinium enhancement cardiovascular magnetic resonance of the systemic right ventricle in adults with previous atrial redirection surgery for transposition of the great arteries. Circulation. 2005;111:2091–8.
60. Babu-Narayan SV, Kilner PJ, Li W, Moon JC, Goktekin O, Davlouros PA, Khan M, Ho SY, Pennell DJ, Gatzoulis MA. Ventricular fibrosis suggested by cardiovascular magnetic resonance in adults with repaired tetralogy of fallot and its relationship to adverse markers of clinical outcome. Circulation. 2006;113:405–13.
61. Aboulhosn JA, Lluri G, Gurvitz MZ, Khairy P, Mongeon FP, Kay J, Valente AM, Earing MG, Opotowsky AR, Lui G, Gersony DR, Cook S, Child J, Ting J, Webb G, Landzberg M, Broberg CS. Alliance for Adult Research in Congenital C. Left and right ventricular diastolic function in adults with surgically repaired tetralogy of Fallot: a multi-institutional study. Can J Cardiol. 2013;29:866–72.
62. Law YM, Ettedgui J, Beerman L, Maisel A, Tofovic S. Comparison of plasma B-type natriuretic peptide levels in single ventricle patients with systemic ventricle heart failure versus isolated cavopulmonary failure. Am J Cardiol. 2006;98(4):520.
63. Flachskampf FA, Wouters PF, Edvardsen T, Evangelista A, Habib G, Hoffman P, Hoffmann R, Lancellotti P, Pepi M, European Association of Cardiovascular Imaging Document reviewers: Erwan D and Fausto R. Recommendations for transoesophageal echocardiography: EACVI update 2014. Eur Heart J Cardiovasc Imaging. 2014;15:353–65.
64. Dimopoulos K, Giannakoulas G, Bendayan I, Liodakis E, Petraco R, Diller GP, Piepoli MF, Swan L, Mullen M, Best N, Poole-Wilson PA, Francis DP, Rubens MB, Gatzoulis MA. 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. 2013;166:453–7.
65. Valente AM, Cook S, Festa P, Ko HH, Krishnamurthy R, Taylor AM, Warnes CA, Kreutzer J, Geva T. Multimodality imaging guidelines for patients with repaired tetralogy of fallot: a report from the American Society of Echocardiography: developed in collaboration with the Society for Cardiovascular Magnetic Resonance and the Society for Pediatric Radiology. J Am Soc Echocardiogr. 2014;27:111–41.
66. Niemann PS, Pinho L, Balbach T, Galuschky C, Blankenhagen M, Silberbach M, Broberg C, Jerosch-Herold M, Sahn DJ. Anatomically oriented right ventricular volume measurements with dynamic three-dimensional echocardiography validated by 3-Tesla magnetic resonance imaging. J Am Coll Cardiol. 2007;50:1668–76.
67. Ait-Ali L, Siciliano V, Passino C, Molinaro S, Pasanisi E, Sicari R, Pingitore A, Festa P. Role of stress echocardiography in operated fallot: feasibility and detection of right ventricular response. J Am Soc Echocardiogr. 2014;27:1319–28.
68. Picano E, Pellikka PA. Stress echo applications beyond coronary artery disease. Eur Heart J. 2014;35:1033–40.
69. Kilner PJ, Geva T, Kaemmerer H, Trindade PT, Schwitter J, Webb GD. Recommendations for cardiovascular magnetic resonance in adults with congenital heart disease from the respective working groups of the European Society of Cardiology. Eur Heart J. 2010;31:794–805.
70. Kempny A, Dimopoulos K, Uebing A, Moceri P, Swan L, Gatzoulis MA, Diller GP. 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. 2012;33:1386–96.
71. Kempny A, Diller GP, Alonso-Gonzalez R, Uebing A, Rafiq I, Li W, Swan L, Hooper J, Donovan J, Wort SJ, Gatzoulis MA, Dimopoulos K. Hypoalbuminaemia predicts outcome in adult patients with congenital heart disease. Heart. 2015;101:699–705.
72. Dimopoulos K, Diller GP, Petraco R, Koltsida E, Giannakoulas G, Tay EL, Best N, Piepoli MF, Francis DP, Poole-Wilson PA, Gatzoulis MA. Hyponatraemia: a strong predictor of mortality in adults with congenital heart disease. Eur Heart J. 2010;31:595–601.
73. Zomer AC, Uiterwaal CS, van der Velde ET, Tijssen JG, Mariman EC, Verheugt CL, Vaartjes I, Pieper PG, Meijboom FJ, Grobbee DE, Mulder BJ. Mortality in adult congenital heart disease: are national registries reliable for cause of death? Int J Cardiol. 2011;152:212–7.

Risk Stratification and Prognosis

4

Vivan J. M. Baggen, Laurie W. Geenen,
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4.1 Introduction

The population of adult patients with congenital heart disease is steadily growing and aging, thanks to the major advances in cardiothoracic surgery and pediatric cardiology in the past decades. Although survival has improved and most of these patients have no complaints, today it is widely acknowledged that congenital heart disease is palliated, not cured. Residual or recurrent structural heart defects are common and may result in late complications such as heart failure and early demise. Therefore, these patients require lifelong surveillance and care in specialized cardiac centers [1]. In order to adequately manage this rapidly expanding population and to optimize patient outcomes, accurate prognostication is of paramount importance.

The etymology of the word "prognosis" dates back from the ancient Greek civilization and is literally translated as "foreknowledge." As a medical term, it is used to indicate the likely course and outcome of a disease. We aim to determine this forecast by a range of patient characteristics and tests, in order to make individualized risk predictions as accurate as possible. This chapter is therefore structured by a range of components that can be useful to stratify the risk of heart failure and other late complications in patients with ACHD. Although state-of-the-art prognostication and treatment in patients with ACHD are often based on extrapolated data from patients with chronic heart failure, this chapter aims to focus on the evidence that is available from congenital patients.

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4.2 Medical History

4.2.1 Congenital Defect and Corrective Surgery

The congenital heart defects can be grouped into mild, moderate, and complex lesions [2]. This classification is important, because it is well known that the survival of patients with a complex heart defect is substantially worse than the survival of patients with a mild type of heart defect [3–6]. Patients with a repaired patent ductus arteriosus or a repaired atrial or ventricular septal defect have the lowest all-cause mortality, being only slightly higher than or even comparable to the general population [4, 6, 7]. In contrast, the long-term survival of patients with a cyanotic defect, Fontan circulation, systemic ventricular heart, or other complex congenital heart disease is clearly diminished with a substantial morbidity [4, 5, 8]. The most frequent cause of death in these patients is chronic heart failure [4].

Among patients with the same congenital defect at birth, it is very important which type of corrective surgery was performed. In patients with transposition of the great arteries (TGA), major differences in ventricular function and functional capacity exist between those with a systemic right ventricle after a Mustard or Senning procedure compared with those who underwent anatomical correction by an arterial switch operation in a more recent surgical era [9]. Consequently, the survival of patients with TGA has markedly improved [10]. Also the preoperative anatomy may vary in severity, and concomitant congenital lesions in other organs may be present. For instance in patients with a Fontan circulation, the preoperative anatomy significantly impacts patient outcomes, with the lowest overall survival in patients with hypoplastic left heart syndrome [11] and heterotaxy syndrome [12]. The presence of concomitant lesions that require more extensive surgical correction, such as atrioventricular valve replacement at the time of Fontan correction, is also related to a higher risk of morbidity and mortality during long-term follow-up [12].

Among patients with the same congenital defect and type of repair, the practice of repair has undergone major changes over the past decades. Apart from improvement in surgical experience and quality of postoperative care, today's surgical techniques are different from those in the past and are adapted based on the late sequelae we now observe more than three decennia after repair. For instance, in patients with tetralogy of Fallot, later age at initial repair and the use of a palliative shunt have been shown to be associated with worse outcomes [13–15]. Corrective surgery is now seldom performed beyond the first half of infancy, and palliative shunts are almost no longer used. Modern strategies that include the avoidance of the use of a transannular patch and pulmonary valve-sparing approaches may improve patient outcomes [15], although comparisons are difficult because of era differences and the lack of long-term follow-up data of newer approaches [16]. In patients with a Fontan circulation, the overall survival has also greatly improved in later surgical eras, with the worst outcomes in patients with an atriopulmonary connection (the original technique) [11, 17] and probably the best outcomes in patients with an extracardiac conduit. Fontan patients with a longer bypass time also have an increased risk of mortality [12].

Table 4.1 Modified Bethesda classification

Mild congenital heart disease	Moderate congenital heart disease	Complex congenital heart disease
Unrepaired PFO or small ASD (no associated lesions)	Unrepaired PDA, ASD II, SVD, VSD (with significant shunt)	Congenitally corrected TGA
Unrepaired small VSD (no associated lesions)	AVSD (partial or complete, repaired or unrepaired)	Systemic right ventricle after Mustard/Senning repair for TGA
Repaired PDA	PAPVR with significant hemodynamic shunt or TAPVR	Truncus arteriosus
Repaired ASD II or SVD without residual shunt	Ebstein's anomaly	Conduits, valved, or nonvalved
Repaired VSD without residual shunt	Aortic coarctation	Double inlet left ventricle or double outlet right ventricle
Mild congenital aortic valve disease	Moderate/severe congenital aortic disease (subvalvar, valvular or supravalvar)	Hypoplastic left or right heart syndrome
Mild congenital mitral valve disease (no associated lesions)	Moderate/severe mitral valve disease (including parachute valve, cleft leaflet)	Mitral or tricuspid atresia
Mild pulmonary valve disease	Moderate/severe pulmonary valve disease or RVOT obstruction	Fontan procedure
	Arterial switch operation for TGA	PAH-CHD
	Repaired tetralogy of Fallot	Eisenmenger syndrome
	Pulmonary atresia with biventricular repair	Cyanotic congenital heart disease

ASD atrial septal defect; *AVSD* atrioventricular septal defect; *PAH-CHD* pulmonary arterial hypertension due to congenital heart disease; *PAPVR* partial anomalous pulmonary venous drainage; *PDA* patent ductus arteriosus; *PFO* patent foramen ovale; *RVOT* right ventricular outflow tract; *SVD* sinus venosus defect; *TAPVR* total anomalous pulmonary venous drainage; *TGA* transposition of the great arteries; *VSD* ventricular septal defect

In conclusion, the severity of the congenital heart disease is not only based on the type of defect but also strongly influenced by the type of corrective surgery, presence of concomitant lesions, and surgical era. Based on these differences, a suggested modification of the original Bethesda classification is provided in Table 4.1, which could be useful for the further guidance of follow-up schemes.

4.2.2 Genetics

The identification of a genetic syndrome or mutation is important, not only because it provides implications for future offspring but also because specific genetic variations are related to the risk of developing associated cardiac complications, such as arrhythmias and heart failure. For instance, ASD patients with an associated NKX2.5 syndrome have a higher risk of the development of atrioventricular block and ventricular dysfunction [18] and may even develop dilated cardiomyopathy. TBX5 is a gene which is involved in Holt-Oram syndrome, which includes

atrioventricular node disease, and also modulates diastolic dysfunction [19]. MYH6 mutations are associated with various forms of congenital heart disease but also with hypertrophic, dilated, and noncompaction cardiomyopathy [20]. In addition, a cardiac congenital abnormality as part of a genetic syndrome (such as Down, Patau, Edward, DiGeorge, Turner, Williams-Beuren, Noonan, or Alagille syndrome) can also involve noncardiac malformations [21]. These may impact perioperative morbidity and can have long-standing ramifications on neurodevelopment and overall health [22].

4.2.3 Age

The presence of chronic pressure or volume overload and cyanosis, as a result of valvular dysfunction, shunts, or other residual lesions, carries long-term effects that steadily increase over time. These effects include atrial and ventricular dilatation, dysfunction, fibrosis, and other forms of disease progression. Accordingly, observational studies show that the risk of heart failure and death continues to increase with age in patients with ACHD [4, 23, 24]. Apart from disease progression, the oldest patients also originate from an earlier surgical era, with a corresponding median later age at corrective surgery and possibly outdated surgical methods [5]. The oldest patients with ACHD therefore carry multiple risk factors for the development of heart failure. However, the strong positive correlation between age and age at initial corrective surgery makes it difficult to distinguish their separate effects and to foresee the rate of disease progression with age in the infants that are operated today with newer techniques.

4.2.4 Sex

Within the general population, men have a shorter life expectancy than women. Leading explanations can be classified as social/environmental (such as risky behavior, smoking, alcohol, homicide, suicide) and biological (such as effects of estrogen versus testosterone) [25]. This sex gap is also observed in patients with ACHD [26] and within specific diagnostic subgroups such as Fontan palliation [11]. It is unknown whether this can be directly translated from the general population or whether other factors such as medical therapy adherence also play a role.

4.2.5 Previous (Re)Interventions

Patients with multiple previous surgical or percutaneous (re)interventions are more frequently followed-up in a tertiary referral center. These patients are likely to represent a more complex congenital group and/or are in a worse clinical condition, with a subsequent higher mortality risk [3]. Multiple previous sternotomies may be present in congenital patients and can also be a risk factor on its own, because these

increase the risk of complications during surgery. Nevertheless, the absolute risk of reentry injury during repeat sternotomy for congenital heart disease is low [27].

4.2.6 Previous Heart Failure or Arrhythmia

A history of heart failure is associated with higher mortality rates, for instance, in patients with repaired tetralogy of Fallot [15]. A history of arrhythmias is also significantly associated with worse outcomes, such as the occurrence of heart failure, late arrhythmias, or mortality in patients with tetralogy of Fallot [14, 28], Mustard [5], and Fontan palliation [12, 17]. The association between early arrhythmias and heart failure may be explained by surgical damage to the conduction system and postoperative scarring. In addition, the presence of a pacemaker has been identified as a risk factor for mortality [29]. Pacemaker implantation in young adults with congenital heart disease is related to higher NT-proBNP levels, lower peak oxygen uptake, and a longer QRS duration, indicating that long-standing abnormal ventricular activation in patients with a pacemaker may contribute to progressive ventricular dysfunction and the occurrence of heart failure [30].

4.2.7 Cardiac Medication Use

Patients who do not use any cardiac medication such as an ACE inhibitor, angiotensin receptor blocker, beta blocker, diuretic, or antiarrhythmic are more likely to be in a good clinical condition and have a much lower risk to develop heart failure [23]. Patients who do use cardiac medication may have a history of heart failure or arrhythmia, with a subsequent higher risk of recurrence. In addition, the chronic use of negative inotropic antiarrhythmic drugs may negatively affect ventricular function. In patients after Fontan correction, diuretic therapy was strongly related to death, transplant [31], or hospitalization for cardiac reasons [17].

Also the lack of adequate medical therapy may increase the risk of complications. In many centers, all Fontan patients are routinely treated with systemic anticoagulation in order to manage the high thromboembolic risk due to low flow in the Fontan circuit, reduced cardiac output, possible Fontan obstruction, and atrial arrhythmias. Fontan patients lacking thromboprophylactic therapy (warfarin or aspirin) have been shown to carry a higher risk of death or transplant [31].

4.2.8 Clinical Symptoms of Heart Failure

Most patients with ACHD have no complaints and do not readily report symptoms. Patients often do not recognize subtle changes in functional class and may have no typical symptoms of heart failure. When present, symptoms of heart failure in congenital heart disease include symptoms of systemic ventricular failure (fatigue, dyspnea, dry cough, reduced exercise tolerance, orthopnea, paroxysmal nocturnal

dyspnea, wheezing) and symptoms of subpulmonary ventricular failure (fatigue, bloating, weight gain, loss of appetite, reduced exercise tolerance, increased abdominal girth) [32]. Clinical heart failure based on history, examination, and further investigations is documented in 22% of patients with Mustard repair for TGA, in 32% of patients with congenitally corrected TGA, and in 40% of patients after Fontan operation [32]. Early recognition and diagnosis of clinical heart failure is very important. The New York Heart Association (NYHA) functional class can be used to classify symptoms of heart failure, with patients who report no limitation in ordinary physical activity considered as NYHA functional class I. NYHA class is known to be significantly associated with adverse outcomes in the overall population of patients with ACHD [4] and also, for instance, in subgroups of patients with repaired tetralogy of Fallot [33] and Fontan palliation [34].

4.3 Physical Examination

4.3.1 Clinical Signs of Heart Failure

Signs of systemic ventricular failure on physical examination in patients with ACHD include a third or fourth heart sound, a laterally displaced apical impulse, basal crackles, absent breath sounds, and dull percussion at the lung basal fields. Signs of subpulmonary failure are elevated jugular venous pressure, hepatomegaly, ascites, pitting leg, and sacral or scrotal edema [32]. Of note, arrhythmias could also be a first clinical manifestation of heart failure. In addition, worsening of cyanosis could be present in patients with intra- or extracardiac shunts or fenestrations.

4.3.2 Oxygen Saturation

Pulse oximetry is routinely carried out alongside clinical examination mostly for diagnostic purposes. However, it also provides prognostic information. Systemic oxygen desaturation is related to a higher risk of cardiovascular events, death, or heart failure in the entire ACHD population [23] and also predicts mortality risk in specific subgroups such as Eisenmenger patients [24] and Fontan patients [29].

4.4 Electrocardiography and Holter Monitoring

Most patients with ACHD have abnormal electrocardiograms (ECGs). Therefore, comparison with previous ECGs in order to detect intraindividual changes in ECG morphology is most relevant to detect underlying disease progression with a higher risk of adverse events.

In concordance with a history of arrhythmia, also the loss of sinus rhythm at standard electrocardiographic evaluation is a strong predictor for clinical outcomes, for instance, in patients with Eisenmenger syndrome [24]. Additional evaluation of

arrhythmias is primarily performed in symptomatic patients and may require ambulatory ECG monitoring (Holter), event recorders, or implantable loop recorders. A grade II or greater ventricular arrhythmia on ambulatory ECG (which includes ≥30 unifocal or multifocal premature ventricular complexes per hour, non-sustained or sustained ventricular tachycardia) has been shown to be a risk marker of sudden death in some cohorts of patients with repaired tetralogy of Fallot [35], but not in all [15, 36].

Increased QRS duration has been shown to be associated with the occurrence of heart failure in ACHD patients with a pacemaker [30]. Also in patients with repaired tetralogy of Fallot, a prolonged QRS duration was predictive of ventricular tachycardia and death [15, 37]; however, conflicting data have been reported [14].

Although the current survival of patients after arterial switch operation for TGA is excellent, the most frequent cause of morbidity and mortality is coronary artery obstruction, which is present in 5–7% of survivors. Annual ECG evaluation for signs of ischemia (with advanced imaging if indicated) is therefore recommended in all arterial switch patients with ostial stenosis identified in childhood [10].

4.5 Transthoracic Echocardiography

Echocardiography is a widely available, portable, cheap, and noninvasive imaging technique that plays a key role in the clinical follow-up of patients with ACHD. However, the quality of echocardiographic measurements is highly user-dependent, and ventricular function and volumes can be challenging to assess in adults with complex congenital heart diseases such as univentricular hearts or systemic right ventricles [38]. An overview of some important echocardiographic predictors that are discussed below is also provided in Fig. 4.1.

4.5.1 Systolic Ventricular Function

The systolic ventricular function is one of the most important prognostic parameters obtained by echocardiography in the ACHD population. A moderately to severely impaired systemic ventricular function (as expressed by an ejection fraction below 40%) is an independent predictor for sudden cardiac death in the overall ACHD population [39]. This is also the case in specific ACHD subpopulations such as in patients with repaired tetralogy of Fallot [40] and in patients with a systemic right ventricle after Mustard procedure [41]. Also the right ventricular (or subpulmonary) systolic function has been shown to be of prognostic importance, for instance, as quantified using fractional area change [42].

The tricuspid annular plane systolic excursion (TAPSE) quantifies the longitudinal right ventricular function in M-mode. In patients with pulmonary arterial hypertension, the TAPSE is frequently reported as an important predictor for adverse clinical outcomes [43]. Accordingly in patients with Eisenmenger syndrome, one study showed that TAPSE was associated with the risk of mortality [44]; however,

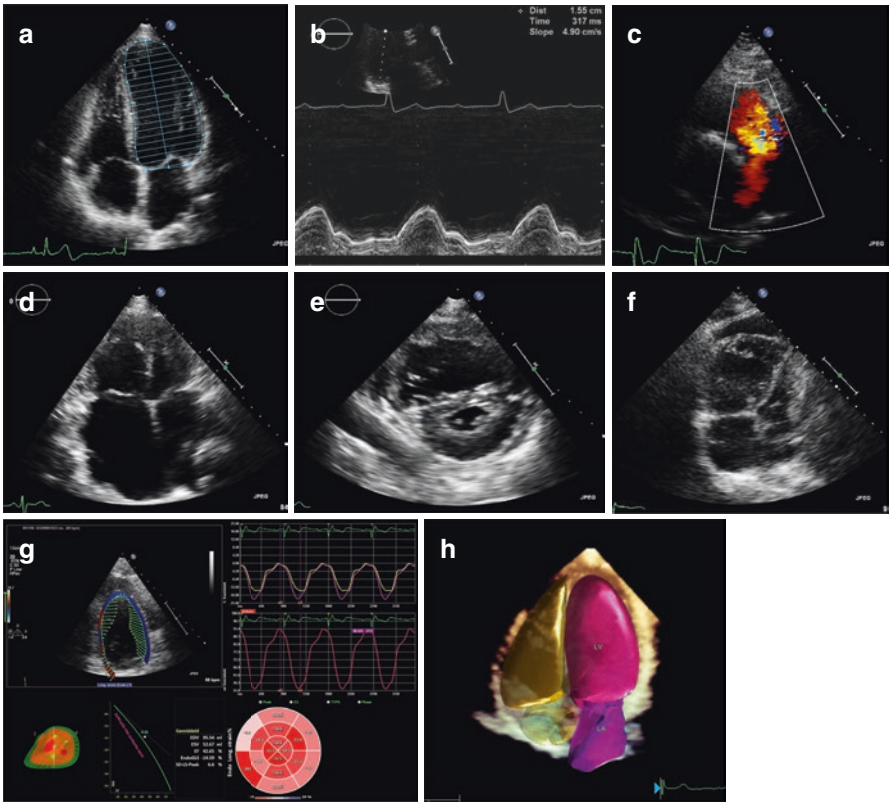


Fig. 4.1 Echocardiographic predictors of adverse clinical outcome in patients with ACHD. (**a**) Measurement of left ventricular ejection fraction using the biplane method of disks (modified Simpson's rule) in a patient with aortic coarctation. (**b**) Mildly reduced TAPSE (<16 mm) in a patient with tetralogy of Fallot. (**c**) Severe pulmonary valve regurgitation visualized using color flow Doppler in a patient with tetralogy of Fallot. (**d**) Severe biatrial dilatation and (**e**) D-shaped left ventricle in a patient with pulmonary arterial hypertension after surgical repair of a sinus venosus defect and partial anomalous pulmonary venous return. (**f**) Pericardial effusion in a patient with pulmonary arterial hypertension. (**g**) Global longitudinal left ventricular strain as quantified with speckle tracking echocardiography (courtesy of R. W. J. van Grootel). (**h**) 3D echocardiography analyzed using automated software (heart model)

contradictory results have been published in this patient group [24]. In patients with a systemic right ventricle after the Mustard procedure, the prognostic value of the lateral versus the septal TAPSE may differ [45]. Nevertheless, the TAPSE was not associated with the right ventricular ejection fraction as measured by cardiac magnetic resonance imaging (CMR) in these patients [46], and the contraction pattern of the systemic right ventricle is thought to shift from longitudinal to circumferential shortening [47]. Therefore, the prognostic value of TAPSE may be limited in this patient group. Although less often used, the mitral annular plane systolic excursion (MAPSE) was found to be associated with sudden cardiac death and ventricular

arrhythmias in patients with repaired tetralogy of Fallot, even beyond the left ventricular ejection fraction [42].

Other measures of the global ventricular function are the myocardial performance index (Tei index) and systolic to diastolic duration ratio. The systolic to diastolic duration has been reported as independent predictor of mortality in patients with a Fontan circulation and is relatively easy to measure, despite of the complex anatomy of the heart [48].

4.5.2 Ventricular and Atrial Dilatation

In patients with a systemic right ventricle, the ejection fraction may not always be a good indicator for the systolic ventricular function due to the frequent occurrence of atrioventricular valve regurgitation, which paradoxically increases the ejection fraction. One study has reported the systemic right ventricular end-diastolic volume to be a better parameter for adverse outcomes in patients with a systemic right ventricle [49]. In patients with repaired tetralogy of Fallot, right ventricular dilatation is often used to in the timing of pulmonary valve replacement, because it is thought that a severely dilated right ventricle is unable to reverse remodel.

Heart failure may lead to atrial dilatation due to chronic diastolic dysfunction [50]. Several studies have shown that both left and right atrial enlargements are related to a worse clinical prognosis [51]. In patients with pulmonary hypertension and in patients with Eisenmenger syndrome, increased right atrial area was found to be a strong predictor for adverse clinical outcomes [43, 44, 52]. Its association with disease severity can be explained by the failure of the right heart to overcome the high pulmonary pressures. As a result, the pressures in the right ventricle and right atrium will increase, which is often reflected by enlargement of the right atrium.

4.5.3 Shunt Lesions and Valve Disease

Doppler echocardiography can also be used to detect shunt lesions and to grade the severity of valve disease. The presence of a substantial shunt lesion or a hemodynamically significant residual shunt after ASD or VSD repair is important to detect and may require transesophageal echocardiography to be adequately visualized, because it impacts the classification of the severity of the heart defect and the follow-up strategy [2]. The presence of a pretricuspid shunt has been reported to be an independent predictor of death in Eisenmenger patients [24].

The grade of valvular stenosis or regurgitation also determines the severity of the heart defect [2] and is important to regularly assess during the routine echocardiographic follow-up of patients with valvular disease. For instance, in patients with repaired tetralogy of Fallot, a moderate or severe tricuspid or pulmonary valve regurgitation has been reported to be associated with an increased risk of sudden cardiac death and arrhythmias [15].

4.5.4 Pulmonary Arterial Hypertension

A substantial proportion of patients with ACHD develops pulmonary arterial hypertension and ultimately Eisenmenger syndrome [53]. Doppler echocardiography can be used to estimate pulmonary pressures based on the maximal tricuspid regurgitation velocity (together with the estimated right atrial pressure, based on inferior vena cava diameter and collapse) or the pulmonary regurgitation maximal and end-diastolic velocity. Long-standing pressure overload of the right ventricle may lead to progressive right ventricular heart failure. Therefore, it is not surprising that elevated pulmonary pressures are strongly indicative of a poor prognosis, and it is important to regularly follow-up right ventricular systolic pressures and function in patients with pulmonary hypertension to timely detect further deterioration.

Pericardial effusion may develop in patients with elevated filling pressures of the right side of the heart [54]. In patients with pulmonary arterial hypertension, pericardial effusion is the most extensively documented parameter that is known to be of prognostic importance [43]. In a multicenter study including patients with Eisenmenger syndrome, in 9.2% of the patients, pericardial effusion was present. The presence of pericardial effusion was found to be a strong predictor for all-cause mortality, even after adjusting for other risk factors such as age, NYHA class, pretricuspid shunt, sinus rhythm, and oxygen saturation [24].

Another specific prognostic parameter in pulmonary arterial hypertension is the septal shift during systole due to elevated pressures in the right ventricle [52], which is also known as the "D-sign" visible on the echocardiography.

4.5.5 Novel Echocardiographic Techniques

Speckle tracking echocardiography is a technique which can be used to obtain the ventricular function based on the quantitative assessment of myocardial deformation (strain) and myocardial displacement of displacement rate (velocity) with a high temporal resolution [55, 56]. One study has shown that systemic right ventricular two-dimensional longitudinal strain was associated with adverse clinical outcomes such as death, arrhythmias, and an increase in NYHA class in patients with a systemic right ventricle [45]. In patients with tetralogy of Fallot, the left ventricular longitudinal strain was related to sudden cardiac death or life-threatening arrhythmias and was associated with a higher NYHA class [42].

Three-dimensional (3D) echocardiography is an excellent imaging technique to visualize complex congenital anatomies, and the technique has improved impressively over the past years. Unfortunately, it is still not widely available and mainly relies on manual input, making it a time-consuming echocardiographic technique. New software has been developed to automatically analyze 3D images to shorten analysis time and to make it more feasible for routine practices. This novel software has been shown to measure the left atrial volume, left ventricular volume, and the left ventricular ejection fraction in strong agreement with CMR measurements [57, 58], also within specific subgroups such as patients with bicuspid aortic valve

disease [59]. 3D echocardiography may significantly contribute to the risk stratification of ACHD patients in the future when the image quality has further improved.

4.6 Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (CMR) is generally accepted as the reference standard when it comes to measurement of the volume, mass, and ejection fraction of both the right and the left ventricle. CMR also has its limitations such as higher costs, less availability, and limited ability to scan patients with intracardiac devices, but it is very useful when echocardiography is unable to provide images of sufficient quality or when echo measurements are borderline or ambiguous [53, 60]. CMR is therefore highly suitable in patients with complex congenital abnormalities in whom it is often difficult to obtain good echocardiographic images of the cardiac anatomy. A graphical illustration of the CMR predictors that are discussed below is provided in Fig. 4.2.

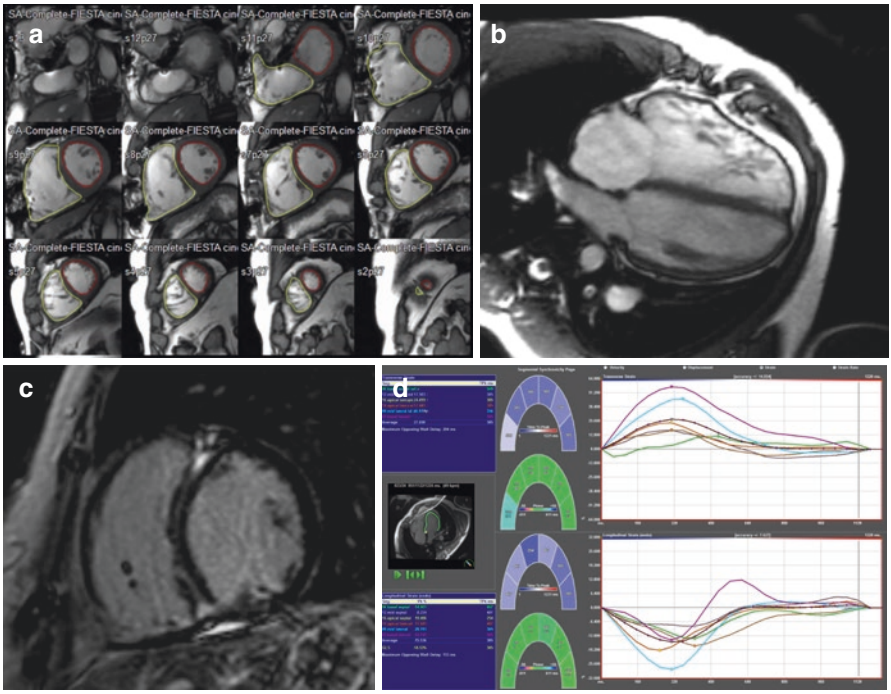


Fig. 4.2 Cardiac magnetic resonance imaging parameters that are reported to be of prognostic importance in patients with ACHD. (**a**) Left and right ventricular ejection fraction as measured by multi-slice short-axis cine imaging in a patient with congenital aortic stenosis. (**b**) Right ventricular dilatation and pronounced trabecularization as visualized on the four-chamber view in a patient with tetralogy of Fallot. (**c**) Late gadolinium enhancement at the right ventricular insertion points. (**d**) Feature tracking to derive regional and global left ventricular strain in a patient with tetralogy of Fallot (courtesy of R. W. J. van Grootel)

4.6.1 Ventricular Function and Volumes

In accordance with the studies that evaluated ventricular function in echocardiography, CMR-derived ejection fraction is strongly predictive of mortality or adverse cardiac events in several subgroups of patients with ACHD, including patients with a systemic right ventricle, repaired tetralogy of Fallot, Eisenmenger syndrome, and pulmonary hypertension [45, 61–63]. In addition, higher ventricular end-diastolic volumes are independently associated with a higher mortality risk in patients with a Fontan circulation [64] and in patients with repaired tetralogy of Fallot [62].

4.6.2 Myocardial Fibrosis

With the help of gadolinium enhancement technique in CMR, myocardial scarring and fibrosis can be detected. Increased late gadolinium enhancement of the left ventricle in patients with repaired tetralogy of Fallot is related to myocardial dysfunction and is associated with adverse outcomes after correcting for age [65]. The presence of late gadolinium enhancement located at the right ventricular insertion points is also thought to reflect a more advanced disease and poor prognosis in patients with tetralogy of Fallot and in patients with pulmonary arterial hypertension [66]. Therefore, myocardial fibrosis quantified by late enhancement could be a valuable additional tool for risk stratification. Myocardial T1 mapping is a relatively novel technique that is able to detect diffuse fibrosis as reflected by prolonged T1 times and to determine the extracellular volume [67]. In patients with a systemic right ventricle after correction of TGA, higher septal extracellular volumes correlate with other prognostic parameters such as NT-proBNP levels and the chronotropic index during CPET [68], suggesting that it may be of prognostic value in these patients.

4.6.3 Deformation Imaging

The deformation imaging technique that is available in CMR is known as feature tracking. Longitudinal and circumferential global left ventricular function measured by feature tracking closely agree with the same parameters measured by speckle tracking. Moreover, right ventricular feature tracking parameters showed to be associated with exercise capacity in patients with repaired tetralogy of Fallot, suggesting that it may be useful as prognostic parameter [69]. Also left ventricular dyssynchrony assessed by myocardial deformation imaging was found to be associated with adverse outcomes in patient with repaired tetralogy of Fallot [62]. However, contradictory results on strain measurements in patients with repaired tetralogy of Fallot have been reported, showing no association between strain measurements and deterioration in left and right ventricular function [70]. Hence, more research is needed to prove the prognostic value of this promising new technique.

4.7 Cardiac Computed Tomography

Computed tomography (CT) angiography has a very high spatial resolution and can therefore reliably evaluate the aortic size and small vasculature of the heart. Therefore, patients with an intrinsic higher risk of aortic dilatation and eventually dissection of the aorta, such as patients with a bicuspid aortic valve, Marfan syndrome, or a SMAD3 mutation, require follow-up by cardiac CT to timely detect any progression in aortic dilatation [71]. An ascending aortic area/height ratio of more than 10 cm^2/m is independently associated with in increased cardiovascular mortality risk in patients with a bicuspid aortic valve [72].

Nevertheless, in the overall population of patients with ACHD, serial cardiac CT measurements are unattractive due to the need of high dosages of ionizing radiation and are therefore not widely used for the risk stratification in patients with ACHD [53]. However, as the population of adults with congenital heart disease is aging, coronary heart disease may begin to develop in this population, which possibly expands the role for CT angiography in the follow-up and risk stratification of elderly patients with ACHD in the future.

4.8 Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing (CPET) consists of the assessment of exercise intolerance and ventilatory gas exchange during exercise and can be considered part of the regular follow-up in ACHD patients. Chronic heart failure is characterized by an impaired cardiac output response to exercise, and therefore CPET is widely used in the clinical follow-up for the development of heart failure in patients with ACHD [73].

4.8.1 Peak Oxygen Uptake

The peak oxygen uptake (peak VO_2) is one of the most important measures to quantify exercise capacity [74]. Peak VO_2 is diminished in symptomatic as well as asymptomatic ACHD patients [75], with the lowest peak VO_2 found in Eisenmenger syndrome and other cyanotic patients [76]. The majority of patients with a Fontan circulation fail to reach >80% of the predicted peak VO_2, independently of the type of Fontan operation [17]. Lower peak VO_2 is associated with a higher risk of hospitalization or death [75], the development of heart failure, and independently predicts mortality [76], indicating that it is a powerful prognostic tool within the entire ACHD population. Studies in specific ACHD populations, such as tetralogy of Fallot, transposition of the great arteries (TGA) corrected by atrial switch procedure, and Ebstein's anomaly, report comparable results regarding the prognostic importance of peak VO_2 [37, 77, 78]. Peak VO_2 may also be suitable for the assessment of perioperative risk in patients with repaired tetralogy of Fallot undergoing surgical pulmonary valve replacement [79].

In patients with a Fontan circulation, contradictory results regarding the predictive ability of the peak VO_2 have been reported. Some studies found an increased risk for mortality or morbidity in patients with a lower peak VO_2, even independent of other risk factors [80]. Others suggest that the impaired peak VO_2 in Fontan circulation does not arise from failure of univentricular circulation but from the intrinsic inability to adequately react to exercise and therefore has no predictive ability [17].

4.8.2 Ventilatory Efficiency

Ventilatory efficiency can be expressed by the slope of the minute ventilation versus the CO_2 production (VE/VCO_2) assessed during CPET. An elevated VE/VCO_2 slope (>30) indicates a pulmonary ventilation-perfusion mismatch due to an adequate ventilation but a poor perfusion due to the inability of the heart to adequately increase the cardiac output during exercise. In the overall ACHD population, a higher VE/VCO_2 slope was found to be associated with a higher risk of mortality; however this association was negated after adjustment for peak VO_2 [76]. Nevertheless, studies that investigated specific diagnostic subgroups such as tetralogy of Fallot, Fontan circulation, and TGA corrected by Mustard or Senning procedure did report that VE/CO_2 slope independently predicted heart failure-related hospitalization or cardiac-related death [37, 78]. Combined interpretation of the VE/CO_2 slope together with the peak VO_2 may further increase the accuracy of risk predictions.

4.8.3 Heart Rate Reserve

The chronotropic response is the ability of the heart to respond to exercise by increasing the heart rate. Most studies use the failure to achieve ≥80% of the heart rate reserve as a cutoff for chronotropic incompetence [81]. In a large cohort of 727 ACHD patients, chronotropic incompetence was present in 62% of the patients and was associated with severity of heart failure symptoms as expressed by the NYHA class [82]. The heart rate reserve and peak heart rate are both predictors for hospitalization or mortality in the overall ACHD population [82]. The heart rate reserve in patients with a Fontan circulation is a strong prognostic parameter to predict mortality or heart transplantation, independent of age, type of Fontan surgery, and the use of antiarrhythmic drugs. However, the prognostic value of heart rate reserve in this population seems to be inferior to other non-CPET-identified risk factors such as signs and symptoms of heart failure, non-total cavopulmonary connection type of Fontan circulation, and a medical history of clinically relevant arrhythmia [17].

Also in patients with Ebstein's anomaly, the heart rate reserve was shown to be a significant predictor of adverse outcomes [77].

4.8.4 Other Prognostic Parameters

In addition to the most clear prognostic parameters as previously mentioned, there are a couple of other CPET parameters that may be of prognostic importance. The peak load (Watt) as a measure for the exercise capacity is relatively easy to obtain in comparison to the peak VO_2, as no gas exchange measurements are required. Peak load may therefore be easier to use in daily clinical practice. Although less extensively investigated, peak load was shown to be associated with a higher risk of mortality in patients with a systemic right ventricle due to congenitally corrected TGA or TGA corrected by the atrial switch procedure [49]. Furthermore, a saturation drop of more than 5% during exercise is a predictor of all-cause mortality in the overall ACHD population [76], and a lower peak exercise systolic blood pressure is associated with an increased risk of adverse cardiac outcomes in patients with a systemic right ventricle [49].

4.9 Biomarkers

4.9.1 Standard Laboratory Testing

Basic laboratory testing should be performed in congenital patients that are suspected of heart failure, which includes a full blood count, iron, kidney function, liver function, protein and albumin, and thyroid function [32]. Anemia is not uncommon in patients with ACHD and is associated with a threefold higher risk of death. Low MCV and diuretic use are related to the presence of anemia in these patients, suggesting that iron depletion and the heart failure syndrome play a role in its pathogenesis. Iron deficiency has also been directly related to adverse outcomes in patients with Eisenmenger syndrome [83], and iron replacement therapy may even improve exercise capacity in these patients [84].

Renal dysfunction is more frequently observed in patients with cyanotic heart disease and is related to a worse prognosis. For instance, Fontan patients with postoperative renal insufficiency or a higher creatinine level have a significantly poorer outcome [12]. Liver dysfunction is most frequently reported in patients with a failing Fontan circuit and is known to have a direct effect on morbidity and mortality. The MELD-XI score, calculated from creatinine and total bilirubin which was originally developed for patients with end-stage liver disease, also predicts cardiac mortality and transplantation in Fontan patients [85].

Fontan patients who develop protein-losing enteropathy (PLE), as diagnosed by enteric loss of alpha-1-antitrypsin or the presence of low-serum total protein/albumin in addition to persistent or intermittent edema, are especially at high risk of death [12, 31]. PLE is difficult to treat; however, with recent advances the 5-year survival after the diagnosis of PLE has improved from 50 to 88% [86].

4.9.2 Natriuretic Peptides

In patients with heart failure, natriuretic peptides are firmly established prognostic tools. Neurohormonal activation of the natriuretic, endothelin, sympathoadrenergic, and renin-aldosterone systems also occurs in all types of congenital heart disease [87]. Accumulating evidence shows that N-terminal pro-B-type natriuretic peptide (NT-proBNP) is related to disease severity and that it is useful for risk stratification in patients with clinically stable ACHD, even beyond conventional risk markers [23, 88]. Interestingly, normal levels of NT-proBNP (<14 pmol/L) can accurately rule out the risk of death and heart failure with a high negative predictive value [23]. Therefore, natriuretic peptides have increasingly gained interest and are currently suggested as a component of the clinical work-up of patients with ACHD [32]. No published data is available yet to confirm that changes in natriuretic peptides over time can be used as a marker for outcome; however, data from acquired heart failure patients suggests that disease progression is related to substantial changes in NT-proBNP over time [89]. A position paper from the working group of grown-up congenital heart disease and the Heart Failure Association of the European Society of Cardiology has therefore suggested that a twofold increase of baseline NT-proBNP within 6 months is regarded as a significant increase which indicates the need for optimization of heart failure medical therapy [32].

4.9.3 Novel Biomarkers

Biomarkers that reflect other pathophysiological mechanisms which are involved in the heart failure syndrome, such as high-sensitive troponin-T (hs-TnT) and growth-differentiation factor 15 (GDF-15), are also related to the occurrence of heart failure in ACHD patients. In a prospective cohort of 595 patients with moderate and complex ACHD, elevated levels of hs-TnT (>14 ng/L, 8% of patients) and GDF-15 (>1109 ng/L, 15% of patients) could predict outcomes in ACHD patients with elevated levels of NT-proBNP, suggesting a potential benefit of a multi-marker approach [23]. Other promising novel cardiac markers are red cell distribution width, galectin-3, and ST-2, but longitudinal studies in patients with ACHD are not available yet.

4.10 Cardiac Catheterization

In patients with ACHD, cardiac catheterization is usually performed for specific anatomical, diagnostic, or physiological questions or for intervention. Some studies have reported hemodynamic variables as predictors for clinical outcome. As described in more detail above, the presence of pulmonary arterial hypertension is an important predictor of mortality [90]. Also in Fontan patients, elevated preoperative pulmonary artery pressures [91], elevated Fontan pressure, portal hypertension [29], and elevated right [31] and left atrial pressure [12] have been identified as risk factors for mortality.

4.11 Risk Stratification in Pregnancy

Although many women with heart disease may be in a stable clinical condition, pregnancy is associated with substantial hemodynamic changes that carry an increased risk of cardiac complications. The risk of complications is strongly influenced by the type of heart defect and presence of residual lesions. The modified World Health Organization (mWHO) classification seems to be the most accurate tool in predicting these risks [92]. It stratifies patients based on their underlying diagnosis into four groups from very low risk patients (mWHO I), to high risk patients in whom a pregnancy is thought to be life threatening and therefore contraindicated (mWHO IV) [93]. Pregnancy is contraindicated (mWHO IV) in women with pulmonary hypertension, severe cyanosis, reduced left ventricular function, previous peripartum cardiomyopathy with incomplete recovery, symptomatic left ventricular outflow tract obstruction, and Marfan patients with a dilated aortic root.

The most frequently encountered complications are heart failure and arrhythmia. Heart failure occurred in 13% of patients in the Registry of Pregnancy and Cardiac disease (ROPAC), a large worldwide registry on patients with cardiac disease becoming pregnant. Heart failure occurred more often at the end of the second trimester and around delivery. At higher risk were patients with cardiomyopathy or presented with heart failure before pregnancy [94]. Although supraventricular ectopy and supraventricular tachycardia are seen often in normal pregnant women, atrial fibrillation or flutter are very rare. In ROPAC, atrial fibrillation or flutter occurred in 1.3% of the pregnant women with structural heart disease and was associated with a marked increase in maternal mortality and low birth weight [95]. Ventricular tachyarrhythmia's occurred in 1.4% of pregnant women with cardiovascular disease in ROPAC, mainly in the third trimester, and was associated with heart failure during pregnancy and impacted fetal outcome [96].

Contraceptive advice and careful planning of the pregnancy are essential for women with cardiac disease [92]. Prepregnancy counseling should be performed in all women with known cardiac disease in an expertise center. An experienced multidisciplinary team should be available to provide care, before, during, and after pregnancy and should timely discuss the mode of delivery. A vaginal delivery is the preferred mode of delivery in most patients, when needed with epidural anesthesia and assisted second stage. A cesarean section is only preferred in specific high-risk groups such as patients with a dilated aorta or severe heart failure [97].

4.12 Risk Prediction

Few studies have attempted to develop risk prediction models specifically for patients with ACHD [76, 98] or to validate existing models designed for the general heart failure population [99, 100]. The Seattle Heart Failure Model (SHFM) allows prediction of survival with the use of easily obtained clinical characteristics, such as age, sex, weight, NYHA class, systemic ejection fraction, systolic blood pressure, cardiac medication use, laboratory values, and presence of a device. In patients with heart failure, the model provides an accurate estimate of mean, 1-, 2-, and 3-year survival and allows estimation of effects of adding medications or devices to a patient's regimen. Although the predicted mortality risks by the SHFM do not represent actual ACHD survival, it may help to identify subjects with ACHD at risk for adverse outcome and poor cardiopulmonary efficiency [100].

4.13 Conclusions and Recommendations

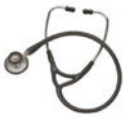
This chapter aimed to provide a comprehensive review of the factors that can be used in day-to-day clinical practice for the risk stratification of patients with ACHD. An overview of the most important reported prognostic factors is provided in Fig. 4.3. Of note, accurate risk stratification does not rely on a single parameter. An integral perspective of the patients' clinical prospects should always be based on a combination of all available information, which is composed of the medical history, physical examination, imaging, exercise testing, and biomarkers. The frequency at which individual patients should be monitored at the outpatient clinic and the type and frequency of additional investigations are based on expert opinion in specialist centers. A suggested follow-up scheme of clinically stable patients with ACHD is provided in Table 4.2. Nonetheless, considering the enormous heterogeneity of the ACHD population, the lack of evidence, and the differences in the availability of additional investigations among centers, it remains challenging to standardize the monitoring and follow-up of individual patients with ACHD.

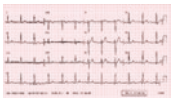
Regular follow-up

Medical History

- Complexity of the congenital heart defect
- Type of corrective surgery
- Pre-operative anatomy and concomitant lesions
- Surgical era and surgical technique
- Genetic syndrome or mutation
- Age and sex
- Previous (re)interventions
- Previous heart failure or arrhythmia
- Cardiac medication use
- Clinical symptoms of heart failure

Physical Examination and ECG

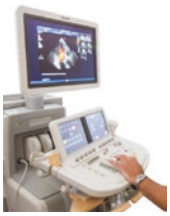




- Clinical signs of heart failure
- Saturation
- Changes in ECG morphology
- Loss of sinus rhythm
- QRS duration

Additional investigations

Echocardiography

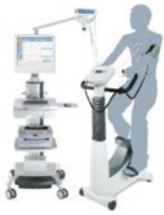


- Systolic ventricular function (LVEF, RVFAC, TAPSE, eyeballing)
- Ventricular and atrial dilatation
- (Residual) shunt lesions
- Severity of valvular disease
- Right ventricular pressure
- Pericardial effusion
- Novel techniques (strain, 3D echocardiography)

Cardiac MRI (CT)

- Systolic ventricular function (LVEF, RVEF)
- Ventricular dilatation
- Novel techniques (late gadolineum enhancement, feature tracking)

Exercise testing



- Peak oxygen uptake (peak VO2)
- Ventilatory efficiency (VE/VCO2 slope)
- Heart rate reserve (chronotropic incompetence)
- Peak load (Watt)

Biomarkers

- Full blood count, iron, kidney function, liver function, protein and albumin, thyroid function.
- NT-proBNP
- High-sensitive Troponin-T
- Growth-differentiation factor 15
- Potential novel biomarkers (galectin-3, ST-2)

Fig. 4.3 Risk factors for heart failure and mortality in patients with ACHD

Table 4.2 Outpatient clinic follow-up scheme of clinically stable patients with ACHD (proposed)

	Mild congenital heart disease	Moderate congenital heart disease	Complex congenital heart disease
Clinical follow-up	Every 2–5 years, depending on hemodynamic residuals; patients long-term (>5 years) after ASD closure without residual shunt or PH may be discharged	Every 1–2 years, depending on severity within subclassification and hemodynamic residuals	At least annually (when in clinically stable condition)
ECG	Routinely (at every checkup)	Routinely (at every checkup)	Routinely (at every checkup)
Chest X-ray	Not routinely advised	Not routinely advised	Not routinely advised
Ambulatory ECG monitoring (Holter)	On indication (palpitations)	On indication (palpitations)	Every 3–5 years and on indication (palpitations)
Ambulatory BP monitoring	On indication	On indication (aortic coarctation)	On indication
Echocardiography	Every 2–5 years, depending on hemodynamic residuals	Every 2 years, annually in case of severe valvular disease	Every 2 years, annually in case of severe valvular disease or on indication
Exercise testing	At least once (for comparison in case of future clinical deterioration)	Every 3–5 years and prepregnancy	Every 3–5 years and prepregnancy
CMR	On indication	Consider every 3–5 years	Consider every 3–5 years
CT	Not routinely advised	On indication (evaluation of aortic size/coarctation)	On indication
Full blood count, iron, kidney function, liver function, protein, albumin, thyroid function	Not routinely advised	At least once and when heart failure is suspected	At least once and when heart failure is suspected; every 2 years in Fontan patients
NT-proBNP	Every 5 years, annually when >15 pmol/L (>125 pg/mL)	Every 5 years, annually when >15 pmol/L (>125 pg/mL)	Every 5 years, annually when >15 pmol/L (>125 pg/mL)

References

1. Moons P, Engelfriet P, Kaemmerer H, et al. Delivery of care for adult patients with congenital heart disease in Europe: results from the Euro Heart Survey. Eur Heart J. 2006;27:1324–30.
2. Warnes CA, Liberthson R, Danielson GK, et al. Task force 1: the changing profile of congenital heart disease in adult life. J Am Coll Cardiol. 2001;37(5):1170.

3. van der Bom T, Mulder BJ, Meijboom FJ, et al. Contemporary survival of adults with congenital heart disease. Heart. 2015;101:1989–95.
4. Diller GP, Kempny A, Alonso-Gonzalez R, et al. Survival prospects and circumstances of death in contemporary adult congenital heart disease patients under follow-up at a Large Tertiary Centre. Circulation. 2015;132:2118–25.
5. Cuypers JA, Eindhoven JA, Slager MA, et al. The natural and unnatural history of the Mustard procedure: long-term outcome up to 40 years. Eur Heart J. 2014;35:1666–74.
6. Cuypers JA, Opic P, Menting ME, et al. The unnatural history of an atrial septal defect: longitudinal 35 year follow up after surgical closure at young age. Heart. 2013;99:1346–52.
7. Menting ME, Cuypers JA, Opic P, et al. The unnatural history of the ventricular septal defect: outcome up to 40 years after surgical closure. J Am Coll Cardiol. 2015;65:1941–51.
8. Engelfriet P, Boersma E, Oechslin E, et al. The spectrum of adult congenital heart disease in Europe: morbidity and mortality in a 5 year follow-up period. The Euro Heart Survey on adult congenital heart disease. Eur Heart J. 2005;26:2325–33.
9. Junge C, Westhoff-Bleck M, Schoof S, et al. Comparison of late results of arterial switch versus atrial switch (mustard procedure) operation for transposition of the great arteries. Am J Cardiol. 2013;111:1505–9.
10. Villafane J, Lantin-Hermoso MR, Bhatt AB, et al. D-transposition of the great arteries: the current era of the arterial switch operation. J Am Coll Cardiol. 2014;64:498–511.
11. d'Udekem Y, Iyengar AJ, Galati JC, et al. Redefining expectations of long-term survival after the Fontan procedure: twenty-five years of follow-up from the entire population of Australia and New Zealand. Circulation. 2014;130:S32–8.
12. Pundi KN, Johnson JN, Dearani JA, et al. 40-year follow-up after the Fontan operation: long-term outcomes of 1,052 patients. J Am Coll Cardiol. 2015;66:1700–10.
13. Van Arsdell GS, Maharaj GS, Tom J, et al. What is the optimal age for repair of tetralogy of Fallot? Circulation. 2000;102:III123–9.
14. Cuypers JA, Menting ME, Konings EE, et al. Unnatural history of tetralogy of Fallot: prospective follow-up of 40 years after surgical correction. Circulation. 2014;130:1944–53.
15. Gatzoulis MA, Balaji S, Webber SA, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. Lancet. 2000;356:975–81.
16. Bichell DP. Fourth decade after repair of tetralogy of Fallot: taking aim at moving targets. Circulation. 2014;130:1931–2.
17. Diller GP, Giardini A, Dimopoulos K, et al. Predictors of morbidity and mortality in contemporary Fontan patients: results from a multicenter study including cardiopulmonary exercise testing in 321 patients. Eur Heart J. 2010;31:3073–83.
18. Pashmforoush M, Lu JT, Chen H, et al. Nkx2-5 pathways and congenital heart disease; loss of ventricular myocyte lineage specification leads to progressive cardiomyopathy and complete heart block. Cell. 2004;117:373–86.
19. Zhu Y, Gramolini AO, Walsh MA, et al. Tbx5-dependent pathway regulating diastolic function in congenital heart disease. Proc Natl Acad Sci U S A. 2008;105:5519–24.
20. Granados-Riveron JT, Ghosh TK, Pope M, et al. Alpha-cardiac myosin heavy chain (MYH6) mutations affecting myofibril formation are associated with congenital heart defects. Hum Mol Genet. 2010;19:4007–16.
21. Egbe A, Lee S, Ho D, Uppu S, Srivastava S. Prevalence of congenital anomalies in newborns with congenital heart disease diagnosis. Ann Pediatr Cardiol. 2014;7:86–91.
22. Pierpont ME, Basson CT, Benson DW Jr, et al. Genetic basis for congenital heart defects: current knowledge: a scientific statement from the American Heart Association Congenital Cardiac Defects Committee, Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. Circulation. 2007;115:3015–38.
23. Baggen VJ, van den Bosch AE, Eindhoven JA, et al. Prognostic value of N-terminal Pro-B-type natriuretic peptide, Troponin-T, and growth-differentiation factor 15 in adult congenital heart disease. Circulation. 2017;135:264–79.
24. Kempny A, Hjortshoj CS, Gu H, et al. Predictors of death in contemporary adult patients with Eisenmenger syndrome: a Multicenter study. Circulation. 2017;135:1432–40.

25. Rogers RG, Everett BG, Onge JM, Krueger PM. Social, behavioral, and biological factors, and sex differences in mortality. Demography. 2010;47:555–78.
26. Zomer AC, Ionescu-Ittu R, Vaartjes I, et al. Sex differences in hospital mortality in adults with congenital heart disease: the impact of reproductive health. J Am Coll Cardiol. 2013; 62:58–67.
27. Kirshbom PM, Myung RJ, Simsic JM, et al. One thousand repeat sternotomies for congenital cardiac surgery: risk factors for reentry injury. Ann Thorac Surg. 2009;88:158–61.
28. Valente AM, Gauvreau K, Assenza GE, et al. Contemporary predictors of death and sustained ventricular tachycardia in patients with repaired tetralogy of Fallot enrolled in the INDICATOR cohort. Heart. 2014;100:247–53.
29. Elder RW, McCabe NM, Hebson C, et al. Features of portal hypertension are associated with major adverse events in Fontan patients: the VAST study. Int J Cardiol. 2013;168:3764–9.
30. Nothroff J, Norozi K, Alpers V, et al. Pacemaker implantation as a risk factor for heart failure in young adults with congenital heart disease. Pacing Clin Electrophysiol. 2006;29: 386–92.
31. Khairy P, Fernandes SM, Mayer JE Jr, et al. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. Circulation. 2008;117:85–92.
32. Budts W, Roos-Hesselink J, Radle-Hurst T, et al. Treatment of heart failure in adult congenital heart disease: a position paper of the Working Group of Grown-Up Congenital Heart Disease and the Heart Failure Association of the European Society of Cardiology. Eur Heart J. 2016;37:1419–27.
33. Sabate Rotes A, Eidem BW, Connolly HM, et al. Long-term follow-up after pulmonary valve replacement in repaired tetralogy of Fallot. Am J Cardiol. 2014;114:901–8.
34. Driscoll DJ, Offord KP, Feldt RH, Schaff HV, Puga FJ, Danielson GK. Five- to fifteen-year follow-up after Fontan operation. Circulation. 1992;85:469–96.
35. Garson A Jr, Nihill MR, McNamara DG, Cooley DA. Status of the adult and adolescent after repair of tetralogy of Fallot. Circulation. 1979;59:1232–40.
36. Cullen S, Celermajer DS, Franklin RC, Hallidie-Smith KA, Deanfield JE. Prognostic significance of ventricular arrhythmia after repair of tetralogy of Fallot: a 12-year prospective study. J Am Coll Cardiol. 1994;23(5):1151.
37. Muller J, Hager A, Diller GP, et al. Peak oxygen uptake, ventilatory efficiency and QRS-duration predict event free survival in patients late after surgical repair of tetralogy of Fallot. Int J Cardiol. 2015;196:158–64.
38. Babu-Narayan SV, Giannakoulas G, Valente AM, Li W, Gatzoulis MA. Imaging of congenital heart disease in adults. Eur Heart J. 2016;37:1182–95.
39. Koyak Z, Harris L, de Groot JR, et al. Sudden cardiac death in adult congenital heart disease. Circulation. 2012;126:1944–54.
40. Ghai A, Silversides C, Harris L, Webb GD, Siu SC, Therrien J. Left ventricular dysfunction is a risk factor for sudden cardiac death in adults late after repair of tetralogy of Fallot. J Am Coll Cardiol. 2002;40:1675–80.
41. Schwerzmann M, Salehian O, Harris L, et al. Ventricular arrhythmias and sudden death in adults after a Mustard operation for transposition of the great arteries. Eur Heart J. 2009; 30:1873–9.
42. Diller GP, Kempny A, Liodakis E, et al. Left ventricular longitudinal function predicts life-threatening ventricular arrhythmia and death in adults with repaired tetralogy of fallot. Circulation. 2012;125:2440–6.
43. Baggen VJ, Driessen MM, Post MC, et al. Echocardiographic findings associated with mortality ortransplant in patients with pulmonary arterial hypertension: a systematic review and meta-analysis. Neth Heart J. 2016;24:374–89.
44. Moceri P, Dimopoulos K, Liodakis E, et al. Echocardiographic predictors of outcome in eisenmenger syndrome. Circulation. 2012;126:1461–8.
45. Diller GP, Radojevic J, Kempny A, et al. Systemic right ventricular longitudinal strain is reduced in adults with transposition of the great arteries, relates to subpulmonary ventricular function, and predicts adverse clinical outcome. Am Heart J. 2012;163:859–66.

46. De Caro E, Bondanza S, Calevo MG, et al. Tricuspid annular plane systolic excursion for the assessment of ventricular function in adults operated on with mustard procedure for complete transposition of the great arteries. Congenit Heart Dis. 2014;9:252–8.
47. Pettersen E, Helle-Valle T, Edvardsen T, et al. Contraction pattern of the systemic right ventricle shift from longitudinal to circumferential shortening and absent global ventricular torsion. J Am Coll Cardiol. 2007;49:2450–6.
48. Cordina R, von Klemperer K, Kempny A, et al. Echocardiographic predictors of mortality in adults with a Fontan circulation. JACC Cardiovasc Imaging. 2017;10:212–3.
49. van der Bom T, Winter MM, Groenink M, et al. Right ventricular end-diastolic volume combined with peak systolic blood pressure during exercise identifies patients at risk for complications in adults with a systemic right ventricle. J Am Coll Cardiol. 2013;62:926–36.
50. Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. Am J Cardiol. 2002;90:1284–9.
51. Baggen VJ, Schut AW, Cuypers JA, et al. Prognostic value of left atrial size and function in adults with tetralogy of Fallot. Int J Cardiol. 2017;236:125–31.
52. Raymond RJ, Hinderliter AL, Willis PW, et al. Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. J Am Coll Cardiol. 2002;39:1214–9.
53. Baumgartner H, Bonhoeffer P, De Groot NM, et al. ESC guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J. 2010;31:2915–57.
54. Natanzon A, Kronzon I. Pericardial and pleural effusions in congestive heart failure-anatomical, pathophysiologic, and clinical considerations. Am J Med Sci. 2009;338:211–6.
55. Voigt JU, Pedrizzetti G, Lysyansky P, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging. 2015;16:1–11.
56. Mondillo S, Galderisi M, Mele D, et al. Speckle-tracking echocardiography: a new technique for assessing myocardial function. J Ultrasound Med. 2011;30:71–83.
57. Tsang W, Salgo IS, Medvedofsky D, et al. Transthoracic 3D echocardiographic left heart chamber quantification using an automated adaptive analytics algorithm. JACC Cardiovasc Imaging. 2016;9:769–82.
58. Medvedofsky D, Mor-Avi V, Amzulescu M, et al. Three-dimensional echocardiographic quantification of the left-heart chambers using an automated adaptive analytics algorithm: multicentre validation study. Eur Heart J Cardiovasc Imaging. 2017.
59. van den Hoven AT, Mc-Ghie JS, Chelu RG, et al. Transthoracic 3D echocardiographic left heart chamber quantification in patients with bicuspid aortic valve disease. Int J Cardiovasc Imaging. 2017.
60. Kilner PJ, Geva T, Kaemmerer H, Trindade PT, Schwitter J, Webb GD. Recommendations for cardiovascular magnetic resonance in adults with congenital heart disease from the respective working groups of the European Society of Cardiology. Eur Heart J. 2010;31:794–805.
61. Jensen AS, Broberg CS, Rydman R, et al. 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. 2015;8.
62. Ortega M, Triedman JK, Geva T, Harrild DM. Relation of left ventricular dyssynchrony measured by cardiac magnetic resonance tissue tracking in repaired tetralogy of fallot to ventricular tachycardia and death. Am J Cardiol. 2011;107:1535–40.
63. Baggen VJ, Leiner T, Post MC, et al. Cardiac magnetic resonance findings predicting mortality in patients with pulmonary arterial hypertension: a systematic review and meta-analysis. Eur Radiol. 2016;26:3771–80.
64. Rathod RH, Prakash A, Kim YY, et al. Cardiac magnetic resonance parameters predict transplantation-free survival in patients with fontan circulation. Circ Cardiovasc Imaging. 2014;7:502–9.
65. Dobson RJ, Mordi I, Danton MH, Walker NL, Walker HA, Tzemos N. Late gadolinium enhancement and adverse outcomes in a contemporary cohort of adult survivors of tetralogy of Fallot. Congenit Heart Dis. 2017;12:58–66.

66. Freed BH, Gomberg-Maitland M, Chandra S, et al. Late gadolinium enhancement cardiovascular magnetic resonance predicts clinical worsening in patients with pulmonary hypertension. J Cardiovasc Magn Reson. 2012;14:11.
67. Riesenkampff E, Messroghli DR, Redington AN, Grosse-Wortmann L. Myocardial T1 mapping in pediatric and congenital heart disease. Circ Cardiovasc Imaging. 2015;8:e002504.
68. Plymen CM, Sado DM, Taylor AM, et al. 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. 2013;14:963–8.
69. Kempny A, Fernandez-Jimenez R, Orwat S, et al. Quantification of biventricular myocardial function using cardiac magnetic resonance feature tracking, endocardial border delineation and echocardiographic speckle tracking in patients with repaired tetralogy of Fallot and healthy controls. J Cardiovasc Magn Reson. 2012;14:32.
70. Jing L, Wehner GJ, Suever JD, et al. Left and right ventricular dyssynchrony and strains from cardiovascular magnetic resonance feature tracking do not predict deterioration of ventricular function in patients with repaired tetralogy of Fallot. J Cardiovasc Magn Reson. 2016;18:49.
71. Tadros TM, Klein MD, Shapira OM. Ascending aortic dilatation associated with bicuspid aortic valve: pathophysiology, molecular biology, and clinical implications. Circulation. 2009;119:880–90.
72. Masri A, Kalahasti V, Svensson LG, et al. Aortic cross-sectional area/height ratio and outcomes in patients with bicuspid aortic valve and a dilated ascending aorta. Circ Cardiovasc Imaging. 2017;10:e006249.
73. Guazzi M, Arena R, Halle M, Piepoli MF, Myers J, Lavie CJ. 2016 focused update: clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. Circulation. 2016;133:e694–711.
74. Guazzi M, Adams V, Conraads V, et al. EACPR/AHA scientific statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. Circulation. 2012;126:2261–74.
75. Diller GP, Dimopoulos K, Okonko D, et al. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. Circulation. 2005; 112:828–35.
76. Inuzuka R, Diller GP, Borgia F, et al. Comprehensive use of cardiopulmonary exercise testing identifies adults with congenital heart disease at increased mortality risk in the medium term. Circulation. 2012;125:250–9.
77. Radojevic J, Inuzuka R, Alonso-Gonzalez R, et al. Peak oxygen uptake correlates with disease severity and predicts outcome in adult patients with Ebstein's anomaly of the tricuspid valve. Int J Cardiol. 2013;163:305–8.
78. Giardini A, Hager A, Lammers AE, et al. Ventilatory efficiency and aerobic capacity predict event-free survival in adults with atrial repair for complete transposition of the great arteries. J Am Coll Cardiol. 2009;53:1548–55.
79. Babu-Narayan SV, Diller GP, Gheta RR, et al. Clinical outcomes of surgical pulmonary valve replacement after repair of tetralogy of Fallot and potential prognostic value of preoperative cardiopulmonary exercise testing. Circulation. 2014;129:18–27.
80. Ohuchi H, Negishi J, Noritake K, et al. Prognostic value of exercise variables in 335 patients after the Fontan operation: a 23-year single-center experience of cardiopulmonary exercise testing. Congenit Heart Dis. 2015;10:105–16.
81. Brubaker PH, Kitzman DW. Chronotropic incompetence: causes, consequences, and management. Circulation. 2011;123:1010–20.
82. Diller GP, Dimopoulos K, Okonko D, et al. Heart rate response during exercise predicts survival in adults with congenital heart disease. J Am Coll Cardiol. 2006;48(6):1250.
83. Van De Bruaene A, Delcroix M, Pasquet A, et al. Iron deficiency is associated with adverse outcome in Eisenmenger patients. Eur Heart J. 2011;32:2790–9.
84. Tay EL, Peset A, Papaphylactou M, et al. 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. 2011;151:307–12.

85. Assenza GE, Graham DA, Landzberg MJ, et al. MELD-XI score and cardiac mortality or transplantation in patients after Fontan surgery. Heart. 2013;99:491–6.
86. John AS, Johnson JA, Khan M, Driscoll DJ, Warnes CA, Cetta F. Clinical outcomes and improved survival in patients with protein-losing enteropathy after the Fontan operation. J Am Coll Cardiol. 2014;64:54–62.
87. Bolger AP, Sharma R, Li W, et al. Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease. Circulation. 2002;106:92–9.
88. Popelova JR, Kotaska K, Tomkova M, Tomek J. Usefulness of N-terminal pro-brain natriuretic peptide to predict mortality in adults with congenital heart disease. Am J Cardiol. 2015;116:1425–30.
89. Masson S, Latini R, Anand IS, et al. Prognostic value of changes in N-terminal pro-brain natriuretic peptide in Val-HeFT (Valsartan Heart Failure Trial). J Am Coll Cardiol. 2008;52:997–1003.
90. Gabriels C, De Meester P, Pasquet A, et al. A different view on predictors of pulmonary hypertension in secundum atrial septal defect. Int J Cardiol. 2014;176:833–40.
91. Burkhart HM, Dearani JA, Mair DD, et al. The modified Fontan procedure: early and late results in 132 adult patients. J Thorac Cardiovasc Surg. 2003;125:1252–9.
92. van Hagen IM, Boersma E, Johnson MR, et al. Global cardiac risk assessment in the registry of pregnancy and cardiac disease: results of a registry from the European Society of Cardiology. Eur J Heart Fail. 2016;18:523–33.
93. Roos-Hesselink JW, Ruys TP, Stein JI, et al. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. Eur Heart J. 2013;34:657–65.
94. Ruys TP, Roos-Hesselink JW, Hall R, et al. Heart failure in pregnant women with cardiac disease: data from the ROPAC. Heart. 2014;100:231–8.
95. Salam AM, Ertekin E, van Hagen IM, et al. Atrial fibrillation or flutter during pregnancy in patients with structural heart disease. JACC Clin Electrophysiol. 2015;1:284–92.
96. Ertekin E, van Hagen IM, Salam AM, et al. Ventricular tachyarrhythmia during pregnancy in women with heart disease: data from the ROPAC, a registry from the European Society of Cardiology. Int J Cardiol. 2016;220:131–6.
97. European Society of G, Association for European Paediatric C, German Society for Gender M et al. ESC guidelines on the management of cardiovascular diseases during pregnancy: the task force on the management of cardiovascular diseases during pregnancy of the European Society of Cardiology (ESC). Eur Heart J. 2011;32:3147–97.
98. Yap SC, Harris L, Chauhan VS, Oechslin EN, Silversides CK. Identifying high risk in adults with congenital heart disease and atrial arrhythmias. Am J Cardiol. 2011;108:723–8.
99. Lin EY, Cohen HW, Bhatt AB, et al. Predicting outcomes using the heart failure survival score in adults with moderate or complex congenital heart disease. Congenit Heart Dis. 2015;10:387–95.
100. Stefanescu A, Macklin EA, Lin E, et al. Usefulness of the Seattle heart failure model to identify adults with congenital heart disease at high risk of poor outcome. Am J Cardiol. 2014;113:865–70.

Co-morbidities

5

Pastora Gallego

5.1 Introduction

Increasing survivorship in patients with CHD leads to a greater chronic exposure to potential risk factors that can contribute to the likelihood of developing HF. It is also recognized that ageing is a key determinant of HF risk, and clinical HF predominantly affects "elderly" individuals [1]. The median age of people alive with severe CHD rose 14 years from 1985 to 2010 and was estimated to be 25 years in 2010 [2]. The population of patients over 60 years old is steadily increasing [3, 4] as is hospitalization in those older than 65 years [5]. In these elderly patients, HF is often accompanied by a range of co-morbidities that add to the disease burden [3, 4]. Adult cardiologists are charged with the coordination of comprehensive care for these complex patients, including the management of extra-cardiac manifestations that arise later in life. This review outlines the prevalence and prognostic relevance of the most prevalent co-morbidities associated with HF in ACHD patients.

5.2 Epidemiology of Co-Morbidities in Adults with CHD

Co-morbidity may be defined as a chronic condition that coexists in an individual with a primary CHD. A distinction is made between noncardiac co-morbidities and cardiac conditions that are directly related to the presence of HF, such as arrhythmias or pulmonary hypertension, or exacerbate it like systemic hypertension or coronary artery disease (CAD) [6]. In addition to other medical conditions existing simultaneously but independently, such as cancer or

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pneumonia, ACHD patients have much extra-cardiac morbidity. These include both syndromes associated with noncardiac abnormalities and, more commonly, sequelae of the underlying heart defect or of prior medical treatments [7]. Table 5.1 summarizes the most frequently occurring co-morbidities in the ACHD population.

In a population of young adults with CHD (average age of 28.1 years,) 2.4–9.3% had important co-morbidities—with both cardiovascular and noncardiac co-morbidities being much more common than in a control population [31]. More recently, Bracher et al. reported a prevalence of 51% of patients with at least one co-morbidity in a contemporary tertiary centre cohort. Systemic arterial hypertension (10.7%), thyroid dysfunction (9.3%), psychiatric disorders (8.5%), neurologic disorders (7.1%), chronic obstructive or restrictive lung disease (6.7%) and previous stroke (6.4%) were the co-morbidities with the highest prevalence. As expected, the distribution of co-morbidities varied with the different individual diagnostic categories. Patients were more likely to have hypertension with repaired aortic coarctation or liver cirrhosis with Fontan palliation. At a median age of 38 years, diabetes or CAD was significantly more frequent in patients with simple defects. In contrast, thyroid dysfunction or gout occurred commonly in patients with moderate/great complexity defects. In this study, near a quarter of all patients (23%) had two or more, and up to seven, co-morbidities and the occurrence of most were dependent. Multiple co-morbidities were also unequally distributed among the different CHD.

In parallel with their high prevalence, extra-cardiac conditions may play an integral role in HF progression and response to therapy and have been recognized as important modifiers of outcomes [7]. Most of the co-morbidities result in a greater number of hospitalizations [42, 43], poorer quality of life and increased mortality [44]. In a cross-sectional study of 122,630 elderly patients with acquired HF, patients with >5 co-morbidities were responsible for 81% of all hospital days [45]. Opotowsky et al. [42] reported a significant increase in the proportion of patients with ≥ 2 co-morbidities among the ACHD admissions between 1998 and 2005. Patients in this study were older (mean age 53.1 ± 0.3 years) and co-morbidities more frequently in those with moderate and complex disease. While numerous studies have shown a strong association between a single co-morbidity and adverse clinical outcomes [22, 26, 46], Bracher et al. [44] examined the impact of multiple co-morbidities on survival of ACHD patients. Their observations support the hypothesis that patients with increasing number of co-morbidities have an increasing risk for death and HF (Fig. 5.1). Given the high morbidity and mortality of HF in ACHD, it is of great importance to diagnose and to treat possible co-morbidities. Unfortunately, these extra-cardiac conditions may be masked by the signs and symptoms of HF and, therefore, may go unnoticed. For example, differentiating ventilatory versus cardiac limitation to exercise can be challenging. The creation of ACHD-specific diagnostic strategies and a multidisciplinary approach can facilitate their detection and improve outcome.

Table 5.1 Co-morbidities in ACHD with heart failure

Acquired cardiovascular co-morbidities	Coronary artery disease [3, 4, 8, 9]	
	Cerebrovascular disease [10]	Stroke Intracranial aneurysms Cerebral complications of cyanosis
	Peripheral vascular disease	Prior catheterizations [11] Chronic venous insufficiency [11] Endothelial dysfunction Aortic aneurysm [12]
Cardiovascular risk factors	Hypertension [3, 8]	
	Dyslipidaemia [13]	
	Lifestyle [14]	Smoking Physical inactivity
	Diabetes [15]	
	Obesity [16]	
	Metabolic syndrome [17]	
Pulmonary disease	Pneumonia [18]	
	Sleep-disordered breathing [19–21]	
	Restrictive lung disease [22, 23]	
	Pulmonary hypertension	
Haematological disorders	Anaemia [24, 25]	
	Cyanosis, erythrocytosis	
	Haemorrhagic diathesis	
Renal dysfunction	Acute kidney injury	
	Chronic renal dysfunction [26]	
	Gout	
Neuropsychological issues	Neurocognitive functioning	Neurodevelopmental disorders [27] Cognitive impairment [27, 28] Dementia [3]
	Psychological issues	Depression [29] Anxiety [30]
	Epilepsy [31]	
Liver disease [32]	Congestive hepatopathy	
	Acute liver injury [33]	
	Cirrhosis	
	Cholelithiasis [34]	
	Iatrogenesis	Drug-related hepatitis Transfusion-related hepatitis
	Hepatocarcinoma [35]	
Endocrine disorders	Thyroid dysfunction [36–38]	
	Neuroendocrine tumours [39, 40]	
	Sexual dysfunction	
Skeletal disorders	Thoracic insufficiency syndrome [41]	
	Scoliosis magna [22]	
Malignancies	Chemotherapy	
	Radiation exposure	

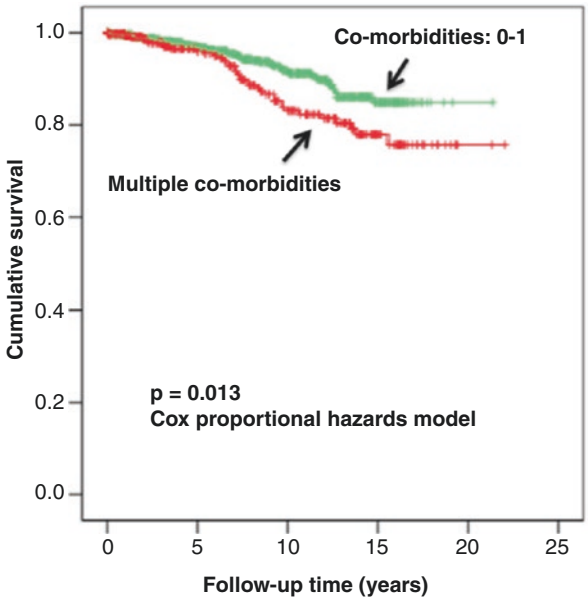

Fig. 5.1 Kaplan-Meier curves for adults with congenital heart disease with multiple co-morbidities vs. with none or one single co-morbidity (adapted with permission from Bracher et al. [44])

5.3 Renal Dysfunction

It is well recognized that cardiovascular and renal functions are closely related. Many patients with HF have evidence of renal dysfunction in the absence of intrinsic renal disease. The prevalence of renal failure in HF patients is estimated to be 40–60% [47]. ACHD patients are also at risk for developing renal dysfunction. Dimopoulos et al. [26] reported an overall prevalence of renal impairment of 50%. Interestingly, it occurred early in adulthood with a mean age of 36 ± 14 years. Renal function was worse in patients with complex lesions, particularly in patients with cyanosis, but a low glomerular filtration rate was present even in those with simple defects. The proportion of individuals with severely reduced glomerular filtration rate (< 60 mL/min m^2) was 35-fold higher in cyanotic patients and 18-fold higher in non-cyanotic patients compared to the general population.

5.3.1 Mechanisms Linking ACHD to Renal Dysfunction

Syndromic associations between familiar forms of left ventricular outflow tract obstructions (Williams-Beuren syndrome) and renal artery stenosis have been reported [48]. However, a number of other risk factors for potential development of renal dysfunction have been recognized. These include erythrocytosis, cyanosis, changes in intra-glomerular haemodynamics and neurohormonal activation [49]. Cyanosis is thought to affect renal function directly via chronic hypoxia and ischaemia but also indirectly through erythrocytosis and increased blood viscosity that can affect glomerular arteriolar resistance, filtration and renal perfusion [26, 50]. Importantly, in the study by Dimopoulos

et al. [26], it was not only cyanotic patients that were at increased risk. As in acquired cardiac dysfunction, chronically elevated central venous pressure (CVP) and depressed cardiac output lead to renal venous congestion and reduced renal blood flow contributing to renal injury. Additionally, even asymptomatic patients may have high levels of neurohormonal factors [51]. Other potential causes of renal dysfunction are prior cardiopulmonary bypass [26, 50], use of diuretics [26] and nephrotoxic medications including contrast agents [7, 49]. In contrast to what happens with intrinsic factors, these extrinsic factors, related to medical management, may be modifiable.

5.3.2 Prognosis

Adults with moderate to severe glomerular filtration rate have lower survival [26]. Afilalo et al. [3] demonstrated that chronic renal failure is one of the most powerful independent predictors of mortality in CHD patients older than 65 years. This is not simply because it is a marker of advanced ACHD HF, but chronic kidney disease itself is also a risk factor for acquired cardiac co-morbidity contributing to death. For example, patients with renal disease suffer accelerated atherosclerotic coronary artery disease, hypertension, anaemia and fluid retention [52]. Additionally, renal dysfunction impacts on both indication for intervention and response of medical treatment [7, 26]. Patients with renal hypoperfusion are less likely to undergo interventions due to high perioperative risk [53]. They have shown an impaired response to diuretics and ACE inhibitors and are at increasing risk of adverse outcomes with digitalis [54].

5.3.3 Management

Although there are no currently clear guidelines in terms of renal assessments and risk stratification, evidence suggests that patients should be monitored from an early age for renal dysfunction. Avoiding dehydration and nephrotoxic drugs and judicious use of contrast administration should be standard. Importantly, quicker identification of acute kidney injury after cardiac surgery or procedures allows early intervention in an attempt to prevent further deterioration. There is also an opportunity to mitigate chronic kidney disease progression and negative renal outcomes by instituting universally accepted interventions including stringent blood pressure control and treatment of proteinuria. Finally, assessment of renal artery anatomy and flow should be desirable in selected populations [48].

5.4 Haematological Disorders

5.4.1 Anaemia

In acquired HF patients, anaemia is common and is a strong marker of adverse outcomes, and it has been recently recognized as a novel therapeutic target [52]. In HF syndrome, anaemia is likely the result of a complex interaction between

cardiac performance, neurohormonal and inflammatory activation, renal dysfunction and bone marrow responsiveness. CHD appears to have systemic manifestations similar to acquired HF and a 13–29% prevalence [24, 25]. Remarkably, in this latter cohort with complex defects and systemic ventricular dysfunction, there was also evidence of a gradual decrease of haemoglobin over time, which presented in 39% of patients during 5 years follow-up [25]. These studies importantly demonstrated the occurrence of anaemia at a much younger age than in acquired HF.

In the ACHD population, decreased renal function, treatment with diuretics and impaired functional class [24, 25] have been found strongly related to anaemia. This may indicate that HF is an important contributing mechanism of anaemia in these patients. However its association with low mean corpuscular volume and warfarin treatment favour iron deficiency being another potential mechanism [24]. In fact, ventricular dysfunction per se has been demonstrated to be associated with impaired iron supply for erythropoiesis [55]. Anaemia remained significantly and independently related to all-cause mortality [24].

ACHD patients should be screened for anaemia, particularly those with congestive HF. At present, there is insufficient data to make a specific treatment recommendation, but erythropoietin and iron administration have resulted in symptomatic improvement in chronic HF [56]. However, diagnostic evaluation for reversible causes of anaemia such as iron deficiency or occult blood loss is appropriate in all patients.

5.4.2 Cyanosis, Erythrocytosis and Hyperviscosity

As optimal haemoglobin concentration depends on the degree of hypoxaemia, defining anaemia in cyanotic CHD is difficult. Relative anaemia, therefore, occurs at much higher levels of haemoglobin and often goes unnoticed [57]. A major cause of relative anaemia is iron deficiency, but microcytosis and hypochromia are often absent. Thus, serum ferritin and transferrin levels are required for diagnosis. Despite high haematocrit, iron supplementation has demonstrated to improve exercise capacity in iron-deficient cyanotic patients without increasing the risk for hyperviscosity [58].

Cyanotic patients with HF have an increased thromboembolic risk [59], and decisions on antithrombotic therapy are challenging balancing the risks of clotting with the increased risk of bleeding. Haemorrhagic diathesis and hypocoagulable haemostatic profiles have been identified in cyanotic CHD, and haematocrit elevations have been related to impaired haemostasis [60]. A small subset of cyanotic patients may experience symptoms of hyperviscosity (such as fatigue, headache, visual changes, and dizziness factors such as dehydration or diuretics use) [61]. Before diagnosing hyperviscosity, iron deficiency, which is much more common, needs to be excluded and, if present, corrected.

5.5 Pulmonary Disease

5.5.1 Pneumonia

Pneumonia is a major case of noncardiac death in older ACHD patients [3, 18]. However reports of the frequency of pneumonia-related death vary. Co-morbid conditions such as diabetes are risk factors. Preventive measures to avoid hospital-acquired pneumonia are important for this at risk HF population.

5.5.2 Sleep-Disordered Breathing

Sleep-disordered breathing (SDB), including obstructive sleep apnoea (OSA) and central sleep apnoea (CSA), has been extensively reported in adults with HF, hypertension, ischaemic heart disease, cardiac arrhythmias and pulmonary hypertension [62]. OSA results from a complete or partial collapse of a normal pharynx during apnoea. By contrary, CSA results from either a decrease in central respiratory drive or instability in feedback control of the central respiratory centre. SDB may occur in 5–15% of the middle-aged population [63], but the prevalence is higher in HF patients: 40% have CSA and 11% have OSA [64]. SDB may increase the risk of morbidity and mortality in cardiovascular diseases. Of a total of 4422 patients aged above 40 years (43.5% males) who did not have known HF or CAD, OSA was an independent predictor of myocardial infarction and CAD-related mortality, particularly with an apnoea-hypopnoea index over 30 (severe OSA) [65]. Figure 5.2

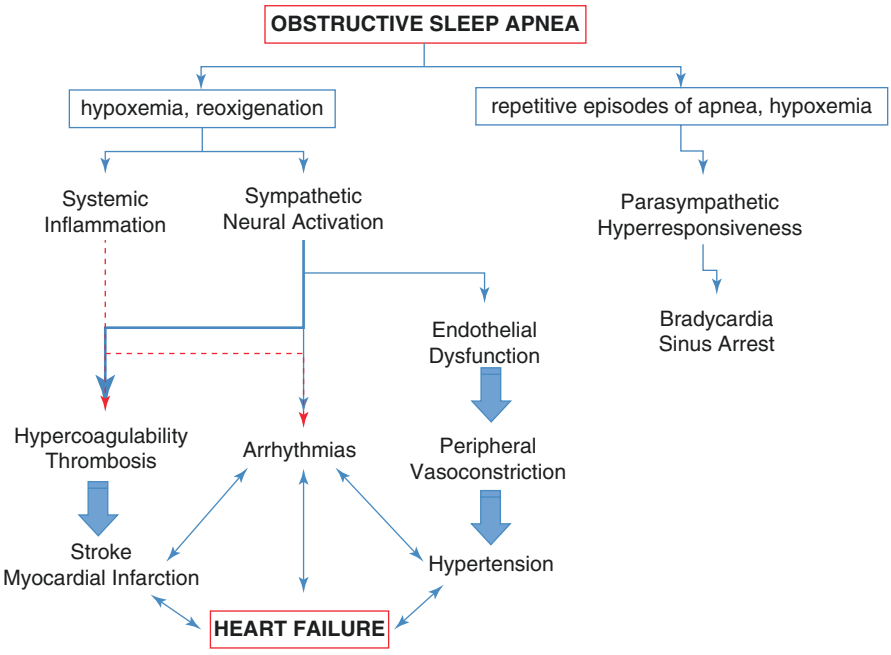

Fig. 5.2 Pathophysiological effects of obstructive sleep apnoea on the cardiovascular system

summarizes the physiological effects of SDB that have a detrimental effect on the cardiovascular system. Both SBD and HF share many aspects of deranged neurohumoral and immunological function.

Few studies to date have investigated SDB in adults with CHD. In a small study of 20 middle-aged Eisenmenger patients, the reported prevalence of SDB was equal to the general population (15%) with body index mass and age as the only predictors for OSA [19]. In contrast Cotts et al. [20] reported the prevalence of SDB in patients after atrial switch procedures to be 44%, even higher than in acquired HF. There are a number of potential explanations. Most of these patients were on HF treatment, 50% had ventricular dysfunction and 41% had a history of atrial arrhythmias. One theory is that soft tissue oedema of the neck (redistributed when lying supine) and increased airway resistance may lead to increased inspiratory force and collapse of upper airway [62].

Alternatively OSA could contribute to ACHD HF by virtue of its effects on neurohormonal activation, endothelial dysfunction, hypertension and ischaemic heart disease [62], which are known to be significant predictors of outcomes [4, 21]. The effects of OSA in cardiac physiology, including hypoxia-induced pulmonary vasoconstriction and reduction in systemic venous return, are especially detrimental in Fontan patients [82]. In summary, the coexistence of haemodynamic impairment and neurohormonal activation in ACHD and OSA may create a vicious circle of progressing HF and further exacerbation of OSA.

Despite its strong association with HF syndrome, it should be noted that the majority of patients with SDB remain undiagnosed. A simple questionnaire to screen patients for OSA or home-based unattended sleep studies helps identify patients at risk [20]. Likewise, treating OSA in HF patients remains challenging. Controlled trials of continuous positive airway pressure (CPAP) have not been conclusive. CPAP only reduces risk in HF patients with CSA [52]. Likewise, CPAP itself is known to impede systemic venous return and reduce cardiac output. Noninvasive positive pressure ventilation titrations in the cardiac catheterization laboratory may be needed to establish safe thresholds [82].

5.5.3 Restrictive Lung Defects

Abnormal lung function is common in ACHD and is associated with decreased exercise capacity and worsened functional status. Nearly half (44–47%) of patients have spirometry-diagnosed restrictive lung disease (RLD) [22], including 89% following Fontan repair and 76% with TOF [66]. HF syndrome patients have similar ventilation and diffusion impairments which are predictors of mortality [23]. Predictors of RLD include multiple prior thoracotomies, diaphragmatic nerve palsy, cardiomegaly, atrial arrhythmias (perhaps related to amiodarone), scoliosis, complex CHD and increased body mass index [22, 66]. Importantly, moderately to severely impaired lung function appears to be an independent predictor of mortality. It has been argued that RLD may be an early marker of subclinical pulmonary congestion, and the association with defect complexity may support this explanation

[22]. However, the role of exercise restriction in early life and other contributors, including early developmental factors, remains to be defined [67]. RLD can also be seen in CHD associated with lung underdevelopment (as in scimitar syndrome—partial anomalous pulmonary venous return with hypoplastic right lung) or related to impaired pulmonary blood flow due to congenital pulmonic stenosis or TOF [68]. The efficacy of interventions on potential, modifiable predictors of abnormal lung function, such as inspiratory muscle training or scoliosis surgery, to improve outcomes remains unclear [23].

5.6 Endocrine Disorders

5.6.1 Thyroid Dysfunction

There are multiple specific syndromic associations between CHD and hyperthyroidism (Di George syndrome) or hypothyroidism (Turner syndrome, Williams-Beuren syndrome and Down syndrome). Chronic lymphocytic thyroiditis is by far the most frequent autoimmune disease affecting Down syndrome patients. The contribution of thyroid hormones, particularly when abnormal, in aggravating cardiovascular disease is recognized. Overt thyroid dysfunction, both thyrotoxicosis and hypothyroidism, increases the risk for arrhythmia and, if untreated, can lead to HF. In parallel, minor changes in circulating hormone concentrations can also adversely affect cardiovascular system [36]. The incidence of thyroid dysfunction varies with the iodine uptake of the region. In a small study of Spanish ACHD patients, the prevalence of subclinical hypothyroidism was 9.6%, equal to the general adult population, but only 2% had values above 10 mUI/L. Cyanosis and Down syndrome were significantly associated [37]. Findings from meta-analysis suggest that young individuals, particularly those with structural heart disease, and individuals with serum TSH value above 10 mUI/L are at increased risk for cardiovascular events and mortality [36]. However, decisions regarding replacement therapy below the threshold of 10 mUI/L remain controversial. If patients exhibit HF symptoms, levothyroxine replacement may be considered. ACHD is also commonly associated with amiodarone-induced thyroid dysfunction due to chronic exposure to high levels of this iodine-rich agent. Female sex, cyanosis, a dose above 200 mg/d, Fontan circulation and low body mass index are risk factors [38]. Substantial liver congestion may explain the thyrotoxicosis observed in patients with severe cardiac dysfunction or in old-style Fontan patients. Since atrial thyrotoxicosis-induced atrial arrhythmias may be fatal, close follow-up of thyroid function is strongly recommended.

5.6.2 Neuroendocrine Tumours

Pheochromocytoma and paraganglioma are neuroendocrine tumours (NETs) derived from neural crest cells that produce catecholamines and localized in the adrenal medulla (90%) or in extra-adrenal chromaffin tissue (10%). They can be

associated with hereditary syndromes (multiple endocrine neoplasms, neurofibromatosis, or von Hippel-Lindau syndrome) but, together with a genetic susceptibility, an increase risk of NETs in cyanotic CHD has been reported [39]. Hypothetically, this is probably due to chronic exposure to hypoxia, which stimulates formation of erythropoietin and growth factors regulated by hypoxia-inducible factor 1, thus favouring tumour genesis. Their prevalence is between 0.2 and 0.6% in hypertensive adults, and a prevalence of 4.6% has been reported in cyanotic CHD [40]. The onset of NET can lead to haemodynamic deterioration, and therefore early diagnosis and treatment are essential. The signs and symptoms of these tumours overlap with those associated with complications of CHD, such as arrhythmias. Thus, the presence of NET should be suspected with the onset of new symptoms in patients with cyanotic CHD, even after surgical correction, as these tumours are a potentially treatable cause of clinical deterioration.

5.6.3 Diabetes

Elderly patients with both CHD and type 2 diabetes (T2DM) have demonstrated higher morbidity and mortality [15]. Early treatment of diabetes and lifestyle modification significantly reduces the risk of microvascular complications and may also reduce late macrovascular complications [69], which are significant predictors of outcome in elderly ACHD patients [3, 4]. In a population-based study, Madsen et al. reported a risk of developing T2DM after an age of 30 years 1.35 higher in CHD compared with controls; cyanotic CHD patients are at highest risk. Chronic hypoxia exposure, renal or hepatic dysfunction and diuretic use are well known to predispose to abnormal glucose metabolism [70]. Additionally, a number of alternative explanations, such as exercise restriction or higher rates of obesity, might be causally related.

5.6.4 Obesity and Metabolic Syndrome

Obesity is common in the ACHD population [71], and there is a twofold increased risk of metabolic syndrome [17]. Metabolic syndrome is a constellation including central obesity, dyslipidaemia, insulin resistance and hypertension. Obesity and metabolic syndrome are strongly related with the development of T2DM, HF, hypertension, renal dysfunction and OSA [16]. Further, obesity results in changes in inflammatory cytokines, which causes a pro-thrombotic state [14]. Physical inactivity and high caloric intake in infancy [17] have been suggested as factors associated with obesity in ACHD. Actions are required to combat the increase in obesity and metabolic syndrome: anthropometry must be evaluated at every visit. As well as reporting over documented cardiovascular risk factors, patients must be educated about their ideal nutrition, weight and exercise regimen [14].

5.7 Cardiovascular Co-morbidities

In the ACHD population, the pathophysiology of the underlying cardiac defect is the main driver of HF. However acquired cardiovascular co-morbidities like hypertension, diabetes or CAD will further contribute.

5.7.1 Cardiovascular Risk Factors

Moons et al. reported in a young population of ACHD patients approximately 80% had at least one cardiovascular risk factor [71] especially hypertension and hyperlipidaemia [8]. In an older cohort, 47% were hypertensive [3]. Worryingly, much of this population had simple lesions. Together with hypertension, diabetes and obesity, cigarette smoking is also associated with an increased risk. Although the proportion of smokers among ACHD patients is not high, encouraging smoking cessation is still an opportunity to reduce cardiovascular risk. Regarding hyperlipidaemia, the evidence in ACHD is still insufficient [13].

5.7.2 Coronary Artery Disease

Atherosclerosis is increasing in ACHD patients [3, 4, 8] especially in those with traditional risk factors [8]. However, myocardial ischaemia in CHD may be due to several causes, and these should also be excluded (see Chap. 2) [9].

5.7.2.1 Clinical Presentation

Late recognition of CAD is not uncommon in CHD patients. Most chest pain in younger ACHD patients is noncardiac. Moreover, cardiac denervation from surgery and autonomic dysfunction may lead to the absence of classic symptoms. Additionally, CAD diagnosis may be challenging due to pre-existing electrocardiographic or segmental wall motion abnormalities that reduce the discriminative value of non-invasive tests [72]. Thus, myocardial infarction is often the first ischaemic event, particularly in elderly patients [3, 9], and it becomes relevant in the development and progression of HF.

5.7.2.2 Prevalence

A prevalence of 1% of atherosclerotic CAD was reported in a single centre study with a mean age at diagnosis of 56 years [8]. Afilalo et al. [3] reported a 7% prevalence of myocardial infarction in a geriatric ACHD population and, in a cohort of patients who underwent routine coronary angiography [72], 9% had evidence of obstructive atherosclerotic CAD. Of note, in this latter study, none of them were under the age of 40 years, and, in a recent report, the absolute risk of ischaemic heart disease was low in the population of children and young adults [9]. Accordingly to underlying heart defect, CAD is more prevalent in patients with coarctation, probably due to the higher prevalence of cardiovascular risk factors in this selected

population [73]. Conversely, although Yalonetsky et al. [8] reported cases of CAD in Eisenmenger patients, cyanosis has been considered as a protection factor for CAD.

5.7.2.3 Prognostic Relevance

As a consequence of ageing population, it is likely that the frequency of acquired atherosclerotic CAD contributing to advanced forms of HF is increasing in ACHD patients. Acute myocardial infarction was a risk factor for mortality during HF-related hospital admission [74], and Stulak et al. demonstrated a trend toward reduced survival in patients who underwent repeat CHD surgery with concomitant coronary artery bypass graft surgery [75]. Giannakoulas et al. [72] reported an association between CAD and ventricular size and functional impairment, and, more importantly, CAD has recently emerged as an important predictor of mortality in elderly patients with CHD [4].

5.7.3 Cerebrovascular Disease

Among CHD survivors who reach the age of 18 years, 8.9% of men and 6.8% of women experienced one cerebrovascular accident before age 65 years, and HF has been recognized as the strongest predictor of stroke. Importantly, for patients with HF, the risk was higher at younger age and decreases with time after incident HF [10]. Thrombi frequently occur in areas of slow flow within the dilated chambers, in particular in low-output situations [59], and haematological and endothelial abnormalities that are prone to thromboembolism have been reported in acquired chronic HF [76]. Moreover, a higher prevalence of atrial arrhythmias or CAD is also seen in HF patients, which can contribute to the risk for stroke.

Before the era of screening for atherosclerotic risk factors and antihypertensive therapies, stroke was a cause of death in aortic coarctation [77]. Additionally, targeting early onset of cardiovascular risk factors will help prevent stroke.

5.7.4 Peripheral Vascular Complications

Peripheral vascular complications are not uncommon. Bicuspid aortic valves, aortic coarctation, conotruncal defects and postoperative states such as Ross procedure are associated with ascending or descending aortic aneurysms and eventually with dissection or rupture [12]. Additionally, catheterizations in infancy can cause both peripheral venous and arterial disease. In addition there is a high prevalence of chronic venous insufficiency in Fontan patients [11], as a result of the unique Fontan physiology and high venous pressures.

5.8 Neuropsychological Functioning

In older non-CHD adults, epidemiological data suggest that there is an association between HF and impairment in global cognition and behavioural problems. Individuals born with CHD are at high risk for structural/acquired neurological abnormalities and for medical co-morbidities that can affect the brain [27]. As adults, there are concerns about the impact of psychological disorders [29, 30] and cognitive decline and dementia [3] on quality of life, employment and survival.

5.8.1 Depression

Antidepressant drug therapy has demonstrated to be associated with increased mortality in male adults with CHD [29]. Depression contributes to smoking, alcohol abuse, poor diet, physical inactivity and poor medication adherence. Moreover, depressed states induce sympathetic activation, hypercoagulability, rhythm disturbances, endothelial dysfunction and a state of elevated cytokines all of which potentially contribute to impairment of cardiac function. Alternatively, depression could also be a symptom of HF-associated cytokine elevation. This could explain the high rate (50%) of mood disorders observed by Kovacs et al. [30].

5.8.2 Neurocognitive Impairment and Dementia

CHD-related syndromes, impaired cardiac function, previous intervention and superimposed traditional cardiac risk factors may all affect neurocognitive functioning [27]. For ACHD patients in middle age, vascular disease in the brain is as prevalent as for the general population at older ages [18], and low cardiac index was a risk factor for dementia in the Framingham Heart Study [78]. This early adult-onset of subclinical and clinical cardiovascular disease will be additive with dysmaturation and acquired injury during childhood [27]. Afilalo et al. [3] reported dementia as the strongest contributor to adverse outcomes in an adult and geriatric survey study, in particular for simple lesions. However, neurocognitive decline is likely underdiagnosed in ACHD patients, particularly those in HF, for several reasons. Cognitive evaluations over time are not performed routinely, neurocognitive impairment may be misclassified as depression and symptoms and drug therapy of HF may impair cognitive evaluation. Recent neuropsychological assessment highlights concerns about executive dysfunction in ACHD patients, especially when cardiac disease is more severe and there are co-morbid vascular risk factors [28]. Longitudinal follow-up of cognitive function in the ageing ACHD patients should, therefore, be desirable.

5.9 Skeletal Disorders

Skeletal disorders in ACHD patients may occur as a result from the underlying condition or from previous surgery, and, generally, they have a substantial impact on the chest wall, spine and, in many situations, both [41]. A 16% prevalence of moderate to severe scoliosis has been reported in a large population of ACHD patients with a fivefold increased risk for ventilatory dysfunction in patients with a Cobb angle >30° [22].

5.10 Liver Disease

The circulatory system is a complex interaction between multiple organs. Involvement of the liver, particularly in right-sided HF, is not uncommon. Normally, the liver receives 70% of its inflow from the portal vein. This inflow is directly related to the gradient between portal and hepatic venous pressures. The remainder one-quarter inflow is from the hepatic artery. The hepatic artery buffer is able to compensate for up to a 60% decrease in portal flow, but beyond that the liver is susceptible to injury. Therefore, in ACHD patients, the liver is sensitive to the long-standing haemodynamic disturbances resulting from the underlying cardiac disease or as a result of palliative surgery. The majority of hepatic complications occur as a consequence of heart disease (see Fontan & Univentricular Heart). Additionally, there are hepatic complications either resulting from transfusion-related infections, from drug-related hepatitis (*amiodarone-induced toxicity*) or from chronic cyanosis and erythrocytosis (*cholelithiasis*) [34]. There are a number of potential heart-liver and liver-heart interactions in HF patients with CHD:

5.10.1 Congestive Hepatopathy

There are several congenital defects that may lead to liver disease (Table 5.2), but the unifying pathophysiology for them is chronically elevated CVP. This high CVP is due to either direct elevation of right atrial pressure, sub-pulmonic ventricular failure or as a result of surgical procedures. Elevation of CVP can cause hepatic sinusoidal dilatation, oedema and hepatic venous hypertension, which in turn may lead to progressive hepatocyte atrophy, centrilobular fibrosis and the development of post-sinusoidal portal hypertension [32]. Hepatic injury ranges from the mild deposition of sinusoidal collage to formation of broad fibrous septa and cardiac liver fibrosis. The final consequence of a cardiac condition that permits long-term survival with marked elevation of CVP is cardiac cirrhosis. The majority of hepatic complications are incidentally discovered, but they will eventually manifest clinically. The typical clinical picture of cardiac cirrhosis includes mild and variable laboratory abnormalities, nodular or heterogeneous appearing liver on imaging studies, portal hypertension and ascites.

5.10.2 Acute Liver Injury

The most common acute liver injury due to heart disease is ischaemic hepatitis. Hypoperfusion due to low cardiac output may lead to hepatocyte necrosis in Rappaport liver zone 3. An interesting observation is that the majority of cases of ischaemic hepatitis occur in the setting of congestive HF, which means that chronic passive venous congestion may predispose hepatocytes to greater hypoxic injury resulting from hypotension [33]. In the presence of portal hypertension, local and systemic vasodilators lead to splanchnic vasodilatation. Systemic hypotension, plasma volume expansion and neoangiogenesis occur. The expected increase of cardiac output in cirrhotic patients is limited in the setting of CHD, making these patients more susceptible to ischaemic hepatitis.

5.10.3 Complications of Liver Disease

Ascites may occur in the absence of cirrhosis. It may be driven by right HF, protein losing enteropathy, narrowing of the venous pathways, renal dysfunction, portal vein thrombosis or portal hypertension [32]. Differential diagnosis of ascites origin may be challenging. There is typically a serum albumin to ascites gradient >1.1 if it is of cardiac origin. Manifestations of portal hypertension also include bleeding from varices and, rarely, hepatic encephalopathy. Variceal bleeding may not be amenable of non-selective beta-blockade or transjugular shunts [32]. It should be desirable to rule out gastro-oesophageal varices before considering anticoagulation in ACHD HF patients with hepatic complications. Portal hypertension may also affect the progression of cardiac dysfunction. Large-vessel, pulmonary-to-systemic venous communications formed as decompressive phenomena from elevated pulmonary vascular pressures or, alternatively, diffuse peripheral pulmonary capillary vasodilation may develop [79]. Finally, hepatocellular carcinoma is increasingly recognized as a late complication [35].

5.10.4 Workup of Hepatic Dysfunction

Assessment relies on clinical, laboratory and radiological findings. This will be more extensively treated in Chap. 6.

5.10.4.1 Serum Markers

The pattern of elevation may guide diagnostic testing [7]. Elevation of serum cholestasis markers is characteristic of congestive hepatopathy. Elevated alkaline phosphatase and GGT reflect a progressive increase in HF class, and mild elevation of indirect bilirubin is also common. INR may be elevated and is often resistant to vitamin K therapy. However, liver enzymes are often normal or only mildly elevated. In contrast, liver transaminases can become markedly elevated in ischaemic hepatitis within 24 h, and bilirubin often peaks later and takes a longer time to

Table 5.2 Congenital heart defects and procedures associated with hepatic dysfunction

Congenital heart defect	Lesion	Haemodynamic consequences	Mechanisms	Hepatic manifestations
Ebstein anomaly	Failure of tricuspid valve delamination Right ventricular myopathy	Tricuspid regurgitation Right ventricle Atrialization Right ventricular dysfunction	Passive congestion Central venous hypertension	Congestive hepatopathy
Atrial septal defect/ atrioventricular canal defect	Left-to-right shunt	Right chamber dilatation Secondary tricuspid regurgitation Pulmonary hypertension	Passive congestion Central venous hypertension	Congestive hepatopathy
Repaired tetralogy of Fallot	Pulmonary regurgitation	Right ventricular dilatation Right ventricular dysfunction Secondary tricuspid regurgitation Ventricular-ventricular interaction	Passive congestion Central venous hypertension Low-flow states	Congestive hepatopathy Ischaemic hepatitis
Pulmonary valve	Pulmonary regurgitation Pulmonary stenosis	Right ventricular dilatation Right ventricular restrictive physiology	Passive congestion Central venous hypertension Low-flow states	Congestive hepatopathy Ischaemic hepatitis
Atrial switch procedure	Venous baffle stenosis Systemic right ventricular failure	Right ventricle dilatation Right ventricle dysfunction Secondary tricuspid regurgitation	Passive congestion Central venous hypertension Low cardiac output	Congestive hepatopathy Ischaemic hepatitis
Fontan palliation	Failure of Fontan physiology over time Narrowing of Fontan pathway Thrombosis	Elevated pulmonary vascular resistance Single ventricle end-diastolic pressure elevation	Non-pulsatile Central venous hypertension Low cardiac output	Congestive hepatopathy Cardiac cirrhosis/portal hypertension Liver fibrosis/ hepatocarcinoma
Left ventricular outflow tract obstruction	Left ventricular dysfunction	Hypotension Secondary pulmonary hypertension	Passive congestion Low cardiac output	Ischaemic hepatitis

resolve. An ALT/LDH ratio < 1.5 is more typical of ischaemic than viral or drug-induced hepatitis. Hypoalbuminaemia is observed with the onset of decompensated cirrhosis. In the presence of cirrhosis, serial monitoring with alpha-fetoprotein (AFP) in patients with focal nodular hyperplasia is desirable since AFP elevations are associated with hepatocarcinoma [32]. Pigment stones should be considered in asymptomatic patients with cholestatic jaundice.

5.10.4.2 Liver Imaging

On computed tomography scans, reticular or zonal enhancement is commonly observed during portal venous phase imaging. While zonal enhancement indicates lower pressures, reticular enhancement is associated with extensive hepatic fibrosis. Hypervascular nodules during arterial phase imaging have been reported in patients with very high venous pressures. Importantly, hepatocellular carcinoma has been reported in Fontan patients [35], and vascular lesions could identify higher-risk patients who warrant closer monitoring. Transient elastography, used for surveying hepatic stiffness, is problematic in that any cause of altered hepatic stiffness (not only fibrosis) impacts on the results, particularly vascular congestion [80].

5.10.4.3 Invasive Assessment

Wedged hepatic vein pressure gradient measurements may not be always an accurate reflection of portal pressures, and direct measurement of portal venous pressure may add complexity in ACHD population. With regard to liver biopsy, liver pathology is not uniformly distributed and is subject to sampling errors. Moreover, the safety of percutaneous liver biopsy in this population is not known [81].

5.10.4.4 Treatment of Concomitant Liver Disease and HF

Currently, there are no data that define an optimal medical treatment algorithm for treating patients with cardiac liver disease. Interestingly, many of medical therapies used to treat HF have detrimental effects on other organs in the setting of liver disease. For example, ACE inhibitor may precipitate hepatorenal syndrome in a patient with significant liver disease. Non-selective beta-blockers are preferred for portal hypertension in liver disease, and carvedilol has shown benefit with HF. Statins are generally safe for patients with liver disease, but the liver enzymes need to be monitored. Diuretics (especially loop diuretics and aldosterone blockers) may be useful in both heart and liver disease, but they may also precipitate hepatorenal syndrome.

When a hospitalized patient with “cardiac cirrhosis” is identified, a common intervention is to give a vasodilator (e.g. ACE inhibitor) or an inotrope (e.g. milrinone) to augment cardiac output. This may work in some patients (i.e. those with a failing left ventricle) but may worsen the picture in others. If systemic ventricle filling pressures are relatively normal, the systemic vascular resistance is low and the primary haemodynamic issue is an inability to augment cardiac output in the setting of right HF, such a treatment strategy can worsen the circulatory status and precipitate acute renal failure. Difficult questions, such as determining if a liver can tolerate cardiac surgery or transplant or if a combined liver and heart transplant should be performed, will be more extensively treated in Chap. 6 “Fontan and Univentricular Heart”.

References

1. Norozi K, Wessel A, Alpers V, Arnhold JO, Geyer S, Zoege M, Buchhorn R. Incidence and risk distribution of heart failure in adolescent and adults with congenital heart disease after cardiac surgery. Am J Cardiol. 2006;97:1238–43.
2. Marelli AJ, Ionescu-Ittu R, Mackie AS, Guo L, Dendukuri N, Kaouache M. Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. Circulation. 2014;130(9):749–56.
3. Afilalo J, Therrien J, Pilote L, Ionescu-Ittu R, Martucci G, Marelli AJ. Geriatric congenital heart disease: burden of disease and predictors of mortality. J Am Coll Cardiol. 2011;58:1509–15.
4. Tutarel O, Kempny A, Alonso-Gonzalez R, Jabbour R, Li W, Uebing A, Dimopoulos K, Swan L, Gatzoulis M, Diller GP. Congenital heart disease beyond the age of 60: emergence of a new population with high resourcce utilization, high morbidity and high mortality. Eur Heart J. 2014;35:725–32.
5. Billet J, Majeed A, Gatzoulis M, Cowie M. Trends in hospital admissions, in-hospital case fatality and population mortality from congenital heart disease in England, 1994 to 2004. Heart. 2008;94:342–8.
6. Lui GK, Fernandes S, MacElhinney DB. Management of cardiovascular risk factors in adult with congenital heart disease. J Am Heart Assoc. 2014;3(6):e001076.
7. Cohen SB, Ginde S, Bartz PJ, Earing MG. Extracardiac complications in adults with congenital heart disease. Congenit Heart Dis. 2013;8:370–80.
8. Yalonetsky S, Horlick EM, Osten MD, Benson LN, Oechslin EN, Silversides CK. Clincal characteristics of coronary artery disease in adults with congenital heart defects. Int J Cardiol. 2013;164:217–20.
9. Fedchenko M, Mandalenakis Z, Rosengren A, Lappas G, Eriksson P, Skoglund K, Dellborg M. Ischemic heart disease in children and young adults with congenital heart disease in Sweden. Int J Cardiol. 2017;248:143–8. https://doi.org/10.1016/j.ijcard.2017.06.120.
10. Lanz J, Brophy JM, Therrien J, Kaouache M, Guo L, Marelli AJ. Stroke in adults with congenital heart disease. Incidence, cumulative risk and predictors. Circulation. 2015;132:2385–94.
11. Valente AM, Bhatt AB, Cook S, Earing MG, Gersony DR, Aboulhosn J, Opotowsky AR, Lui G, Gurvitz M, Graham D, Fernandes SM, Khairy P, Webb G, Gerhard-Herman M, Landzberg MJ, Investigators A. The CALF (congenital heart disease in adults lower extremities systemic venous health in Fontan patients) study. J Am Coll Cardiol. 2010;56:144–50.
12. Kuijpers JM, Mulder BJM. Aortopathies in adult congenital heart disease and genetic aortopathy syndromes: management strategies and indications for surgery. Heart. 2017;103(12):952–66.
13. Martinez-Quintana E, Rodriguez-Gonzalez F, Nieto-Lago V, Novoa FJ, Lopez-Rios L, Riaño-Ruiz M. Serum glucose and lipid levels in adult congenital heart disease. Metabolism. 2010;59:1642–8.
14. Rosenthal TM, Leung ST, Ahmad R, Young T, Lavie CJ, Moodie DS, Shah S. Lifestyle modification for the prevention of morbidity and mortality in adult congenital heart disease. Congenit Heart Dis. 2016;11:1189–98.
15. Dellborg M, Björk A, Pirouzi Fard MN, Ambring A, Eriksson P, Svensson AM, Gudbjörnsdottir S. High mortality and morbidityamong adults with congenital heart disease and type 2 diabetes. Scand Cardiovasc J. 2015;49:344–50.
16. Tsai AG, Wadden TA. In the clinic: obesity. Ann Intern Med. 2013;159(5):ITC3-1–ITC3-15.
17. Deen JF, Krieger EV, Slee AE, Arslan A, Arterburn D, Stout K, Portman MA. Metabolic syndrome in adults with congenital heart disease. J Am Heart Assoc. 2016;5:e001132.
18. Diller GP, Kempny A, Alonso-Gonzalez R, Swan L, Uebing A, Li W, Babu-Narayan S, Wort SJ, Dimopoulus K, Gatzoulis M. Survival prospects and circumstances of death in contemporary adult congenital heart disease patients under follow up at a large tertiary Centre. Circulation. 2015;132(22):2118–25.
19. Hjortshoj CS, Jensen AS, Christiensen JAE, Jennum P, Sondergaard L. Sleep-disordered breathing in Eisenmenger syndrome. Am J Cardiol. 2016;214:23–4.

20. Cotts T, Smith KR, Lu J, Dorfman AL, Norris MD. Risk for sleep-disordered breathing in adults after atrial switch repairs for d-looped transposition of the great arteries. Pediatr Cardiol. 2014;35:888–92.
21. Pillutla P, Shetty KD, Foster E. Mortality associated with adult congenital heart disease: trends in the US population from 1979 to 2005. Am J Cardiol. 2009;158:874–9.
22. Alonso-Gonzalez R, Borgia F, Diller GP, Inuzuka R, Kempny A, Martinez-Naharro A, Tutarel O, Marino P, Wurstmann K, Charalambides M, Silva M, Swan L, Dimopoulos K, Gatzoulis M. Abnormal lung function in adults with congenital heart disease: prevalence, relation to cardiac anatomy and association with survival. Circulation. 2013;127:882–90.
23. Iversen KK, Kjaergaard J, Akkan D, Kober L, Torp-Pedersen C, Hassager C, Vestbo J, Kjoller E, ECHOS Lung Function Study Group. The prognosic importance of lung function in patients admitted with heart failure. Eur J Heart Fail. 2010;12:685–91.
24. Dimopoulos K, Diller GP, Petrarco R, Chamaidi A, Karaoli E, Mullen M, Swan L, Piepoli MF, Poole-Wilson PA, Francis DP, Gatzoulis M, Giannakoulas G. Anaemia in adults with congenital heart disease relates to adverse outcomes. J Am Coll Cardiol. 2009;54:2093–100.
25. Collins N, Piran S, Harrison J, Azevedo E, Oechslin E, Silversides C. Prevalence and determinants of anaemia in adults with congenital heart disease and ventricular dysfunction (subaortic right ventricle and single ventricle physiology). Am J Cardiol. 2008;102:625–8.
26. Dimopoulos K, Diller GP, Koltsida E, Pijuan-Domenech A, Papadopoulos SA, Babu-Narayan S, Salukhe TV, Piepoli MF, Pool-Wilson PA, Best N, Francis DP, Gatzoulis M. Prevalence, predictors and prognostic value of renal dysfuncion in adults with congenital heart disease. Circulation. 2008;117:2320–8.
27. Marelli AJ, Miller SP, Marino BL, Jefferson AL, Newburger JW. Brain in congenital heart disease across the lifespan: the cumulative burden of injury. Circulation. 2016;133:1951–62.
28. Ilardi D, Ono KE, McCartney R, Book W, Stringer AY. Neurocongnitive functioning in adults with congenital heart disease. Congenit Heart Dis. 2017;12(2):166–73.
29. Diller GP, Bräutingam A, Kempny A, Uebing A, Alonso-Gonzalez R, Swan L, Babu-Narayan SV, Baumgartner H, Dimopoulus K, Gatzoulis M. Depression requiring anti-depressant drug therapy in adult congenital heart disease: prevalence, risk factors and prgnostic value. Eur Heart J. 2016;37:771–82.
30. Kovacs AH, Saidi AS, Kuhl EA, Sears SF, Silversides C, Harrison JL, Ong L, Colman J, Oechslin E, Nolan RP. Depression and anxiety in adult congenital heart disease: predictors and prevalence. Int J Cardiol. 2009;137:158–64.
31. Billet J, Cowie MR, Gatzoulis MA, Vonder Muhl JF, Majeed A. Comorbidity, healthcare utilisation and process of care measures in patients with congenital heart disease in the UK: cross-sectional, population-based study with case-control analysis. Heart. 2008;94:1194–9.
32. Asrani SK, Asrani NS, Freese DK, Phillips SD, Warnes CA, Heimbach J, Kamath PS. Congenital heart disease and the liver. Hepatology. 2012;56:1160–9.
33. Birrer R, Takuda Y, Takara T. Hypoxic hepatopathy: pathophysiology and prognosis. Intern Med. 2007;46:1063–70.
34. Shiina Y, Toyoda T, Kawasoe Y, Tateno S, Shirai T, Matsuo K, et al. The prevalence and risk factors for cholelitiasis and asymptomatic gallstones in adults with congenital heart disease. Int J Cardiol. 2011;152:171–6.
35. Bryant T, Ahmad Z, Millward-Sadler H, Burney K, Stedman B, Kendall T, et al. Arterialised hepatic nodules in the Fontan circulation: hepatico-cardiac complications. Int J Cardiol. 2010;151:268–72.
36. Floriani C, Gencer B, Collet TH, Rondoni N. Subclinical thyroid dysfunction and cardiovascular disease: 2016 update. Eur Heart J. 2018;39(7):503–7. https://doi.org/10.1093/eurheartj/ehx050.
37. Martínez-Quintana E, Rodriguez-Gonzalez F, Nieto-Lago V. Subclinical hypothyroidism in grown-up congenital heart disease patients. Pediatr Cardiol. 2013;34:912–7.
38. Thorne SA, Barnes I, Cullinan P, Somerville J. Amiodarone associated thyroid dysfunction. Risk factors in adults with congenital heart disease. Circulation. 1999;100:149–54.

39. Opotowsky AR, Moko LE, Ginns J, Rosenbaum M, Gretumann M, Aboulhosn J, Hageman A, Kim Y, Deng LX, Grewal J, Zaidi AN, Almanssori G, Oechsling E, Earing M, Landzberg M, Singh MN, Wu F, Vaidya A. Pheochromocytoma and paraganglioma in cyanotic congenital heart disease. J Clin Endocrinol Metab. 2015;100(4):1325–34.
40. Ponz de Antonio I, Ruiz-Cantador J, Gonzalez AE, Oliver JM, Sanchez-Recalde A, Lopez-Sendon JL. Prevalence of neuroendocrine tumors in patients with cyanotic congenital heart disease. Rev Esp Cardiol. 2017;70(8):669–81.
41. Mayer O, Campbell R, Cahill P, Redding G. Thoracic insufficiency syndrome. Curr Probl Pediatr Adolesc Health Care. 2016;46(3):72–97.
42. Opotowsky AR, Siddiqi OK, Webb GD. Trends in hospitalizations for adults with congenital heart disease in the US. J Am Coll Cardiol. 2009;54(5):460–7.
43. Vergeut G, Uiterwaal CSPM, van der Velde ET, Meijboom FJ, Pieper PG, Sieswerd GT, Plokker HW, Grobbee DE, Mulder BJ. The emerging burden of hospital admissions of adults with congenital heart disease. Heart. 2010;96:872–8.
44. Bracher I, Padrutt M, Bonassin F, Santos Lopes B, Gruner C, Stämpfli SF, Oxenious A, De Pasquuale G, Seliger T, Lüscher TF, Attenhoffer Jost C, Greutmann M. Burden and impact of congenital syndromes and comorbidities among adults with congenital heart disease. Int J Cardiol. 2017;240:159–64.
45. Braunstein JB, Anderson G, Gerstenblith GF, Weller W, Niefeld M, Herbert R, Wu AW. Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. J Am Coll Cardiol. 2003;42:1226–33.
46. Dimopoulos K, Diller GP, Giannakoulas G, Petrarco R, Chamaidi A, Karaoli E, Mullen M, Swan L, Piepoli MF, Pool-Wilson PA, Francis DP, Gatzoulis M. Anaemia in adults with congenital heart disease relates to adverse outcomes. J Am Coll Cardiol. 2009;54(22): 2093–100.
47. Damman K, Valente AM, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J. 2014;35:455–69.
48. Pankau R, Partsch CJ, Winter M, Gosch A, Wessel A. Incidence and spectrum of renal abnormalities in Williams-Beuren syndrome. Am J Med Genet. 1996;63:301–4.
49. Morgan C, Al-Alklabi M, Garcia Guerra G. Chronic kidney disease in congenital heart disease patients: a narrative review of evidence. Can J Kidney Health Dis. 2015;2:163–9.
50. Buelow MW, Dall A, Bartz PJ, Tweddell JS, Sowinski J, Rudd N, Karzmark L, Earing MG. Renal dysfunction is common among adults after palliation for previous tetralogy of Fallot. Pediatr Cardiol. 2013;34(1):165–9.
51. Ohuchi H, Diller GP. Biomarkers in adult congenital heart disease heart failure. Heart Fail Clin. 2014;10:43–56.
52. Chong VH, Singh J, Parry H, Saunders J, Chowdhury F, Mancini DM, Lang CC. Management of noncardiac comorbidities in chronic heart failure. Cardiovasc Ther. 2015;33:300–15.
53. Aydin SI, Seiden HS, Blaufox AD, Parnell VA, Choudhury T, Punnose A, et al. Acute kidney injury after surgery for congenital heart disease. Ann Thorac Surg. 2012;945:1589–95.
54. Lam CC, Mancini D. Noncardiac comorbidities in chronic heart failure. Heart. 2007;93: 665–71.
55. Opasich C, Cazzola M, Scelsi L, De Feo S, Bosimini E, Lagioia R, Febo O, Ferrari R, Fucili A, Moratti R, et al. Blunted erythropoietin productivo and defective iron supply for erythropoiesis as major causses of anaemia in patients with chronic heart failure. Eur Heart J. 2005;26: 2232–7.
56. Silverberg DS, Wexler D, Blum M, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anaemia of severe, resistant congestive heart failure improves cardiac and renal function and functional class and markedly reduces hospitalizations. J Am Coll Cardiol. 2000;35:1737–44.
57. Broberg CS, Jayaweera AR, Diller GP, Prasad SK, Lay Thein S, Bax BE, Burman J, Gatzoulis M. Seeking optimal relation between oxygen saturation and hemoglobine concentration in adults with cyanosis from congenital heart disease. Am J Cardiol. 2011;107(4):595–9.

58. Tay ELW, Peset A, Papaphylactou M, Inuzuka R, Alonso-Gonzalez R, Giannakoulas G, Tzifa A, Goletto S, Broberg C, Dimopoulos K, Gatzoulis M. Replacement therapy for iron deficiency improves exercise capacity and quality of life in patients with cyanotic congenital heart disease and/or Eisenmenger syndrome. Int J Cardiol. 2011;151(3):307–12.
59. Jensen AS, Idorn L, Thomsen C, Von der Recke P, Mortensen J, Sorensen KE, Thilen U, Nagy E, Kofoed KF, Ostrowski SR, Sondergaard L. Prevalence of cerebral and pulmonar thrombosis in patients with cyanotic congenital heart disease. Heart. 2015;101(19):1540–6.
60. Jensen AS, Johanson PI, Sorensen KE, Thilen U, Nagy E, Furenäs L, Sondergaard L. The haematocrit- an importan factor causing impaired haemostasis in patients with cyanotic congental heart disease. Int J Cardiol. 2013;167:1317–21.
61. Rosove MH, Perloff JK, Hocking WG, Child JS, Cannnobbio MM, Skorton DJ. Chronic hypoxemia and decompensated erythrocytosis in cyanotic congenital heart disease. Lancet. 1996; 2:313–5.
62. Wolk R, Kara T, Somers VR. Sleep-disordered breathing and cardiovascular disease. Circulation. 2003;108:9–12.
63. Young T, Palta J, Dempsey J, Skatrud j WS, Bardr S. The occurrence if sleep-disordered breathing among middle-aged adults. N Engl J Med. 1993;328:1230–5.
64. Cormican LJ, Williams A. Sleep-disordered breathing and its treatment in chronic heart failure. Heart. 2005;91:1264–70.
65. Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, et al. Prospective study of obstructive sleep apnea and incident coronary disease and heart failure: the sleep heart health study. Circulation. 2010;122:352–60.
66. Ginde S, Bartz PJ, Hill GD, Danduran MJ, Sowinski J, Biller J, et al. Restrictive lung disease is an independent predictor of exercise intolerance in the adult with congenital heart disease. Congenit Heart Dis. 2013;8:246–54.
67. Opotowsky AR. Abnormal spirometry in congenital heart disease. Where do we go from here? Circulation. 2013;127:865–7.
68. Pianosi PT, Johnson JN, Turchetta A, Johnson BD. Pulmonary function and ventilatory limitation to exercise in congenital heart disease. Congenit Heart Dis. 2009;4:2–11.
69. Hollman RR, Paul SK, Bethel MA, Mathews DR, Neal HA. 10-year follow up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359:1577–89.
70. Ohuchi H, Miyamoto Y, Yamamoto M, Ishihara H, Takata H, Miyazaki A, Yamada O, Yagihara T. High prevalence of abnormal glucose metabolism in young adult patients with complex congenital heart disease. Am Heart J. 2009;158:30–9.
71. Moons P, Van Deyk K, Dedroog D, Troost E, Budts W. Prevalence of cardiovascular risk factors in adults with congenital heart disease. Eur J Cardiovasc Prev Rehabil. 2006;13:612–6.
72. Giannakoulas G, Dimpopulos K, Engel R, Goktekin O, Kucukdurmaz Z, Vantankulu MA, Berdard E, Diller GP, Papaphylactou M, Francis DP, Di Mario C, Gatzoulis M. Burden of coronary artery disease in adults with congenital heart disease and its relation to congenital and traditional heart risk factors. Am J Cardiol. 2009;103:1445–50.
73. Roifmann I, Therrien J, Ionescu-Itu r, Pilote L, Guo L, Kotowyckz MA, Martucci G, Marelli AJ. Coarctation of the aorta and coronary artery disease: fact or fiction? Circulation. 2012; 126(1):16–21.
74. Rodriguez FH, Moodie DS, Parekh DR, Franklin WJ, Morales DL, Zafar F, Adams GJ, Fiedman RA, Rossano JW. Outcomes of heart failure-related hospitalizations in adults with congenital heart disease in the United States. Congenit Heart Dis. 2013;8:513–9.
75. Stulak JM, Dearani JA, Bukhart HM, Ammash NM, Philips SD, Schaff HV. Coronary artery disease in adult congenital heart disease: outcome after coronary artery bypass grafting. Ann Thorac Surg. 2012;93:116–22.
76. Gibbs CR, Blann AD, Watson RD, Lip GY. Abnormalities of hemorheological, endothelial and platelet function in patients with chronic heart failure in sinus rhythm: effects of angiotensin-converting enzyme inhibito and beta-blocker therapy. Circulation. 2001;103:1746–51.
77. Cohen M, Fuster V, Steele PM, Driscoll D, McGoon DC. Coarctation of the aorta. Long-term follow-up and prediction of outcome after surgical correction. Circulation. 1989;80:840–5.

78. Jefferson AL, Beiser AS, Himali JJ, Seshadri S, O'Donnell CJ, Manning WJ, Wolf PA, Au R, Benjamin EJ. Low cardiac indez is associated with incident dementia and Alzheimer disease: the Framingham Heart Study. Circulation. 2015;131:1333–9.
79. Krowka MJ. Hepatopulmonary syndrome and portopulmonary hypertension. Curr Treat Options Cardiovasc Med. 2002;4:267–73.
80. Wong VW-S, Chan HL-Y. Transient elastography. J Gastroenterol Hepatol. 2010;25:1726–31.
81. Rychik J, Veldman G, Rand E, Russo P, Rome JJ, Krok K, Goldberg DJ, Cahill AM, Wells R. The precarious state of the liver after a Fontan operation. Summary of a multidisiciplinary symposium. Pediatr Cardiol. 2012;33:1001–12.
82. Watson NF, Bushnell T, Jones TK, Stout K. A novel method for the evaluation and treatment of obstructive sleep apnea in four adults with complex congenital heart disease and Fontan repairs. Sleep Breath. 2009;13:421–4.

Part II

Specific Conditions

The Palliated Univentricular Heart

6

Rafael Alonso-Gonzalez

6.1 Introduction

The majority of adult patients with univentricular heart will have undergone some form of palliative procedure to restrict or increase pulmonary blood flow in childhood. In the majority of them, this will be followed by complete redirection of the systemic venous return with a cavopulmonary connection (Fontan procedure). The price for this form of palliation is a unique form of heart failure characterized by chronic systemic venous hypertension and low cardiac output [1]. In some patients, the Fontan circulation is not performed, and mechanisms of heart failure in this population differ from those who have a completed Fontan circuit. In this chapter, we will focus primarily in heart failure in patients with Fontan circulation.

6.2 Fontan Failure

Fontan procedure is a palliative procedure for patients with complex congenital heart disease and an anatomical contraindication for biventricular repair. Since the description of the Fontan operation in 1971 [2], multiple modifications have been described [3–6] (Fig. 6.1). Although the Fontan operation has changed completely the outcome of thousands of patients with univentricular heart, it remains a palliative procedure and limited in its ability to fully eliminate the problems associated with single ventricle physiology.

The term Fontan failure has been introduced to describe an inefficient circulation leading to a constellation of complications including limited exercise capacity,

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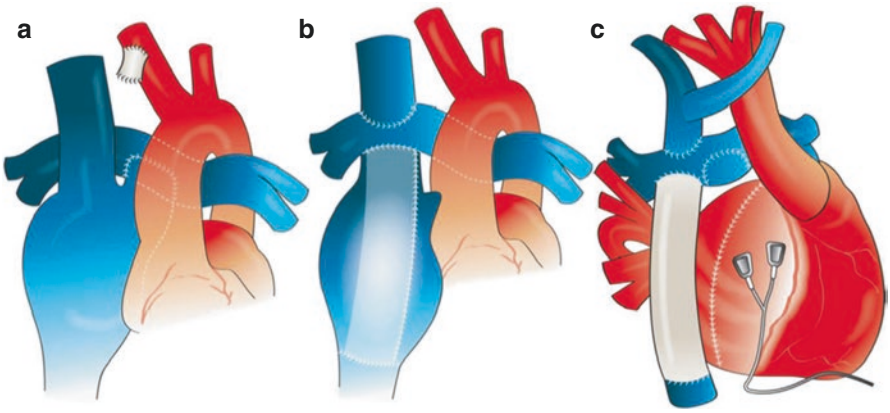

Fig. 6.1 Variations of Fontan surgery. (**a**) Modified classic Fontan; (**b**) intracardiac lateral tunnel Fontan; and (**c**) extracardiac Fontan. In (**a**) the modified Blalock-Taussig shunt, shown in white, was taken down and oversewn. In (**c**), permanent atrial epicardial pacemaker leads are illustrated in grey. Reprinted from Mondesert et al. [12] with permission from Elsevier

reduced cardiac output, recurrent atrial arrhythmias, chronic cyanosis, hepatomegaly with extensive fibrosis, cirrhosis, hepatocarcinoma, protein-losing enteropathy, plastic bronchitis, chronic ascites, venous insufficiency, thrombosis and chronic peripheral oedema [7, 8]. The lack of a standard definition of Fontan failure limits the understanding of the prevalence of heart failure in this population. Estimates of heart failure prevalence range from 10 to 20% early after Fontan surgery, rising to 50% in the adult population [9, 10]. Fontan failure presents gradually over the years, and patients may not recognize symptoms or present overt manifestations of decline until deterioration is quite advanced. This makes managing these patients extremely challenging. Standard heart failure treatment might help symptomatically but is not thought to change outcome; therefore early transplant referral should be considered in this population.

Some authors have divided the failure of the Fontan circulation in three categories: ventricular dysfunction, systemic complications of Fontan physiology and chronic Fontan failure [11, 12]. Although there is some overlap between these categories, this approach might be relevant when considering treatment options.

6.2.1 Ventricular Dysfunction

The Fontan circulation is characterized by the absence of a subpulmonary pumping chamber relying upon changes in intrathoracic pressure during breathing to draw blood through the lungs and systemic venous hypertension to provide the "pumping" pressure in the circulation. The pulmonary blood flow in this setting will be determined by the trans-pulmonary gradient, which depends on the pressure in the systemic veins (preload), the pressure in the pulmonary veins (afterload) and by the pulmonary vascular resistance. Since the body tolerates limited pressures in the systemic veins (up to 20 mmHg) and has a narrow window of filling pressures, the

pulmonary vascular resistance will be the main determinant of the cardiac output in this circulation [7].

Before the Fontan completion, the systemic ventricle is subjected to high volumes and frequently to high pressures leading to ventricular overgrowth, eccentric hypertrophy and, if excessive, spherical reconfiguration and dysfunction [13]. Immediately after Fontan completion, there will be a rapid reduction of preload of the systemic ventricle resulting in an under-filled single ventricle, leading to a mismatch in diastolic volume and ventricular mass. Although hypertrophy might decrease over time, abnormal ventricular relaxation and reduced ventricular compliance will persist, leading to progressive decline in diastolic function and subsequent increased venous congestion with further reduction of cardiac output [7, 8, 13]. Patients with Fontan procedure have a significant reduction in contractile and diastolic function with normal afterload, impaired ventricular-arterial coupling and reduced ventricular efficiency with heightened sensitivity to heart rate. Therefore, maintenance of cardiac output will depend on lower afterload, eccentric remodelling and relative preservation of diastolic function [14].

The systolic ventricular function is generally preserved in childhood. The systolic wall stress restores to normal in most individuals if the Fontan procedure is done before 10 years of age [15]; however long-term systolic ventricular dysfunction is seen in some adult patients with a Fontan circulation. This is attributed to chronic hypoxia and volume overload, ventriculotomy during various palliative procedures and ventricle morphology of the single ventricle [16]. In children, right ventricular morphology of the single ventricle is associated with poorer ventricular function [16] and worse atrioventricular valve regurgitation [17] and is also, along with protein-losing enteropathy (PLE) and higher right atrial pressure, an independent predictor of heart failure death in this population [18]. d'Udekem et al. showed in 499 consecutive patients undergoing univentricular palliation that children with morphologically right ventricle have 2.2-fold risk of death prior to the bidirectional Glenn stage [19]. In adults, there has been no definitive evidence of significantly different outcomes between those with right ventricular and left ventricular morphology. Data from the Australian and New Zealand Fontan registry, however, showed that adult patients with hypoplastic left heart syndrome have higher risk of developing Fontan failure, arrhythmias, thromboembolism and PLE compare with left ventricular morphology [20].

Furthermore, the distinction between Fontan failure and preserved or reduced systolic function is important because therapeutic options, expected responses and long-term outcomes may vary, depending on systolic function. Understanding the specific mechanisms associated with heart failure in a patient with a Fontan repair is crucial.

6.2.2 Systemic Complications of Fontan Physiology

6.2.2.1 Arrhythmias

Atrial arrhythmias, most typically atrial macro re-entrant tachycardias, are the most common cardiac complication affecting individuals after Fontan operation, accounting for 75% of supraventricular arrhythmias. Factors contributing to the high risk of

atrial arrhythmias include extensive atrial suture lines, high systemic venous pressure, atrial dilation and hypertrophy [21], heterotaxy syndrome [20], older age at Fontan and atrioventricular valve regurgitation [18]. The risk of arrhythmias also depends on the type of Fontan with higher prevalence in patients with atrio-pulmonary Fontan and lateral tunnel than in patients with extracardiac conduit [20].

Atrial arrhythmias are poorly tolerated in patients with Fontan physiology as preload-dependant Fontan patients respond very poorly to the rapid ventricular rate, particularly in the setting of high pulmonary vascular resistance and poor contractility [8]. Sustained atrial arrhythmias may lead to rapid deterioration of the haemodynamic status, due to the loss of atrioventricular (AV) synchrony and reduction in cardiac output and systemic ventricular function leading to decompensated heart failure. Termination of acute episodes is recommended whenever possible either with antiarrhythmic drugs or, more often, with electrical cardioversion. Patients with an atrio-pulmonary Fontan may develop intracardiac thrombus even in presence of optimal anticoagulation; thus, a transoesophageal echocardiogram should be performed prior cardioversion. In the presence of a thrombus in the Fontan circuit, the risk/benefit of restoring sinus rhythm should be carefully considered. In selective stable patients, rate control can be a useful initial strategy, but close monitoring of the patient is paramount, with special attention to signs of haemodynamic instability, such as hypotension, low urine output or worse renal function. These findings should prompt attempts to quickly restore sinus rhythm. Long-term treatment options include antiarrhythmic medication and catheter ablation, although the latter should be considered early after the first episode of arrhythmia. Conventional catheter ablation has lower rate of success and higher rate of recurrence in Fontan patients compared with other forms of congenital heart disease [22]. However, the use of new technology, such as magnetic navigation, irrigated catheters and imaging integration, significantly increases the rate of success in this challenging population [23]. The development of significant arrhythmias in patients with atrio-pulmonary Fontan when presenting with signs of heart failure is associated with a 3-year mortality rate of 25% [24]. This should also be a trigger to consider early referral for transplantation.

Sinus node dysfunction and chronotropic incompetence are common in patients with Fontan physiology [25, 26], whereas AV conduction problems are rare. Loss of normal sinus rhythm has been associated with atrial tachycardia and liver fibrosis [27]. Pacemaker insertion can be challenging in these patients due to their underlying anatomy. Transvenous atrial pacing might be possible in patients with atrio-pulmonary Fontan or lateral tunnel, but patients with extracardiac conduit will require an epicardial approach.

6.2.2.2 Liver Disease

Liver disease is one of the most galling complications in patients with Fontan circulation. Some recent data suggest that liver disease is universal in patients with Fontan physiology [28, 29]; it may begin immediately after Fontan completion, if not before then [30, 31], and progresses with age [28]. The spectrum of liver disease varies from mild liver congestion to severe fibrosis with nodular regeneration and

cirrhosis. It is important to differentiate between "true cirrhosis" and "cardiac cirrhosis". Patients with "true cirrhosis" have higher grade of portal fibrosis and portal hypertension, which is absent in most of the cases of "cardiac cirrhosis" [32]. Although the presence of "true cirrhosis" does not predict earlier time to death or heart transplant in this population [32], "true cirrhosis" is less likely to regress after isolated heart transplantation. Therefore, concomitant liver transplant might need to be considered. In addition, there have been reports of malignant transformation of hepatic fibrosis in hepatocellular carcinoma which is more likely to occur in patients with "true cirrhosis".

The mechanisms leading to hepatic dysfunction in the Fontan population are poorly understood but are likely to be multifactorial, including chronic elevation of central venous pressure, hypoxaemia and increased mesenteric vascular resistance [33]. Chronically elevated central venous pressure induces hepatic injury through sinusoidal stasis, stromal stretch and compression of the adjacent plates. This is generally a primarily sinusoidal process with portal tract involvement in only the most advanced cases [29]. Fibrosis in the portal distribution is more typically associated with inflammatory liver diseases such as viral hepatitis, toxic injury related to alcohol or medications or non-alcoholic fatty liver disease, but recent studies have shown portal involvement in patients with Fontan circulation at all stages of sinusoidal fibrosis [28, 29] (Fig. 6.2), suggesting that factors other than central venous hypertension may be contributing to liver injury. In patients with Fontan circulation, there is a heterogeneous liver involvement which might explain the poor correlation between liver biopsy and outcomes and highlights the potential for sampling error and/or the high degree of interobserver/intraobserver variability in liver biopsy interpretation.

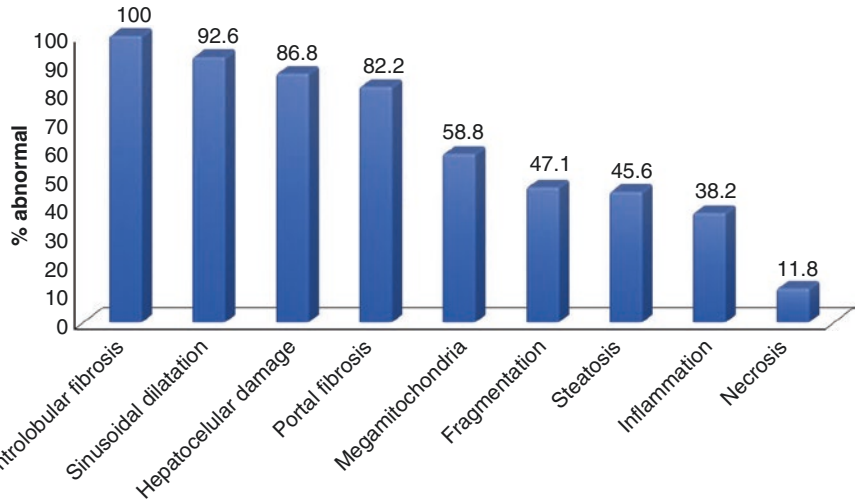

Fig. 6.2 Liver histopathology findings in 68 Fontan subjects who had liver biopsy or autopsy. Data extracted from Wu et al. [32]

The absence of ascites does not exclude advanced liver disease or Fontan failure, and standard serologic liver tests poorly correlate with degree of liver disease in this population. The most common abnormal test is gamma-glutamyl transpeptidase (GGT), elevated in almost 75% of patients with Fontan circulation [29]. Other findings include prolongation of the prothrombin time or of the INR, mild aminotransferase elevation [34, 35], mild thrombocytopenia [29] and decreased serum albumin [17, 29, 35]. Abnormal biomarkers of hepatic fibrosis are common in adults with Fontan circulation, but standard serologic tests to assess liver fibrosis do not predict the degree of histologic hepatic fibrosis in these patients [36]. The VAST (varices, ascites, splenomegaly, thrombocytopenia) score, which gives a point each for varices, ascites, splenomegaly (>13 cm on any imaging) or thrombocytopenia (<150,000 platelets/mL), is a strong marker for portal hypertension and has been utilized in the Fontan population to predict risk for adverse events such as death, transplant or hepatocellular carcinoma. Newer modalities, such as diffusion-weighted magnetic resonance imaging, may allow for more reproducible and representative quantification of hepatic fibrosis.

Regular surveillance of the liver is paramount in Fontan patients. Annual liver ultrasound is recommended after 10 years of the Fontan completion [35], and it is reasonable to consider liver elastography at baseline and follow-up. Patients with more advanced fibrosis and arterialized nodular lesions warrant further imaging with triple-phase computed tomography or liver magnetic resonance gadoxetate disodium (Eovist, Bayer, Whippany, New Jersey) and alpha-fetoprotein measurements every 6 months to rule out hepatocellular carcinoma.

6.2.2.3 Lymphatic Dysfunction

The lymphatic vessels play an important role in maintaining a capillary filtration equilibrium. Capillary filtration equilibrium depends on mean capillary hydrostatic pressure which is greatest at the arteriolar end, leading to filtration, and least at the venular end leading to reabsorption. Approximately 10% of tissue fluid, which fails to reabsorb, is taken up by small lymphatic capillaries, which then drain into larger lymphatic channels and ultimately in the thoracic duct, the largest lymphatic channel in the body, which itself drains into the innominate vein [16]. Patients with Fontan circulation have chronic systemic venous hypertension which will results in increase lymph production and difficulty for the thoracic duct to drain into the great veins. This will lead to significant lymphatic congestion, dilatation of the thoracic duct, chylous pleural effusions and formation of new lymphatic collaterals [37]. Early evidence of lymphatic abnormalities (lymphangiectasia and lymphatic collaterals) has been demonstrated in patients after bidirectional cavopulmonary connection or Fontan procedure even in the absence of plastic bronchitis or PLE [38, 39].

Lymphatics are difficult structures to evaluate because of their small size and variable anatomy. Nuclear scintigraphy is widely used in the diagnosis of PLE and has demonstrated the dilated thoracic duct and perihilar lymphangiectasia [40]. Magnetic resonance (MR) lymphangiography has shown lymphangiectasia and lymphatic collateralization in patients with Fontan palliation [16]. Dynamic contrast MR lymphangiography has demonstrated abnormal dilated lymphatic channels

arising from the thoracic duct and retrograde flow of contrast in these channels towards the carina or hilum of the lung in patients with plastic bronchitis [39].

Several strategies have been developed in an attempt to treat failing Fontan by targeting the lymphatic abnormalities. These include thoracic duct ligation, decompression of the thoracic duct, thoracic duct embolization and selective embolization of abnormal lymphatic collaterals. Although thoracic duct ligation and thoracic duct embolization have been reported as useful in the treatment of plastic bronchitis [41], since the thoracic duct is the structure that drains abdominal chyle, duct ligation/embolization could potentially initiate or worsen ascites and/or PLE. However, selective embolization of the abnormal lymphatic channel or isolation of the branches of the thoracic duct [42] appears promising in the management of these patients. Decompression of the thoracic duct by diverting the innominate vein to the atrial appendage has been reported as a successful option to treat patients with PLE [43].

6.2.2.4 Protein-Losing Enteropathy

Plastic bronchitis and PLE are serious complications associated with significant morbidity and mortality. The exact prevalence is unknown; however, studies suggest their presence in 5–15% of patients after palliation of the single ventricle and can occur in the setting of good ventricular function and low central venous pressure. Although classic data report a mortality rate of 50% at 5 years after initial diagnosis [44], more recent data suggest an 88% and 72% survival rate at 5 and 10 years, respectively [45]. Factors related with decreased survival include Fontan pressure >15 mmHg, decreased ventricular function (ejection fraction <55%) and New York Heart Association (NYHA) > II [45]. PLE can lead to severe hypoproteinaemia with significant reduction in oncotic pressure and development of oedema, ascites and pleural-pericardial effusions and frequently chronic diarrhoea.

The exact physiopathology of PLE is not completely understood. While all patients who have undergone a Fontan procedure have elevated venous pressure, the finding that only a minority develop PLE has led to speculation as to the aetiology of the PLE. Ostrow et al. propose that the chronic state of low cardiac output after the Fontan operation leads to a redistribution of flow away from nonvital organs such as the mesenteric circulation. This will diminish mesenteric blood flow which in combination with elevated venous pressures can lead to a decrease in the gut perfusion profile. Impaired mesenteric perfusion may result in modulation of intestinal cell membrane function and promote cellular apoptosis, factors which contribute to increased intestinal permeability and protein leakage [46].

In patients with chronic heart failure, there is a significant stimulation of the inflammatory system, a phenomenon that may similarly occur in patients with Fontan circulation. Several studies have shown elevation in inflammatory markers such as cytokines, tumour necrosis factor alpha (TNF-α) and C-reactive protein (CRP) in patients with Fontan circulation and PLE. Cytokines can induce vasoconstriction and impair endothelium-dependent vasodilation in resistance arteries; hence they may play a role in increasing mesenteric vascular resistance and contribute to a predisposition to PLE in patients after the Fontan circulation. TNF-α may play a direct role in altering intestinal cell membrane permeability to intravascular protein. Bode et al.

demonstrated in an in vitro model of PLE that TNF-α disrupts the tight junctions in the gut mucosa and increases fourfold the albumin flux across a monolayer of intestinal HT29 cells [47]. They also showed in a knockout of syndecan-1 that the predominant heparan sulphate proteoglycan, on the basolateral surface of intestinal epithelial cells, increased rate of protein leak by almost twofold. Combination of the knockout with TNF-α and/or increased venous pressure produced a synergistic effect with a sevenfold increase in albumin permeability [48]. This could explain why treatment with unfractionated heparin may be effective in treating PLE.

Patients with constrictive pericarditis can develop PLE secondary to high venous pressure (>24 mmHg) which resolves after pericardiectomy [49]. Markedly increased systemic venous pressure will increase intestinal lymphatic pressure which, in selected cases, cause localized rupture of the intestinal lymphatics into the gut lumen decompressing the entire systemic lymphatic system [50]. In patients with Fontan circulation, there is a correlation of PLE with the central venous pressure at the time of development of PLE, but this correlation disappears during the chronic phase [51]. However, this correlation is weak, with some patients developing PLE even with "normal" systemic venous pressures. A possible explanation is that the lymphatic system is operating near capacity in most subjects following the Fontan procedure and either some predisposing defect (e.g. congenital lymphatic malformation) or an event such as infection results in the rupture of the lymphatics in a localized area of the intestine. The mucosal histology in PLE of these subjects is identical to that found in primary intestinal lymphangiectasia and constrictive pericarditis, suggesting that high venous pressure plays a significant role in the pathogenesis of PLE.

The primary diagnostic test for PLE is stool testing for the presence of alpha-1 antitrypsin (α1-AT) in a 24-h stool collection. An α1-AT clearance (α1-AT clearance = [(mL stool) × (stool α1-AT mg/dL)]/[serum α1-AT mg/dL]) greater than 27 mL/24 h or an abnormal faecal α1-AT concentration greater than 54 mg/dL is diagnostic for PLE. α1-AT testing of a spot stool specimen may also show elevated levels in PLE, but this is a less sensitive approach and is not recommended in the initial diagnosis. The use of a random stool α1-AT level coupled with serum α1-AT level, however, may serve as a convenient surveillance method for patients with known PLE undergoing treatment or in remission.

As the cause of PLE is multifactorial, it is important to individualize the treatment plan for each patient. After the diagnosis of PLE is made, a thorough systematic approach is needed to address all possible aetiologies. The first step in treatment should be aimed at addressing any cardiac aetiologies, specifically relieving any mechanical obstructions and improving cardiac output. Dietary recommendations for these patients include high-protein (≥2 g/kg/day) and low-fat diet (≤25% of calories from fat) with medium-chain triglyceride supplementation. Medium-chain triglycerides are transported directly into portal blood rather than the lymphatic system bypassing the damaged lymphatic system in patients with PLE [45]. Optimal diuretic treatment is paramount including spironolactone. Spironolactone has diuretics and cardiac properties but also improves endothelial cell function and reduces inflammation [52]. A trial of pharmacological agents such as heparin,

corticosteroids and octreotide may be used. Subcutaneous unfractionated heparin decreases permeability of the gut membrane to large molecules and may decrease inflammation and potential microthrombi to the mesenteric arteries [45, 53]. Budesonide is an enteric-specific steroid, thus targeting inflammation, and has been reported to be successful in the treatment of PLE [54, 55]. Octreotide is a somatostatin analogue that decreases lymphatic flow but increases gallstone formation and therefore should not be used as a first-line treatment [45]. Despite which treatment is used, the majority of patients will benefit from pulmonary vasodilators, such as sildenafil, to reduce pulmonary pressures and optimize the Fontan circulation.

6.2.2.5 Cyanosis

A certain degree of cyanosis is common in patients with Fontan circulation, due to coronary sinus drainage to the systemic circulation or pulmonary shunting. In addition, the presence of a fenestration to decompress the circuit might contribute to the degree of cyanosis. After Glenn or Fontan operations, the increased central venous pressure may induce recanalization of embryologically formed systemic venous collaterals. Systemic venous collaterals are defined as venous channels draining desaturated blood from the high-pressure system of the upper half of the body into the low-pressure system of the lower part of the body and should be suspected when oxygen saturation is <90%. In Fontan patients, the most common veno-venous collateral vessels are from the brachiocephalic angles, superior vena cava and pericardial veins to the pulmonary veins or directly into the left atrium [56]. Patients with Fontan circulation can also develop pulmonary arteriovenous malformations (PAVMs) as well as recanalized pulmonary veno-venous collaterals between the bronchial and pulmonary veins, increasing the degree of cyanosis. PAVMs are thin-walled vascular malformations that are located pleurally or subpleurally and may range from microscopic telangiectasia to 1–5 cm in size [57]. Patients with PAVMs may be entirely asymptomatic, suggesting a smaller physiologic burden of intrapulmonary right-left shunt in which oxygenation is not significantly affected. However, advanced stages of PAVMs formation may present with hypoxaemia, cyanosis, cerebral embolization and brain abscesses [58]. Embolization may be successful with isolated or large PAVMs and is commonly used to treat isolated PAVMs. However, embolization therapy is rarely feasible after a superior vena cava to pulmonary artery connection as the disease usually presents in the diffuse form. Embolization of veno-venous collaterals is also possible, but since these appear to decompress the Fontan circuit, the decision to close these collateral vessels should be individualized.

6.2.2.6 Thromboembolism

Thrombus formation in patients with Fontan circulation is likely to be multifactorial. Numerous abnormalities in the coagulation cascade have been reported in this population, such as low levels of protein C, protein S and antithrombin III. This would suggest a hypercoagulable state, but these patients also have deficiency of coagulation factors such as II, V, VII, VIII and X that might increase bleeding risk [59, 60]. These findings appear to be more relevant in patient with chronic cyanosis.

Although patients with atrio-pulmonary Fontan are more likely to form thrombus within the Fontan circulation, mainly in presence of atrial arrhythmias, the actuarial incidence of thromboembolic complications with extracardiac conduits has been estimated to be 7.1% at 10 years [61]. In fact, the largest studies comparing extracardiac and intracardiac tunnels reported no differences in thromboembolic event rates. It is common practice to anticoagulate all patients with atrio-pulmonary Fontan; however the optimal preventive strategy in patients with total cavopulmonary connections remains to be determined, with no current consensus.

6.2.3 Chronic Fontan Failure

Even in absence of ventricular dysfunction or systemic complications, one can consider the Fontan circulation as a state of chronic heart failure. Cardiac output is reduced and venous pressure is increased from the moment of the Fontan completion and both worsen with time. In addition, patients with Fontan circulation have a limited ability to boost cardiac output during exercise due to their limited or absent pulmonary vascular reactivity and recruitment of pulmonary segments limiting their exercise capacity. The latter is significantly reduced in adolescents with Fontan circulation [62, 63] and continues to fall at a rate of approximately 2.6% predicted per year [64] with a significant increase in risk of hospitalization and symptoms when crosses a threshold of approximately 45% of predicted [11]. In a recent study, Cunningham et al. have shown that a decline in peak oxygen consumption between consecutive cardiopulmonary exercise tests predicts increased risk for death or transplant in adults with a Fontan circulation independent of their baseline peak oxygen consumption [65].

Progressive decline in the efficiency of the Fontan circulation is also well recognized. Pulmonary vascular resistance increases with time and plays a significant role in this deterioration. In addition, the end-diastolic pressure of the single ventricle will also increase leading to worsening of venous congestion and further deterioration of the cardiac output [7]. Another important contributing factor is the size of the extracardiac conduit in patients with total cavopulmonary connection. As the patient grows, there will be a significant increase of blood volume across the Fontan pathway, and associated power loss will become more important [11]. Although it is accepted that patients with Fontan circulation will deteriorate, there is no clear strategies designed to improve the Fontan circulation and, perhaps, to increase the period of symptom-free survival.

6.3 Treatment of Circulatory Failure in Fontan Circulation

The circulatory problem in the Fontan circuit is created by the damming effect of the Fontan system and the subsequent limit on cardiac preload. Therefore, strategies aimed at optimizing the efficiency of the Fontan system, such as reducing systemic venous pressure, reducing the resistance in the Fontan circuit or the creation of a fenestration, may be more effective than traditional heart failure therapies [1].

An acute increase of the systemic venous pressure, as occurs during exercise, can temporarily increase cardiac output. However, chronic high venous pressures in excess of 18–20 mmHg are poorly tolerated in patients with Fontan circulation resulting in symptoms such as congestion, oedema, ascites, lymphatic dysfunction and progressive veno-venous collaterals with cyanosis. Diuretics can control some of these symptoms but at the risk of aggravating the chronic effects of the pre-existing ventricular underfilling [7].

In the current era, the surgical technique used to create a total cavopulmonary connection is usually satisfactory with minimal focal stenosis and reduced turbulence. However, in patients with elevated Fontan pressure and reduced exercise capacity, special care should be taken to ensure areas of stenosis, hypoplasia or distortion are detected early and managed.

Pulmonary vascular resistance increases physiologically over time leading to Fontan failure. Pulmonary vasodilator drugs aimed at reducing pulmonary vascular resistance appear as an attractive option in this setting, but the available data are contradictory. Sildenafil has been tested in different studies in this population. Giardini et al. [66] 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 being administrated. Unfortunately, this effect has not been confirmed in subsequent randomized-controlled trials. Goldberg et al. [67] studied in a double-blind, placebo-controlled, crossover trial, conducted in children and young adults after Fontan surgery, the effects of sildenafil after 6 weeks of treatment. The study showed a significant reduction in respiratory rate and minute ventilation at peak exercise. There was also a significant decrease in ventilatory equivalents of carbon dioxide at anaerobic threshold. However, although there was a trend of improved oxygen consumption at anaerobic threshold, this was not confirmed at peak exercise. Bosentan has also been studied in patients with Fontan circulation, again with contradictory results. Schuuring et al. [68] reported in a cohort of 42 patients with Fontan circulation that 6 months' treatment with bosentan did not improve neither exercise capacity nor quality of life but increased NT-proBNP. More recently, Hebert A et al. [69] randomized 75 stable patients with Fontan circulation to bosentan or placebo. After 12 weeks, there was a significant increase 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 proven positive effects of pulmonary vasodilators in patients with Fontan circulation, there is no sufficient evidence suggesting that pulmonary vasodilators are beneficial in this population, and further studies are warranted before therapeutic recommendations can be made.

One way of increasing cardiac output in patients with Fontan circulation is creating a small fenestration. Although a fenestration at the time of the Fontan is well tolerated and may be viable for years or decades after surgery, a creation of a fenestration in presence of a failing Fontan circulation is not as well tolerated. In this setting, a small fenestration will not allow the degree of decompression necessary to improve symptoms, and a larger fenestration might reduce venous congestion and

increase cardiac output but will result in severe cyanosis. Nevertheless, in selected cases a fenestration might be considered as a bridge to transplantation.

Fontan patients with excessive bradycardia will benefit from pacing with a heart rate in the physiologic range to increase cardiac output and reduce venous congestion [70]; however excessive tachycardia may result in a decrease in cardiac output related to the inability of increasing diastolic filling. Patients with biventricular circulation have ventricular preload reserve; thus an increase in heart rate will result in increased stroke volume and subsequently cardiac output. However, in patients with Fontan circulation with no ventricular preload reserve, an increase in heart rate will result in a proportional reduction in stroke volume with no significant change in cardiac output [71].

Modification of the afterload could be another potential therapeutic target in patients with failing Fontan circulation. As any patient with chronic low cardiac output, systemic afterload is increased in these patients to maintain blood pressure. In a patient with biventricular heart, impaired left ventricular systolic function and preload dependent circulation, a reduction in afterload will lead to increase in cardiac output, counteracting for the hypotension induced by these drugs. However, in a Fontan patient with no preload reserve, a significant reduction in afterload will not lead to increase in cardiac output and, in fact, could be detrimental if it causes hypotension. Whether or not there is a role for low-dose afterload reduction in attempting to modulate ventricular diastolic function remains as yet unknown [1]. In the larger randomized trial of enalapril after Fontan, no beneficial effect was seen [72]. However, the time course in this trial was 10 weeks; it may be that the benefit of afterload reducing agents lies in the chronic impact on diastolic function rather than the short-term impact on systemic vascular resistance [1].

Optimal medical therapy of heart failure in patients with Fontan circulation remains uncertain. Multicentre, randomized trials are needed to elucidate the effect of treatments of heart failure in these complex and growing population.

6.4 Mechanical Support and Transplantation in Patients with Fontan Circulation

Heart or heart-lung transplant should always be considered in patients with univentricular heart and refractory heart failure. Whereas, the proportion of transplants in patients with univentricular heart has not changed over the last 10 years, the number of transplanted congenital patients with biventricular circulation and systemic right ventricle has doubled. Standard risk factors used for listing patients with acquired heart disease for transplantation may not be applicable to patients with Fontan circulation. High sensitization, elevated PVR, distorted pulmonary artery anatomy, anatomical abnormalities including abnormal position of organs or vessels (e.g. situs inversus, malposition of the great arteries or venous anomalies) as well as previous cardiac operations may add significant technical problems. All of these factors should be considered in the assessment of these patients prior to transplantation. In addition, patients with Fontan circulation, as has been

already discussed, are prone to develop liver failure; thus a detailed assessment of the liver with a multidisciplinary team, including cardiologists with expertise in adult congenital heart disease and gastroenterologists with expertise in liver failure, is paramount.

Timing for referral is challenging in this group of patients. Progressive deterioration of exercise capacity is expected, leading to gradual adaptation of their physical activity making it difficult to assess functional class. In addition, patients normally "feel well" and do not see the benefit of having a heart transplant. However, long-standing low cardiac output will have an impact in renal function which will also be affected by cyanosis. Moreover, chronic venous congestion will impact on the liver function leading to cardiac liver cirrhosis. Both renal and hepatic failure might preclude patients for having isolated heart transplant, and therefore referral for transplantation should be considered before these organs fail.

Although there are conflicting reports as to whether or not patients after the Fontan operation are at higher risk of death after heart transplantation, recent data suggest a significant improvement in the outcome of this population [73]. Patients with Fontan circulation presenting for transplantation with preserved ventricular function but failing Fontan physiology (e.g. symptoms and signs of poor cardiac output, raised right atrial pressure, PLE, ascites and oedema) are at higher risk of dying than those who present with heart failure and reduced ventricular function [74]. Other aspects of the Fontan operation and postoperative physiology that can lead to increased risk after heart transplantation in these patients include multiple previous surgeries, chronic cyanosis, coagulation dysfunction, elevated pulmonary vascular resistance and an elevated circulating anti-HLA antibodies.

Experience with ventricular assist devices (VAD) in patients with single ventricle physiology is limited. Recent data from the INTERMACS registry suggest that survival of patients with congenital heart disease and left VAD (LVAD), including patients with single ventricle physiology, is similar to non-adult congenital heart disease patients [75]. Mortality, however, was higher for patients requiring biventricular assist device (BiVAD) or total artificial heart (TAH) [75]. Over the last decade, several investigators have tested different mechanical pumps for use within the Fontan circulation to improve cardiac output and reduce systemic venous congestions. Some of these investigations are quite advanced but not ready for testing in humans.

Conclusion

As the survival of patients with univentricular heart and Fontan circulation continues to improve, the challenges of the management of this circulation are becoming more apparent. While the Fontan operation has radically changed the outcome of patients with univentricular heart, we, adult congenital heart disease clinicians, will have to intensify our efforts to improve our ability of dealing with the complications of this unnatural circulation. Complications are complex and involve multiple organs requiring a multidisciplinary approach. Continued research is needed to develop therapies to manage ventricular dysfunction and the systemic complications in these patients. Further investigation of the role of

mechanical assist devices in this complex circulation is also required. Novel mechanical devices are under development, but they are not ready for clinical use. As the number of Fontan survivors continues to grow, rational and systematic diagnostic and treatment protocols will need to be established and tested.

References

1. Gewillig M, Goldberg DJ. Failure of the fontan circulation. Heart Fail Clin. 2014;10:105–16.
2. Fontan F, Baudet E. Surgical repair of tricuspid atresia. Thorax. 1971;26:240–8.
3. Bjork VO, Olin CL, Bjarke BB, Thoren CA. Right atrial-right ventricular anastomosis for correction of tricuspid atresia. J Thorac Cardiovasc Surg. 1979;77:452–8.
4. de Leval MR, Kilner P, Gewillig M, Bull C. Total cavopulmonary connection: a logical alternative to atriopulmonary connection for complex Fontan operations. Experimental studies and early clinical experience. J Thorac Cardiovasc Surg. 1988;96:682–95.
5. Kreutzer G, Galindez E, Bono H, De Palma C, Laura JP. An operation for the correction of tricuspid atresia. J Thorac Cardiovasc Surg. 1973;66:613–21.
6. Marcelletti C, Corno A, Giannico S, Marino B. Inferior vena cava-pulmonary artery extracardiac conduit. A new form of right heart bypass. J Thorac Cardiovasc Surg. 1990;100:228–32.
7. Gewillig M, Brown SC. The Fontan circulation after 45 years: update in physiology. Heart. 2016;102:1081–6.
8. Lastinger L, Zaidi AN. The adult with a Fontan: a panacea without a cure? Circ J. 2013;77:2672–81.
9. Norozi K, Wessel A, Alpers V, Arnhold JO, Geyer S, Zoege M, Buchhorn R. Incidence and risk distribution of heart failure in adolescents and adults with congenital heart disease after cardiac surgery. Am J Cardiol. 2006;97:1238–43.
10. Piran S, Veldtman G, Siu S, Webb GD, Liu PP. Heart failure and ventricular dysfunction in patients with single or systemic right ventricles. Circulation. 2002;105:1189–94.
11. Goldberg DJ, Shaddy RE, Ravishankar C, Rychik J. The failing Fontan: etiology, diagnosis and management. Expert Rev Cardiovasc Ther. 2011;9:785–93.
12. Mondesert B, Marcotte F, Mongeon FP, Dore A, Mercier LA, Ibrahim R, Asgar A, Miro J, Poirier N, Khairy P. Fontan circulation: success or failure? Can J Cardiol. 2013;29:811–20.
13. Nakamura Y, Yagihara T, Kagisaki K, Hagino I, Kobayashi J. Ventricular performance in long-term survivors after Fontan operation. Ann Thorac Surg. 2011;91:172–80.
14. Saiki H, Eidem BW, Ohtani T, Grogan MA, Redfield MM. Ventricular-arterial function and coupling in the adult Fontan circulation. J Am Heart Assoc. 2016;5:e003887.
15. Sluysmans T, Sanders SP, van der Velde M, Matitiau A, Parness IA, Spevak PJ, Mayer JE Jr, Colan SD. Natural history and patterns of recovery of contractile function in single left ventricle after Fontan operation. Circulation. 1992;86:1753–61.
16. Menon S, Chennapragada M, Ugaki S, Sholler GF, Ayer J, Winlaw DS. The lymphatic circulation in adaptations to the Fontan circulation. Pediatr Cardiol. 2017;38:886–92.
17. Anderson PA, Sleeper LA, Mahony L, Colan SD, Atz AM, Breitbart RE, Gersony WM, Gallagher D, Geva T, Margossian R, McCrindle BW, Paridon S, Schwartz M, Stylianou M, Williams RV, Clark BJ III, Pediatric Heart Network I. Contemporary outcomes after the Fontan procedure: a Pediatric Heart Network Multicenter study. J Am Coll Cardiol. 2008;52:85–98.
18. Khairy P, Fernandes SM, Mayer JE Jr, Triedman JK, Walsh EP, Lock JE, Landzberg MJ. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. Circulation. 2008;117:85–92.
19. d'Udekem Y, Xu MY, Galati JC, Lu S, Iyengar AJ, Konstantinov IE, Wheaton GR, Ramsay JM, Grigg LE, Millar J, Cheung MM, Brizard CP. Predictors of survival after single-ventricle palliation: the impact of right ventricular dominance. J Am Coll Cardiol. 2012;59:1178–85.

20. d'Udekem Y, Iyengar AJ, Galati JC, Forsdick V, Weintraub RG, Wheaton GR, Bullock A, Justo RN, Grigg LE, Sholler GF, Hope S, Radford DJ, Gentles TL, Celermajer DS, Winlaw DS. Redefining expectations of long-term survival after the Fontan procedure: twenty-five years of follow-up from the entire population of Australia and New Zealand. Circulation. 2014;130:S32–8.
21. Elder RW, Wu FM. Clinical approaches to the patient with a failing Fontan procedure. Curr Cardiol Rep. 2016;18:44.
22. Yap SC, Harris L, Silversides CK, Downar E, Chauhan VS. Outcome of intra-atrial re-entrant tachycardia catheter ablation in adults with congenital heart disease: negative impact of age and complex atrial surgery. J Am Coll Cardiol. 2010;56:1589–96.
23. Ueda A, Suman-Horduna I, Mantziari L, Gujic M, Marchese P, Ho SY, Babu-Narayan SV, Ernst S. Contemporary outcomes of supraventricular tachycardia ablation in congenital heart disease: a single-center experience in 116 patients. Circ Arrhythm Electrophysiol. 2013;6:606–13.
24. Diller GP, Giardini A, Dimopoulos K, Gargiulo G, Muller J, Derrick G, Giannakoulas G, Khambadkone S, Lammers AE, Picchio FM, Gatzoulis MA, Hager A. Predictors of morbidity and mortality in contemporary Fontan patients: results from a multicenter study including cardiopulmonary exercise testing in 321 patients. Eur Heart J. 2010;31:3073–83.
25. Diller GP, Dimopoulos K, Okonko D, Uebing A, Broberg CS, Babu-Narayan S, Bayne S, Poole-Wilson PA, Sutton R, Francis DP, Gatzoulis MA. Heart rate response during exercise predicts survival in adults with congenital heart disease. J Am Coll Cardiol. 2006;48(6):1250.
26. Diller GP, Okonko DO, Uebing A, Dimopoulos K, Bayne S, Sutton R, Francis DP, Gatzoulis MA. Impaired heart rate response to exercise in adult patients with a systemic right ventricle or univentricular circulation: prevalence, relation to exercise, and potential therapeutic implications. Int J Cardiol. 2009;134:59–66.
27. Deal BJ, Jacobs ML. Management of the failing Fontan circulation. Heart. 2012;98:1098–104.
28. Goldberg DJ, Surrey LF, Glatz AC, Dodds K, O'Byrne ML, Lin HC, Fogel M, Rome JJ, Rand EB, Russo P, Rychik J. Hepatic fibrosis is universal following Fontan operation, and severity is associated with time from surgery: a liver biopsy and hemodynamic study. J Am Heart Assoc. 2017;6:e004809.
29. Wu FM, Kogon B, Earing MG, Aboulhosn JA, Broberg CS, John AS, Harmon A, Sainani NI, Hill AJ, Odze RD, Johncilla ME, Ukomadu C, Gauvreau K, Valente AM, Landzberg MJ, Alliance for Adult Research in Congenital Cardiology I. Liver health in adults with Fontan circulation: a multicenter cross-sectional study. J Thorac Cardiovasc Surg. 2017;153:656–64.
30. Schwartz MC, Sullivan L, Cohen MS, Russo P, John AS, Guo R, Guttenberg M, Rand EB. Hepatic pathology may develop before the Fontan operation in children with functional single ventricle: an autopsy study. J Thorac Cardiovasc Surg. 2012;143:904–9.
31. Schwartz MC, Sullivan LM, Glatz AC, Rand E, Russo P, Goldberg DJ, Rome JJ, Cohen MS. Portal and sinusoidal fibrosis are common on liver biopsy after Fontan surgery. Pediatr Cardiol. 2013;34:135–42.
32. Wu FM, Jonas MM, Opotowsky AR, Harmon A, Raza R, Ukomadu C, Landzberg MJ, Singh MN, Valente AM, Egidy Assenza G, Perez-Atayde AR. Portal and centrilobular hepatic fibrosis in Fontan circulation and clinical outcomes. J Heart Lung Transplant. 2015;34:883–91.
33. Alonso-Gonzalez R. Liver dysfunction and congenital heart disease: are we ready for the epidemic? Int J Cardiol. 2017;249:169–70.
34. Asrani SK, Asrani NS, Freese DK, Phillips SD, Warnes CA, Heimbach J, Kamath PS. Congenital heart disease and the liver. Hepatology. 2012;56:1160–9.
35. Hilscher MB, Johnson JN, Cetta F, Driscoll DJ, Poterucha JJ, Sanchez W, Connolly HM, Kamath PS. Surveillance for liver complications after the Fontan procedure. Congenit Heart Dis. 2017;12:124–32.
36. Wu FM, Earing MG, Aboulhosn JA, Johncilla ME, Singh MN, Odze RD, Ukomadu C, Gauvreau K, Landzberg MJ, Valente AM, Alliance for Adult Research in Congenital

Cardiology I. Predictive value of biomarkers of hepatic fibrosis in adult Fontan patients. J Heart Lung Transplant. 2017;36:211–9.
37. Wegria R, Zekert H, Walter KE, Entrup RW, De Schryver C, Kennedy W, Paiewonsky D. Effect of systemic venous pressure on drainage of lymph from thoracic duct. Am J Phys. 1963;204:284–8.
38. Dori Y, Keller MS, Fogel MA, Rome JJ, Whitehead KK, Harris MA, Itkin M. MRI of lymphatic abnormalities after functional single-ventricle palliation surgery. Am J Roentgenol. 2014;203:426–31.
39. Dori Y, Keller MS, Rychik J, Itkin M. Successful treatment of plastic bronchitis by selective lymphatic embolization in a Fontan patient. Pediatrics. 2014;134:e590–5.
40. Connor FL, Angelides S, Gibson M, Larden DW, Roman MR, Jones O, Currie BG, Day AS, Bohane TD. Successful resection of localized intestinal lymphangiectasia post-Fontan: role of (99m)technetium-dextran scintigraphy. Pediatrics. 2003;112:e242–7.
41. Parikh K, Witte MH, Samson R, Teodori M, Carpenter JB, Lowe MC, Morgan W, Hardin C, Brown M, Naughton Y, Sinha S, Barber BJ. Successful treatment of plastic bronchitis with low fat diet and subsequent thoracic duct ligation in child with fontan physiology. Lymphology. 2012;45:47–52.
42. Dori Y, Keller MS, Rome JJ, Gillespie MJ, Glatz AC, Dodds K, Goldberg DJ, Goldfarb S, Rychik J, Itkin M. Percutaneous lymphatic embolization of abnormal pulmonary lymphatic flow as treatment of plastic bronchitis in patients with congenital heart disease. Circulation. 2016;133:1160–70.
43. Hraska V. Decompression of thoracic duct: new approach for the treatment of failing Fontan. Ann Thorac Surg. 2013;96:709–11.
44. Mertens L, Hagler DJ, Sauer U, Somerville J, Gewillig M. Protein-losing enteropathy after the Fontan operation: an international multicenter study. PLE study group. J Thorac Cardiovasc Surg. 1998;115:1063–73.
45. John AS, Johnson JA, Khan M, Driscoll DJ, Warnes CA, Cetta F. Clinical outcomes and improved survival in patients with protein-losing enteropathy after the Fontan operation. J Am Coll Cardiol. 2014;64:54–62.
46. Ostrow AM, Freeze H, Rychik J. Protein-losing enteropathy after fontan operation: investigations into possible pathophysiologic mechanisms. Ann Thorac Surg. 2006;82:695–700.
47. Bode L, Eklund EA, Murch S, Freeze HH. Heparan sulfate depletion amplifies TNF-alpha-induced protein leakage in an in vitro model of protein-losing enteropathy. Am J Physiol Gastrointest Liver Physiol. 2005;288:G1015–23.
48. Bode L, Salvestrini C, Park PW, Li JP, Esko JD, Yamaguchi Y, Murch S, Freeze HH. Heparan sulfate and syndecan-1 are essential in maintaining murine and human intestinal epithelial barrier function. J Clin Invest. 2008;118:229–38.
49. Wilkinson P, Pinto B, Senior JR. Reversible protein-losing enteropathy with intestinal lymphangiectasia secondary to chronic constrictive pericarditis. N Engl J Med. 1965;273:1178–81.
50. Levitt DG, Levitt MD. Protein losing enteropathy: comprehensive review of the mechanistic association with clinical and subclinical disease states. Clin Exp Gastroenterol. 2017;10:147–68.
51. Ohuchi H, Yasuda K, Miyazaki A, Kitano M, Sakaguchi H, Yazaki S, Tsuda E, Yamada O. Haemodynamic characteristics before and after the onset of protein losing enteropathy in patients after the Fontan operation. Eur J Cardiothorac Surg. 2013;43:e49–57.
52. Ringel RE, Peddy SB. Effect of high-dose spironolactone on protein-losing enteropathy in patients with Fontan palliation of complex congenital heart disease. Am J Cardiol. 2003;91:1031–2. A9.
53. Ryerson L, Goldberg C, Rosenthal A, Armstrong A. Usefulness of heparin therapy in protein-losing enteropathy associated with single ventricle palliation. Am J Cardiol. 2008;101:248–51.
54. Schumacher KR, Cools M, Goldstein BH, Ioffe-Dahan V, King K, Gaffney D, Russell MW. Oral budesonide treatment for protein-losing enteropathy in Fontan-palliated patients. Pediatr Cardiol. 2011;32:966–71.

55. Turner Z, Lanford L, Webber S. Oral budesonide as a therapy for protein-losing enteropathy in patients having undergone Fontan palliation. Congenit Heart Dis. 2012;7:24–30.
56. Heinemann M, Breuer J, Steger V, Steil E, Sieverding L, Ziemer G. Incidence and impact of systemic venous collateral development after Glenn and Fontan procedures. Thorac Cardiovasc Surg. 2001;49:172–8.
57. McMullan DM, Reddy VM, Gottliebson WM, Silverman NH, Perry SB, Chan F, Hanley FL, Riemer RK. Morphological studies of pulmonary arteriovenous shunting in a lamb model of superior cavopulmonary anastomosis. Pediatr Cardiol. 2008;29:706–12.
58. Kavarana MN, Jones JA, Stroud RE, Bradley SM, Ikonomidis JS, Mukherjee R. Pulmonary arteriovenous malformations after the superior cavopulmonary shunt: mechanisms and clinical implications. Expert Rev Cardiovasc Ther. 2014;12:703–13.
59. Jahangiri M, Kreutzer J, Zurakowski D, Bacha E, Jonas RA. Evaluation of hemostatic and coagulation factor abnormalities in patients undergoing the Fontan operation. J Thorac Cardiovasc Surg. 2000;120:778–82.
60. Odegard KC, McGowan FX Jr, Zurakowski D, Dinardo JA, Castro RA, del Nido PJ, Laussen PC. Procoagulant and anticoagulant factor abnormalities following the Fontan procedure: increased factor VIII may predispose to thrombosis. J Thorac Cardiovasc Surg. 2003;125:1260–7.
61. Marrone C, Galasso G, Piccolo R, de Leva F, Paladini R, Piscione F, Santoro G. Antiplatelet versus anticoagulation therapy after extracardiac conduit Fontan: a systematic review and meta-analysis. Pediatr Cardiol. 2011;32:32–9.
62. Kempny A, Dimopoulos K, Uebing A, Moceri P, Swan L, Gatzoulis MA, Diller GP. 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. 2012;33:1386–96.
63. Paridon SM, Mitchell PD, Colan SD, Williams RV, Blaufox A, Li JS, Margossian R, Mital S, Russell J, Rhodes J, Pediatric Heart Network I. A cross-sectional study of exercise performance during the first 2 decades of life after the Fontan operation. J Am Coll Cardiol. 2008;52:99–107.
64. Giardini A, Hager A, Pace Napoleone C, Picchio FM. Natural history of exercise capacity after the Fontan operation: a longitudinal study. Ann Thorac Surg. 2008;85:818–21.
65. Cunningham JW, Nathan AS, Rhodes J, Shafer K, Landzberg MJ, Opotowsky AR. Decline in peak oxygen consumption over time predicts death or transplantation in adults with a Fontan circulation. Am Heart J. 2017;189:184–92.
66. Giardini A, Balducci A, Specchia S, Gargiulo G, Bonvicini M, Picchio FM. Effect of sildenafil on haemodynamic response to exercise and exercise capacity in Fontan patients. Eur Heart J. 2008;29:1681–7.
67. Goldberg DJ, French B, McBride MG, Marino BS, Mirarchi N, Hanna BD, Wernovsky G, Paridon SM, Rychik J. 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. 2011;123:1185–93.
68. Schuuring MJ, Vis JC, van Dijk AP, van Melle JP, Vliegen HW, Pieper PG, Sieswerda GT, de Bruin-Bon RH, Mulder BJ, Bouma BJ. Impact of bosentan on exercise capacity in adults after the Fontan procedure: a randomized controlled trial. Eur J Heart Fail. 2013;15:690–8.
69. Hebert A, Mikkelsen UR, Thilen U, Idorn L, Jensen AS, Nagy E, Hanseus K, Sorensen KE, Sondergaard L. 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. 2014;130:2021–30.
70. Cohen MI, Rhodes LA, Wernovsky G, Gaynor JW, Spray TL, Rychik J. Atrial pacing: an alternative treatment for protein-losing enteropathy after the Fontan operation. J Thorac Cardiovasc Surg. 2001;121(3):582.
71. Barber G, Di Sessa T, Child JS, Perloff JK, Laks H, George BL, Williams RG. Hemodynamic responses to isolated increments in heart rate by atrial pacing after a Fontan procedure. Am Heart J. 1988;115:837–41.

72. Kouatli AA, Garcia JA, Zellers TM, Weinstein EM, Mahony L. Enalapril does not enhance exercise capacity in patients after Fontan procedure. Circulation. 1997;96:1507–12.
73. Menachem JN, Golbus JR, Molina M, Mazurek JA, Hornsby N, Atluri P, Fuller S, Birati EY, Kim YY, Goldberg LR, Wald JW. Successful cardiac transplantation outcomes in patients with adult congenital heart disease. Heart. 2017;103:1449–54.
74. Ross HJ, Law Y, Book WM, Broberg CS, Burchill L, Cecchin F, Chen JM, Delgado D, Dimopoulos K, Everitt MD, Gatzoulis M, Harris L, Hsu DT, Kuvin JT, Martin CM, Murphy AM, Singh G, Spray TL, Stout KK, American Heart Association Adults With Congenital Heart Disease Committee of the Council on Clinical C, Council on Cardiovascular Disease in the Young tCoCR, Intervention, the Council on Functional G and Translational B. Transplantation and mechanical circulatory support in congenital heart disease: a scientific statement from the American Heart Association. Circulation. 2016;133:802–20.
75. VanderPluym CJ, Cedars A, Eghtesady P, Maxwell BG, Gelow JM, Burchill LJ, Maltais S, Koehl DA, Cantor RS, Blume ED. Outcomes following implantation of mechanical circulatory support in adults with congenital heart disease: an analysis of the interagency registry for mechanically assisted circulatory support (INTERMACS). J Heart Lung Transplant. 2018;37:89–99.

Systemic Right Ventricle

7

Lorna Swan

7.1 Introduction

The systemic right ventricle (RV) occurs in a spectrum of congenital cardiac disorders. This chapter will focus on heart failure in the context of a biventricular heart in the two main groups of adult patients with systemic RV patients (Fig. 7.1). Single ventricle physiology with a dominant RV will be discussed elsewhere. The systemic RV is most commonly seen in two settings—situs solitus and atrioventricular (AV) and ventriculo-arterial (VA) discordance (alternatively called congenitally corrected

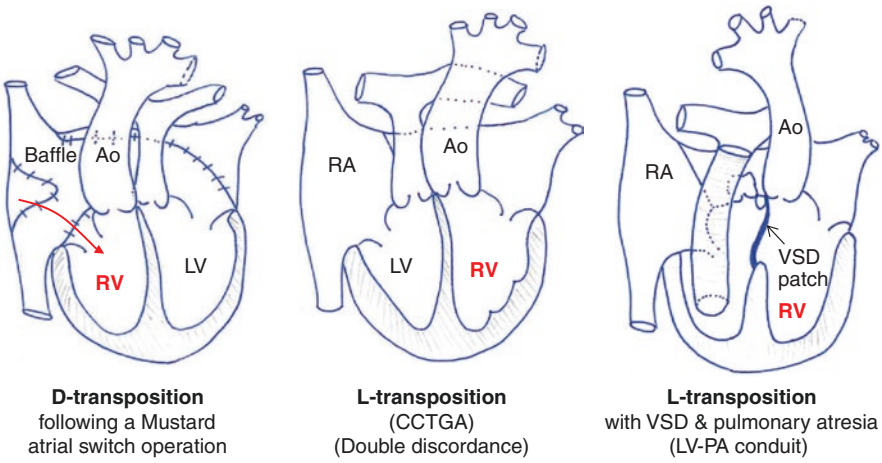

Fig. 7.1 Common types of systemic right ventricles (RV) in biventricular hearts

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transposition, ventricular inversion, double discordance or levo-transposition) and in those with AV concordance and VA discordance (D-transposition of the great arteries (TGA)). At birth this second form of transposition is incompatible with life, and therefore various early palliative operations are performed. Of these types of intervention, this chapter will focus on those with previous atrial switch (the Mustard or the Senning) operations. The population of patients with atrial switch operations is diminishing as newer surgical techniques replaced this operative approach in the early 1980s. However, many of these patients are now in their 30s and 40s and are commonly presenting with issues related to heart failure and arrhythmia.

7.2 Epidemiology and Long-Term Outcome

D-TGA and CCTGA are rare congenital cardiac lesions in the adult population, and there are approximately 0.04 cases per 1000 in the general population [1]. Little is known about the genetics of these lesions, but it is infrequent that patients have an underlying chromosomal abnormality, extra-cardiac anomalies or a positive family history. There are rare case reports of D-TGA being associated with chromosome 22 deletions or with specific mutations on the X chromosome [2]. However these are the exceptions and most cases are sporadic.

Long-term outcome for those with a previous atrial switch operation is well documented. In a large Scandinavian study, mortality in childhood was high, and after 30 years of follow-up, 40% of patients had died [3]. Other studies report better outcome with an 80% survival at 28 years [4]. Long-term outcome is adversely affected by the presence of additional lesions—for example, mortality is 2.7 times greater in those with an additional VSD [5]. Survival is more difficult to estimate in those with CCTGA given its variable age at presentation. Case of very late presentation is reported, but in those with a known diagnosis by the age of 45 years, heart failure (25–67%) and RV dysfunction (32–67%) are common with the risks of both being linked to the presence of other associated lesions [6].

Heart failure is common in those with previous atrial switch. In a study from the Netherlands, 50 long-term Mustard/Senning survivors were studied 40 years after their initial surgery. All but one of these subjects had systemic RV dysfunction—14% of which had only developed in the last decade [5]. As might be expected, the prevalence of heart failure increases over time with age being a major determinant [6]. The most common causes of death in the atrial switch population are progressive heart failure and sudden cardiac death, presumably arrhythmic. In the CCTGA group, heart failure predominates [7].

7.3 Causes of Heart Failure

The systemic RV is fundamentally different from a left ventricle in the systemic position. This is true from cellular function to microscopic myocyte organization through to gross anatomy and geometry. The understanding of the interplay of these

factors is still limited, but appreciation of the forebears of heart failure in this population is increasing. The right ventricle must learn to adapt to the "abnormal" subaortic environment. In its usual position, the RV is ideally designed to cope with changes in preload and to a relatively low and fixed afterload. In the systemic position, the reverse is true—preload is less variable and afterload is significantly elevated. This different environment results in significant changes to the geometry of the ventricle and to marked ventricular hypertrophy.

7.3.1 Geometry

The normal RV is wrapped around the LV in its short axis, and its function is intimately related to the LV. This ventricular-ventricular interaction is highlighted to be the fact that 30% of the contractile energy of the RV is generated by the LV [8]. Normal RV contraction has a peristaltic-like pattern with contraction from the base and apex spreading up to the outflow tracts. There is greater longitudinal shortening than radial shortening. Unlike the LV the RV lacks the ability to have significant torsion during systole and lacks many of the circular myofibres seen in the middle layer of the LV [9]. The RV is in almost every way not a left ventricle and not intrinsically designed to operate in the sub-aortic position. In addition, the tricuspid valve anatomy is also not ideally suited to the systemic circulation, and tricuspid regurgitation is common (Fig. 7.2).

However there are occasional patients who present with undiagnosed CCTGA in later life—these patients have managed, despite all of these issues, to maintain

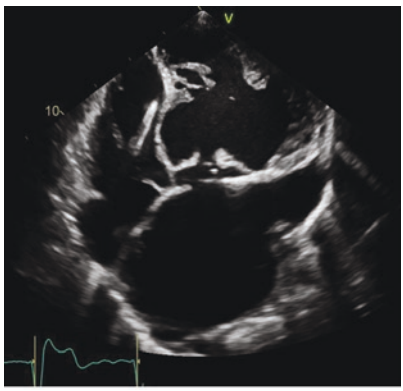

Fig. 7.2 Mechanisms of heart failure in systemic right ventricle

systolic function and exercise capacity [10]. It is clear that the RV has the ability, at least to some extent, to modify its structure in response to sub-aortic haemodynamics. In other settings the RV hypertrophies and develops patterns of muscle fibre orientation similar to the LV when subjected to pressure and volume overload [11]. There is therefore a spectrum of these adaptive and pathological modifications and much to learn about why some patients can maintain RV function for many years when others have accelerated dysfunction.

7.3.2 Cellular Structure

Patients with D-TGA and a previous atrial switch have a distinct pattern of circulating microRNA expression. MicroRNAs have a potential role in myocardial hypertrophy, regulation of cardiac apoptosis and regulation of the cardiomyocyte cytoskeleton. Their relationship in cardiac remodelling and the development of failure of the systemic RV is unclear, but they do correlate with measurements of relatively load-independent systemic ventricular contractility [12]. In addition little is known about how the cellular receptors of the RV are regulated in the sub-aortic position. Receptor signalling in the subpulmonary RV is thought to be different than that of the LV [13], but how this impacts on possible response to treatment is not clear in these complex congenital patients.

7.3.3 Ischaemic

There are several potential mechanisms by which ischaemia may drive ventricular dysfunction. Patients with CCTGA often have associated lesions. The most common of these are pulmonary stenosis and VSD. These patients are chronically hypoxic, and over many years this may adversely impact on ventricular function and potentially lead to further myocardial fibrosis [14]. The second mechanism is via inadequate coronary perfusion. Although in D-TGA the coronary arteries are macroscopically normal, the hypertrophied RV demonstrates reduced capillary density. The myocardial oxygen demand can therefore outstrip the coronary perfusion. Impaired coronary flow reserve and subclinical ischaemia have been documented in this settling and may lead to ventricular dysfunction and electrical instability [15]. In myocardial scintigraphy studies, the majority of atrial switch patients had documented myocardial perfusion defects [16]. In addition to progressive heart failure, ischaemia may have an important role in the risk of sudden cardiac death in these patients, 80% of which occurs during exercise adding weigh to this hypothesis [17].

In CCTGA the coronary arteries are “inverted” with the left coronary usually originating from the right sinus and the right from the left sinus. There may also in some patients be a single coronary from the right sinus. The right coronary artery will supply the hypertrophied and often dilated RV. Again, even in the absence of luminal narrowing, demand may outweigh supply [18].

7.3.4 Myocardial Fibrosis

Microscopic and macroscopic myocardial fibrosis appears to be common in patients following atrial switch surgery. Various biomarkers (such as procollagen type III amino-terminal propeptide (PIIINP), collagen type I carboxy-terminal telopeptide (CITP) and procollagen type I N-terminal propeptide (PINP)) are thought to be surrogate markers approximating the intensity of myocardial fibrosis. These markers are elevated in patients with a systemic RV especially in those with larger ventricles [19]. The level of PIIINP was higher in patients with an above average end-diastolic volume, and CITP was elevated in patients with late gadolinium enhancement (LGE) on MRI. Markers of collagen turnover such as C-terminal propeptide of type I procollagen (CICP) and C-terminal telopeptide of type I collagen (ICTP) are also increased [20]. Many of these markers are also related to outcome (MMP9, TIMP1, late GAD defects) suggesting potential common pathological pathways [19, 21].

On magnetic resonance imaging, LGE is common in those with a systemic RV, and a 1% increase in LGE was associated with a 38% increase in cardiac end points (death, arrhythmia, transplantation) [22]. Indeed RV LGE was a stronger predictor of outcome than RV ejection fraction. Newer imaging techniques have also been attempting to quantify diffuse myocardial fibrosis (as opposed to localized macroscopic fibrosis). This also appears to be increased in the systemic RV, and the extent of interstitial expansion is related to other markers of disease progression (such as NT-proBNP and markers of chronotropic function) [23].

In the systemic RV, myocardial fibrosis is also thought to be progressive and not solely related to perioperative insult in early life [21]. It is unclear if patchy fibrosis is inevitable over a certain age or a certain RV mass, but ongoing pathological remodelling is highly probable. Several groups have suggested that RV fibrosis could be a target for therapy and ongoing studies with agents such as eplerenone, which improves collagen turnover biomarkers, are awaited.

7.3.5 Baffle Function

One of the unique features of HF post-atrial switch is the role of the baffle function. Extensive atrial surgery in infancy leads to stiff and poorly compliant atrial pathways. Even in the absence of obstruction, these pathways limit the ability of the heart to increase its stroke volume especially at higher heart rates. This is important both on exercise and during atrial arrhythmias when the time for ventricular filling is shorter. This was demonstrated on dobutamine stress echo where, unlike the CCTGA population, those with an atrial switch were less able to increase stroke volume [24]. When the ability to increase stroke volume is diminished, the ability to increase cardiac output becomes more dependent on appropriately increasing heart rate. This limitation to preload is also important when considering the relative benefits and limitations of any medical therapy that may either impact on preload or on heart rate.

When there are specific baffle issues such as narrowings and obstructions, these should be stented both to optimize cardiac function but also to facilitate future transvenous lead placing if required [25].

7.3.6 Heart Rate

Both D-TGA and CCTGA may be associated with a blunted ability to increase heart rate on effort. This chronotropic incompetence may have several mechanisms. Post-atrial switch this is often due to abnormal sinus node function, and many of these patients have a junctional rhythm as their background rhythm [26]. In CCTGA AV block is common, and this should be carefully looked for both at rest and on exercise testing. As mentioned above in D-TGA, in particular, cardiac output and exercise capacity is often dependent on heart rate, and this needs to be borne in mind when considering therapies such as beta-blockers.

7.3.7 Tricuspid Regurgitation

Tricuspid regurgitation is common in the setting of a systemic RV (Fig. 7.3). As the RV takes on a more rounded shape, the tricuspid valve is distorted. The tricuspid valve septal chordal attachments are also displaced. Although much of the tricuspid regurgitation in systemic RV is functional, a subset of patients will have structurally abnormal valves related to an Ebstein-like anomaly or post-VSD repair. In CCTGA up to 60% of patients have a structurally abnormal valve [27]. The presence of significant tricuspid regurgitation is an important determinant of outcome, and surgical repair or replacement of the AV valve should be considered early in the disease trajectory before RV function becomes prohibitive. Outcomes from tricuspid valve surgery are poorer if the preoperative RV ejection fraction is less than 40% or if the subpulmonary ventricular systolic pressure is elevated (>50 mmHg) [28]. Progressive tricuspid regurgitation and systemic RV dysfunction can be linked together in a viscous circle of volume loading, ventricular dilatation, ventricular dysfunction and further AV valve regurgitation. Novel trans-catheter techniques are now being employed to address TR in patients who are thought to be too high risk for conventional surgery in much the same way as those with functional mitral regurgitation in those with systemic LV dysfunction [29].

7.3.8 Other Mechanisms of Heart Failure

There is very little data available regarding the influence of diastolic dysfunction on HF presentations in systemic RV. Distinguishing between abnormalities of baffle function, ventricular filling and intrinsic stiffness of the ventricle is challenging for even the most sophisticated imaging techniques. However, in such grossly hypertrophied, ischaemic and potentially fibrosed ventricles, a long prodrome of diastolic dysfunction prior to overt HF symptoms would not be unexpected. Other

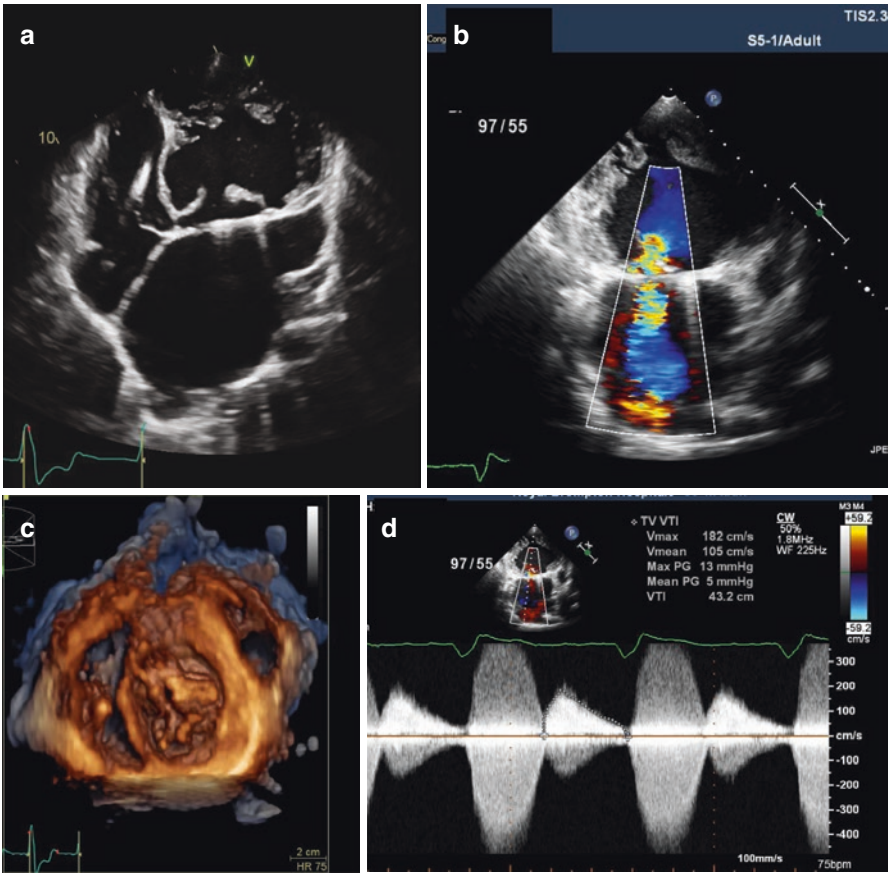

Fig. 7.3 Transthoracic echo of 34-year-old with CCTGA and previous (unsuccessful) repair of systemic AV valve. (**a**) Massively dilated LA and RV with ring from previous valve repair. Pacing lead noted in LV. (**b**) Severe systemic AV valve regurgitation (tricuspid valve). (**c**) Short axis of systemic AV valve—trileaflet valve with thickened abnormal leaflets. (**d**) Severe Tricuspid regurgitation (systemic pressures)

contributors to progressive ventricular dysfunction may include pathological myocardial-pericardial interactions and comorbidity such as thyroid dysfunction. Pregnancy in patients with a systemic RV may accelerate disease progression, and those with significant ventricular dysfunction should be counselled against pregnancy and offered effective non-oestrogen-based contraception [30, 31].

7.3.9 Systemic RV in Complex Hearts

CCTGA in particular is often associated with other cardiac lesions. These commonly include VSD and varying forms of pulmonary outflow tract obstruction. Pulmonary hypertension is often seen in those with unrestricted VSD and no

pulmonary obstruction and in a subset of transposition patients with no other detectable cause. Pulmonary hypertension in some settings may act to limit the dilatation of the systemic RV (in much the same way as a pulmonary artery band). However over time, the subpulmonary ventricle will suffer and biventricular failure will ensue. In general, the addition of other associated lesions is associated with a poorer outcome.

7.4 Diagnostic Workup

The diagnostic workup for HF in this population is as for other forms of ACHD-related HF (see Chap. 3). Cardiopulmonary exercise test and established biomarkers as NT-proBNP may be used as both diagnostic (serial tests) and prognostic tools. Particular attention should be focused on baffle function (post-atrial switch), coronary perfusion and diastolic function. The impact of tricuspid regurgitation as either a cause or result of ventricular dysfunction required careful assessment, and in this setting techniques such as stress echo may be informative. In complex patients MRI assessment of RV function is more reproducible than traditional echo.

7.5 Treatment Options

7.5.1 Medical Therapy

There is little to no evidence base for medical treatment of HF. However this does not equate to evidence of lack of efficacy. Previous studies have been limited by lack of consistent definitions of abnormal RV function, heterogenous low-risk study subjects (often asymptomatic with only mild RV dysfunction), poor study design and short follow-up. Many of these studies have been under powered with a high risk of type II errors. As previously mentioned caution needs to be exercised in the use of vasodilators on those with non-distensible atria or restrictive physiology where altering venous capacitance may decrease ventricular filling rather than increasing cardiac output. When initiating beta-blocker therapy, patients should be assessed for significant chronotropic incompetence and occult AV block.

One of the few largest studies in patient with a systemic RV was a randomized clinical trial (RCT) of valsartan [32]. Again this was in a low-risk population with many patients being asymptomatic. However in those with symptoms, valsartan appeared to be associated with a stabilization of RV ejection fraction compared to controls. Data on ß-blockers in this population are even scarcer although small observational studies suggested improvement in HF symptoms after treatment with ß-blockers. There is also evidence that ß-blockers may reduce SCD in those with atrial switches [33]. As discussed previously there are ongoing studies of mineralocorticoid receptor antagonists in this population and other newer agents. Chapter 11 discussed drug therapies in greater detail.

7.5.2 Pulmonary Artery Banding

A rather novel therapeutic option for the treatment of HF in adults with a systemic RV is to band the pulmonary artery (effectively creating significant pulmonary stenosis) and render the left ventricle "hypertensive". This was initially done as a staging procedure towards a late double switch operation with the plan of training the LV prior to it becoming the systemic ventricle. However, in adults the results of late switch operations were disappointing [34]. Incidentally it was noted that a few patients with simple banding reported a symptomatic improvement. In these patients banding resulted in a significant change in the RV-LV interaction with the septum moving towards the right ventricle and altering RV geometry and volume. In particular the tricuspid annulus reduced and, in some patients, tricuspid regurgitation improved. Age is, however, a major determinant of the LV response to banding and in older individuals the risk of acute, or chronic, LV failure is a limiting factor. For this reason these techniques have not been widely adopted in adult HF practice. Minimally invasive banding and other catheter-based therapies require further evaluation.

7.5.3 Device Therapies

Sudden cardiac death is a particular risk for the post-atrial switch patients (4–5 per 1000 patient years) [1]. There are no reliable risk scoring systems to effectively stratify risk, and most clinicians will rely on systemic RV function/ejection fraction as the main determinant of risk and the need for a primary prevention implantable cardiac defibrillator (ICD) (Fig. 7.4). Late gadolinium enhancement on MRI, atrial arrhythmias, surgery at older age and elevated circulating levels of NT-proBNP are also associated with SCD. Most authors would suggest the implantation of a primary prevention ICD in those with a systemic EF of less than 35% (Class IIb indication from the recent PACES/HRS expert consensus statement) [35]. As discussed previously baffles should be fully accessed prior to device therapy and stented if narrowed or associated with a baffle leak that may cause paradoxical embolism. If present atrial arrhythmias should be treated aggressively with catheter ablation. This will reduce the burden of arrhythmia on ventricular function and also reduce the risk of inappropriate shocks. The risk of sudden cardiac death in those with CCTA is approximately 1 death per 100 patient years of follow-up and is associated with tricuspid regurgitation and impaired RV function [36]. Again an EF of less than 35% is quoted as an indication for a primary prevention ICD.

Cardiac resynchronization therapies are discussed in Chap. 12. Care needs to be taken prior to device implantation to fully assess the coronary sinus anatomy which may, in the atrial switch patients, have been baffled to the pulmonary venous component of the atria. Variations in coronary sinus anatomy, such as atretic or multiple ostia, are also common in CCTGA [37]. As in other populations, the patients who appear to most benefit from CRT are those, often the CCTGA group, with long-term brady pacing and pacing-induced dys-synchrony.

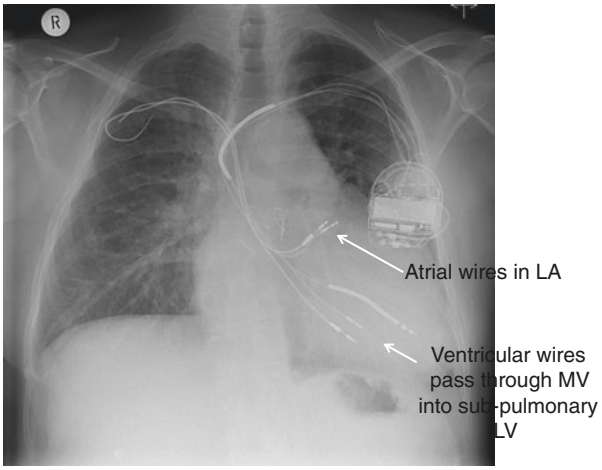

Fig. 7.4 CXR showing typical position for pacing/defibrillator leads in Mustard patient

7.5.4 Mechanical Support and Transplantation

Mechanical support and transplantation is discussed in Chap. 13. Patients with a systemic RV are often good candidates for transplantation as many will have had limited previous cardiac surgery. Elevated pulmonary artery resistance is the most common barrier to transplantation, as it is often related to ventricular function, which may improve after full heart failure treatment with/without ventricular assist device (VAD) implantation. Initial difficulties with outlet cannula from the apex of the hypertrophied RV have now been overcome with new generation of devices and with implanter experience [38].

7.6 Unanswered Questions in Systemic RV Heart Failure

Like the post-Fontan surgery group, our understanding of the optimal treatment strategy for the failing systemic RV patient is still rudimentary. Particular questions remain regarding the cellular and receptor profile of the systemic RV and how these may be pharmacologically manipulated to best improve function. In addition, novel therapies such as PA banding or trans-catheter valve treatments may need to be reinvestigated to assess if there are innovative ways of addressing declining EF. One of the most significant mysteries of the systemic RV is why some ventricles fail early and others have preserved function for many years. The impact of genotype and protein expression is yet to be adequately explored in this group.

References

1. Silka MJ, Hardy BG, Menashe VD, Morris CD. A population-based prospective evaluation of risk of sudden cardiac death after operation for common congenital heart defects. J Am Coll Cardiol. 1998;32:245–51.

2. D'Alessandro LC, Latney BC, Paluru PC, Goldmuntz E. The phenotypic spectrum of ZIC3 mutations includes isolated d-transposition of the great arteries and double outlet right ventricle. Am J Med Genet A. 2013;161A:792–802.
3. Vejlstrup N, Sorensen K, Mattsson E, Thilen U, Kvidal P, Johansson B, Iversen K, Sondergaard L, Dellborg M, Eriksson P. Long-term outcome of Mustard/Senning correction for transposition of the great arteries in Sweden and Denmark. Circulation. 2015;132:633–8.
4. Wilson NJ, Clarkson PM, Barratt-Boyes BG, Calder AL, Whitlock RM, Easthope RN, Neutze JM. Long-term outcome after the mustard repair for simple transposition of the great arteries. 28-year follow-up. J Am Coll Cardiol. 1998;32:758–65.
5. Cuypers JA, Eindhoven JA, Slager MA, Opic P, Utens EM, Helbing WA, Witsenburg M, van den Bosch AE, Ouhlous M, van Domburg RT, Rizopoulos D, Meijboom FJ, Bogers AJ, Roos-Hesselink JW. The natural and unnatural history of the Mustard procedure: long-term outcome up to 40 years. Eur Heart J. 2014;35:1666–74.
6. Norozi K, Wessel A, Alpers V, Arnhold JO, Geyer S, Zoege M, Buchhorn R. Incidence and risk distribution of heart failure in adolescents and adults with congenital heart disease after cardiac surgery. Am J Cardiol. 2006;97:1238–43.
7. Zomer AC, Vaartjes I, Uiterwaal CS, van der Velde ET, van den Merkhof LF, Baur LH, Ansink TJ, Cozijnsen L, Pieper PG, Meijboom FJ, Grobbee DE, Mulder BJ. Circumstances of death in adult congenital heart disease. Int J Cardiol. 2012;154:168–72.
8. Santamore WP, Dell'Italia LJ. Ventricular interdependence: significant left ventricular contributions to right ventricular systolic function. Prog Cardiovasc Dis. 1998;40:289–308.
9. Pettersen E, Helle-Valle T, Edvardsen T, Lindberg H, Smith HJ, Smevik B, Smiseth OA, Andersen K. Contraction pattern of the systemic right ventricle shift from longitudinal to circumferential shortening and absent global ventricular torsion. J Am Coll Cardiol. 2007;49:2450–6.
10. Beauchesne LM, Warnes CA, Connolly HM, Ammash NM, Tajik AJ, Danielson GK. Outcome of the unoperated adult who presents with congenitally corrected transposition of the great arteries. J Am Coll Cardiol. 2002;40:285–90.
11. Sanchez-Quintana D, Anderson RH, Ho SY. Ventricular myoarchitecture in tetralogy of Fallot. Heart. 1996;76:280–6.
12. Lai CT, Ng EK, Chow PC, Kwong A, Cheung YF. Circulating microRNA expression profile and systemic right ventricular function in adults after atrial switch operation for complete transposition of the great arteries. BMC Cardiovasc Disord. 2013;13:73.
13. Guillory AN, Clayton RP, Prasai A, El Ayadi A, Herndon DN, Finnerty CC. Biventricular differences in beta-adrenergic receptor signaling following burn injury. PLoS One. 2017;12:e0189527.
14. Broberg CS, Chugh SS, Conklin C, Sahn DJ, Jerosch-Herold M. Quantification of diffuse myocardial fibrosis and its association with myocardial dysfunction in congenital heart disease. Circ Cardiovasc Imaging. 2010;3:727–34.
15. Hauser M, Meierhofer C, Schwaiger M, Vogt M, Kaemmerer H, Kuehn A. Myocardial blood flow in patients with transposition of the great arteries—risk factor for dysfunction of the morphologic systemic right ventricle late after atrial repair. Circ J. 2015;79:425–31.
16. Millane T, Bernard EJ, Jaeggi E, Howman-Giles RB, Uren RF, Cartmill TB, Hawker RE, Celermajer DS. Role of ischemia and infarction in late right ventricular dysfunction after atrial repair of transposition of the great arteries. J Am Coll Cardiol. 2000;35:1661–8.
17. Kammeraad JA, van Deurzen CH, Sreeram N, Bink-Boelkens MT, Ottenkamp J, Helbing WA, Lam J, Sobotka-Plojhar MA, Daniels O, Balaji S. Predictors of sudden cardiac death after Mustard or Senning repair for transposition of the great arteries. J Am Coll Cardiol. 2004;44:1095–102.
18. Hauser M, Bengel FM, Hager A, Kuehn A, Nekolla SG, Kaemmerer H, Schwaiger M, Hess J. Impaired myocardial blood flow and coronary flow reserve of the anatomical right systemic ventricle in patients with congenitally corrected transposition of the great arteries. Heart. 2003;89:1231–5.
19. Lipczynska M, Szymanski P, Kumor M, Klisiewicz A, Hoffman P. Collagen turnover biomarkers and systemic right ventricle remodeling in adults with previous atrial switch procedure for transposition of the great arteries. PLoS One. 2017;12:e0180629.

20. Dos L, Pujadas S, Estruch M, Mas A, Ferreira-Gonzalez I, Pijuan A, Serra R, Ordonez-Llanos J, Subirana M, Pons-Llado G, Marsal JR, Garcia-Dorado D, Casaldaliga J. Eplerenone in systemic right ventricle: double blind randomized clinical trial. The evedes study. Int J Cardiol. 2013;168:5167–73.
21. Rydman R, Gatzoulis MA, Ho SY, Ernst S, Swan L, Li W, Wong T, Sheppard M, McCarthy KP, Roughton M, Kilner PJ, Pennell DJ, Babu-Narayan SV. Systemic right ventricular fibrosis detected by cardiovascular magnetic resonance is associated with clinical outcome, mainly new-onset atrial arrhythmia, in patients after atrial redirection surgery for transposition of the great arteries. Circ Cardiovasc Imaging. 2015;8.
22. Babu-Narayan SV, Goktekin O, Moon JC, Broberg CS, Pantely GA, Pennell DJ, Gatzoulis MA, Kilner PJ. Late gadolinium enhancement cardiovascular magnetic resonance of the systemic right ventricle in adults with previous atrial redirection surgery for transposition of the great arteries. Circulation. 2005;111:2091–8.
23. Plymen CM, Sado DM, Taylor AM, Bolger AP, Lambiase PD, Hughes M, Moon JC. 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. 2013;14:963–8.
24. Winter MM, van der Plas MN, Bouma BJ, Groenink M, Bresser P, Mulder BJ. Mechanisms for cardiac output augmentation in patients with a systemic right ventricle. Int J Cardiol. 2010;143:141–6.
25. Daehnert I, Hennig B, Wiener M, Rotzsch C. Interventions in leaks and obstructions of the interatrial baffle late after Mustard and Senning correction for transposition of the great arteries. Catheter Cardiovasc Interv. 2005;66:400–7.
26. Vetter VL, Tanner CS, Horowitz LN. Electrophysiologic consequences of the Mustard repair of d-transposition of the great arteries. J Am Coll Cardiol. 1987;10:1265–73.
27. Acar P, Sidi D, Bonnet D, Aggoun Y, Bonhoeffer P, Kachaner J. Maintaining tricuspid valve competence in double discordance: a challenge for the paediatric cardiologist. Heart. 1998;80:479–83.
28. Mongeon FP, Connolly HM, Dearani JA, Li Z, Warnes CA. Congenitally corrected transposition of the great arteries ventricular function at the time of systemic atrioventricular valve replacement predicts long-term ventricular function. J Am Coll Cardiol. 2011;57:2008–17.
29. Picard F, Tadros VX, Asgar AW. From tricuspid to double orifice morphology: percutaneous tricuspid regurgitation repair with the MitraClip device in congenitally corrected-transposition of great arteries. Catheter Cardiovasc Interv. 2017;90:432–6.
30. Cataldo S, Doohan M, Rice K, Trinder J, Stuart AG, Curtis SL. Pregnancy following Mustard or Senning correction of transposition of the great arteries: a retrospective study. BJOG. 2016;123:807–13.
31. European Society of Gynecology, Association for European Paediatric Cardiology, German Society for Gender Medicine, Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, Gibbs JS, Gohlke-Baerwolf C, Gorenek B, Iung B, Kirby M, Maas AH, Morais J, Nihoyannopoulos P, Pieper PG, Presbitero P, Roos-Hesselink JW, Schaufelberger M, Seeland U, Torracca L, ESC Committee for Practice Guidelines. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the task force on the management of cardiovascular diseases during pregnancy of the European Society of Cardiology (ESC). Eur Heart J. 2011;32:3147–97.
32. van der Bom T, Winter MM, Bouma BJ, Groenink M, Vliegen HW, Pieper PG, van Dijk AP, Sieswerda GT, Roos-Hesselink JW, Zwinderman AH, Mulder BJ. Effect of valsartan on systemic right ventricular function: a double-blind, randomized, placebo-controlled pilot trial. Circulation. 2013;127:322–30.
33. Khairy P, Harris L, Landzberg MJ, Fernandes SM, Barlow A, Mercier LA, Viswanathan S, Chetaille P, Gordon E, Dore A, Cecchin F. Sudden death and defibrillators in transposition of the great arteries with intra-atrial baffles: a multicenter study. Circ Arrhythm Electrophysiol. 2008;1:250–7.

34. Winlaw DS, McGuirk SP, Balmer C, Langley SM, Griselli M, Stumper O, De Giovanni JV, Wright JG, Thorne S, Barron DJ, Brawn WJ. Intention-to-treat analysis of pulmonary artery banding in conditions with a morphological right ventricle in the systemic circulation with a view to anatomic biventricular repair. Circulation. 2005;111:405–11.
35. Khairy P, Van Hare GF, Balaji S, Berul CI, Cecchin F, Cohen MI, Daniels CJ, Deal BJ, Dearani JA, Groot N, Dubin AM, Harris L, Janousek J, Kanter RJ, Karpawich PP, Perry JC, Seslar SP, Shah MJ, Silka MJ, Triedman JK, Walsh EP, Warnes CA. PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult Congenital Heart Disease: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology (ACC), the American Heart Association (AHA), the European Heart Rhythm Association (EHRA), the Canadian Heart Rhythm Society (CHRS), and the International Society for Adult Congenital Heart Disease (ISACHD). Heart Rhythm. 2014;11:e102–65.
36. McCombe A, Touma F, Jackson D, Canniffe C, Choudhary P, Pressley L, Tanous D, Robinson PJ, Celermajer D. Sudden cardiac death in adults with congenitally corrected transposition of the great arteries. Open Heart. 2016;3:e000407.
37. Bottega NA, Kapa S, Edwards WD, Connolly HM, Munger TM, Warnes CA, Asirvatham SJ. The cardiac veins in congenitally corrected transposition of the great arteries: delivery options for cardiac devices. Heart Rhythm. 2009;6:1450–6.
38. Peng E, O'Sullivan JJ, Griselli M, Roysam C, Crossland D, Chaudhari M, Wrightson N, Butt T, Parry G, MacGowan GA, Schueler S, Hasan A. Durable ventricular assist device support for failing systemic morphologic right ventricle: early results. Ann Thorac Surg. 2014;98:2122–9.

Pulmonary Arterial Hypertension

8

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Abbreviations

ASD	Atrial septal defect
CHD	Congenital heart disease
CMR	Cardiac magnetic resonance
CT	Computed tomography
ES	Eisenmenger syndrome
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
PDA	Patent ductus arteriosus
PH	Pulmonary hypertension
RV	Right ventricle
TAPSE	Tricuspid annular plane systolic excursion
VSD	Ventricular septal defect

8.1 Introduction

Over the last decades, pulmonary arterial hypertension (PAH) associated with congenital heart disease (CHD) has been studied in greater detail. However, these patients face numerous complications and still have poorer long-term survival prospects compared to the rest of the CHD population mainly due to heart failure (HF)-related issues [1].

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8.2 Definition and Classification of PAH

Pulmonary hypertension (PH) is defined as an increase in mean pulmonary arterial pressure ≥ 25 mmHg at rest, assessed by right heart catheterization [2]. Pulmonary arterial hypertension (PAH) is further characterized by pulmonary artery wedge pressure ≤ 15 mmHg and a pulmonary vascular resistance >3 Wood units (precapillary PH) in the absence of other causes. In 1998, the classification of PH was first developed, establishing groups with similar characteristics [2, 3]. PAH-CHD belongs to Group 1 PH, together with idiopathic PAH, familial PAH, portal hypertension, and PAH associated with connective tissue disease, infection, and drugs. PAH-CHD is further divided into four main groups based on clinical phenotypes: (1) Eisenmenger syndrome (ES), (2) PAH associated with prevalent systemic to pulmonary shunt lesions, (3) PAH with small/coincidental defect, and (4) PAH after defect correction.

8.3 Epidemiology

Approximately, 5–10% of adults with CHD will eventually develop PAH [4, 5]. However, the epidemiology of PAH-CHD is likely to change with a reduction in the number of patients with simple CHD defects (classic Eisenmenger patients) and an increase in those with complex lesions and those with closed defects who develop PAH [6].

8.4 Pathophysiology and Natural History

PAH can be developed in patients suffering from simple or complex CHD, but the likelihood of pulmonary vascular obstructive disease is higher among patients with larger shunts [6]. Furthermore, the location of the cardiac defect is important, as patients with a post-tricuspid shunt (unrepaired complete atrioventricular septal defect or large patent ductus arteriosus (PDA)) develop Eisenmenger physiology more often than patients with a pre-tricuspid shunt (atrial septal defect (ASD), anomalous pulmonary venous connection) [4, 7].

Median survival is reduced by around 20 years in patients with ES compared to the general population [8, 9]. Notably, the location of the cardiac defect seems to affect the long-term prognosis of the disease. This may be attributed to the ability of the right ventricle (RV) to offload and to adapt [10]. It should be noted, however, that studies showing better prognosis of PAH-CHD compared to idiopathic PAH are limited by immortal bias, since patients have not been observed from birth to end of

follow-up [5, 11, 12]. Among subgroups of PAH-CHD, patients with ES or PAH associated with prevalent systemic to pulmonary shunt lesions have better survival rates compared to patients after defect closure [13].

8.5 Evaluation of PAH-CHD Patients

8.5.1 Clinical Evaluation

Symptoms such as dyspnea on exertion, fatigue, weakness, angina, and syncope may raise the suspicion for PAH in patients with CHD [2]. Presence of cyanosis is the clinical hallmark of patients with ES and distinguishes these patients from patients with other types of PAH [14]. Chronic cyanosis leads to further myocardial impairment and is the cause of multiorgan dysfunction.

8.5.2 Functional Capacity

World Health Organization (WHO) classification is the most common classification for quantifying functional capacity in PAH-CHD patients. A 6-min walk distance <450 m equates to a maximal oxygen consumption in the cardiopulmonary exercise test between 10 and 16 mL/min/kg and BNP >100 pg/mL [15].

Cardiopulmonary exercise test is an accurate objective method for quantifying exercise tolerance. Patients with ES along with patients with complex CHD have the lowest maximal oxygen consumption and the highest minute ventilation-carbon dioxide production slope values [16–18].

8.5.3 Natriuretic Peptides

Pulmonary vascular disease causes RV wall stress and deterioration in RV function, which can be reflected by an increase in plasma brain natriuretic peptide (BNP) and the N-terminal prohormone of BNP (NT-proBNP) [19]. Indeed, in PAH-CHD, the elevation of the BNP and NT-proBNP are established prognostic markers of right heart failure and death [20, 21]. Serial changes in NT-proBNP levels along with changes in WHO functional class, peak oxygen saturation, 6-min walk distance, and tricuspid annular plane systolic excursion (TAPSE) predict mortality and were more potent predictors compared to parameters at baseline assessment [22].

8.5.4 Imaging

Echocardiography cannot be used for establishing the diagnosis of PH [23]. Indirect signs of the development of PAH in CHD patients include the presence of bidirectional or right-to-left shunt, RV hypertrophy, flattening of the interventricular septum, short pulmonary acceleration time, high pulmonary regurgitation velocity, and inferior vena cava dilatation [24]. Moreover, echocardiography is valuable in assessing prognosis and monitoring the efficacy of PAH-targeted therapy (Fig. 8.1) [25]. Cardiac magnetic resonance (CMR) is the gold standard for quantitative assessment of RV dimensions and function (Fig. 8.2) [24]. Furthermore, CMR has a role in risk stratification [26]. In ES patients, the presence of obstruction or in situ pulmonary artery thrombosis or pulmonary artery dilation can be detected with the aid of computerized tomography (CT) (Fig. 8.3). In PAH-CHD patients with chest pain and/or unexplained left ventricle wall motion abnormalities or infarction, CT can be used to image the coronary arteries. Compression of the left main stem coronary by a very

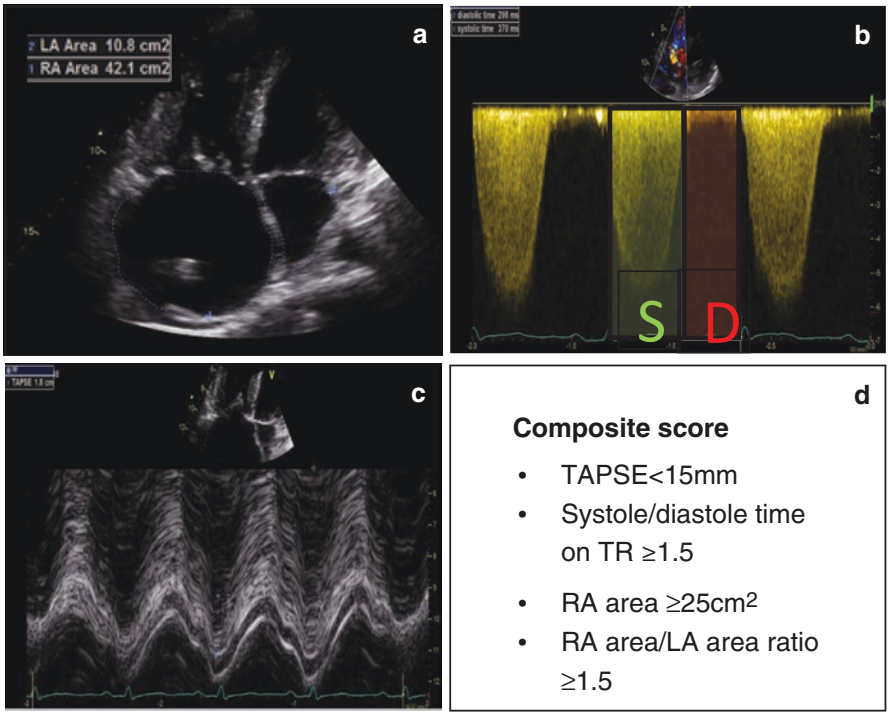

Fig. 8.1 Estimation of the echocardiographic predictors (**a**–**d**) of mortality in a woman suffering from Eisenmenger syndrome due to a large ventricular septal defect. Large right atrial area (RA) and the high ratio of right to left atrial (LA) area indicate poor outcome (**a**), while systole/diastole time of tricuspid regurgitation = 1.24 (**b**) and TAPSE = 1.8 cm (**c**) are favorable prognostic markers. *TAPSE* tricuspid annular plane systolic excursion, *TR* tricuspid regurgitation

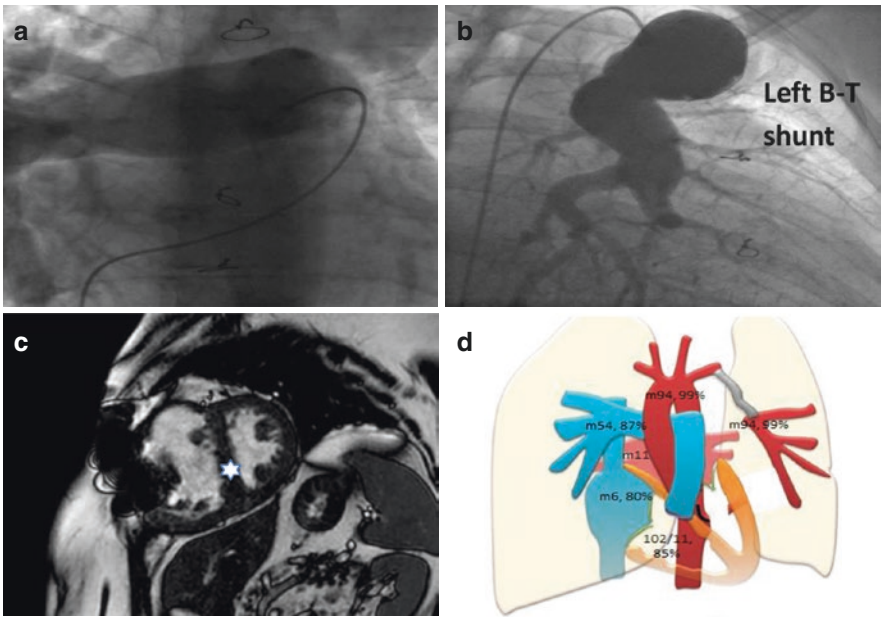

Fig. 8.2 This is a 45-year-old female with tetralogy of Fallot (TOF), who had initially undergone a Blalock-Taussig (B-T) shunt and later TOF correction. Patient was lost to follow-up and returned to tertiary care three decades later after experiencing severe symptoms. At last assessment it was discovered that the left B-T shunt was not taken down and the two pulmonary arteries were separated. In (**a**) infusion is performed via (right) pulmonary artery and only right lung is perfused. Angiographic opacification of left lung is performed with selective infusion in the left B-T shunt (**b**). Cardiac magnetic resonance indicates flattening of the septum (asterisk) and right ventricular hypertrophy due to elevated pulmonary pressures in the right lung (**c**). Schematic visualization of the pressures and the saturations (**d**)

dilated pulmonary artery is a well-recognized cause of angina [27]. However, CT does not provide information on hemodynamics, and care needs to be taken when using nephrotoxic iodinated contrast agents especially in cyanotic patients [28].

8.6 Treatment

8.6.1 General Management

PAH-CHD patients, especially those with ventricular dysfunction, should be referred to specialized tertiary centers [2, 29]. This was highlighted both in Canada where specialized ACHD care was independently associated with mortality reduction and also in Germany suggesting a better outcome mainly mediated by the early and proper initiation of PAH-targeted therapy [30, 31].

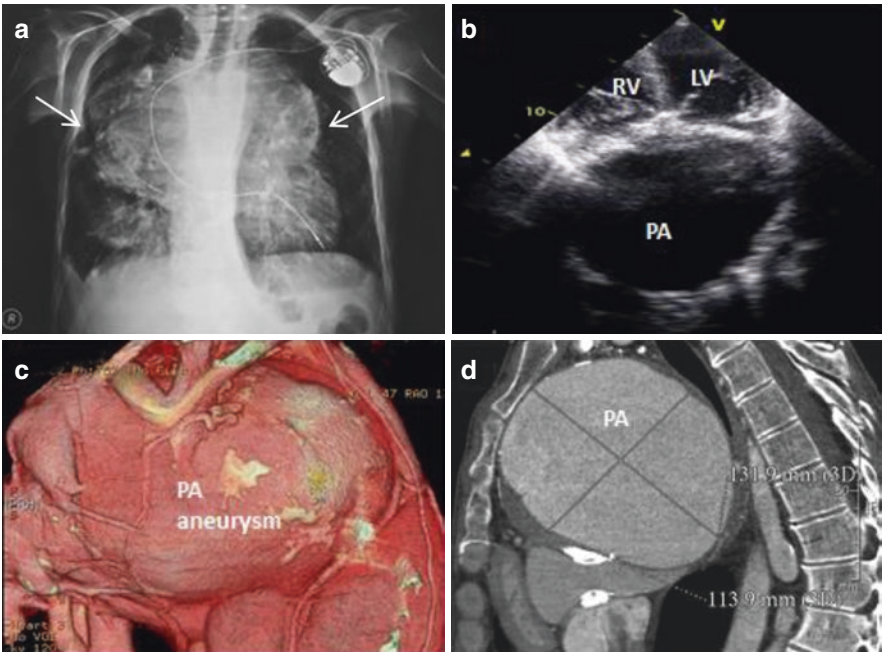

Fig. 8.3 Complex congenital heart disease associated with Eisenmenger syndrome. This is a 37-year-old male with transposition of the great arteries and large ventricular septal defect, who had undergone a palliative Mustard procedure and subsequently insertion of a pacemaker. When he was referred to a specialized PAH-CHD center, he was found to have a giant pulmonary artery aneurysm on the chest radiogram (**a**, arrows), echocardiography study (**b**), and cardiac computed tomography (**c** and **d**). *PA* pulmonary artery, *LV* left ventricle, *RV* right ventricle

Avoidance of pregnancy and adequate contraceptive measures are additional issues of high importance for these patients [32]. Endocarditis prophylaxis, prevention of dehydration, regular immunization against influenza and pneumococcal infections, as well as supervised exercise training are recommended [2]. The effectiveness of exercise training as add-on to medical therapy is recognized, as it improves working capacity and quality of life [33–35]. Iron deficiency is frequently encountered in cyanotic patients and is the result of secondary erythrocytosis due to chronic hypoxemia [36]. Phlebotomy is only indicated in cases of moderate to severe symptomatic hyperviscosity syndrome in the absence of dehydration [5]. Iron supplementation is recommended as it improves exercise tolerance and quality of life [37]. Oxygen therapy is not routinely recommended since it has not impacted on survival of ES patients [38].

Patients with ES have a substantial risk of in situ pulmonary artery thrombus formation [39]. In contrast, the predisposition of ES patients to bleeding, including life-threatening pulmonary hemorrhage, discourages the routine use of anticoagulants [29, 40]. Anticoagulation should only be considered in cases of atrial arrhythmias and pulmonary artery thrombosis, especially in the setting of RV systolic impairment [29, 41]. The role of novel oral anticoagulants is yet to be defined.

Non-cardiac surgeries in PAH-CHD patients should be performed only when necessary and in expert centers due to the risks of right heart failure and other life-threatening complications [42, 43].

8.6.2 Treating PAH-Related HF

8.6.2.1 Acute Right HF

The keys to managing acute RV failure in these patients are as follows:

- To identify and treat any reversible triggers such as arrhythmia or sepsis.
- To optimize the Frank-Starling curve of the failing RV using loop diuretics and central venous pressure (CVP) monitoring. It may be necessary to maintain a narrow window of CVP to stabilize the patient as an over- or underfilled RV may further diminish cardiac output and adversely impact on RV-LV interaction. Serial echocardiography can be very useful in carefully titrating diuretic therapy against RV function and measures of cardiac output.
- To try to improve myocardial contractility with inotropic support (see Chap. 9).
- To reduce RV afterload using pulmonary vasodilator therapy.

Intravenous prostacyclin is the pulmonary vasodilator of choice in severely decompensated patient, while nitric oxide is recommended in intubated patients [44–46].

Intravenous diuretics are preferred over oral therapies especially in edematous patients who may have edema of the gut wall. Following the acute event, chronic diuretics may also be required to treat symptomatic fluid overload and optimize RV filling. In the midterm spironolactone is very valuable in treating the associated secondary hyperaldosteronism and is a useful adjuvant when patients are difficult to diurese with loop diuretics alone [47].

8.6.2.2 Chronic Right HF

Disease-modifying drugs in acquired left heart failure have been extrapolated in PAH-CHD with RV deterioration. Theoretically, renin-angiotensin system inhibition with angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs) may worsen right-to-left shunting and further compromise oxygen saturation [48]. Notably, the administration of angiotensin-converting enzyme inhibitors in 60 cyanotic CHD patients showed favorable results, while recent data from the German registry reported no association of the clinical outcome of ES patients and the use of ACEIs/ARBs [31, 49]. The use of β-blockers has been very limited in PAH patients due to their theoretical negative inotropic effect on the RV [50]. Nonetheless, carvedilol was reported initially to improve RV function in pulmonary hypertensive rats, and their use in PAH patients is currently being assessed [51, 52]. As above loop diuretics, aldosterone antagonists and targeted pulmonary vasodilators are the bedrock of ongoing management.

8.6.3 Targeted PAH Treatment

Advanced PAH therapies are now widely used in patients with PAH-CHD and have been shown to improve functional capacity and survival [12, 31, 53–56]. Targets for PAH-specific therapy are the three pathophysiological pathways: (1) endothelin, (2) nitric oxide, and (3) prostacyclin.

8.6.3.1 Endothelin-1 Receptor Antagonists

Endothelin-1 is a strong vasoconstrictor and mitogen for smooth muscle, produced by endothelial cells [57, 58]. Endothelin receptor antagonists include bosentan, ambrisentan, and macitentan. The results of the Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) were the first strong evidence on the efficacy of endothelin receptor antagonists in ES patients [59]. The prolonged beneficial effect of bosentan on exercise capacity was confirmed by a prospective study, in which the increase in mean 6-min walk distance continued to exist during at least 2.5 years of follow-up [60].

Data on efficacy of ambrisentan in PAH-CHD patients is limited. A retrospective study of 17 ES patients, who were administered ambrisentan, showed an improvement in 6-min walk distance without serious adverse events [61].

Approval of macitentan in PAH-CHD was based on the Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome (SERAPHIN), which included 62 CHD-PAH patients with a closed defect [62]. The efficacy of macitentan in ES patients has also been evaluated at the MAESTRO study (clinicaltrials.gov NCT01743001). After 16 weeks of treatment, 6-min walk distance was increased in both groups (macitentan and placebo), while NT-proBNP was decreased by 20% in macitentan arm [63]. In a small study of 15 patients with ES, macitentan was well tolerated and seemed to have positive effect on 6-min walk distance and resting oxygen saturation [64]. Of note, in a study of 40 patients that switched from bosentan to macitentan, an improvement was recorded in WHO functional class, NT-proBNP, and TAPSE compared to those that received bosentan, while no difference was reported in hospitalization for heart failure and syncope [65].

8.6.3.2 Phosphodiesterase-5 Inhibitors and Guanylate Cyclase Stimulators

Sildenafil was the first drug of this category which was proved effective in patients with symptomatic PAH [66]. Later a small randomized trial with ten ES patients demonstrated that sildenafil improved exercise capacity, NYHA class, and hemodynamic parameters [67]. Prospective, nonrandomized trials resulted in similar findings [68–70]. Similarly, the PHIRST trial proved the efficacy and safety of tadalafil in PAH, including patients with CHD (closed defects or PDA) [71]. In another observational study of ES patients, tadalafil was shown to be safe and to improve exercise capacity, NYHA class, and hemodynamics, and this was also confirmed by a randomized placebo-controlled, double-blind crossover study [72, 73].

Riociguat acts on the nitric oxide pathway as a guanylate cyclase stimulator. The randomized controlled trial PATENT-1 (Pulmonary Arterial hyperTENsion sGC-stimulator Trial-1) and its extension PATENT-2 demonstrated the role of riociguat in patients with PAH (including patients with PAH after CHD correction), improving the WHO functional class, exercise capacity, hemodynamics, and NT-proBNP [74, 75].

8.6.3.3 Prostacyclin Receptor Agonists

The pulmonary vasodilators that were initially used, were the intravenous prostacyclin analogues. Administration of epoprostenol seemed to have favorable clinical and hemodynamic results in PAH-CHD patients [76, 77]. However, its use is limited by the risk of line sepsis and paradoxical embolism in patients with shunts. A double-blind, randomized, placebo-controlled trial showed that subcutaneous treprostinil administration was effective (109 out of 470 were patients with systemic to pulmonary shunts), having an acceptable safety profile, with the most common side effect being the infusion site pain [78]. The EIGER study reported that inhaled iloprost improved exercise capacity, quality of life, and RV function in 13 Eisenmenger patients, albeit no improvement was recorded in their hemodynamics [79]. Recently, the Prostacyclin (PGI_2) Receptor Agonist In Pulmonary Arterial Hypertension (GRIPHON) study proved the safety and efficacy of selexipag, an oral prostacyclin receptor agonist [80]. This study included 110 PAH-CHD patients with a closed defect, and therefore, the role of selexipag in PAH-CHD patients is promising, but yet to be defined.

8.6.3.4 Combination Therapy

While the administration of combination therapy in PAH is increasing over the years [81], data in PAH-CHD is limited. A randomized, placebo-controlled, double-blind crossover study showed that bosentan as monotherapy in 21 patients with ES improved 6-min walk distance, pulmonary vascular resistance, and pulmonary blood flow, while the addition of sildenafil to bosentan increased only saturation at rest [82]. However, D'Alto et al. reported that addition of sildenafil in PAH-CHD patients after oral bosentan therapy improved clinical status, effort oxygen saturation, exercise tolerance, and hemodynamics [83].

8.6.3.5 Special Entities

Segmental PH is a newly recognized PH condition that was described in PH guidelines as "PH observed in discrete lung areas perfused by aortopulmonary collaterals in congenital heart diseases such as pulmonary or tricuspid atresia" [2]. There is very limited data on the role of drug therapies in this group [84].

A large proportion of ES patients have Trisomy 21 (Down syndrome). Although these patients are often difficult to assess, in three small studies, bosentan administration appeared to be safe and had favorable results [85–87].

8.6.4 Transplantation

Patients with advanced right heart failure, despite maximal medical treatment, are eligible candidates for heart transplantation [88–90]. Notably, in the ACHD cohort of the United Network for Organ Sharing database, pulmonary vascular resistance exceeding 4 Wood units was a predictor of 30-day mortality; however, no difference in long-term survival based on pretransplantation pulmonary vascular resistance was found [91].

In a UK center, early and late outcome with heart-lung transplantation was compared between ES and non-ES patients, and no difference in overall survival was reported. Indeed, the 10-year survival was 26% and 27.6%, respectively [92]. Furthermore, over a 10-year period, 605 transplants in end-stage ES patients were recorded in the United Network for Organ Sharing/International Society for Heart and Lung Transplantation Joint Thoracic Registry [93]. The underlying cause of ES predicted the posttransplantation survival. Heart-lung transplantation seemed to have better results compared to lung transplantation with shunt correction (see Chap. 13).

Conclusion

Even though patients with PAH-CHD live longer in the era of PAH-targeted treatment, mortality remains high. Right heart failure is currently the predominant cause of death in these patients. Therefore, the prevention and the optimal management of heart failure in these patients play a key role, and research should be oriented in this direction.

References

1. Diller GP, Kempny A, Alonso-Gonzalez R, et al. Survival prospects and circumstances of death in contemporary adult congenital heart disease patients under follow-up at a Large Tertiary Centre. Circulation. 2015;132(22):2118–25.
2. Galie N, Humbert M, Vachiery JL, et al. ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37(1):67–119.
3. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D34–41.
4. Duffels MG, Engelfriet PM, Berger RM, et al. Pulmonary arterial hypertension in congenital heart disease: an epidemiologic perspective from a Dutch registry. Int J Cardiol. 2007;120(2):198–204.
5. Bouzas B, Gatzoulis MA. Pulmonary arterial hypertension in adults with congenital heart disease. Rev Esp Cardiol. 2005;58(5):465–9.
6. Gatzoulis MA, Alonso-Gonzalez R, Beghetti M. Pulmonary arterial hypertension in paediatric and adult patients with congenital heart disease. Eur Respir Rev. 2009;18(113):154–61.
7. Van de Bruaene A, Delcroix M, Pasquet A, et al. The Belgian Eisenmenger syndrome registry: implications for treatment strategies? Acta Cardiol. 2009;64(4):447–53.

8. Engelfriet PM, Duffels MG, Moller T, et al. Pulmonary arterial hypertension in adults born with a heart septal defect: the Euro Heart Survey on adult congenital heart disease. Heart. 2007;93(6):682–7.
9. Lange RA, Brickner ME. Improving survival in patients with Eisenmenger syndrome: are we any closer? Circulation. 2017;135(15):1441–3.
10. Moceri P, Kempny A, Liodakis E, et al. Physiological differences between various types of Eisenmenger syndrome and relation to outcome. Int J Cardiol. 2015;179:455–60.
11. Hopkins WE, Ochoa LL, Richardson GW, Trulock EP. Comparison of the hemodynamics and survival of adults with severe primary pulmonary hypertension or Eisenmenger syndrome. J Heart Lung Transplant. 1996;15(1 Pt 1):100–5.
12. Diller GP, Kempny A, Inuzuka R, et al. Survival prospects of treatment naive patients with Eisenmenger: a systematic review of the literature and report of own experience. Heart. 2014;100(17):1366–72.
13. Manes A, Palazzini M, Leci E, et al. Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: a comparison between clinical subgroups. Eur Heart J. 2014;35(11):716–24.
14. Dimopoulos K, Wort SJ, Gatzoulis MA. Pulmonary hypertension related to congenital heart disease: a call for action. Eur Heart J. 2014;35(11):691–700.
15. Niedeggen A, Skobel E, Haager P, et al. Comparison of the 6-minute walk test with established parameters for assessment of cardiopulmonary capacity in adults with complex congenital cardiac disease. Cardiol Young. 2005;15(4):385–90.
16. Diller GP, Dimopoulos K, Okonko D, et al. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. Circulation. 2005;112(6):828–35.
17. Kempny A, Dimopoulos K, Uebing A, et al. 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. 2012;33(11):1386–96.
18. Inuzuka R, Diller GP, Borgia F, et al. Comprehensive use of cardiopulmonary exercise testing identifies adults with congenital heart disease at increased mortality risk in the medium term. Circulation. 2012;125(2):250–9.
19. Yasue H, Yoshimura M, Sumida H, et al. Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. Circulation. 1994;90(1):195–203.
20. Reardon LC, Williams RJ, Houser LS, et al. Usefulness of serum brain natriuretic peptide to predict adverse events in patients with the Eisenmenger syndrome. Am J Cardiol. 2012;110(10):1523–6.
21. Giannakoulas G, Mouratoglou SA, Gatzoulis MA, Karvounis H. Blood biomarkers and their potential role in pulmonary arterial hypertension associated with congenital heart disease. A systematic review. Int J Cardiol. 2014;174(3):618–23.
22. Schuijt MTU, Blok IM, Zwinderman AH, et al. Mortality in pulmonary arterial hypertension due to congenital heart disease: serial changes improve prognostication. Int J Cardiol. 2017.
23. D'Alto M, Romeo E, Argiento P, et al. Accuracy and precision of echocardiography versus right heart catheterization for the assessment of pulmonary hypertension. Int J Cardiol. 2013;168(4):4058–62.
24. D'Alto M, Dimopoulos K, Budts W, et al. Multimodality imaging in congenital heart disease-related pulmonary arterial hypertension. Heart. 2016;102(12):910–8.
25. D'Alto M, Romeo E, Argiento P, et al. Pulmonary arterial hypertension: the key role of echocardiography. Echocardiography. 2015;32 Suppl 1:S23–37.
26. Jensen AS, Broberg CS, Rydman R, et al. 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. 2015;8(12).
27. Devaraj A, Hansell DM. Computed tomography signs of pulmonary hypertension: old and new observations. Clin Radiol. 2009;64(8):751–60.

28. Babu-Narayan SV, Giannakoulas G, Valente AM, Li W, Gatzoulis MA. Imaging of congenital heart disease in adults. Eur Heart J. 2016;37(15):1182–95.
29. Baumgartner H, Bonhoeffer P, De Groot NM, et al. ESC guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J. 2010;31(23):2915–57.
30. Mylotte D, Pilote L, Ionescu-Ittu R, et al. Specialized adult congenital heart disease care: the impact of policy on mortality. Circulation. 2014;129(18):1804–12.
31. Diller GP, Korten MA, Bauer UM, et al. Current therapy and outcome of Eisenmenger syndrome: data of the German National Register for congenital heart defects. Eur Heart J. 2016;37(18):1449–55.
32. Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, et al. ESC guidelines on the management of cardiovascular diseases during pregnancy: the task force on the management of cardiovascular diseases during pregnancy of the European Society of Cardiology (ESC). Eur Heart J. 2011;32(24):3147–97.
33. Becker-Grunig T, Klose H, Ehlken N, et al. Efficacy of exercise training in pulmonary arterial hypertension associated with congenital heart disease. Int J Cardiol. 2013;168(1):375–81.
34. Budts W, Borjesson M, Chessa M, et al. Physical activity in adolescents and adults with congenital heart defects: individualized exercise prescription. Eur Heart J. 2013;34(47):3669–74.
35. Giannakoulas G, Dimopoulos K. Exercise training in congenital heart disease: should we follow the heart failure paradigm? Int J Cardiol. 2010;138(2):109–11.
36. Rosove MH, Perloff JK, Hocking WG, et al. Chronic hypoxaemia and decompensated erythrocytosis in cyanotic congenital heart disease. Lancet. 1986;2(8502):313–5.
37. Tay EL, Peset A, Papaphylactou M, et al. 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. 2011;151(3):307–12.
38. Sandoval J, Aguirre JS, Pulido T, et al. Nocturnal oxygen therapy in patients with the Eisenmenger syndrome. Am J Respir Crit Care Med. 2001;164(9):1682–7.
39. Silversides CK, Granton JT, Konen E, et al. Pulmonary thrombosis in adults with Eisenmenger syndrome. J Am Coll Cardiol. 2003;42(11):1982–7.
40. Broberg C, Ujita M, Babu-Narayan S, et al. Massive pulmonary artery thrombosis with haemoptysis in adults with Eisenmenger's syndrome: a clinical dilemma. Heart. 2004;90(11):e63.
41. Broberg CS, Jayaweera AR, Diller GP, et al. Seeking optimal relation between oxygen saturation and hemoglobin concentration in adults with cyanosis from congenital heart disease. Am J Cardiol. 2011;107(4):595–9.
42. Ammash NM, Connolly HM, Abel MD, Warnes CA. Noncardiac surgery in Eisenmenger syndrome. J Am Coll Cardiol. 1999;33(1):222–7.
43. Bennett JM, Ehrenfeld JM, Markham L, Eagle SS. Anesthetic management and outcomes for patients with pulmonary hypertension and intracardiac shunts and Eisenmenger syndrome: a review of institutional experience. J Clin Anesth. 2014;26(4):286–93.
44. Granton J, Mercier O, De Perrot M. Management of severe pulmonary arterial hypertension. Semin Respir Crit Care Med. 2013;34(5):700–13.
45. Hoeper MM, Granton J. Intensive care unit management of patients with severe pulmonary hypertension and right heart failure. Am J Respir Crit Care Med. 2011;184(10):1114–24.
46. Price LC, Wort SJ, Finney SJ, Marino PS, Brett SJ. Pulmonary vascular and right ventricular dysfunction in adult critical care: current and emerging options for management: a systematic literature review. Crit Care. 2010;14(5):R169.
47. Bansal S, Lindenfeld J, Schrier RW. Sodium retention in heart failure and cirrhosis: potential role of natriuretic doses of mineralocorticoid antagonist? Circ Heart Fail. 2009;2(4):370–6.
48. Trojnarska O. Heart failure in the adult patient with congenital heart disease. Cardiol J. 2007;14(2):127–36.
49. Hopkins WE, Kelly DP. Angiotensin-converting enzyme inhibitors in adults with cyanotic congenital heart disease. Am J Cardiol. 1996;77(5):439–40.
50. Peacock A, Ross K. Pulmonary hypertension: a contraindication to the use of {beta}-adrenoceptor blocking agents. Thorax. 2010;65(5):454–5.

51. Bogaard HJ, Natarajan R, Mizuno S, et al. Adrenergic receptor blockade reverses right heart remodeling and dysfunction in pulmonary hypertensive rats. Am J Respir Crit Care Med. 2010;182(5):652–60.
52. Grinnan D, Bogaard HJ, Grizzard J, et al. Treatment of group I pulmonary arterial hypertension with carvedilol is safe. Am J Respir Crit Care Med. 2014;189(12):1562–4.
53. van Riel AC, Schuuring MJ, van Hessen ID, et al. Treatment of pulmonary arterial hypertension in congenital heart disease in Singapore versus the Netherlands: age exceeds ethnicity in influencing clinical outcome. Neth Heart J. 2016;24(6):410–6.
54. Dimopoulos K, Inuzuka R, Goletto S, et al. Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension. Circulation. 2010;121(1):20–5.
55. Diller GP, Alonso-Gonzalez R, Dimopoulos K, et al. Disease targeting therapies in patients with Eisenmenger syndrome: response to treatment and long-term efficiency. Int J Cardiol. 2013;167(3):840–7.
56. Adriaenssens T, Delcroix M, Van Deyk K, Budts W. Advanced therapy may delay the need for transplantation in patients with the Eisenmenger syndrome. Eur Heart J. 2006;27(12):1472–7.
57. Cacoub P, Dorent R, Maistre G, et al. Endothelin-1 in primary pulmonary hypertension and the Eisenmenger syndrome. Am J Cardiol. 1993;71(5):448–50.
58. Galie N, Manes A, Branzi A. The endothelin system in pulmonary arterial hypertension. Cardiovasc Res. 2004;61(2):227–37.
59. Galie N, Beghetti M, Gatzoulis MA, et al. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. Circulation. 2006;114(1):48–54.
60. Vis JC, Duffels MG, Mulder P, et al. 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. 2013;164(1):64–9.
61. Zuckerman WA, Leaderer D, Rowan CA, Mituniewicz JD, Rosenzweig EB. Ambrisentan for pulmonary arterial hypertension due to congenital heart disease. Am J Cardiol. 2011;107(9):1381–5.
62. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med. 2013;369(9):809–18.
63. Ltd AP. Actelion announces results of the MAESTRO study with macitentan in patients with pulmonary arterial hypertension due to Eisenmenger syndrome. 2017.
64. Herbert S, Gin-Sing W, Howard L, Tulloh RM. Early experience of Macitentan for pulmonary arterial hypertension in adult congenital heart disease. Heart Lung Circ. 2017.
65. Blok IM, van Riel A, van Dijk APJ, Mulder BJM, Bouma BJ. From bosentan to macitentan for pulmonary arterial hypertension and adult congenital heart disease: further improvement? Int J Cardiol. 2017;227:51–2.
66. Galie N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med. 2005;353(20):2148–57.
67. Singh TP, Rohit M, Grover A, Malhotra S, Vijayvergiya R. A randomized, placebo-controlled, double-blind, crossover study to evaluate the efficacy of oral sildenafil therapy in severe pulmonary artery hypertension. Am Heart J. 2006;151(4):851.e851–5.
68. Tay EL, Papaphylactou M, Diller GP, et al. Quality of life and functional capacity can be improved in patients with Eisenmenger syndrome with oral sildenafil therapy. Int J Cardiol. 2011;149(3):372–6.
69. Chau EM, Fan KY, Chow WH. Effects of chronic sildenafil in patients with Eisenmenger syndrome versus idiopathic pulmonary arterial hypertension. Int J Cardiol. 2007;120(3):301–5.
70. Zhang ZN, Jiang X, Zhang R, et al. Oral sildenafil treatment for Eisenmenger syndrome: a prospective, open-label, multicentre study. Heart. 2011;97(22):1876–81.
71. Galie N, Brundage BH, Ghofrani HA, et al. Tadalafil therapy for pulmonary arterial hypertension. Circulation. 2009;119(22):2894–903.
72. Mukhopadhyay S, Sharma M, Ramakrishnan S, et al. Phosphodiesterase-5 inhibitor in Eisenmenger syndrome: a preliminary observational study. Circulation. 2006;114(17):1807–10.

73. Mukhopadhyay S, Nathani S, Yusuf J, Shrimal D, Tyagi S. Clinical efficacy of phosphodiesterase-5 inhibitor tadalafil in Eisenmenger syndrome—a randomized, placebo-controlled, double-blind crossover study. Congenit Heart Dis. 2011;6(5):424–31.
74. Ghofrani HA, Galie N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med. 2013;369(4):330–40.
75. Rosenkranz S, Ghofrani HA, Beghetti M, et al. Riociguat for pulmonary arterial hypertension associated with congenital heart disease. Heart. 2015;101(22):1792–9.
76. Rosenzweig EB, Kerstein D, Barst RJ. Long-term prostacyclin for pulmonary hypertension with associated congenital heart defects. Circulation. 1999;99(14):1858–65.
77. Thomas IC, Glassner-Kolmin C, Gomberg-Maitland M. Long-term effects of continuous prostacyclin therapy in adults with pulmonary hypertension associated with congenital heart disease. Int J Cardiol. 2013;168(4):4117–21.
78. Simonneau G, Barst RJ, Galie N, et al. 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. 2002;165(6):800–4.
79. Cha KS, Cho KI, Seo JS, et al. 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. 2013;112(11):1834–9.
80. Sitbon O, Channick R, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension. N Engl J Med. 2015;373(26):2522–33.
81. Fox BD, Shtraichman O, Langleben D, Shimony A, Kramer MR. Combination therapy for pulmonary arterial hypertension: a systematic review and meta-analysis. Can J Cardiol. 2016;32(12):1520–30.
82. Iversen K, Jensen AS, Jensen TV, Vejlstrup NG, Sondergaard L. Combination therapy with bosentan and sildenafil in Eisenmenger syndrome: a randomized, placebo-controlled, double-blinded trial. Eur Heart J. 2010;31(9):1124–31.
83. D'Alto M, Romeo E, Argiento P, et al. Bosentan-sildenafil association in patients with congenital heart disease-related pulmonary arterial hypertension and Eisenmenger physiology. Int J Cardiol. 2012;155(3):378–82.
84. Schuuring MJ, Bouma BJ, Cordina R, et al. Treatment of segmental pulmonary artery hypertension in adults with congenital heart disease. Int J Cardiol. 2013;164(1):106–10.
85. Duffels MG, Vis JC, van Loon RL, et al. Down patients with Eisenmenger syndrome: is bosentan treatment an option? Int J Cardiol. 2009;134(3):378–83.
86. Duffels MG, Vis JC, van Loon RL, et al. 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. 2009;103(9):1309–15.
87. D'Alto M, Romeo E, Argiento P, et al. Therapy for pulmonary arterial hypertension due to congenital heart disease and Down's syndrome. Int J Cardiol. 2013;164(3):323–6.
88. Stout KK, Broberg CS, Book WM, et al. Chronic heart failure in congenital heart disease: a scientific statement from the American Heart Association. Circulation. 2016;133(8):770–801.
89. Ross HJ, Law Y, Book WM, et al. Transplantation and mechanical circulatory support in congenital heart disease: a scientific statement from the American Heart Association. Circulation. 2016;133(8):802–20.
90. Budts W, Roos-Hesselink J, Radle-Hurst T, et al. Treatment of heart failure in adult congenital heart disease: a position paper of the Working Group of Grown-Up Congenital Heart Disease and the Heart Failure Association of the European Society of Cardiology. Eur Heart J. 2016;37(18):1419–27.
91. Patel ND, Weiss ES, Allen JG, et al. Heart transplantation for adults with congenital heart disease: analysis of the United Network for organ sharing database. Ann Thorac Surg. 2009;88(3):814–21. discussion 821-812.
92. Stoica SC, McNeil KD, Perreas K, et al. Heart-lung transplantation for Eisenmenger syndrome: early and long-term results. Ann Thorac Surg. 2001;72(6):1887–91.
93. Waddell TK, Bennett L, Kennedy R, Todd TR, Keshavjee SH. Heart-lung or lung transplantation for Eisenmenger syndrome. J Heart Lung Transplant. 2002;21(7):731–7.

Acute Heart Failure in Adult Patients with Congenital Heart Disease

9

Alexander Van De Bruaene and S. Lucy Roche

9.1 Introduction

The population of adult patients with moderate and complex congenital heart disease (CHD) continues to grow [1]. As this cohort ages, symptomatic heart failure (HF) episodes and end-stage HF have become increasingly prevalent [2–4]. The hospital admission rate of ACHD patients is twice that of the general population, and 16% of ACHD admissions are directly to intensive care [5, 6]. In 2016, both the European Society of Cardiology and the American Heart Association published papers on the management of HF in ACHD (ACHD-HF) [7, 8]. These ACHD-specific consensus documents mainly relate to chronic HF and provide only limited, if any, guidance on acute HF. In an absence of evidence or consensus recommendations for the management of acute ACHD-HF, current practice is based largely on clinical experience.

In the main, acute ACHD-HF presents in four ways:

(1) *Patients with previously unrecognised and unrepaired CHD*. The management of these patients is complex, requires an expert multidisciplinary team and depends on the underlying heart defect and haemodynamics at the time of presentation [9].

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(2) *Repaired CHD patients with residual haemodynamic lesions who decompensate in response to an acute trigger*. Such patients may have been stable for decades but deteriorate suddenly when they develop arrhythmia, systemic infection and noncardiac illness or undergo noncardiac surgery. Unfortunately this scenario is all too often linked to lapses in care or loss to specialist follow-up.

(3) *Patients who develop infective endocarditis (IE)*. ACHD patients most at risk are patients with prosthetic valve material or a previous history of IE [10].

(4) *Patients who despite adequate follow-up and appropriately timed re-interventions, due to the 'natural' history of their cardiac lesion, develop chronic HF with acute-on-chronic presentations*.

This chapter will focus on patients with acute HF in patients with repaired CHD reviewing the most relevant residual lesions and explaining how, in the presence of certain triggers, they predispose patients to acute decompensation. This is particularly relevant to patients who have been lost to specialist ACHD follow-up. The importance of searching for reversible mechanical and electrical causes will be emphasised. Strategies to stabilise acute-on-chronic patients, buying time to consider advanced HF therapies, will also be discussed.

9.2 Acute Heart Failure Caused by Residual Abnormalities

9.2.1 Related to Valves and Conduits

Many patients with repaired or palliated congenital heart disease live with residual atrioventricular and/or semilunar valve abnormalities, and those with conduits often develop conduit stenosis and/or regurgitation as they age [11]. The ventricles of such patients are exposed to ongoing and progressive haemodynamic effects with pressure overload, volume overload or both. Unchecked, an indolent pathophysiology with neurohormonal activation, cardiac remodelling and effects on the peripheral and pulmonary vasculature eventually results in clinical HF. The impact of residual pulmonary regurgitation in patents with repaired tetralogy of Fallot (TOF) is probably one of the most studied and best understood examples [12].

ACHD patients with valve and conduit problems tend to experience a protracted, well-compensated, asymptomatic phase. In an ideal world, this permits careful tracking of their course and the timely re-intervention. Alas, in reality, thresholds for re-intervention remain uncertain [13], patients get lost to follow-up [14], and intervening events can trigger sudden decompensation. These factors mean that ACHD patients with residual valve and conduit abnormalities can and do experience acute clinical HF episodes. However, as long as the patient's ventricular mechanics and overall status have not progressed too far (something best assessed by ACHD specialists), it may be possible to treat the HF by treating the underlying valve/conduit disease.

Case 1: Pulmonary valve replacement in TOF can acutely improve heart function:

A 24-year-old woman, born with TOF, had surgery in infancy and then a 25 mm Hancock porcine conduit at the age of 17 years. She failed to transition to adult care

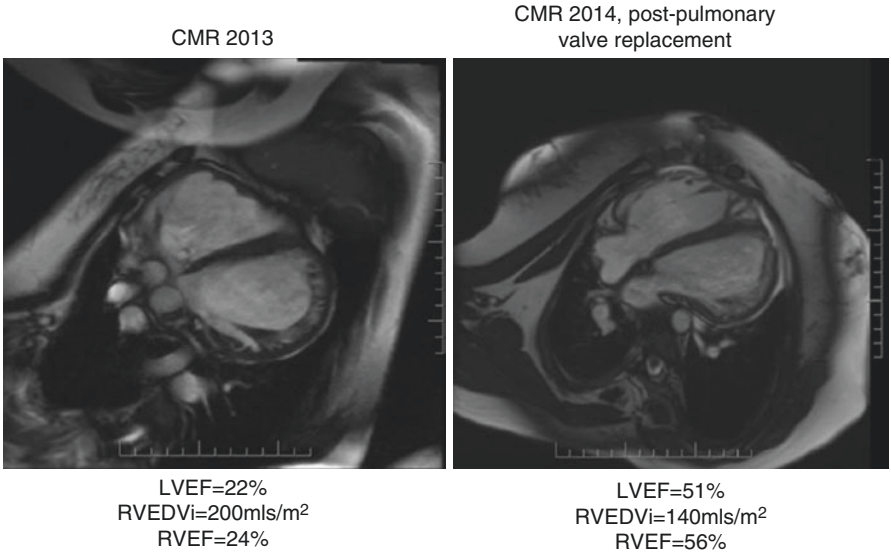

Fig. 9.1 CMR of a TOF patient before (left panel) and after (right panel) pulmonary valve replacement (*CMR* cardiac magnetic resonance, *LVEF* left ventricular ejection fraction, *RVEDVI* right ventricular end-diastolic volume index, *RVEF* right ventricular ejection fraction)

and had been without specialist follow-up for the previous 6 years. She presented to her local emergency department with a 2-week history of swollen legs and orthopnoea on a background of a 3-month history of lethargy. Previously she had been fit and well. She had signs of right heart failure with severe bilateral peripheral oedema, mild ascites and hepatomegaly. Electrocardiogram (ECG) demonstrated sinus rhythm, right bundle branch block and QRS duration of 180 ms. Echocardiography and cardiac magnetic resonance (CMR) confirmed severe pulmonary regurgitation, severe tricuspid regurgitation, right ventricular (RV) dilatation and biventricular dysfunction. Her BNP was 893 pg/ml. She was transferred to the specialist centre where she required intravenous diuretics. She underwent surgical pulmonary valve replacement and tricuspid valve repair 12 weeks later. Post discharge she was followed up in a specialist ACHD-HF clinic, and she continued on an ACEI for poor LV function. Five years later she remains asymptomatic with mildly impaired biventricular function and BNP 23 pg/ml and no further hospital admissions (Fig. 9.1).

9.2.2 Related to the Subaortic (Systemic) Right Ventricle

Patients with a systemic right ventricle (Mustard, Senning and congenital corrected transposition of the great arteries (CCTGA)) are vulnerable to the development of late HF. The RV myocardial architecture and tricuspid valve anatomy are intrinsically ill-suited to the high afterload of systemic arterial resistance (see Chap. 7. The

RV subaortic RV does adapt—it becomes hypertrophied and dilated and changes its contraction pattern [15]). In this way, although they may have evidence of a chronic HF state, most patients remain well compensated for decades [16, 17].

One trigger for acute HF in this group is atrial tachyarrhythmia (Fig. 9.1). These are particularly concerning for transposition patients with atrial baffle repairs where the patients in whom the capacitance and conduit function of the baffles is limited [18]. Unlike CCTGA patients, those with a baffle are unable to increase their stroke volume in response during exercise or dobutamine stress [18, 19]. This response occurs despite increased ventricular contraction and suggests that the interatrial baffles limit ventricular filling during fast heart rates. These patients tolerate fast heart rates poorly and may even cause haemodynamic collapse, especially in the presence of baffle obstruction [20]. Treatment with prompt electrical cardioversion is almost always required.

9.2.3 Related to a Fontan Circulation

Fontan patients have a finally balanced circulation with little reserve [21]. Ventricular function, atrioventricular vale regurgitation, pulmonary venous obstruction, branch pulmonary artery stenosis, obstruction of the Fontan connection or outflow tract obstruction (ascending aorta and aortic arch, especially after Damus-Kaye-Stansel procedure) could all contribute to HF. The systemic ventricle usually evolves from volume overloaded, dilated and/or hypertrophied when shunted or banded to overgrown and preload insufficient after Fontan completion [22]. Therefore, classic indices of ventricular function may be difficult to evaluate [23]. It may be even more difficult to identify patients with impaired diastolic dysfunction [24, 25]. In Fontan patients, the inherent vulnerability of the cardiovascular system can acutely be revealed, and their condition can spiral downwards rapidly. Triggers for this often include atrial arrhythmia, sepsis, pregnancy, undergoing noncardiac surgery or developing thrombosis within the Fontan pathway.

Case 2: Acute HF in a Fontan patient secondary to a complicated postoperative course following noncardiac surgery:

A 29-year-old woman with a history of right atrial isomerism, bilateral superior caval veins, pulmonary stenosis and single right ventricle had undergone a Fontan palliation as a child. She had residual severe atrioventricular valve regurgitation with moderate ventricular dysfunction. At baseline, she was asymptomatic. She had a surgical termination of pregnancy and experienced postoperative pain secondary to endometriosis. She was prescribed ibuprofen 600 mg, of which she took 60 tablets in 7 days. She presented with oliguria an acute kidney injury. She was treated with intravenous fluids and developed IART. She was transferred to the specialist centre. On day 2, she worsened with cardiogenic shock (hypotension, ischaemic hepatitis, high lactate). She was transferred to cardiac intensive care unit (CICU), started on IV inotropes and required dialysis. She had three unsuccessful DC cardioversion attempts. She stabilised but remained inotrope dependent for 8 weeks in the CICU. Eventually, with aggressive afterload reduction, she was

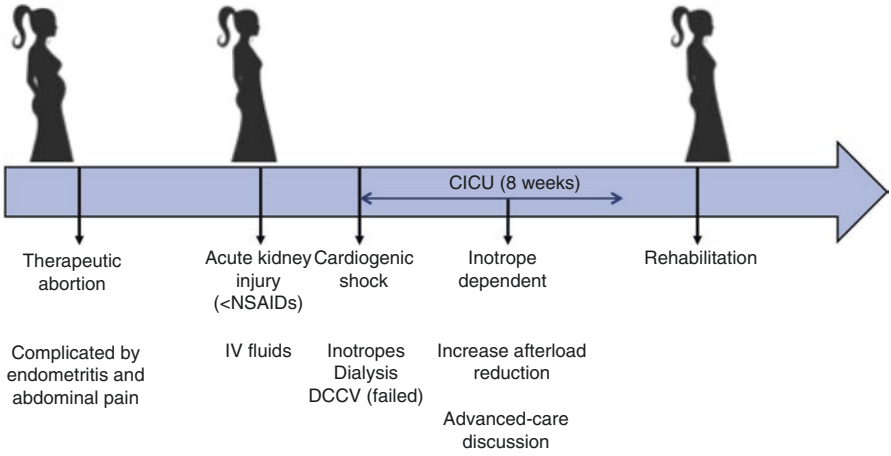

Fig. 9.2 Timetable of complications and recovery of a patient with univentricular heart post-therapeutic abortion (*CICU* cardiac intensive care unit, *IV* intravenous, *NSAIDs* non-steroidal anti-inflammatory drugs, *DCCV* DC cardioversion)

weaned off inotropes and transferred to the ward. She required intensive rehabilitation but eventually recovered with stable cardiac function (Fig. 9.2).

9.2.4 Related to Pulmonary Vasculature

The pulmonary vascular system maximises the surface area for gas exchange whilst minimising resistance to blood flow, so as to decrease the work the subpulmonary ventricle needs to perform [26, 27]. Evaluation of the pulmonary circulation is important in patients presenting with subpulmonary RV failure and also in patients with Fontan circulation. The increase in pulmonary vascular resistance (PVR) can be gradual due to elevated pulmonary blood flow (intra- or extra-cardiac left-to-right shunt, palliative shunts), due to non-pulsatile flow instead of laminar flow (Fontan circulation) or acutely due to pulmonary embolism or other severe lung insults [28, 29]. Thrombus formation is a major concern in patients with a Fontan circulation, occurring in about 25% of patients, especially in patients with a right atrium to pulmonary artery (RA-PA) Fontan connection or atrial arrhythmias [30, 31]. Pulmonary embolism may result in ventilation/perfusion mismatch or a significant increase in PVR, both of which are poorly tolerated. Likewise, pulmonary artery thrombus is present in about 25% of patients with Eisenmenger physiology [32, 33].

Case 3: Acute circulatory failure caused by increased resistance to pulmonary blood flow in a Fontan patient with a massive thrombus:

A 60-year-old gentleman was born with tricuspid atresia and VSD. He underwent a classic Glenn procedure, followed by RA-PA Fontan palliation in 1983. He was lost to follow up and represented with a short history decreasing exercise

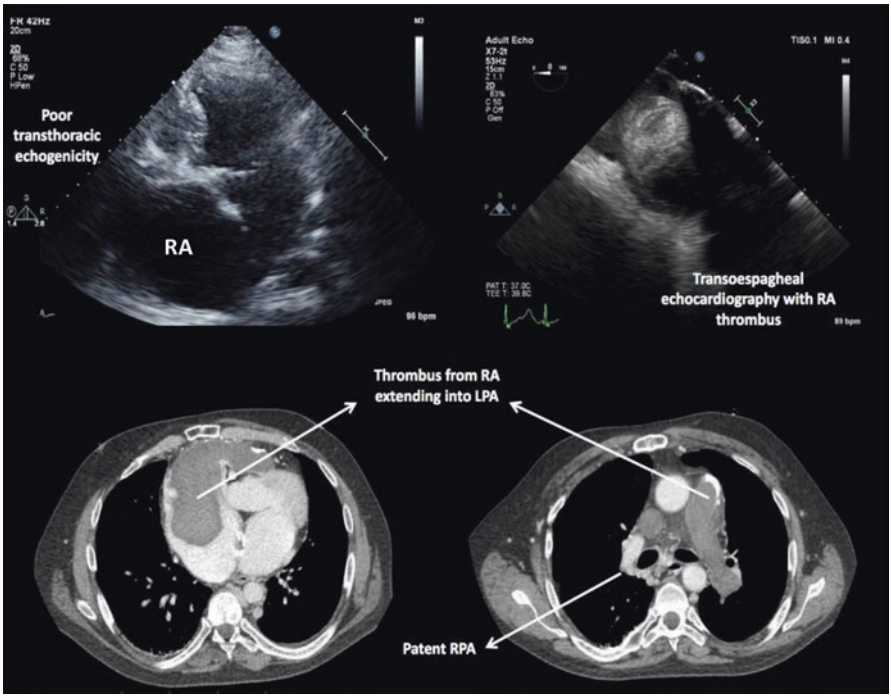

Fig. 9.3 Echo (upper panels) and computed tomography (lower panels) imaging a giant thrombus in RA (upper right panel) extending into LPA. RPA was free of thrombus (*RA* right atrium, *LPA* left pulmonary artery, *RPA* right pulmonary artery)

tolerance and worsening desaturation. Transoesophageal echocardiography and cardiac CT revealed extensive thrombus from the RA into distal left pulmonary artery. The classic Glenn connected to the right pulmonary artery was free. Due to incapacitating cyanosis, he underwent surgical thrombectomy but unfortunately died due to postoperative complications (Fig. 9.3).

9.2.5 Related to Residual Shunts and/or Collaterals

It is important to consider the presence of shunts and collaterals as an additional volume and/or pressure load causing HF. Pre-tricuspid shunt lesions, such as atrial septal defects (ASD) result in volume load of the right heart [34], whereas post-tricuspid shunt lesions, such as ventricular septal defect (VSD), result in volume load of the LV, but both may cause pulmonary vascular disease. Both systemic RV patients with a baffle repair and Fontan patients may also have shunts at atrial level. Aorta-pulmonary arterial collaterals are another cause of left-to-right shunting which may volume load the subaortic ventricle. In CHD patients with chronically elevated venous pressure, venous-venous collaterals can occur (Fontan patients, patients with Glenn shunt) [35]. These collaterals cause right-to-left shunt with

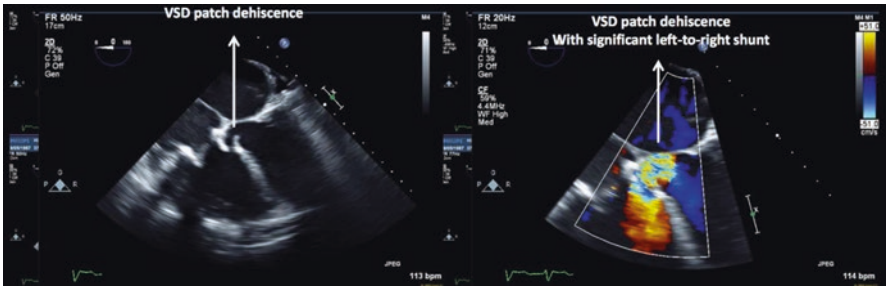

Fig. 9.4 VSD patch dehiscence as pictured with transesophageal echocardiography without (left panel) and with colour Doppler (right panel). *VSD* ventricular septal defect

cyanosis. Patients who lack circulating hepatic factor in the pulmonary blood flow (in case of a classic Glenn connection) are more prone to form pulmonary arteriovenous malformations causing an intrapulmonary right-to-left shunt [36].

When patients with shunts acutely deteriorate (e.g. Eisenmenger, Fontan with fenestration and/or collaterals, univentricular heart physiology), the ratio of systemic vascular resistance (SVR) to PVR should be closely guarded. Any state that decreases SVR and/or increases PVR will result in increased right-to-left shunting and systemic arterial desaturation. Care should be taken to avoid and treat septicaemia, elevated temperatures and medical therapies that could reduce afterload.

Case 4: Acute HF secondary to VSD patch dehiscence:

A 27-year-old gentleman with previous VSD patch closure and bioprosthetic tricuspid valve replacement presented with acute severe HF with poor peripheral perfusion. Echocardiogram showed a severely dilated RV with severely reduced RV systolic function and complete dehiscence of the VSD patch (Fig. 9.4). Cardiac catheterisation showed a right atrial pressure of 28 mmHg, RV end-diastolic pressure of 25 mmHg, mean PA pressure of 54 mmHg and Qp/Qs estimated at 4:1. As he was haemodynamically unstable despite aggressive HF management, including inotropes, he underwent successful emergent surgery with VSD patch closure. Three years later he remains well with normal biventricular function.

9.3 Arrhythmia as a Trigger for Acute Heart Failure

Both tachyarrhythmias and brady-arrhythmias can easily disrupt the delicate haemodynamic balance in CHD patients [37]. Although appearing to be benign, atrial arrhythmias in ACHD are associated with a 50% increase in mortality and a 100% increase in stroke and HF [38]. Intra-atrial re-entrant tachycardia (IART) is frequent in CHD patients [39–41]. As mentioned above particular sub-groups of patients are preload dependent and especially sensitive to arrhythmias with a rapid ventricular response [20]. Atrial fibrillation will become more frequent as the ACHD population ages [41]. Ventricular tachycardia is most typically encountered in patients with tetralogy of Fallot, TGA or Ebstein anomaly [42, 43]. Brady-arrhythmias include

sinus node dysfunction (CCTGA, TGA-baffle and Fontan) and atrioventricular block (CCTGA and AVSD). When patients present with HF secondary to arrhythmia, the cornerstone of treatment is the restoration of sinus rhythm.

9.4 Infective Endocarditis

Infective endocarditis (IE), which has a prevalence in CHD of 1.3 per 1000 patient years, is especially common in patients with prosthetic valves [10]. This risk varies with the type of valve—1% per year in homograft conduits to 2–3% per year for Contegra conduits or Melody valves [44]. One-year IE-associated mortality in CHD patients is 16%, and around 20% of patients will experience worsening of HF because of IE [10]. The presence of HF during the course of IE significantly increases mortality risk [45]. Patch dehiscence in the setting of endocarditis, outflow tract obstruction and worsening valve regurgitation are often poorly tolerated. The presence of HF in left-sided IE is a clear indication for surgical intervention [46]. Early surgery in left-sided native IE in patients without CHD is independently associated with reduced mortality [47] and probably also applies to patients with CHD.

Case 5: Infective endocarditis of a Melody valve:

A 29-year-old man with pulmonary atresia and VSD who underwent multiple previous interventions, including a 20 mm Melody valve implanted 10 years prior. He presented with MRSA IE of the Melody valve, which was stenotic resulting in significant RV pressure load. He had runs of nonsustained ventricular tachycardia but was inoperable because of cavitating lung lesions with severe haemorrhage, which required emergent intubation. He underwent salvage stenting of the RVOT, which was successful in reducing the RV pressure load and allowed stabilisation of the patient with antibiotics so that he could undergo surgical revision of his RV outflow tract some weeks later (Fig. 9.5).

9.5 Heart Failure Secondary to Complications of Noncardiac Surgery and Interventions

Patients with ACHD undergoing noncardiac surgery have an increased perioperative morbidity and mortality [48] and longer intensive care unit (ICU) stay [49]. A multidisciplinary preoperative assessment is essential [50]. For reasons discussed above, patients with a Fontan circulation, pulmonary hypertension and cyanotic CHD have an especially high risk of developing acute HF even during minor surgical procedures. A carefully considered plan should incorporate issues such as which environment the surgery is best performed in (ACHD centre or elsewhere), who should provide anaesthesia and where the patient should recover from surgery. Careful fluid management, perioperative monitoring of the SVR/PVR ratio, invasive monitoring if necessary and postoperative ICU stay if needed can all reduce the potential for acute ACHD-HF in the perioperative setting [51].

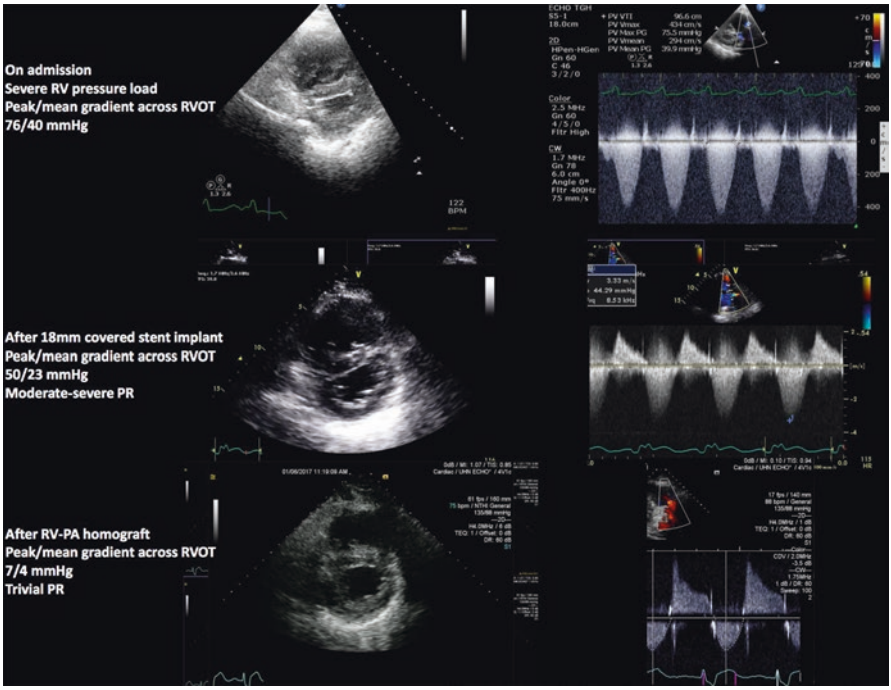

Fig. 9.5 Appearance of RV in echo (left) and RVOT gradient (right) before stenting (upper panel), after stenting (middle panel) and postsurgical revision of RVOT (bottom panel) (*RV* right ventricle, *RVOT* right ventricular outflow tract, *PR* pulmonary regurgitation)

9.6 Diagnosis of Acute Heart Failure

Initial clinical assessment of ACHD patients with (sub)acute HF should be similar to general HF patients as in the European Society of Cardiology HF guidelines [52]. In addition, all of the particular risks described above should be assessed with a sound understanding of the patient's anatomy and physiology. Identification of precipitating causes, evaluation of the severity of the patient's condition and multiorgan assessment are all key.

9.6.1 Oxygen Saturations, Arterial Blood Gases, Chest XR and Biomarkers

In patients with cyanotic CHD, it is important to compare current saturation with the saturation measured at the last outpatient clinic visit. In case of differential cyanosis (patent ductus arteriosus (PDA)-Eisenmenger), care should be taken to follow saturation in the lower extremities. Arterial blood gas (and if available mixed venous blood gas) analysis is more reliable and more complete. A chest X-ray will provide

information about pulmonary venous congestion. Biomarkers, such as BNP and NT-proBNP, are related with adverse outcome in ACHD patients with HF [53].

9.6.2 Examination, Electrocardiogram and Cardiac Enzymes

Low blood pressure with signs of reduced peripheral and vital organ perfusion requires immediate attention. An *electrocardiogram* to detect arrhythmias is crucial as they may cause or exacerbate heart failure.

9.6.3 Ischaemia (Serial ECG and High-Sensitive Troponin)

Ischaemia in ACHD is often thromboembolic in origin, especially in the presence of intracardiac shunts, severe subaortic ventricular dysfunction, atrial arrhythmias and/or mechanical subaortic atrioventricular valves. Anomalous coronary arteries may also carry a risk [54, 55]. About 10% of children with anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) survive into adulthood and can present with HF, ischaemia and even cardiac arrest [56]. Post surgical reimplantation, there is a risk of ostial coronary artery stenosis (aortic root replacement, Ross procedure, arterial switch procedure). Coronary complications are present in 5% of patients with arterial switch operations [57]. Coronary fistulae, if large enough, may cause coronary arterial steal leading to ischaemia [35]. As the ACHD population ages, myocardial ischaemia due to atherosclerosis-related coronary artery disease will also increase [4, 58].

9.6.4 Structure and Function (Echocardiography)

Echocardiography is mandated in the initial evaluation of all acute ACHD-HF patients. Attention should be paid to lesion-specific residual lesions, subpulmonary ventricle, conduits if present, valvular function and in Fontan patients the presence of a thrombus in the Fontan connection and Fontan obstruction.

9.6.5 Magnetic Resonance Imaging (MRI), Computed Tomography (CT) and Catheterisation

MRI and CT are powerful diagnostic tools that can inform both the diagnostics and treatment decision-making in the acute HF patient [59]. *Cardiac catheterisation* may provide additional information including pulmonary vascular resistance, RV and LV filling pressures and pressure gradients and permits the evaluation of collateral vessels and shunt fraction in selected patients with CHD [59].

9.7 Therapeutic Management

The acuity of management will be driven by the patient's clinical status. Haemodynamically unstable patients need immediate support according to acute cardiac life-support protocols. In less urgent scenarios, it is always helpful if the non-specialist has a straightforward means of communicating with an ACHD cardiologist. Since oftentimes the patient may be well known to the specialist and whilst general acute heart failure management is often appropriate, there may be specific caveats related to the specific underlying diagnosis.

Oxygen is given to treat hypoxaemia but not recommended as an adjunctive therapy for non-hypoxaemic ACHD patients as it may decrease cardiac output through an increase in SVR and may increase myocardial ischaemia [60–62]. An effort should be made to establish what the baseline saturations of the patient were when well. Erroneously targeting normal oxygen saturations or paO_2 in a patient baseline saturations are in the 80s can lead to haemodynamic disaster, for example, if the patient is intubated and their 'just-compensated' physiology destabilised by positive-pressure ventilation. Conversely, in patients with subpulmonary ventricular failure and/or right-to-left shunt, hypoxaemia should be avoided as it may increase PVR. Diuretics are the cornerstones for symptomatic relief of patients presenting with fluid overload due to immediate venodilator action and fluid removal. Careful assessment of volume status in patients with subpulmonary failure (preload-dependent circulation) is required as both hypo- and hypervolaemia will decrease cardiac output [63]. Limited volume loading with evaluation of fluid responsiveness may be useful but may worsen subpulmonary function in patients with pulmonary hypertension [64].

Patients with cavopulmonary shunts (Glenn or Fontan) and atrial switch (Mustard or Senning) and those who are haemodynamically unstable require prompt treatment of atrial arrhythmias [37]. When electrical cardioversion is performed, the team needs to be prepared for the possibility of prolonged bradycardia. Many Fontan patients do not have ready venous access to the ventricular mass (for temporary pacing), and this should be anticipated by having options such as atropine, isoprenaline and other forms of nonvenous pacing [37].

Intravenous vasodilators, such as nitroglycerine, isosorbide dinitrate and nitroprusside, may be important in the treatment of subaortic ventricular failure as they reduce preload (thereby reducing congestion) and afterload (thereby increasing stroke volume and cardiac output) [65]. Patients with isolated subpulmonary failure are unlikely to benefit from vasodilator therapy. The presence of a right-to-left shunt is a relative contraindication (i.e. decreased SVR/PVR ratio).

Norepinephrine causes peripheral arterial vasoconstriction through α-1 agonism and mild positive inotropic effect through β-1 receptor agonism. It may be indicated in subaortic ventricular failure in case of severe hypotension to redistribute blood from the extremities to the vital organs at the expense of increased afterload [62]. In patients with subpulmonary failure and right-to-left shunts, it is important to keep SVR well above PVR to preserve right coronary artery blood flow and avoid myocardial ischaemia and increased cyanosis, respectively [63]. Interestingly, in patients

with acute or chronic subpulmonary RV pressure load, increased LV afterload (induced by norepinephrine) also resulted in improved RV function and even remodelling [66, 67]. It should be noted that norepinephrine may also increase PVR at higher doses [63]. Vasoconstrictors should be used with caution in Fontan patients.

Milrinone is a phosphodiesterase-3 inhibitor that reduces afterload by vasodilation and has inotropic properties. If subpulmonary RV failure is due to volume load (pulmonary regurgitation), milrinone increases contractility of the failing RV and reduces PVR and SVR whilst maintaining mean arterial blood pressure [68]. It has become the main inotrope in paediatric intensive care after cardiac surgery [69]. Caution is required as milrinone increases the frequency of ventricular arrhythmias [70]. Dobutamine is a β-1 agonist that increases myocardial contractility and reduces SVR and PVR at doses up to 5 μg/kg/min [63, 71]. Although it improves RV contractility and RV-pulmonary artery coupling [71], doses exceeding 10 μg/kg/min may cause pulmonary vasoconstriction, which should be avoided in patients with subpulmonary failure. Levosimendan is a calcium sensitiser with positive inotropic effect by increasing calcium sensitivity of myocytes without increasing oxygen demand. By opening adenosine triphosphate (ATP)-sensitive potassium channels, it also has vasodilatory effects. In patients with severe, low-output heart failure, levosimendan improved haemodynamic performance more effectively than dobutamine [72]. By not affecting intracellular calcium levels, it may also have less pro-arrhythmogenic effects.

Pulmonary vasodilation in case of increased PVR may be provided by inhaled NO [73] or the inhaled prostacyclin analogue iloprost [74]. Inhaled agents, if possible, are preferred over intravenous agents which may cause hypotension [63, 75]. Rebound pulmonary hypertension can occur when administration is interrupted. If the patient was on pulmonary vasodilators prior to admission, it is important to continue and consider upgrading.

Primary systemic ventricular disease will benefit from positive-pressure ventilation (PPV) as it decreases systemic ventricular afterload [76]. In contrast, in patients with subpulmonary ventricular failure or a Fontan circulation, PPV can decrease cardiac output. Ventilation can be used to decrease PVR and increase blood flow. Hypoxia, hypercapnia and compression of the pulmonary vasculature at the extremes of lung volumes should be avoided [63].

9.8 The Role of Extracorporeal Membrane Oxygenation

Many surgical ACHD centres will also have experience with extracorporeal member oxygenation (ECMO), either in the context of an associated paediatric cardiac programme or an associated adult heart transplant programme. When ACHD patients develop acute heart failure in a setting where there are clinicians experienced in ECMO, the use of this supportive therapy can be considered. Potential indications, contraindications and options for modes of ECMO are similar to those in other adults [77]. Review of the literature and our clinical experience suggest ECMO in ACHD patients is most often performed in the setting of post-cardiotomy

myocardial dysfunction. A 2016 paper from the Mayo Clinic (Rochester, USA) described postoperative ECMO support in 24 ACHD patients, 1.1% of their ACHD cardiac surgical cohort during the 13-year study period [78]. Both biventricular and single-ventricle physiology patients were supported, and 46% survived to hospital discharge, which is comparable with outcomes for non-ACHD, post-cardiotomy ECMO [78]. There are occasions when ECMO might be considered for ACHD patients outside of the setting of cardiac surgery, usually as an option to buy time (e.g. intractable arrhythmia inducing acute heart failure, acute heart failure in the setting of endocarditis, acute thrombosis of a Fontan circulation). Vohra et al. published a case report of a 21-year-old, complex ACHD patient who developed septic shock secondary to infective endocarditis on a Melody valve and was successfully supported by ECMO until stabile enough for surgical treatment [79]. In 2016, Aydin et al. published data from the Extracorporeal Life Support Organization (ELSO) registry looking at ECMO in patients with a single-ventricle anatomy. Although all patients were children, the primary indication for ECMO was respiratory failure, rather than post-cardiotomy [80].

Even when ECMO is suggested in an emergency situation, pre-cannulation evaluation of multi-organ function and neurological status is essential. ECMO can maintain patients despite severe, unrecoverable impairment, and assessment can be difficult once support is initiated. It is also advisable to seek information as to whether the patient has previously provided details regarding their views on advanced care or their likely philosophy in this regard. Establishing ECMO in ACHD patients may be complicated by challenges related to venous access. Large-bore cannulas are required for cannulation, and the patient's chart should be reviewed for information regarding patency of the femoral and neck vessels as well as any documented vascular abnormalities. Ultrasound imaging of the vessels and review of any previous cross-sectional imaging are invaluable. In patients placed on ECMO percutaneously, left ventricular distension can compromise myocardial recovery. We and others have used percutaneous, trans-septal techniques to vent the left atrium in this situation. The durability of ECMO support tends to be limited by complications such as sepsis, thrombosis and bleeding. It should be considered a short-term support option which may, in some circumstances, buy an ACHD patient time for recovery, bridge them to a definitive surgical strategy or permit transition to a more durable form of mechanical support. For each individual, the potential exit strategy, timeframe and goals of support should be discussed by the team and with the patient (or their family) before ECMO cannulation.

9.9 The Multidisciplinary Approach to Acute HF

Complex ACHD is often a multisystem disorder. ACHD patients may have diminished pulmonary reserve due to lung hypoplasia, scoliosis, diaphragmatic paralysis and/or restrictive lung disease [76]. Renal dysfunction is frequent especially in patients with cyanotic CHD [81]. If a patient is admitted to the intensive care unit, specific attention should be given to deterioration in renal function. Patients with

subpulmonary failure may have a decreased renal perfusion pressure gradient. The same patients may have increased intra-abdominal pressures (in case of ascites) [81, 82]. Invasive haemodynamic monitoring and measurements of bladder pressures may be useful in this scenario.

The impact of associated haematological and liver abnormalities on acute HF management is discussed in Chapter 5.

Conclusion

Whilst chronic ACHD-HF is the more prevalent problem, patients do present acutely and sometimes in severe distress. These are often young patients and the stakes are high. This chapter has described several common modes of presentation. As in all other aspects of ACHD care, a thorough understanding of the underlying anatomy/physiology is the starting point for any diagnostic and therapeutic algorithm. Although more studies, specific to acute ACHD-HF patients, are needed, a better knowledge of CHD anatomy/physiology and provision of clear lines of communication for early consultation with the ACHD specialist team will result in better outcomes for our patients.

References

1. Moons P, Bovijn L, Budts W, Belmans A, Gewillig M. Temporal trends in survival to adulthood among patients born with congenital heart disease from 1970 to 1992 in Belgium. Circulation. 2010;122:2264–72.
2. Warnes CA, Liberthson R, Danielson GK, Dore A, Harris L, Hoffman JI, Somerville J, Williams RG, Webb GD. Task force 1: the changing profile of congenital heart disease in adult life. J Am Coll Cardiol. 2001;37(5):1170.
3. Bolger AP, Gatzoulis MA. Towards defining heart failure in adults with congenital heart disease. Int J Cardiol. 2004;97(Suppl 1):15–23.
4. Diller GP, Kempny A, Alonso-Gonzalez R, Swan L, Uebing A, Li W, Babu-Narayan S, Wort SJ, Dimopoulos K, Gatzoulis MA. Survival prospects and circumstances of death in contemporary adult congenital heart disease patients under follow-up at a large tertiary centre. Circulation. 2015;132(22):2118–25.
5. Verheugt CL, Uiterwaal CS, van der Velde ET, Meijboom FJ, Pieper PG, Sieswerda GT, Plokker HW, Grobbee DE, Mulder BJ. The emerging burden of hospital admissions of adults with congenital heart disease. Heart. 2010;96:872–8.
6. Mackie AS, Pilote L, Ionescu-Ittu R, Rahme E, Marelli AJ. Health care resource utilization in adults with congenital heart disease. Am J Cardiol. 2007;99:839–43.
7. Budts W, Roos-Hesselink J, Radle-Hurst T, Eicken A, McDonagh TA, Lambrinou E, Crespo-Leiro MG, Walker F, Frogoudaki AA. Treatment of heart failure in adult congenital heart disease: a position paper of the Working Group of Grown-Up Congenital Heart Disease and the Heart Failure Association of the European Society of Cardiology. Eur Heart J. 2016;37:1419–27.
8. Stout KK, Broberg CS, Book WM, Cecchin F, Chen JM, Dimopoulos K, Everitt MD, Gatzoulis M, Harris L, Hsu DT, Kuvin JT, Law Y, Martin CM, Murphy AM, Ross HJ, Singh G, Spray TL, American Heart Association Council on Clinical Cardiology CoFG, Translational B, Council on Cardiovascular R, Imaging. Chronic heart failure in congenital heart disease: a scientific statement from the American Heart Association. Circulation. 2016;133:770–801.
9. 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, Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas P, Widimsky P, Swan L, Andreotti F, Beghetti M, Borggrefe M, Bozio A, Brecker S, Budts W, Hess J, Hirsch R, Jondeau G, Kokkonen J, Kozelj M, Kucukoglu S, Laan M, Lionis C, Metreveli I, Moons P, Pieper PG, Pilossoff V, Popelova J, Price S, Roos-Hesselink J, Uva MS, Tornos P, Trindade PT, Ukkonen H, Walker H, Webb GD, Westby J. ECS guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J. 2010;31:2915–57.

10. Kuijpers JM, Koolbergen DR, Groenink M, Peels KC, Reichert CL, Post MC, Bosker HA, Wajon EM, Zwinderman AH, Mulder BJ, Bouma BJ. Incidence, risk factors, and predictors of infective endocarditis in adult congenital heart disease: focus on the use of prosthetic material. Eur Heart J. 2017;38:2048–56.
11. Kim HW, Seo DM, Shin HJ, Park JJ, Yoon TJ. Long term results of right ventricular outflow tract reconstruction with homografts. Korean J Thorac Cardiovasc Surg. 2011;44:108–14.
12. Wald RM, Valente AM, Marelli A. Heart failure in adult congenital heart disease: emerging concepts with a focus on tetralogy of Fallot. Trends Cardiovasc Med. 2015;25:422–32.
13. Bhagra CJ, Hickey EJ, Van De Bruaene A, Roche SL, Horlick EM, Wald RM. Pulmonary valve procedures late after repair of tetralogy of fallot: current perspectives and contemporary approaches to management. Can J Cardiol. 2017;33:1138–49.
14. Wray J, Frigiola A, Bull C, Adult Congenital Heart disease Research N. Loss to specialist follow-up in congenital heart disease; out of sight, out of mind. Heart. 2013;99:485–90.
15. Pettersen E, Helle-Valle T, Edvardsen T, Lindberg H, Smith HJ, Smevik B, Smiseth OA, Andersen K. Contraction pattern of the systemic right ventricle shift from longitudinal to circumferential shortening and absent global ventricular torsion. J Am Coll Cardiol. 2007;49:2450–6.
16. Cuypers JA, Eindhoven JA, Slager MA, Opic P, Utens EM, Helbing WA, Witsenburg M, van den Bosch AE, Ouhlous M, van Domburg RT, Rizopoulos D, Meijboom FJ, Bogers AJ, Roos-Hesselink JW. The natural and unnatural history of the Mustard procedure: long-term outcome up to 40 years. Eur Heart J. 2014;35:1666–74.
17. Graham TP Jr, Bernard YD, Mellen BG, Celermajer D, Baumgartner H, Cetta F, Connolly HM, Davidson WR, Dellborg M, Foster E, Gersony WM, Gessner IH, Hurwitz RA, Kaemmerer H, Kugler JD, Murphy DJ, Noonan JA, Morris C, Perloff JK, Sanders SP, Sutherland JL. Long-term outcome in congenitally corrected transposition of the great arteries: a multi-institutional study. J Am Coll Cardiol. 2000;36:255–61.
18. Derrick GP, Narang I, White PA, Kelleher A, Bush A, Penny DJ, Redington AN. Failure of stroke volume augmentation during exercise and dobutamine stress is unrelated to load-independent indexes of right ventricular performance after the Mustard operation. Circulation. 2000;102:III154–9.
19. Fratz S, Hager A, Busch R, Kaemmerer H, Schwaiger M, Lange R, Hess J, Stern HC. Patients after atrial switch operation for transposition of the great arteries can not increase stroke volume under dobutamine stress as opposed to patients with congenitally corrected transposition. Circ J. 2008;72:1130–5.
20. Khairy P. Sudden cardiac death in transposition of the great arteries with a Mustard or Senning baffle: the myocardial ischemia hypothesis. Curr Opin Cardiol. 2017;32:101–7.
21. Gewillig M, Brown SC, Eyskens B, Heying R, Ganame J, Budts W, La Gerche A, Gorenflo M. The Fontan circulation: who controls cardiac output? Interact Cardiovasc Thorac Surg. 2010;10:428–33.
22. Gewillig M. Ventricular dysfunction of the functionally univentricular heart: management and outcomes. Cardiol Young. 2005;15(Suppl 3):31–4.
23. Cordina R, von Klemperer K, Kempny A, West C, Senior R, Celermajer DS, Gatzoulis MA, Babu-Narayan SV, Li W. Echocardiographic predictors of mortality in adults with a Fontan circulation. JACC Cardiovasc Imaging. 2017;10:212–3.
24. Cheung YF, Penny DJ, Redington AN. Serial assessment of left ventricular diastolic function after Fontan procedure. Heart. 2000;83(4):420.

25. Gewillig MH, Lundstrom UR, Deanfield JE, Bull C, Franklin RC, Graham TP Jr, Wyse RK. Impact of Fontan operation on left ventricular size and contractility in tricuspid atresia. Circulation. 1990;81:118–27.
26. Murray CD. The physiological principle of minimum work: I. The vascular system and the cost of blood volume. Proc Natl Acad Sci U S A. 1926;12:207–14.
27. Glenny RW. Emergence of matched airway and vascular trees from fractal rules. J Appl Physiol. 2011;110:1119–29.
28. Duffels MG, Engelfriet PM, Berger RM, van Loon RL, Hoendermis E, Vriend JW, van der Velde ET, Bresser P, Mulder BJ. Pulmonary arterial hypertension in congenital heart disease: an epidemiologic perspective from a Dutch registry. Int J Cardiol. 2007;120:198–204.
29. Engelfriet PM, Duffels MG, Moller T, Boersma E, Tijssen JG, Thaulow E, Gatzoulis MA, Mulder BJ. Pulmonary arterial hypertension in adults born with a heart septal defect: the Euro Heart Survey on adult congenital heart disease. Heart. 2007;93:682–7.
30. Egbe AC, Connolly HM, Niaz T, Yogeswaran V, Taggart NW, Qureshi MY, Poterucha JT, Khan AR, Driscoll DJ. Prevalence and outcome of thrombotic and embolic complications in adults after Fontan operation. Am Heart J. 2017;183:10–7.
31. Egbe AC, Connolly HM, McLeod CJ, Ammash NM, Niaz T, Yogeswaran V, Poterucha JT, Qureshi MY, Driscoll DJ. Thrombotic and embolic complications associated with atrial arrhythmia after Fontan operation: role of prophylactic therapy. J Am Coll Cardiol. 2016;68:1312–9.
32. Silversides CK, Granton JT, Konen E, Hart MA, Webb GD, Therrien J. Pulmonary thrombosis in adults with Eisenmenger syndrome. J Am Coll Cardiol. 2003;42:1982–7.
33. Broberg CS, Ujita M, Prasad S, Li W, Rubens M, Bax BE, Davidson SJ, Bouzas B, Gibbs JS, Burman J, Gatzoulis MA. Pulmonary arterial thrombosis in eisenmenger syndrome is associated with biventricular dysfunction and decreased pulmonary flow velocity. J Am Coll Cardiol. 2007;50:634–42.
34. Van De Bruaene A, La Gerche A, Prior DL, Voigt J-U, Delcroix M, Budts W. Pulmonary vascular resistance as assessed by bicycle stress echocardiography in patients with ASD type secundum. Circ Cardiovasc Imaging. 2011;4:237–45.
35. Inglessis I, Landzberg MJ. Interventional catheterization in adult congenital heart disease. Circulation. 2007;115:1622–33.
36. Srivastava D, Preminger T, Lock JE, Mandell V, Keane JF, Mayer JE Jr, Kozakewich H, Spevak PJ. Hepatic venous blood and the development of pulmonary arteriovenous malformations in congenital heart disease. Circulation. 1995;92:1217–22.
37. Karbassi A, Nair K, Harris L, Wald RM, Roche SL. Atrial tachyarrhythmia in adult congenital heart disease. World J Cardiol. 2017;9:496–507.
38. Bouchardy J, Therrien J, Pilote L, Ionescu-Ittu R, Martucci G, Bottega N, Marelli AJ. Atrial arrhythmias in adults with congenital heart disease. Circulation. 2009;120:1679–86.
39. Gewillig M, Wyse RK, de Leval MR, Deanfield JE. Early and late arrhythmias after the Fontan operation: predisposing factors and clinical consequences. Br Heart J. 1992;67:72–9.
40. Moons P, Gewillig M, Sluysmans T, Verhaaren H, Viart P, Massin M, Suys B, Budts W, Pasquet A, De Wolf D, Vliers A. Long term outcome up to 30 years after the Mustard or Senning operation: a nationwide multicentre study in Belgium. Heart. 2004;90:307–13.
41. Labombarda F, Hamilton R, Shohoudi A, Aboulhosn J, Broberg CS, Chaix MA, Cohen S, Cook S, Dore A, Fernandes SM, Fournier A, Kay J, Macle L, Mondesert B, Mongeon FP, Opotowsky AR, Proietti A, Rivard L, Ting J, Thibault B, Zaidi A, Khairy P, Aarcc. Increasing prevalence of atrial fibrillation and permanent atrial arrhythmias in congenital heart disease. J Am Coll Cardiol. 2017;70:857–65.
42. Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, Rosenthal M, Nakazawa M, Moller JH, Gillette PC, Webb GD, Redington AN. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. Lancet. 2000;356:975–81.
43. Kammeraad JA, van Deurzen CH, Sreeram N, Bink-Boelkens MT, Ottenkamp J, Helbing WA, Lam J, Sobotka-Plojhar MA, Daniels O, Balaji S. Predictors of sudden cardiac death

after Mustard or Senning repair for transposition of the great arteries. J Am Coll Cardiol. 2004;44:1095–102.
44. Van Dijck I, Budts W, Cools B, Eyskens B, Boshoff DE, Heying R, Frerich S, Vanagt WY, Troost E, Gewillig M. Infective endocarditis of a transcatheter pulmonary valve in comparison with surgical implants. Heart. 2015;101:788–93.
45. Yoshinaga M, Niwa K, Niwa A, Ishiwada N, Takahashi H, Echigo S, Nakazawa M. Japanese Society of Pediatric C, Cardiac S. Risk factors for in-hospital mortality during infective endocarditis in patients with congenital heart disease. Am J Cardiol. 2008;101:114–8.
46. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, El Khoury G, Erba PA, Iung B, Miro JM, Mulder BJ, Plonska-Gosciniak E, Price S, Roos-Hesselink J, Snygg-Martin U, Thuny F, Tornos Mas P, Vilacosta I, Zamorano JL, Document R, Erol C, Nihoyannopoulos P, Aboyans V, Agewall S, Athanassopoulos G, Aytekin S, Benzer W, Bueno H, Broekhuizen L, Carerj S, Cosyns B, De Backer J, De Bonis M, Dimopoulos K, Donal E, Drexel H, Flachskampf FA, Hall R, Halvorsen S, Hoen B, Kirchhof P, Lainscak M, Leite-Moreira AF, Lip GY, Mestres CA, Piepoli MF, Punjabi PP, Rapezzi C, Rosenhek R, Siebens K, Tamargo J, Walker DM. 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. 2015;36:3075–128.
47. Nadji G, Rusinaru D, Remadi JP, Jeu A, Sorel C, Tribouilloy C. Heart failure in left-sided native valve infective endocarditis: characteristics, prognosis, and results of surgical treatment. Eur J Heart Fail. 2009;11:668–75.
48. Maxwell BG, Wong JK, Kin C, Lobato RL. Perioperative outcomes of major noncardiac surgery in adults with congenital heart disease. Anesthesiology. 2013;119:762–9.
49. Price S, Jaggar SI, Jordan S, Trenfield S, Khan M, Sethia B, Shore D, Evans TW. Adult congenital heart disease: intensive care management and outcome prediction. Intensive Care Med. 2007;33:652–9.
50. Howard-Quijano K, Schwarzenberger JC. Acute care medicine: perioperative management of adult congenital heart disease. Am J Ther. 2014;21:288–95.
51. Heggie J, Karski J. The anesthesiologist's role in adults with congenital heart disease. Cardiol Clin. 2006;24:571–85. vi
52. 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, Authors/Task Force M. 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. 2016;37:2129–200.
53. Van De Bruaene A, Hickey EJ, Kovacs AH, Crean AM, Wald RM, Silversides CK, Redington AN, Ross HJ, Alba AC, Billia F, Nair K, Benson L, Horlick E, Osten M, Colman J, Heggie J, Oechslin EN, Roche SL. Phenotype, management and predictors of outcome in a large cohort of adult congenital heart disease patients with heart failure. Int J Cardiol. 2018;252:80–7.
54. Frescura C, Basso C, Thiene G, Corrado D, Pennelli T, Angelini A, Daliento L. Anomalous origin of coronary arteries and risk of sudden death: a study based on an autopsy population of congenital heart disease. Hum Pathol. 1998;29:689–95.
55. Taylor AJ, Rogan KM, Virmani R. Sudden cardiac death associated with isolated congenital coronary artery anomalies. J Am Coll Cardiol. 1992;20:640–7.
56. Alsara O, Kalavakunta JK, Hajjar V, Alsarah A, Cho N, Dhar G. Surviving sudden cardiac death secondary to anomalous left coronary artery from the pulmonary artery: a case report and literature review. Heart Lung. 2014;43:476–80.
57. Raisky O, Bergoend E, Agnoletti G, Ou P, Bonnet D, Sidi D, Vouhe PR. Late coronary artery lesions after neonatal arterial switch operation: results of surgical coronary revascularization. Eur J Cardiothorac Surg. 2007;31:894–8.

58. Pillutla P, Shetty KD, Foster E. Mortality associated with adult congenital heart disease: Trends in the US population from 1979 to 2005. Am Heart J. 2009;158:874–9.
59. Bhatt AB, Foster E, Kuehl K, Alpert J, Brabeck S, Crumb S, Davidson WR Jr, Earing MG, Ghoshhajra BB, Karamlou T, Mital S, Ting J, Tseng ZH. Congenital heart disease in the older adult: a scientific statement from the American Heart Association. Circulation. 2015;131:1884–931.
60. Stub D, Smith K, Bernard S, Nehme Z, Stephenson M, Bray JE, Cameron P, Barger B, Ellims AH, Taylor AJ, Meredith IT, Kaye DM. Air versus oxygen in ST-segment-elevation myocardial infarction. Circulation. 2015;131:2143–50.
61. Park JH, Balmain S, Berry C, Morton JJ, McMurray JJ. Potentially detrimental cardiovascular effects of oxygen in patients with chronic left ventricular systolic dysfunction. Heart. 2010;96:533–8.
62. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher AESC. 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. 2012;33:1787–847.
63. Price LC, Wort SJ, Finney SJ, Marino PS, Brett SJ. Pulmonary vascular and right ventricular dysfunction in adult critical care: current and emerging options for management: a systematic literature review. Crit Care. 2010;14:R169.
64. Delcroix M, Naeije R. Optimising the management of pulmonary arterial hypertension patients: emergency treatments. Eur Respir Rev. 2010;19:204–11.
65. Mullens W, Abrahams Z, Francis GS, Skouri HN, Starling RC, Young JB, Taylor DO, Tang WH. Sodium nitroprusside for advanced low-output heart failure. J Am Coll Cardiol. 2008;52:200–7.
66. Apitz C, Honjo O, Friedberg MK, Assad RS, Van Arsdell G, Humpl T, Redington AN. Beneficial effects of vasopressors on right ventricular function in experimental acute right ventricular failure in a rabbit model. Thorac Cardiovasc Surg. 2012;60:17–23.
67. Apitz C, Honjo O, Humpl T, Li J, Assad RS, Cho MY, Hong J, Friedberg MK, Redington AN. Biventricular structural and functional responses to aortic constriction in a rabbit model of chronic right ventricular pressure overload. J Thorac Cardiovasc Surg. 2012;144:1494–501.
68. Hyldebrandt JA, Agger P, Siven E, Wemmelund KB, Heiberg J, Frederiksen CA, Ravn HB. Effects of milrinone and epinephrine or dopamine on biventricular function and hemodynamics in right heart failure after pulmonary regurgitation. Am J Physiol Heart Circ Physiol. 2015;309:H860–6.
69. Hoffman TM, Wernovsky G, Atz AM, Kulik TJ, Nelson DP, Chang AC, Bailey JM, Akbary A, Kocsis JF, Kaczmarek R, Spray TL, Wessel DL. Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. Circulation. 2003;107:996–1002.
70. Smith AH, Owen J, Borgman KY, Fish FA, Kannankeril PJ. Relation of milrinone after surgery for congenital heart disease to significant postoperative tachyarrhythmias. Am J Cardiol. 2011;108:1620–4.
71. Kerbaul F, Rondelet B, Motte S, Fesler P, Hubloue I, Ewalenko P, Naeije R, Brimioulle S. Effects of norepinephrine and dobutamine on pressure load-induced right ventricular failure. Crit Care Med. 2004;32:1035–40.
72. Follath F, Cleland JG, Just H, Papp JG, Scholz H, Peuhkurinen K, Harjola VP, Mitrovic V, Abdalla M, Sandell EP, Lehtonen L, Steering C, Investigators of the Levosimendan Infusion versus Dobutamine S. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. Lancet. 2002;360:196–202.

73. Bhorade S, Christenson J, O'Connor M, Lavoie A, Pohlman A, Hall JB. Response to inhaled nitric oxide in patients with acute right heart syndrome. Am J Respir Crit Care Med. 1999;159:571–9.
74. Hoeper MM, Olschewski H, Ghofrani HA, Wilkens H, Winkler J, Borst MM, Niedermeyer J, Fabel H, Seeger W. A comparison of the acute hemodynamic effects of inhaled nitric oxide and aerosolized iloprost in primary pulmonary hypertension. German PPH study group. J Am Coll Cardiol. 2000;35:176–82.
75. Van De Bruaene A, La Gerche A, Claessen G, De Meester P, Devroe S, Gillijns H, Bogaert J, Claus P, Heidbuchel H, Gewillig M, Budts W. Sildenafil improves exercise hemodynamics in Fontan patients. Circ Cardiovasc Imaging. 2014;7:265–73.
76. Allan CK. Intensive care of the adult patient with congenital heart disease. Prog Cardiovasc Dis. 2011;53:274–80.
77. Makdisi G, Wang IW. Extra Corporeal Membrane Oxygenation (ECMO) review of a lifesaving technology. J Thorac Dis. 2015;7:E166–76.
78. Acheampong B, Johnson JN, Stulak JM, Dearani JA, Kushwaha SS, Daly RC, Haile DT, Schears GJ. Postcardiotomy ECMO support after high-risk operations in adult congenital heart disease. Congenit Heart Dis. 2016;11:751–5.
79. Vohra HA, Jones C, Viola N, Haw MP. Use of extra corporeal membrane oxygenation in the management of sepsis secondary to an infected right ventricle-to-pulmonary artery Contegra conduit in an adult patient. Interact Cardiovasc Thorac Surg. 2009;8:272–4.
80. Aydin SI, Duffy M, Rodriguez D, Rycus PT, Friedman P, Thiagarajan RR, Weinstein S. Venovenous extracorporeal membrane oxygenation for patients with single-ventricle anatomy: a registry report. J Thorac Cardiovasc Surg. 2016;151(6):1730.
81. Dimopoulos K, Diller GP, Koltsida E, Pijuan-Domenech A, Papadopoulou SA, Babu-Narayan SV, Salukhe TV, Piepoli MF, Poole-Wilson PA, Best N, Francis DP, Gatzoulis MA. Prevalence, predictors, and prognostic value of renal dysfunction in adults with congenital heart disease. Circulation. 2008;117:2320–8.
82. Mullens W, Abrahams Z, Skouri HN, Francis GS, Taylor DO, Starling RC, Paganini E, Tang WH. Elevated intra-abdominal pressure in acute decompensated heart failure: a potential contributor to worsening renal function? J Am Coll Cardiol. 2008;51:300–6.

Part III

Treatment of Chronic Heart Failure

Role of Intervention and Surgery

10

Anselm Uebing

10.1 Introduction

Many congenital cardiac lesions result in an abnormal ventricular load, and if significant and long-standing, this may adversely, and potentially irreversibly, impact on myocardial contractility. Therefore, all diagnostic efforts in CHD primarily aim at accurate assessment not only of heart function but also of its loading conditions. Situations of ventricular volume or pressure overload need to be recognised in time in order to preserve ventricular function in the long term.

Transcatheter interventions and surgery aim to normalise the loading conditions of the heart and in this way play a central role in the prevention and treatment of heart failure in patients with CHD. They are complementary to medical therapies for the failing heart and when carried out timely may help avoid the need for long-term drug treatment.

This chapter will present an overview of the main CHD lesions potentially associated with heart failure that can be treated by transcatheter and surgical procedures. These lesions predominantly cause chronic alternations in volume or pressure load of the respective ventricle. The most commonly encountered examples are discussed. Of course, many patients have complex forms of CHD with multiple lesions competing for physiological dominance. Their treatment is challenging and needs an individualised multidisciplinary approach.

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10.2 Lesions Primarily Affecting the Right Ventricle

10.2.1 Atrial Septal Defect

Atrial septal defects (ASDs) are one of the most common forms of CHD and are still often first diagnosed in adulthood.

There are three major types of ASDs: the ostium primum, ostium secundum and sinus venosus defects. The ostium secundum defect is centrally located in the fossa ovalis region of the interatrial septum. The ostium primum defect is part of the spectrum of atrioventricular septal defects and can therefore be combined with a ventricular septal defect and a common atrioventricular valve. If there is only an atrial communication in this setting, it can also be called partial AV septal defect. The sinus venosus defect is usually located in the superior interatrial septum at the junction of the superior vena cava with the right atrium. An anomalous connection of the right pulmonary veins to the superior vena cava is typical part of this defect. A rarer variant is called inferior sinus venosus defect and is located at the junction of the inferior vena cava with the right atrium.

ASDs allow shunting of blood between the atria. The magnitude and direction of blood flow depend on the size and relative diastolic filling properties of the ventricles. As compliance of the low-pressure right ventricle is usually lower than that of the left ventricle, shunting is left to right in most cases. Large defects allow for a large shunt. Small defects (<1 cm in diameter) may be insignificant.

The left-to-right shunt through the defects leads to a chronic increase in volume load to the right atrium and ventricle resulting in enlargement of the right heart structures. Over time, the additional workload to the right heart can lead to right ventricular dysfunction and failure often preceded by atrial arrhythmia. Paradoxical systemic embolic events are rare but can be the first clinical hint to the presence of the defect. Pulmonary arterial hypertension develops slowly in patients with a large left-to-right shunt on atrial level and is therefore usually a feature only of the older patient with this condition.

Besides the obvious chronic volume-loading effects of ASDs on the right heart, there are important effects on the left heart too. The overflow of blood from the left to the right heart leaves the left ventricle chronically under-filled with concomitant impairment in systemic cardiac output particularly during exercise.

There is consensus that ASD closure is indicated in patients with significant left-to-right shunting indicated by right heart dilatation unless pulmonary arterial hypertension and left ventricular dysfunction are not too advanced. ASD closure in this setting should be considered as soon as the diagnosis is established, irrespective of age. If there is significant pulmonary arterial hypertension, an ASD may be beneficial and should not be completely closed as it can act as an “overflow valve” to the right heart. Similarly, when severe left ventricular dysfunction (systolic or diastolic) is present, the ASD can decompress the left heart avoiding pulmonary congestion.

10.2.1.1 Surgical ASD Closure

Surgical ASD closure is needed for all patients with an ASD other than a secundum ASD and is also necessary if a secundum ASD is too large or has insufficient rims to anchor a transcatheter closure device. Therefore, surgical ASD closure is still regularly performed and usually involves insertion of a pericardial or Dacron patch. In patients with a primum ASD, surgery may include left atrioventricular valve repair. Surgical ASD closure for all forms of ASDs is safe and effective with a very low procedural mortality and excellent long-term outcome [1, 2].

10.2.1.2 Transcatheter ASD Closure

Today, transcatheter ASD closure is most commonly performed using double-disc devices such as the Amplatzer Septal Occluder® (St Jude Medical, St Paul, MN, USA) or the Occlutech® device (Occlutech, Helsingborg, Sweden). These are both self-expanding and self-centring devices formed from a nitinol wire mesh (Fig. 10.1). The ASO was the first device introduced into clinical practice using that principle, and its introduction into clinical practice in 1997 has transformed transcatheter ASD closure from a complex procedure with considerable complication rates to a safe and effective routine procedure [3]. Only secundum-type defects with a rim of 4–5 mm between the defect and the atrioventricular valve, the inferior vena cava and the pulmonary veins are suitable for transcatheter closure.

ASD closure with the ASO has been shown to be safe and effective with closure rates as high as 95% and compared with surgery catheter closure minimises hospital stay, shortens recovery and avoids wound infections [4]. However, serious complications such as device embolisation, cardiac perforation, arrhythmia including heart block, thrombus formation and embolization and erosion do rarely occur [5, 6].

10.2.1.3 Effects of ASD Closure

Long-term survival of patients with an ASD is impaired, and ASD closure has been shown to result in improved survival [7, 8]. Historic data from the Mayo Clinic show that patients who underwent surgical ASD closure before the age of 25 years and survived to hospital discharge showed normal long-term survival compared to healthy controls [9]. A recent Danish nationwide cohort study reporting on a median follow-up period of 18.1 years (range 1–53 years) confirmed the survival benefit for patients who underwent ASD closure compared to those that did not and also showed that ASD closure in childhood or adolescence (before the age of 18 years) results in best long-term survival [8].

In addition to the clear prognostic benefit of ASD closure irrespective of age, a reduction in morbidity can also be expected following the procedure. Atrial tachy- or bradyarrhythmia is more common in ASD patients than in the general population and is the result of long-standing abnormal atrial load. As expected, the incidence of arrhythmia increases with age. Despite ASD closure, new-onset atrial arrhythmia remains a concern especially in patients that undergo ASD closure late in life [10].

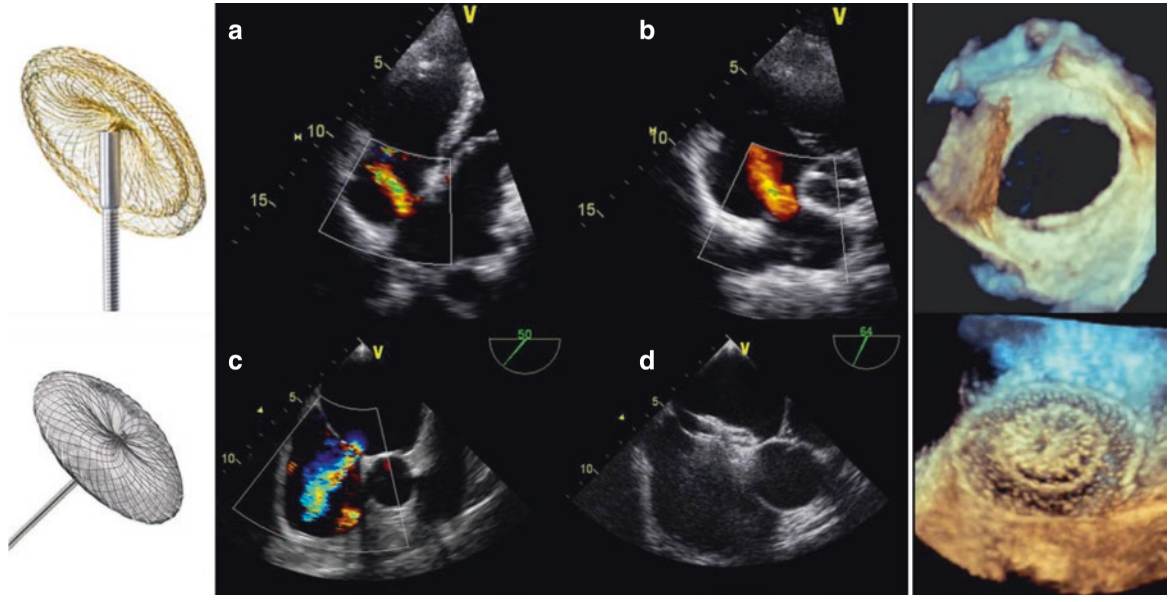

Fig. 10.1 Transcatheter ASD closure is most commonly performed with the Occlutech® and Amplatzer Septal Occluder® (left-sided panel). Transthoracic and transoesophageal echocardiography of an ASD (**a**–**c**) is performed to assess the defect and control device placement (**d**). 3D echocardiography of the defect before and after device implantation (right-sided panel)

Many ASD patients report few symptoms, but there is a favourable impact of ASD closure on exercise tolerance irrespective of age [11, 12]. Improved left ventricular filling with improved systemic cardiac output seems the likely mechanism by which ASD closure improves exercise capacity [13]. Cardiac reverse remodelling with reduction in right atrial and right ventricular volumes occurs soon after ASD closure and is more pronounced and often complete in younger patients [14]. Complete normalisation in right heart size cannot be expected in older patients following ASD closure—another argument for timely closure of ASDs earlier in life [15].

10.2.2 Right Ventricular Outflow Tract Lesion

Reconstruction of, or intervention to, the right ventricular outflow tract (RVOT) is part of treatment of a series of congenital cardiac conditions. Defects such as tetralogy of Fallot, double outlet right ventricle, pulmonary atresia or stenosis need enlargement or reconstruction of the RVOT or connection of the right (or subpulmonary) ventricle to the pulmonary artery. As a result, RVOT dysfunction, i.e. regurgitation or stenosis, is commonly observed in these lesions. Surgical repair of tetralogy of Fallot often involves patch augmentation of the RVOT with patch enlargement of the pulmonary valve and almost universally results in pulmonary regurgitation (PR) with right ventricular volume load. Prosthetic conduits connecting the subpulmonary ventricle with the pulmonary artery as used for primary repair of truncus arteriosus or pulmonary atresia have a limited lifespan; they will degenerate with time and can become stenotic, regurgitant or both. Conduit dysfunction is a common cause of chronic right ventricular volume or pressure overload.

Chronic volume overload from PR is not a benign lesion as it results in right ventricular dilatation [16] and prolongation of QRS duration, which is in turn linked with malignant arrhythmia and sudden cardiac death [17]. Though PR as an isolated lesion or as a result of surgical reconstruction of the RVOT is usually clinically well tolerated for decades, right (and later left) ventricular function worsens with time and exercise intolerance develops [18, 19]. There is evidence that the compensatory mechanisms of the right ventricular myocardium ultimately fail and that right ventricular volume load has to be normalised by PVR to avoid irreversible ventricular dysfunction [20].

Chronic pressure overload from stenosis at the level of the right ventricular outflow tract results in right ventricular hypertrophy, restriction and right atrial enlargement with an increased risk for atrial arrhythmia and is associated with reduced exercise tolerance. In most cases RVOT obstruction increases gradually, and the right ventricle can adapt to a slow increase in afterload with increased contractility and maintains cardiac output. An increase in ventricular contractility is, however, mirrored by an increase in diastolic stiffness, and diastolic dysfunction may well persist when the RV has been exposed to RV pressure overload for too long [21].

10.2.2.1 Management of Pulmonary Regurgitation

The indication for pulmonary valve replacement (PVR) to reduce PR has evolved in recent years. However, the optimal timing for PVR in this context remains a matter of debate. It is widely accepted that in the presence of significant PR, valve replacement should not be delayed until the patient presents with symptoms as complete reverse remodelling of the right ventricle after intervention becomes less likely with this strategy [22]. Nowadays, emphasis is placed on RV volumetric and functional data usually obtained from cardiac magnetic resonance imaging in the hope to find markers that best predict post-procedural normalisation of RV size and function. It seems that the end-systolic volume index contains information on both, RV size and function, and is best suitable to guide decision-making for PVR at least for the asymptomatic patient with PR after Fallot repair [23, 24].

10.2.2.2 Management of RVOT Obstruction

The indications for relief of RVOT obstruction including valvar pulmonary stenosis are less controversial. Surgical or interventional treatment is indicated in symptomatic patients and in those with significant increase in RV pressure. A gradient >64 mmHg (peak velocity >4 m/s) is accepted as a threshold above which to intervene using interventional techniques in patients with normal RV function. In asymptomatic patients where the only treatment option is surgical valve replacement, guidelines suggest treatment in the presence of a systolic RV pressure above 80 mmHg (>4.3 m/s). Patients with less severe RV outflow tract obstruction should be considered for intervention or surgery in the presence of symptoms, RV dysfunction, likely progression of the condition (e.g. double-chambered right ventricle), significant atrial or ventricular arrhythmia and right-to-left shunt across an atrial or ventricular communication [25].

10.2.2.3 Surgery for RVOT Dysfunction

Most data exists on the effects of surgical PVR for PR in repaired Fallot patients. Many centres have moved towards earlier PVR based primarily on data on RV size and function in these patients. However, the risk of surgical PVR is not negligible. It must be carefully balanced against the expected benefit of the procedure. A meta-analysis that aimed to determine the outcomes and effect of surgical PVR in patients with repaired tetralogy of Fallot reported a pooled early mortality rate of 2.1% [26]. The Royal Brompton group recently reported a similar early mortality rate following PVR for a group of 220 adult repaired Fallot patients [27]. An overall survival rate of 97% at 1 year, 96% at 3 years and 92% at 10 years was also reported with significantly better survival in the later era (2005–2010) compared with survival in the earlier era (1993–2004; 99% versus 94% at 1 year and 98% versus 92% at 3 years, respectively; $P = 0.019$). Interestingly, patients operated in the earlier era were more symptomatic with a lower preoperative peak oxygen uptake. Peak oxygen uptake was found to be the strongest predictor of early mortality in this report. This result is supporting current common practice with a tendency towards earlier surgical PVR in patients that are less symptomatic with better exercise tolerance.

PVR for PR is effective in reducing RV volumes, but RV functional improvement has been questioned as postoperative improvement in RV ejection fraction has not been found [26]. However, the absence of improvement in ejection fraction following a procedure that reduces PR and hence RV end-diastolic volume and stroke volume at the same time does not necessarily exclude improvement in ventricular contractility. Ventricular ejection fraction is no valid marker of ventricular contractility when comparing states of different ventricular loading conditions. RV end-systolic volume has been suggested as a valid estimate of intrinsic, load-independent RV function in repaired Fallot patients [23]. It reduces immediately after PVR as a result of acute unloading of the ventricle when reinstating pulmonary valve competence but progressively improves during midterm follow-up likely reflecting ongoing functional recovery of the RV function [24].

Data on the effects of surgical PVR in repaired Fallot patients with PR have recently been summarised in another meta-analysis [28]. PVR reduces PR and RV size, likely improves RV function and improves left ventricular filling and LV ejection fraction and also clinical status and functional class.

10.2.2.4 Transcatheter Pulmonary Valve Implantation

Since its introduction in 2000, transcatheter pulmonary valve implantation (TPVI) has emerged as an alternative to conventional surgery for patients with RVOT dysfunction [29, 30]. The valve used for the first patient was a valved segment of a bovine jugular vein that was sutured into a balloon expandable stent. This prototype was refined and introduced into the European market by Medtronic as the Melody® Transcatheter Pulmonary Valve (TPV) in 2006. As per the instructions for use for implantation of the Melody® valve system, TPVI is indicated for patients with regurgitant prosthetic RVOT conduits with a clinical indication for invasive or surgical intervention or patients with stenotic prosthetic RVOT conduits where the risk of worsening regurgitation is a relative contraindication to balloon dilatation or stenting. The existence of a full (circumferential) RVOT conduit that was equal to or greater than 16 mm in diameter when originally implanted is also warranted for implantation of the Melody® valve. The valve can be delivered using a 22 Fr delivery system (Ensemble®, Medtronic) which is available with an 18, 20 and 22 mm balloon. The outer diameter of the valve will be 24 mm when the valve is inserted on a 22 mm delivery system. An alternative to the Melody TPV is the Edwards SAPIEN XT valve (Edwards Lifesciences, Irvine, CA, USA). This valve is originally designed for implantation into the aortic position. The most recent version of the valve type (SAPIEN XT) has been CE marked for the use in the pulmonary position in 2016. It is available with external diameters of 23, 26 and 29 mm. The valve is manufactured of bovine pericardium mounted in a short cobalt-chromium stent. Valve implantation is prepared by pre-dilatation of the RVOT conduit with high-pressure balloon inflation of the intended landing zone with simultaneous coronary angiography followed by presenting of the conduit (Fig. 10.2).

TPVI has been shown to reduce and often normalise the RVOT gradient and to abolish pulmonary regurgitation immediately. It results in reduction in RV volumes and improved RV function, LV filling and stroke volumes. Significant improvement

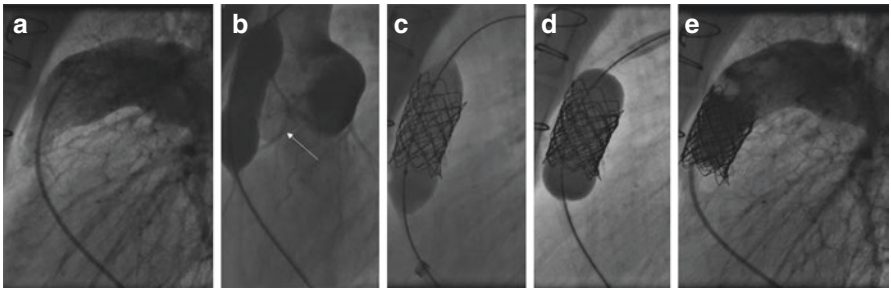

Fig. 10.2 Transcatheter pulmonary valve implantation of the Melody® valve into a stenotic and mildly regurgitant RV to PA conduit (**a**). Balloon dilatation with simultaneous aortic root injection is performed to exclude coronary artery compression prior to valve implantation (**b**, arrow is indicated the patent left coronary artery). Pre-stenting—in this case with CP stents (NuMed, Hopkinton, New York, USA)—is performed (**c**) followed by Melody® valve implantation (**d**). The final angiogram shows valve competence (**e**). The peak systolic gradient across the valve could be reduced from 55 to 5 mmHg by valve implantation

in functional capacity and RV systolic function has also been reported [31, 32]. The beneficial effect of PPVI on objective exercise capacity is clearly documented for patients with stenotic RVOT conduits [33]. In patients where pulmonary regurgitation was the leading lesion, TPVI did not always result in improved oxygen uptake, but improvement in the ability to recover from maximal exercise has been documented [34].

Re-intervention rate after TPVI is satisfactory. Most recent reports document 5-year freedom from re-intervention and valve explantation of 76 ± 4% and 92 ± 3%, respectively [32]. Risk factors for re-intervention include a high post-procedural RVOT gradient, stent compression and recoil. The most common cause of re-intervention is fracture of the valve stent with RVOT obstruction. Pre-stenting has been shown to reduce the risk of valve stent fracture and is therefore nowadays recommended part of the procedure [35].

Infective endocarditis remains a concern after PPVI. An annual risk of infective endocarditis of about 2% per patient year has been reported [36]. Comparative studies with surgically implanted biological valves and conduits do not exist but are needed to clarify whether TPVI is riskier than surgery with regard to this potentially life-threatening condition.

10.2.2.5 Balloon Valvuloplasty of Pulmonary Valve Stenosis

Congenital pulmonary valve stenosis can progress and first present in adulthood with symptoms of heart failure. As in children, first-line treatment of this condition in adults is balloon valvuloplasty. The procedure is effective in reducing the gradient across the pulmonary valve and right ventricular pressure [37]. In adults with long-standing pulmonary stenosis and right ventricular hypertension, hypertrophy of the RV can be intense so that relief of valvar stenosis may result in a dynamic subvalvar muscular stenosis which generally resolves with time.

Procedural complications of balloon valvuloplasty of pulmonary stenosis include pulmonary regurgitation potentially resulting in RV enlargement and later need for pulmonary valve replacement.

10.2.2.6 Isolated Peripheral Pulmonary Artery Stenosis

Isolated peripheral pulmonary artery (*PA*) stenosis rarely causes a significant impact on RV function. However multiple areas of stenosis, such as seen in Williams syndrome or in some forms of pulmonary atresia or after the arterial switch operation, may lead to a significant pressure load to the subpulmonary ventricle. Balloon angioplasty and stenting are beneficial when there are discrete haemodynamically significant obstructive lesions in the pulmonary tree [38].

10.2.3 Ebstein Anomaly

Ebstein anomaly is a malformation of the tricuspid valve and the right ventricle associated with failure of delamination of the septal, inferior and anterior leaflets of the tricuspid valve. It results in tricuspid regurgitation and right ventricular dysfunction. The morphology of the tricuspid valve is highly variable as is the clinical presentation, which ranges from severely diseased in neonatal life to an asymptomatic incidental finding in adulthood. The condition is often combined with an interatrial communication allowing for right-to-left shunting. Common symptoms include decreased exercise capacity, cyanosis (at rest or during exercise), paradoxical embolic events, progressive cardiomegaly, right ventricular enlargement and dysfunction and supraventricular or ventricular arrhythmia.

Surgery for Ebstein anomaly is indicated for the symptomatic adult patient or for patients with progressive cardiomegaly, right heart enlargement or dysfunction or those with arrhythmia not amenable to electrophysiology treatment [25]. This is predominantly tricuspid valve repair or replacement, if surgical repair of the valve is not possible or has failed [39]. Many surgical techniques have been applied for primary tricuspid valve repair. Early techniques (Danielson and Carpentier-Chauvaud techniques) aimed at creating a monocusp valve making use of the usually enlarged anterior leaflet often combined with plication of the atrialised portion of the right ventricle, resection of redundant tissue of the enlarged right atrium and the use of an annuloplasty ring [40, 41]. The most modern technique is the cone reconstruction of the tricuspid valve introduced by da Silva (Fig. 10.3) [42]. With this technique all available tricuspid valve tissue is delaminated from the right ventricular walls. A cone is created from the valve tissue that is anchored at the level of the anatomic annulus. Ventricular and atrial plication/resection, annular stabilisation using a ring, leaflet plication and augmentation and the creation of autologous neo-chordae are surgical modifications that are used as part of this operation. As a result of this operation, a tricuspid valve is created that approximates the anatomy of the normal valve. All 360° of the right AV junction is surrounded by tricuspid valve tissue, and neo-annulus diameter of 20–22 mm is the aim in a normal-sized

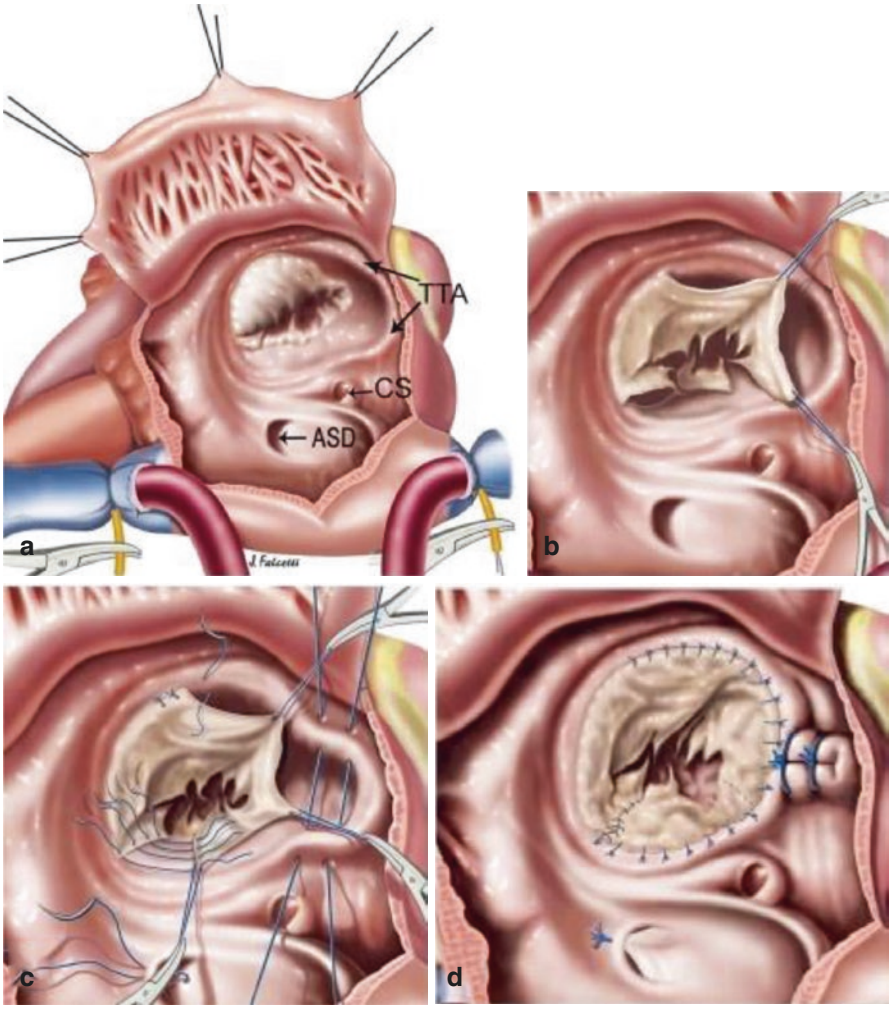

Fig. 10.3 Operative steps for Ebstein anomaly repair with the cone procedure. (**a**) Opened right atrium showing displacement of the tricuspid valve. *TTA* true tricuspid annulus, *ASD* atrial septal defect, *CS* coronary sinus. (**b**) Detached part of the anterior and posterior leaflet forming a single piece. (**c**) Clockwise rotation of the posterior leaflet edge to be sutured to the anterior leaflet septal edge and plication of the true tricuspid annulus. (**d**) Complete valve attachment to the true tricuspid annulus and valved closure of the atrial septal defect (from da Silva et al. [42])

adult. Nowadays, the cone reconstruction of the tricuspid valve is considered the surgical option of choice for symptomatic Ebstein patients younger than 55–60 years with no significant pulmonary hypertension, left ventricular dysfunction, extensive enlargement of the right ventricle and tricuspid annulus and poor delamination of the tricuspid valve leaflets [43].

Tricuspid valve replacement is an excellent surgical option for patients that can be operated using reparative techniques. It is preferred in older patients or those with massive annular or right ventricular dilatation [43]. Bioprosthetic (porcine)

valves are preferred over mechanical valve because of satisfactory durability of the valve and no need for permanent anticoagulation. Furthermore, mechanical valves should be avoided in the tricuspid position when right ventricular function is significantly compromised. Impaired leaflet movement may result in an increased risk for thrombus formation despite effective anticoagulation in this scenario.

Early mortality of operative management of Ebstein anomaly has improved in recent years, and early mortality rates between 2% and 5% are reported [39]. Surgical success of valve repair and early and longer-term outcome of tricuspid valve repair are highly dependent on institutional and operator experience reflecting the complexity of the procedure due to the variability of the morphological substrate. The largest body of data on surgical repair of the tricuspid in Ebstein patients exists from the Mayo Clinic. From this institution an ~85% repair rate is reported for the adult Ebstein patient with about a quarter of the patients having been operated with the cone procedure during the last decade [43]. The Mayo Clinic experience (before adoption of the cone procedure) demonstrated a long-term survival rate after valve repair of 90% and 76% and survival rate free of late reoperation of 74% and 46% at 10 and 20 years, respectively (mean age at surgery 24 years; range 8 days to 79 years) [44]. Improvement in functional class is also reported. Predictors of mortality included the presence of left ventricular disease (mitral regurgitation, more than moderate LV dysfunction), cyanosis, RV outflow tract obstruction and more than moderate RV dysfunction. These data suggest that early tricuspid valve repair in specialised centres should be aimed for.

When biological tricuspid valve prostheses fail, percutaneous valve-in-valve insertion of a transcatheter valve is an option to expand the lifespan of the surgical valve prosthesis and delay redo surgery. Transcatheter valve-in-valve tricuspid valve replacement has been performed using the same valve systems approved for percutaneous pulmonary valve implantation (Melody® and Edwards SAPIEN® valves) (Fig. 10.4). Low procedural complication rates have been reported, but longer-term functional data are still missing [45].

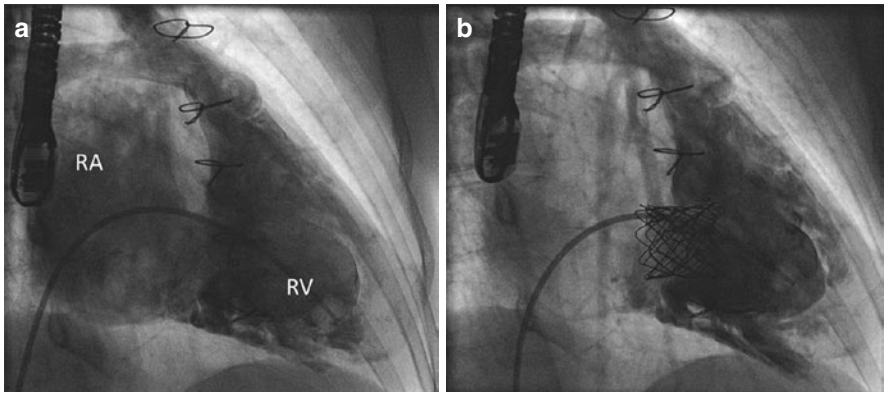

Fig. 10.4 Transcatheter valve-in-valve implantation of a Melody® valve system into a failing tricuspid valve prosthesis. The patient with Ebstein anomaly presented with severe regurgitation of the bioprosthesis only 3 years after implantation (**a**). The final angiogram (**b**) showed valve competence and transoesophageal echocardiography did not show significant stenosis

10.3 Lesions Primarily Affecting the Left Ventricle

10.3.1 Post-tricuspid Left-to-Right Shunt Lesion

Lesions allowing for left-to-right shunting comprise the largest proportion of congenital cardiac conditions. Post-tricuspid shunt lesions such as ventricular septal defects (VSD) and patent ductus arteriosus (PDA) allow for excessive pulmonary blood flow that results in an increased pulmonary venous return to the left heart with increased filling of the left ventricle through the left-sided AV valve. In this way, these lesions result in volume overload to the left heart with left atrial and left ventricular enlargement. The magnitude and direction of blood flow through a VSD or PDA depend on the size of the defect and the state of the pulmonary vascular resistance. A left-to-right shunt that causes left heart chamber dilatation can usually be considered significant.

Small restrictive defects only present with a murmur but not with signs of heart failure. Large defects result in large shunt volumes with pulmonary overcirculation and volume overload to the left heart. Children with such defects present with heart failure early in life. If large defects are left unclosed, pulmonary vascular resistance increases ultimately leading to irreversible and progressive pulmonary vascular disease. When pulmonary vascular resistance exceeds systemic vascular resistance, reversal of shunting from left to right to right to left ensues, leading to Eisenmenger physiology with cyanosis.

The majority of adult patients with a VSD or PDA will have their defects closed in childhood or in the presence of a large, non-restrictive defect will have developed Eisenmenger physiology. However, there is a proportion of patients presenting in adulthood with signs of heart failure that is induced by long-standing volume overload with left heart enlargement without advanced pulmonary vascular disease. Heart failure in these patients can be induced by left ventricular dysfunction, atrial arrhythmia or both. Patients with an enlarged left ventricle may also develop AV valve regurgitation. Those with a perimembranous or outlet VSD may develop aortic regurgitation causing additional volume overload the left ventricle.

Asymptomatic patients with a small shunt across the VSD or PDA with normal left ventricular size and no pulmonary hypertension or any additional cardiac lesion do not need closure of the defect. Regular follow-up for patients with a small VSD seems however recommendable. Follow-up data on this patient group confirm that adult patients with a small and restrictive VSD can present with arrhythmia, progressive aortic regurgitation, infective endocarditis and a double-chambered right ventricle. These complications can indicate surgery in a significant proportion of these patients. The development of systolic and diastolic left ventricular dysfunction has also been reported in a significant proportion of these patients [46].

Patients with a small PDA that does not lead to LV enlargement may be considered candidates for prophylactic closure to abolish the risk for infective endarteritis. Those with a moderately sized PDA that did not lead to pulmonary vascular disease present with a continuous murmur and left-sided heart dilatation and often with symptoms with heart failure and arrhythmia (atrial fibrillation resulting from

long-standing left atrial dilatation). LV systolic and diastolic dysfunction can also develop in these patients. Closure is indicated in these patients as well as long as pulmonary vascular resistance is not prohibitively high [25].

10.3.1.1 Surgery

Surgical closure of a VSD in adulthood can be performed using prosthetic patches or by direct suture. Early mortality of surgical VSD closure is low (approximately 1%), and late survival is excellent as long as left ventricular disease is not advanced. Patients with preoperative elevation in pulmonary artery pressure may present with increasing, decreasing or unchanged pulmonary hypertension, and lifelong follow-up is needed for these patients.

Catheter device closure of ventricular septal defects is considered the method of choice for patients with a muscular VSD as these defects can be poorly accessible for the surgeon. Percutaneous closure of perimembranous VSDs carries the risk for aortic or tricuspid valve damage and significant conduction abnormalities including late complete heart block [47].

Surgery for PDA is rarely performed but might be indicated for the rare patient with a large PDA not amenable to device closure, for example, for patients with ductal aneurysms or recent endarteritis. Operative closure consists of ductal ligation or division and is usually performed via a left lateral thoracotomy. Complications include recurrent laryngeal nerve palsy or phrenic nerve damage.

Device closure is the technique of choice for PDA closure. It is preferred over surgery in adult patients with an isolated duct as PDAs in adults are often calcified with friable tissue that can complicate surgery. Closure is nowadays performed either by coils or in PDAs larger than 3 mm by duct occluder devices such as the Amplatzer Duct Occluder I (St Jude Medical, St Paul, MN, USA). The Amplatzer Duct Occluder I is most commonly used to close a PDA in an adult. The device is formed of a self-expanding nitinol wire mesh similar to the Amplatzer Septal Occluder of VSD occluder devices. Implantation is from the pulmonary artery side. Procedural success and closure rates are high (almost 100% success rate with more than 95% long-term closure rate), and complication rates (device embolisation) are low when using this device [48].

Other rare forms of left-to-right shunting may present with acute left ventricular failure. These include a ruptured sinus of Valsalva aneurysm with acute shunting from the aortic root often to the right ventricle. Again both surgical and catheter-based techniques can address the shunt and offload the left heart.

10.3.2 Aortic Coarctation

Aortic coarctation is a juxtaductal obstructive lesion in the descending aorta that is commonly associated with hypoplasia of the aortic arch. Collateral vessels arising from the proximal arterial tree may bypass the stenotic aortic segment providing blood flow to the distal arterial bed. Coarctation occurs in 5–8% of patients with CHD and is more frequent in men.

Untreated the outcome for patients with CoA is poor. Historical natural history data show a mean age of death of 34 years with a 75% mortality rate at the age of 43 years [49]. Death is from congestive heart failure, aortic dissection or rupture, endocarditis, bleeding from intracranial aneurysms and premature atherosclerotic disease.

Adults with coarctation present with either native, uncorrected lesion or after previous CoA repair in childhood. Most adults with CoA are symptomatic. The leading symptom is upper limb hypertension. However, heart failure resulting from LV systolic and/or diastolic dysfunction can also be the reason for presentation.

According to current guidelines, treatment of CoA is indicated in all patients with CoA (residual or native) with a noninvasive blood pressure gradient between the upper and lower limbs >20 mmHg, in patients with upper limb hypertension (>140/90 mmHg), abnormal blood pressure response to exercise or left ventricular hypertrophy regardless of symptoms. Hypertensive patients with significant narrowing (>50% relative to the descending aortic diameter at the level of the diaphragm) should also be considered for treatment [25].

10.3.2.1 Surgery for Coarctation

Surgery is treatment of choice for coarctation in infancy and early childhood and is performed as soon as the diagnosis is made. The preferred technique is the extended end-to-end anastomosis as with this the lowest re-coarctation and aneurysm rates can be achieved at low mortality [50].

Primary surgical repair in adulthood carries a higher mortality risk than in childhood due to the degenerative changes of the aortic wall tissue and comorbidities such as coronary artery disease or ventricular dysfunction. Techniques used are end-to-end anastomosis, interposition grafts, extra-anatomic jump grafts and patch augmentation. Access for these is usually via a lateral thoracotomy. These surgical techniques carry a high risk of complications including aneurysm formation (most commonly after patch augmentation), restenosis and laryngeal nerve damage especially when used for repair of re-coarctation and have therefore greatly been abandoned [51].

Surgery still has a role for adult patients with coarctation or re-coarctation without aneurysm but complex arch anatomy (e.g. long-segment arch hypoplasia, stenosis of a previously implanted graft). For these patients, a conduit can be placed between the ascending and descending aorta through the posterior pericardium via a median thoracotomy. This approach seems advantageous as it deals with the aortic arch pathology but avoids dissection of the lung and collateral circulation, injury to the laryngeal nerve and sutures in friable aortic tissue and allows reliable chord protection as cross-clamping of the aorta can usually be avoided [51]. This approach can also be considered for patients that need surgery for associated cardiac lesions (e.g. aortic valve replacement or ascending aortic replacement) at the same time.

10.3.2.2 Transcatheter Therapy for Coarctation

In adolescents and adult with native or recurrent aortic coarctation and no adverse anatomic features such as long-segment arch hypoplasia, aneurysm formation or

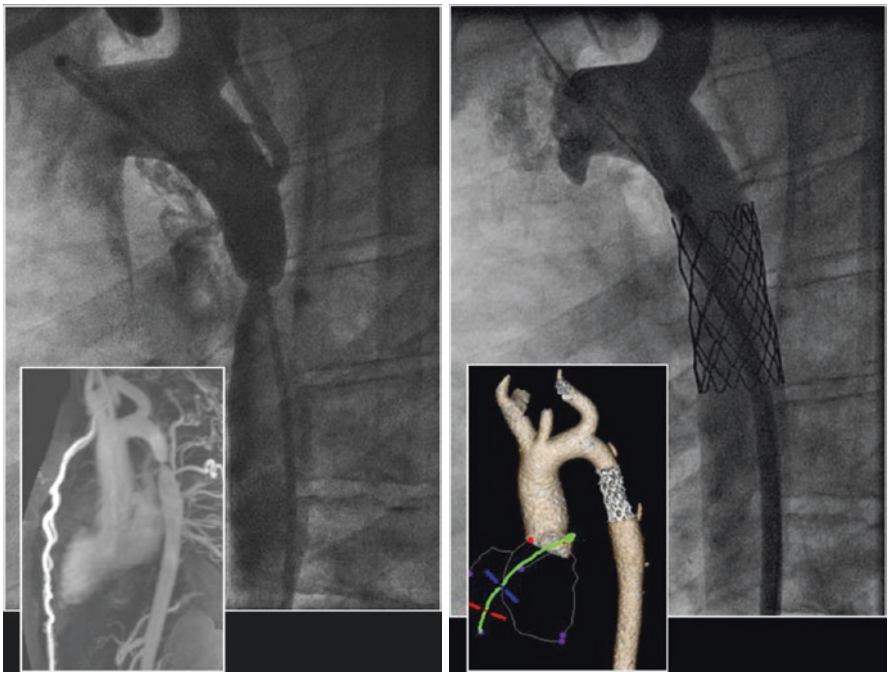

Fig. 10.5 Severe aortic coarctation with collateralisation (angiography and magnetic resonance imaging shown in the left-sided panel) with a peak systolic pressure gradient of 45 mmHg is treated by implantation of 39 mm covered CP stent (NuMed, Hopkinton, New York, USA). Post-procedural angiography and a CT scan (right-sided panel) did not show any evidence of damage to the aortic wall with good stent apposition. No residual gradient was recorded after stent implantation

adjacent aortic arch vessels, balloon dilatation with simultaneous stent implantation is considered the preferred treatment option (Fig. 10.5). Balloon dilatation alone has greatly been abandoned as multicentre observational data have shown that stenting results in lower aneurysm and re-coarctation rates [52]. In the largest series on coarctation stenting to date, high procedural success rates of 98% could be documented [53]. Improved blood pressure control and reduced LV mass with improved LV function have also been demonstrated [54–56].

Complications of coarctation stenting, albeit rare, can be serious. Aortic rupture and extensive dissection are the most feared complications and have been reported to occur in about 1 in 200 cases [53]. These complications are more likely to occur in the older patients and can be the result of balloon oversizing or post-dilatation. Other potential complications include stent migration, vascular access injury, intimal tear, small dissection or false aneurysm formation and stroke [53]. Covered stents are increasingly used to stent aortic coarctation even in the absence of an aneurysm that may need sealing. They are clearly recommended for patients that are considered higher risk for aortic damage (i.e. the older patient with a non-compliant aorta, the patient with atresia or sub-atresia of the coarctation segment).

Despite the high procedural success rate of coarctation treatment, long-term survival after repair remains impaired. Data on the survival prospects of the Royal Brompton cohort of repaired coarctation patients have been published in 2015. The projected 5-year mortality rate for a 40-year-old coarctation patient is comparable to that of the subgroup of 47-year-olds of the general UK population [57]. Impaired survival is due to the long-term effects of persistent arterial hypertension including premature coronary artery and cerebrovascular disease and persistent systolic and diastolic left ventricular disease.

10.4 Intervention in Complex Congenital Heart Disease

Catheter lab-based interventions play a key role in the management of patients with complex congenital lesions. The interventions performed are widely variable in type, including stenting of stenotic vessels, closure of abnormal communications such as collaterals and baffle leaks, the creation of new fenestrations and many more. Baffle obstruction or leaks are challenging complications after the atrial switch operation. Traditional treatment options include intravascular stenting or, less commonly, surgery. Hybrid procedures such as minimally invasive intraoperative surgical stent placement are becoming increasingly common. In the setting of venous hypertension associated with stenosis in a Fontan pathway, stent implantation can have a dramatic impact on the detrimental haemodynamic effect or even a mild narrowing in patients with functionally univentricular circulation. In patients who fail after Fontan procedure, creation of a fenestration is often performed, with variable technique depending on the underlying anatomic substrate. To increase chances of patency of the fenestration, implantation of a stent is often required, particularly in the setting of an extracardiac conduit. For those patients with cyanosis and favourable Fontan haemodynamics, closure of a fenestration may be performed using atrial septal occluder devices with high success rate. Coils compatible with magnetic resonance imaging are used widely to treat collateral vessels, although on occasion other specific embolisation tools are required, such as particles or vascular plugs [58, 59].

10.5 Novel Device-Based Therapies for Left-Sided Heart Failure

Left ventricular enlargement is a compensatory mechanism of ventricular myocardial dysfunction but comes at the cost of increased regional wall stress and in turn oxygen demand. Reduction of wall stress by shrinking the ventricle has therefore been attempted surgically. New ventricular reduction devices such as the Parachute device (CardioKinetix Inc., Menlo Park, CA, USA) have recently been introduced to restore the geometry of the ventricle [60]. These devices that exclude the apical portion of the left ventricle are therefore of potential benefit more for the patients with apical dyskinesia and dilatation resulting from anterior myocardial infarction and rarely of use in patient with ventricular failure in the context of congenital heart disease.

Diastolic heart failure with preserved or mildly reduced ejection fraction (HFpEF), however, is common amongst patients with CHD. Therapeutic options for this condition are limited. Diastolic heart failure is characterised by abnormal ventricular relaxation and increased diastolic stiffness resulting in increased left atrial pressure and pulmonary congestion. Reflecting on the historic observation that patients with mitral stenosis who had a coexisting atrial septal defect (Lutembacher syndrome) are less symptomatic than those with an intact atrial septum and the more recent observation of acute pulmonary oedema and breathlessness in patients with diastolic left ventricular dysfunction after closure of an atrial septal defect, creation of an atrial septal defect has been introduced as treatment for patients with diastolic heart failure [61, 62]. Indeed, implantation of a device creating a permanent atrial communication (Fig. 10.6) has recently been demonstrated to reduce left atrial pressure and improve symptoms.

As the population of patient with ACHD is not only increasing in number but also ageing, we can expect an increasing number of ACHD patients presenting with HFpEF [63]. Left atrial depressurisation by device implantation may therefore become a more common procedure also in the ACHD catheter laboratory.

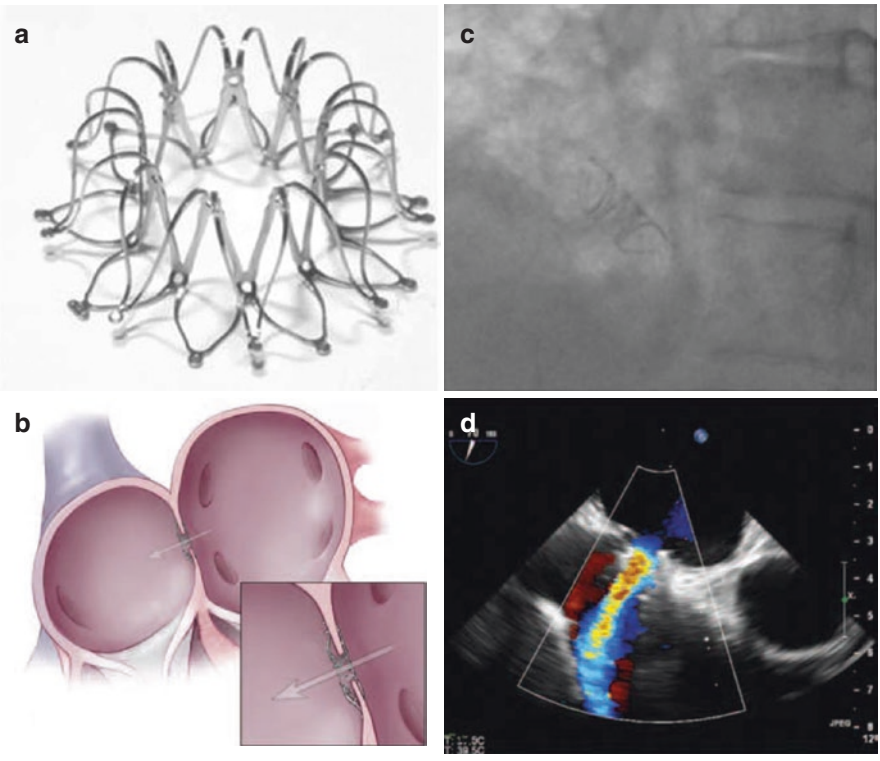

Fig. 10.6 Expanded interatrial septal defect system (**a**), schematic drawing showing the device implanted into the interatrial septum (**b**), fluoroscopic image (**c**) and transoesophageal echocardiographic image showing left-to-right shunt across the defect (**d**) (from Søndergaard et al. [61])

Atrioventricular valve (AV) dysfunction is integrally related to the onset and propagation of ventricular dysfunction. There is currently a boom in new transcatheter techniques to repair functional systemic AV valve regurgitation [64]. Percutaneous techniques that deal with AV valve dysfunction either aim at repair of the valve leaflets [65], reduction of the valve annulus diameter [66] or replacement of the valve either in the anatomic [67] or an extra-anatomic position [68]. Although developed in the acquired heart failure setting, these devices and techniques are now being applied to CHD, and this is an exciting area for further research and development [65].

References

1. Kotowycz MA, Therrien J, Ionescu-Ittu R, Owens CG, Pilote L, Martucci G, Tchervenkov C, Marelli AJ. Long-term outcomes after surgical versus transcatheter closure of atrial septal defects in adults. JACC Cardiovasc Interv. 2013;6:497–503.
2. Gatzoulis MA, Hechter S, Webb GD, Williams WG. Surgery for partial atrioventricular septal defect in the adult. Ann Thorac Surg. 1999;67:504–10.
3. Fischer G, Stieh J, Uebing A, Hoffmann U, Morf G, Kramer HH. Experience with transcatheter closure of secundum atrial septal defects using the Amplatzer septal occluder: a single centre study in 236 consecutive patients. Heart. 2003;89:199–204.
4. Du ZD, Hijazi ZM, Kleinman CS, Silverman NH, Larntz K, Investigators A. Comparison between transcatheter and surgical closure of secundum atrial septal defect in children and adults: results of a multicenter nonrandomized trial. J Am Coll Cardiol. 2002;39:1836–44.
5. DiBardino DJ, McElhinney DB, Kaza AK, Mayer JE. Analysis of the US Food and Drug Administration Manufacturer and User Facility Device Experience database for adverse events involving Amplatzer septal occluder devices and comparison with the Society of Thoracic Surgery congenital cardiac surgery database. J Thorac Cardiovasc Surg. 2009;137:1334–41.
6. Amin Z, Hijazi ZM, Bass JL, Cheatham JP, Hellenbrand WE, Kleinman CS. Erosion of Amplatzer septal occluder device after closure of secundum atrial septal defects: review of registry of complications and recommendations to minimize future risk. Catheter Cardiovasc Interv. 2004;63:496–502.
7. Campbell M. Natural history of atrial septal defect. Br Heart J. 1970;32:820–6.
8. Nyboe C, Karunanithi Z, Nielsen-Kudsk JE, Hjortdal VE. Long-term mortality in patients with atrial septal defect: a nationwide cohort-study. Eur Heart J. 2017. https://doi.org/10.1093/eurheartj/ehx687.
9. Murphy JG, Gersh BJ, McGoon MD, Mair DD, Porter CJ, Ilstrup DM, McGoon DC, Puga FJ, Kirklin JW, Danielson GK. Long-term outcome after surgical repair of isolated atrial septal defect. Follow-up at 27 to 32 years. N Engl J Med. 1990;323:1645–50.
10. Gatzoulis MA, Freeman MA, Siu SC, Webb GD, Harris L. Atrial arrhythmia after surgical closure of atrial septal defects in adults. N Engl J Med. 1999;340:839–46.
11. Diller G-P, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, Johansson B, Bouzas B, Mullen MJ, Poole-Wilson PA, Francis DP, Gatzoulis MA. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. Circulation. 2005;112:828–35.
12. Helber U, Baumann R, Seboldt H, Reinhard U, Hoffmeister HM. Atrial septal defect in adults: cardiopulmonary exercise capacity before and 4 months and 10 years after defect closure. J Am Coll Cardiol. 1997;29:1345–50.
13. Giardini A, Donti A, Formigari R, Specchia S, Prandstraller D, Bronzetti G, Bonvicini M, Picchio FM. Determinants of cardiopulmonary functional improvement after transcatheter atrial septal defect closure in asymptomatic adults. J Am Coll Cardiol. 2004;43:1886–91.

14. Veldtman GR, Razack V, Siu S, El-Hajj H, Walker F, Webb GD, Benson LN, McLaughlin PR. Right ventricular form and function after percutaneous atrial septal defect device closure. J Am Coll Cardiol. 2001;37:2108–13.
15. Attenhofer Jost CH, Oechslin E, Seifert B, Maly F, Fatio R, Turina J, Jenni R. Remodelling after surgical repair of atrial septal defects within the oval fossa. Cardiol Young. 2002;12:506–12.
16. Uebing A, Fischer G, Bethge M, Scheewe J, Schmiel F, Stieh J, Brossmann J, Kramer HH. Influence of the pulmonary annulus diameter on pulmonary regurgitation and right ventricular pressure load after repair of tetralogy of Fallot. Heart. 2002;88:510–4.
17. Gatzoulis MA, Till JA, Somerville J, Redington AN. Mechanoelectrical interaction in tetralogy of Fallot. QRS prolongation relates to right ventricular size and predicts malignant ventricular arrhythmias and sudden death. Circulation. 1995;92:231–7.
18. Eyskens B, Reybrouck T, Bogaert J, Dymarkowsky S, Daenen W, Dumoulin M, Gewillig M. Homograft insertion for pulmonary regurgitation after repair of tetralogy of fallot improves cardiorespiratory exercise performance. Am J Cardiol. 2000;85:221–5.
19. Frigiola A, Redington AN, Cullen S, Vogel M. Pulmonary regurgitation is an important determinant of right ventricular contractile dysfunction in patients with surgically repaired tetralogy of Fallot. Circulation. 2004;110:II153–7.
20. Geva T. Repaired tetralogy of Fallot: the roles of cardiovascular magnetic resonance in evaluating pathophysiology and for pulmonary valve replacement decision support. J Cardiovasc Magn Reson. 2011;13:9.
21. Gaynor SL, Maniar HS, Bloch JB, Steendijk P, Moon MR. Right atrial and ventricular adaptation to chronic right ventricular pressure overload. Circulation. 2005;112:I212–8.
22. Therrien J, Provost Y, Merchant N, Williams W, Colman J, Webb G. Optimal timing for pulmonary valve replacement in adults after tetralogy of Fallot repair. Am J Cardiol. 2005;95:779–82.
23. Uebing A, Fischer G, Schlangen J, Apitz C, Steendijk P, Kramer H-H. Can we use the end systolic volume index to monitor intrinsic right ventricular function after repair of tetralogy of Fallot? Int J Cardiol. 2011;147:52–7.
24. Heng EL, Gatzoulis MA, Uebing A, Sethia B, Uemura H, Smith GC, Diller G-P, McCarthy KP, Ho SY, Li W, Wright P, Spadotto V, Kilner PJ, Oldershaw P, Pennell DJ, Shore DF, Babu-Narayan SV. Immediate and midterm cardiac remodeling after surgical pulmonary valve replacement in adults with repaired tetralogy of Fallot: a prospective cardiovascular magnetic resonance and clinical study. Circulation. 2017;136:1703–13.
25. Baumgartner H, Bonhoeffer P, NMS DG, de Haan F, Deanfield JE, Galie N, Gatzoulis MA, Gohlke-Baerwolf C, Kaemmerer H, Kilner P, Meijboom F, BJM M, Oechslin E, Oliver JM, Serraf A, Szatmari A, Thaulow E, Vouhe PR, Walma E. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J. 2010;31:2915–57.
26. Cheung EW-Y, Wong WH-S, Cheung Y-F. Meta-analysis of pulmonary valve replacement after operative repair of tetralogy of Fallot. Am J Cardiol. 2010;106:552–7.
27. Babu-Narayan SV, Diller G-P, Gheta RR, Bastin AJ, Karonis T, Li W, Pennell DJ, Uemura H, Sethia B, Gatzoulis MA, Shore DF. Clinical outcomes of surgical pulmonary valve replacement after repair of tetralogy of Fallot and potential prognostic value of preoperative cardiopulmonary exercise testing. Circulation. 2014;129:18–27.
28. Ferraz Cavalcanti PE, Sá MPBO, Santos CA, Esmeraldo IM, De Escobar RR, De Menezes AM, De Azevedo OM, De Vasconcelos Silva FP, RFDA L, RDC L. Pulmonary valve replacement after operative repair of Tetralogy of Fallot: meta-analysis and meta-regression of 3,118 patients from 48 studies. J Am Coll Cardiol. 2013;62:2227–43.
29. Bonhoeffer P, Boudjemline Y, Saliba Z, Merckx J, Aggoun Y, Bonnet D, Acar P, Le BJ, Sidi D, Kachaner J. Percutaneous replacement of pulmonary valve in a right-ventricle to pulmonary-artery prosthetic conduit with valve dysfunction. Lancet. 2000;356:1403–5.
30. Ansari MM, Cardoso R, Garcia D, Sandhu S, Horlick E, Brinster D, Martucci G, Piazza N. Percutaneous pulmonary valve implantation: present status and evolving future. J Am Coll Cardiol. 2015;66:2246–55.

31. Khambadkone S, Coats L, Taylor A, Boudjemline Y, Derrick G, Tsang V, Cooper J, Muthurangu V, Hegde SR, Razavi RS, Pellerin D, Deanfield J, Bonhoeffer P. Percutaneous pulmonary valve implantation in humans: results in 59 consecutive patients. Circulation. 2005;112:1189–97.
32. Cheatham JP, Hellenbrand WE, Zahn EM, Jones TK, Berman DP, Vincent JA, McElhinney DB. Clinical and hemodynamic outcomes up to 7 years after transcatheter pulmonary valve replacement in the US melody valve investigational device exemption trial. Circulation. 2015;131:1960–70.
33. Lurz P, Giardini A, Taylor AM, Nordmeyer J, Muthurangu V, Odendaal D, Mist B, Khambadkone S, Schievano S, Bonhoeffer P, Derrick G. Effect of altering pathologic right ventricular loading conditions by percutaneous pulmonary valve implantation on exercise capacity. Am J Cardiol. 2010;105:721–6.
34. Lurz P, Riede FT, Taylor AM, Wagner R, Nordmeyer J, Khambadkone S, Kinzel P, Derrick G, Schuler G, Bonhoeffer P, Giardini A, Daehnert I. Impact of percutaneous pulmonary valve implantation for right ventricular outflow tract dysfunction on exercise recovery kinetics. Int J Cardiol. 2014;177:276–80.
35. Nordmeyer J, Lurz P, Khambadkone S, Schievano S, Jones A, McElhinney DB, Taylor AM, Bonhoeffer P. Pre-stenting with a bare metal stent before percutaneous pulmonary valve implantation: acute and 1-year outcomes. Heart. 2011;97:118–23.
36. Uebing A, Rigby ML. The problem of infective endocarditis after transcatheter pulmonary valve implantation. Heart. 2015;10:749–51.
37. Chen CR, Cheng TO, Huang T, Zhou YL, Chen JY, Huang YG, Li HJ. Percutaneous balloon valvuloplasty for pulmonic stenosis in adolescents and adults. N Engl J Med. 1996;335:21–5.
38. Zampi JD, Loccoh E, Armstrong AK, Yu S, Lowery R, Rocchini AP, Hirsch-Romano JC. Twenty years of experience with intraoperative pulmonary artery stenting. Catheter Cardiovasc Interv. 2017;90:398–406.
39. Brown ML, Dearani JA, Danielson GK, Cetta F, Connolly HM, Warnes CA, Li Z, Hodge DO, Driscoll DJ, Mayo Clinic Congenital Heart Center. The outcomes of operations for 539 patients with Ebstein anomaly. J Thorac Cardiovasc Surg. 2008;135:1120–36. 1136–7
40. Danielson GK, Maloney JD, Devloo RA. Surgical repair of Ebstein's anomaly. Mayo Clin Proc. 1979;54:185–92.
41. Carpentier A, Chauvaud S, Macé L, Relland J, Mihaileanu S, Marino JP, Abry B, Guibourt P. A new reconstructive operation for Ebstein's anomaly of the tricuspid valve. J Thorac Cardiovasc Surg. 1988;96:92–101.
42. da Silva JP, Baumgratz JF, da Fonseca L, Franchi SM, Lopes LM, Tavares GMP, Soares AM, Moreira LF, Barbero-Marcial M. The cone reconstruction of the tricuspid valve in Ebstein's anomaly. The operation: early and midterm results. J Thorac Cardiovasc Surg. 2007;133:215–23.
43. Dearani JA, Mora BN, Nelson TJ, Haile DT, O'Leary PW. Ebstein anomaly review: what's now, what's next? Expert Rev Cardiovasc Ther. 2015;13:1101–9.
44. Brown ML, Dearani JA, Danielson GK, Cetta F, Connolly HM, Warnes CA, Li Z, Hodge DO, Driscoll DJ. Functional status after operation for Ebstein anomaly: the Mayo Clinic experience. J Am Coll Cardiol. 2008;52:460–6.
45. Roberts PA, Boudjemline Y, Cheatham JP, Eicken A, Ewert P, McElhinney DB, Hill SL, Berger F, Khan D, Schranz D, Hess J, Ezekowitz MD, Celermajer D, Zahn E. Percutaneous tricuspid valve replacement in congenital and acquired heart disease. J Am Coll Cardiol. 2011;58:118–22.
46. Karonis T, Scognamiglio G, Babu-Narayan SV, Montanaro C, Uebing A, Diller GP, Alonso-Gonzalez R, Swan L, Dimopoulos K, Gatzoulis MA, Li W. Clinical course and potential complications of small ventricular septal defects in adulthood: Late development of left ventricular dysfunction justifies lifelong care. Int J Cardiol. 2016;208:102–6.
47. Carminati M, Butera G, Chessa M, Giovanni J De, Fisher G, Gewillig M, Peuster M, Piechaud JF, Santoro G, Sievert H, Spadoni I, Walsh K, Investigators of the European VSD Registry A, Lillehei C, Cohen M, Warden H, Varco R, Kouchoukos N, Blackstone E, Doty D, Hanley F, Karp R, Ross-Hesselink J, Mejiboom F, Spitaels S, Domberg R Van, Rijen E Van, Utens

E, Bogers A, Simons M, et al. Transcatheter closure of congenital ventricular septal defects: results of the European Registry. Eur Heart J 2007;28:2361–8.
48. Liddy S, Oslizlok P, Walsh KP. Comparison of the results of transcatheter closure of patent ductus arteriosus with newer Amplatzer devices. Catheter Cardiovasc Interv. 2013;82:253–9.
49. Campbell M. Natural history of coarctation of the aorta. Br Heart J. 1970;32:633–40.
50. Torok RD, Campbell MJ, Fleming GA, Hill KD. Coarctation of the aorta: Management from infancy to adulthood. World J Cardiol. 2015;7:765–75.
51. Massey R, Shore DF. Surgery for complex coarctation of the aorta. Int J Cardiol. 2004;97:67–73.
52. Forbes TJ, Kim DW, Du W, Turner DR, Holzer R, Amin Z, Hijazi Z, Ghasemi A, Rome JJ, Nykanen D, Zahn E, Cowley C, Hoyer M, Waight D, Gruenstein D, Javois A, Foerster S, Kreutzer J, Sullivan N, Khan A, Owada C, Hagler D, Lim S, Canter J, Zellers T, CCISC Investigators. Comparison of surgical, stent, and balloon angioplasty treatment of native coarctation of the aorta: an observational study by the CCISC (Congenital Cardiovascular Interventional Study Consortium). J Am Coll Cardiol. 2011;58:2664–74.
53. Forbes TJ, Garekar S, Amin Z, Zahn EM, Nykanen D, Moore P, Qureshi SA, Cheatham JP, Ebeid MR, Hijazi ZM, Sandhu S, Hagler DJ, Sievert H, Fagan TE, Ringewald J, Du W, Tang L, Wax DF, Rhodes J, Johnston TA, Jones TK, Turner DR, CAC P, Hellenbrand WE, Congenital Cardiovascular Interventional Study Consortium (CCISC). Procedural results and acute complications in stenting native and recurrent coarctation of the aorta in patients over 4 years of age: a multi-institutional study. Catheter Cardiovasc Interv. 2007;70:276–85.
54. Fawzy ME, Sivanandam V, Pieters F, Stefadouros MA, Galal O, Dunn B, Kinsara A, Khan B, Al-Halees Z. Long-term effects of balloon angioplasty on systemic hypertension in adolescent and adult patients with coarctation of the aorta. Eur Heart J. 1999;20:827–32.
55. Lam Y-Y, Kaya MG, Li W, Mahadevan VS, Khan AA, Henein MY, Mullen M. Effect of endovascular stenting of aortic coarctation on biventricular function in adults. Heart. 2007;93:1441–7.
56. Hassan W, Awad M, Fawzy ME, Al OA, Malik S, Akhras N, Shoukri M. Long-term effects of balloon angioplasty on left ventricular hypertrophy in adolescent and adult patients with native coarctation of the aorta. Up to 18 years follow-up results. Catheter Cardiovasc Interv. 2007;70:881–6.
57. Diller G-P, Kempny A, Alonso-Gonzalez R, Swan L, Uebing A, Li W, Babu-Narayan S, Wort SJ, Dimopoulos K, Gatzoulis MA. Survival prospects and circumstances of death in contemporary adult congenital heart disease patients under follow-up at a large tertiary centre. Circulation. 2015;132:2118–25.
58. Kreutzer J, Graziano JN, Stapleton G, Rome JJ. Late catheter interventions in hypoplastic left heart syndrome. Cardiol Young. 2011;21(Suppl 2):65–76.
59. Hansen JH, Runge U, Uebing A, Scheewe J, Kramer H-H, Fischer G. Cardiac catheterization and interventional procedures as part of staged surgical palliation for hypoplastic left heart syndrome. Congenit Heart Dis. 2012;7:565–74.
60. Sagic D, Otasevic P, Sievert H, Elsasser A, Mitrovic V, Gradinac S. Percutaneous implantation of the left ventricular partitioning device for chronic heart failure: a pilot study with 1-year follow-up. Eur J Heart Fail. 2010;12:600–6.
61. Søndergaard L, Reddy V, Kaye D, Malek F, Walton A, Mates M, Franzen O, Neuzil P, Ihlemann N, Gustafsson F. Transcatheter treatment of heart failure with preserved or mildly reduced ejection fraction using a novel interatrial implant to lower left atrial pressure. Eur J Heart Fail. 2014;16:796–801.
62. Hasenfuß G, Hayward C, Burkhoff D, Silvestry FE, McKenzie S, Gustafsson F, Malek F, Van der HJ, Lang I, Petrie MC, Cleland JGF, Leon M, Kaye DM. A transcatheter intracardiac shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF): a multicentre, open-label, single-arm, phase 1 trial. Lancet. 2016;387:1298–304.
63. Tutarel O, Kempny A, Alonso-Gonzalez R, Jabbour R, Li W, Uebing A, Dimopoulos K, Swan L, Gatzoulis MA, Diller GP. Congenital heart disease beyond the age of 60: emergence of a

new population with high resource utilization, high morbidity, and high mortality. Eur Heart J. 2014;35:725–32.
64. Taramasso M, Hahn RT, Alessandrini H, Latib A, Attinger-Toller A, Braun D, Brochet E, Connelly KA, Denti P, Deuschl F, Englmaier A, Fam N, Frerker C, Hausleiter J, Juliard J-M, Kaple R, Kreidel F, Kuck KH, Kuwata S, Ancona M, Malasa M, Nazif T, Nickenig G, Nietlispach F, Pozzoli A, Schäfer U, Schofer J, Schueler R, Tang G, Vahanian A, et al. The International Multicenter TriValve Registry: which patients are undergoing transcatheter tricuspid repair? JACC Cardiovasc Interv. 2017;10:1982–90.
65. Franzen O, von Samson P, Dodge-Khatami A, Geffert G, Baldus S. Percutaneous edge-to-edge repair of tricuspid regurgitation in congenitally corrected transposition of the great arteries. Congenit Heart Dis. 2011;6:57–9.
66. Stephan von Bardeleben R, Tamm A, Emrich T, Münzel T, Schulz E. Percutaneous transvenous direct annuloplasty of a human tricuspid valve using the Valtech Cardioband. Eur Heart J. 2017;38:690.
67. Duncan A, Daqa A, Yeh J, Davies S, Uebing A, Quarto C, Moat N. Transcatheter mitral valve replacement: long-term outcomes of first-in-man experience with an apically tethered device—a case series from a single centre. EuroIntervention. 2017;13:e1047–57.
68. Lauten A, Laube A, Schubert H, Bischoff S, Nietzsche S, Horstkötter K, Poudel-Bochmann B, Franz M, Lichtenberg A, Figulla HR, Akhyari P. Transcatheter treatment of tricuspid regurgitation by caval valve implantation—experimental evaluation of decellularized tissue valves in central venous position. Catheter Cardiovasc Interv. 2015;85:150–60.

Drug Therapy in Adult Congenital Heart Disease Heart Failure

11

Pieter De Meester and Werner Budts

11.1 Introduction

Heart failure (HF) is the predominant cause of death in adult patients with repaired congenital heart disease [1, 2]. Treatment consists of timely intervention for correctable causes of impaired functionality, oxygen desaturation or heart failure, physical rehabilitation, initiation of drug therapy, device therapy and assist device implantation or heart transplantation.

Drug therapy should be aimed at either symptom relief, preventing progression of HF, prevention of HF-related complications or reduction of mortality. Moreover, drug therapy also intends to reduce the number of hospitalisations and, consequently, stabilise or improve quality of life. Blockade of the renin-angiotensin-aldosterone system (RAAS blockade) together with beta-blockade has become the cornerstone of chronic HF treatment in general cardiology [3]. In recent years, the addition of a neprilysin inhibitor has proven to be of clinical benefit (i.e. the angiotensin II receptor blocker and neprilysin inhibitor molecule or ARNI) [4]. Although medical therapy in patients from the general population with HF and reduced ejection fraction is based on large, well-executed studies, the evidence for drug therapy in patients with repaired and unrepaired congenital heart disease is scarce. The presence of a systemic morphologic left or right ventricle, the unique haemodynamics of pressure and volume loading, the presence of intracardiac and extracardiac shunts, a history of preload deprivation, chronic systemic desaturation and the importance of the pulmonary vasculature represent each congenital defect, and even each patient, as a unique clinical and haemodynamic challenge. This patient specificity makes it difficult to initiate large randomised studies to prove the potential

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value of medical HF treatment. However, neurohormonal activation also takes place in patients with congenital heart disease with HF, making a case in favour of classical HF therapy in these patients [5].

In this chapter, we summarise the rationale, evidence and expert consensus for initiation of drug therapy in patients with adult congenital heart disease and chronic HF.

11.2 Systolic Failure of the Morphological Systemic Left Ventricle

Despite the lack of clinical studies performed in this patient group, the pathophysiology of HF in case of systemic left ventricular (LV) failure can be considered to be the same as in patients with HF due to acquired heart disease [3, 6]. Therefore, it is suggested that diuretics, renin-angiotensin-aldosterone system (RAAS) blockers, beta-blockers and mineralocorticoid receptor antagonists can be used in the congenital heart disease population [6]. This is especially true if neurohormonal and cardiac autonomic activity is increased [7].

In patients with left ventricular outflow tract obstruction (e.g. aortic stenosis, supra- and subvalvular stenosis), the cornerstone of treatment is corrective surgery. However, after correction, HF symptoms sometimes persist. In this patient population, classical HF treatment can be initiated [8]. In case of persisting arterial hypertension after coarctation repair, antihypertensive treatment should be started. In these patients beta-blockers to reduce exercise-related hypertension are often the first-line choice [9].

In both *asymptomatic* and *symptomatic* patients with systemic left ventricular dysfunction, RAAS blockade, beta-blockers and mineralocorticoid receptor antagonists should be considered [6]. Digoxin was previously used extensively in paediatric practice, but its role is now very limited due to its lack of mortality benefit and potential risks associated with its prescription. Loop diuretics have never shown improved survival in the treatment of chronic HF and should only be for decongestion and relief from symptoms [3]. The addition of a thiazide is indicated in case of refractory oedema under close monitoring of clinical status and renal function [10].

11.3 Systemic Right Ventricle

The long-term pressure overload on the systemic right ventricle will almost always lead to progressive dysfunction and HF [11, 12]. However, even in asymptomatic patients, most adults have some degree of what would be considered as RV dysfunction [13]. Furthermore right ventricular function at rest might not be indicative for contractile reserve during exercise, making it a blunt measure of cardiac performance [14]. It is unclear at what time point drug therapy should be initiated in patients with a systemic RV. BNP levels have been shown to correlate with clinical status, RV ejection fraction, exercise capacity and worsening tricuspid regurgitation, but a specific

cut-off value to discriminate patients with significant neurohormonal activation has not been identified [15–17].

All of the HF drug studies performed in the systemic RV have been flawed. Many include mixed populations of patients, non-randomised controlled methodologies and short follow-up. In addition most are underpowered, and it is not possible to exclude important Type II errors when reviewing the results. Studies on RAAS blockade have mainly focused on surrogate endpoints such as ejection fraction, maximum oxygen uptake and cardiac index. Although some studies have shown improvement, data are often conflicting [13, 18–20]. No clear benefit has been observed in studies with ACE-I in patients after atrial switch repair for d-TGA [21–23]. Furthermore, patients with ccTGA have never been investigated in isolation.

Although therapy with losartan initially showed promise by improving ejection fraction and exercise duration, no differences have been observed in two small randomised clinical trials [18, 19, 24]. It has to be said that most of the patients included in these studies were asymptomatic and had a reasonably preserved right ventricular function.

Beta-blockade has shown to improve symptoms, lessen systemic tricuspid regurgitation, improve functional status and have positive effects on right ventricular remodelling [20, 25, 26]. However, no effects on hospital admission, sudden death and HF-related death are reported in literature [20].

Eplerenone has been investigated in one limited trial showing a trend towards reduction in collagen turnover biomarkers, but no detectable clinical benefit [27].

It is important to emphasise that the surrogate endpoints, often used in the beforementioned studies, often don't correlate with outcome even in patients with HF due to acquired heart disease. Furthermore, if using the data from the acquired HF studies, the 'number needed to treat' to obtain measurable benefit often greatly exceeds the study population especially when asymptomatic or low-risk patients are included.

Although, from a theoretical point of view, initiation of RAAS blockade and beta-blockade at an early stage might help to prevent negative remodelling, the use of this medication in the *asymptomatic* population is generally not recommended [6, 8]. The lack of evidence and the risk of accentuating pre-existing structural and electrical abnormalities make it hard to justify early initiation of therapy. RAAS blockade leads to vasodilatation and might impair ventricular filling due to restrictive atrial baffles, atria or right ventricle, in particular in patients who underwent atrial switch repair. Beta-blockade might accentuate sinus node dysfunction and AV node conduction leading to complete heart block. In these patients the risk of harm may be greater than the potential benefit. Again the number needed to treat will be high when patients are asymptomatic, and this will often tip the balance towards not initiating therapy in this situation.

If *symptoms* of HF occur, and no correctable cause can be identified, initiation of RAAS blockade and beta-blockade can be considered, with careful up-titration and with close monitoring of the patient's symptoms and oxygen saturation [6, 8]. In these patients, neurohormonal and sympathetic activation can be presumed, and initiation of HF treatment can be considered equal as in patients with systemic left

ventricular dysfunction [27, 28]. In Table 11.1 are summarised clinical trials for HF drugs in this group of patients.

11.4 Systolic Failure of the Morphological Sub-pulmonary Right Ventricle

In patients with volume loading due to valvular regurgitation (i.e. patients with Ebstein anomaly or pulmonary valve regurgitation after tetralogy of Fallot repair) or a pre-tricuspid shunt lesion, timely surgical correction is indicated by valve surgery or closure of the shunt lesion, respectively [29–31]. Although volume loading is well tolerated for a long time, right ventricular dilatation and dysfunction will occur over time. Furthermore, the right ventricle can evolve towards a restrictive physiology [32]. Although increased sympathetic nervous system activity has been described in patients after tetralogy of Fallot repair, trials could not show the added benefit of RAAS blockade and beta-blockade [33, 34]. However, in case of a restrictive right ventricular physiology, administration of ramipril has shown favourable effects on *left* ventricular function and ejection fraction [33].

Other studies evaluating the effect of RAAS blockade and beta-blockers have not been performed in right-sided HF due to dysfunction of the sub-pulmonary right ventricle.

If pulmonary arterial hypertension is the cause of right ventricular failure, drug therapy should focus on the pulmonary circulation and follow the recommendation of the respective guideline to lower the afterload of the right ventricle [35].

Because of this, in *asymptomatic* patients, no medical treatment is indicated. When *symptomatic*, correction of congestion by loop diuretics with or without the addition of a thiazide can be started, with close monitoring of clinical parameters and renal function [6, 8, 10]. Likewise, the addition of spironolactone or eplerenone is reasonable. Spironolactone is of particular benefit if there is the suspicion of secondary hyperaldosteronism.

11.5 Palliated Single Ventricle and Fontan

The Fontan circulation represents a complex series of haemodynamic and anatomic changes, each of which can fail. Adequate filling, laminar flow from the caval veins towards the pulmonary artery, a healthy pulmonary vasculature, good run-off of oxygenated blood towards the systemic atrium and ventricle and good systolic and diastolic function of the single ventricle are all necessary in order to have a well-functioning Fontan circulation. When symptoms of HF occur, each of these segments of the Fontan circulation should be considered to be the culprit.

No study has proven the benefit of diuretics in the ACHD population nor, for that matter, in acquired heart disease, but it is reasonable to titrate the dose of loop diuretics to treat congestion and relieve symptoms. However, caution should be taken to avoid under-filling, as this may reduce preload and cause deterioration of

Table 11.1 Clinical trials for heart failure drugs in patients with systemic right ventricle

References	Design	Population	*n*	Intervention	Duration	Comparison	Outcome
Shaddy [54]	Multicentre RCT/ double blind/ placebo	Children and adolescents with symptomatic systolic HF	101	Carvedilol	8 months	Placebo	*Negative*: composite endpoint of heart failure outcomes
Ishibashi [48]	Prospective cohort study	Fontan, bidirectional Glenn, univentricular heart without intervention	51	Carvedilol	11 months	Before and after beta-blockade	*Positive*: cardiothoracic ratio, dose of diuretics, ejection fraction, clinical signs, symptoms and NYHA class
Kouatli [47]	RCT/double blind/ placebo	Fontan	18	Enalapril	10 weeks	Placebo	*Negative*: exercise time, echo parameters of diastolic function, increased cardiac output on exertion
Hsu [45]	Multicentre RCT/ double blind/ placebo	Infants with single-ventricle physiology	230	Enalapril	14 months	Placebo	*Negative*: somatic growth, ventricular function or heart failure therapy
Mahle [36]	Prospective cohort study	Fontan	10	Spironolactone	4 weeks	Before and after MRA	*Negative*: endothelial function
Ringel [37]	Retrospective observational	Fontan	3	Spironolactone	2–3 years	Observational	*Positive*: improvement on protein-losing enteropathy
Giardini [38]	Intervention	Fontan	27	Single-dose sildenafil	Single dose	Before and after PDE2-I	*Positive*: exercise capacity, haemodynamic response to exercise
Van De Bruaene [39]	Intervention	Fontan	10	Single-dose sildenafil	Single dose	Before and after PDE2-I	*Positive*: cardiac index during exercise and decreased total pulmonary vascular resistance index (MRI)
Goldberg [40]	RCT/double blind/ crossover	Fontan	27	Sildenafil	6 weeks	Placebo/crossover	*Positive*: myocardial performance index and VTI x HR (echo)
Shabanian [41]	Prospective cohort study	Fontan	23	Sildenafil	1 week	Before and after PDE2-I	*Positive*: ventriculo-arterial coupling (echo)

(continued)

Table 11.1 (continued)

References	Design	Population	*n*	Intervention	Duration	Comparison	Outcome
Ovaert [42]	Prospective cohort study	Fontan	10	Bosentan	16 weeks	Before and after endothelin receptor antagonist	*Negative*: oxygen saturation, exercise performance, QoL
Schuuring [43]	Multicentre, prospective randomised, open label	Fontan	42	Bosentan	6 months	Before and after endothelin receptor antagonist	*Negative*: exercise capacity, NT-proBNP, cardiac output, Short Form-36, QoL, NYHA

RCT randomised controlled trial, *QoL* quality of life, *NYHA* New York Heart Association functional class, *VTI* velocity time integral, *HR* heart rate, *PDE2-I* phosphodiesterase 2 inhibitors, *MRA* mineralocorticoid receptor antagonist

renal function. Alternatively, spironolactone has shown to have an impact on protein-losing enteropathy and endothelial function [36, 37].

If pulmonary vascular resistance is elevated, the use of specific pulmonary vasodilator therapy might be considered. One should be cautious in case of a restrictive systemic ventricle, as the increased volume load might be poorly tolerated. Most evidence has emerged for the phosphodiesterase inhibitors with improvement of oxygen uptake, increased pulmonary and systemic blood flow at peak exercise, improved myocardial performance index and systolic arterial and ventricular elastance [38–41]. The effect of endothelin receptor antagonists is less certain; some authors showed a benefit, whereas others did not [42, 43]. This might be due to simultaneous reduction of both afterloads whilst increasing preload, which is more pronounced with PDE2 inhibitors [39].

Although ACE-I is often used in patients with a single ventricle, either a morphological right or left ventricle, evidence for improved ventricular function is lacking [44]. Enalapril was tested in two studies, both in asymptomatic children and in adults, and has failed to show a benefit on a number of endpoints, including functional class, BNP levels, ejection fraction, diastolic function, systemic vascular resistance, survival and freedom from heart transplantation [45–47]. However, no data are available on the use of ACE-I in patients with symptomatic HF.

There is one report on the use of beta-blockade in patients with a single-ventricle physiology, showing improved clinical parameters and less symptoms of HF with the use of carvedilol on top of standard medical therapy, consisting of diuretics, digoxin and ACE-I [48].

Again the use of digoxin is not supported by evidence.

Therefore, careful examination of the weakest part of the Fontan circulation is necessary before initiation of therapy. The largest evidence is there for PDE2 inhibition. Treatment of fluid overload with diuretics should be titrated carefully. Furthermore, standard HF treatment, although not supported by trials, is reasonable in those whose predominant issue is ventricular dysfunction. Lastly, in case of persisting right-to-left shunting, cyanosis might be aggravated after the initiation of RAAS inhibition because of the lowering of the systemic vascular resistance [49]. It is a usual practice to start RAAS blockade, beta-blockers and mineralocorticoid receptor antagonists in case of decreasing ejection fraction (>40%) in asymptomatic and symptomatic patients with a morphological left ventricle and titrating diuretics in the latter. In case of a morphological right ventricle, initiation of therapy is recommended only when symptoms occur [6, 8]. In Table 11.2 are summarised clinical trials for HF drugs in this group of patients.

11.6 Heart Failure with Preserved Ejection Fraction

In HF with preserved ejection fraction due to acquired heart disease, no medical treatment has shown to reduce morbidity or mortality [3]. Similarly, no data are available in patients with congenital heart disease. As patients with HF with preserved ejection fraction function on the steep part of the Starling curve, prevention of both volume over- and underload and good blood pressure control is key.

Table 11.2 Clinical trials for heart failure drugs in patients with univentricular heart and/or post-Fontan-type surgery

References	Design	Population	*n*	Intervention	Duration	Comparison	Outcome
Hechter [23]	Observational retrospective	TGA Mustard	14	ACE-I	2 years	Before and after ACE-I	*Negative*: exercise capacity and MRI measured ejection fraction
Lester [24]	RCT/crossover	TGA atrial switch	7	Losartan	8 weeks	Placebo/crossover	*Positive*: exercise duration, TR, ejection fraction
Robinson [21]	Prospective cohort study	TGA atrial switch	9	Enalapril	12 months	Before and during ACE-I	*Negative*: exercise performance, cardiac index
Dore [18]	Multicentre RCT/ double blind/ crossover	TGA atrial switch	29	Losartan	15 weeks	Placebo/crossover	*Negative*: exercise capacity, BNP
Therrien [22]	RCT/double blind/ placebo	TGA atrial switch	17	Ramipril	1 year	Placebo	*Negative*: RV function (MRI), RV size (MRI), exercise capacity, QoL
Van Der Bom [19]	Multicentre RCT/ double blind	ccTGA or TGA atrial switch	88	Valsartan	3 years	Placebo	*Positive*: RV volumes and mass (MRI) *Negative*: clinical event rate, RV function (MRI), exercise capacity, TR, QoL, neurohormonal activation
Tutarel [28]	Retrospective observational control	TGA Mustard	14	Enalapril	13 months	Before and after ACE-I	*Positive*: NT-proBNP *Negative*: NYHA, echo parameters, exercise capacity
Josephson [26]	Retrospective observational cohort	TGA atrial switch	8	Beta-blockers	36 months	Before and after beta-blockade	*Trend* towards improved symptoms, less TR and improved NYHA
Bouallal [55]	Prospective cohort study	ccTGA or TGA atrial switch	14	Bisoprolol carvedilol	13 months	Before and after beta-blockade	*Positive*: NYHA, QoL, RV ejection fraction (radionuclide ventriculography) *Negative*: ejection fraction (MRI), exercise capacity, BNP
Giardini [25]	Prospective cohort study	ccTGA or TGA atrial switch	8	Carvedilol	12 months	Before and after beta-blockade	*Positive*: RV and LV ejection fraction (MRI) *Negative*: exercise capacity
Doughan [20]	Retrospective cohort study	TGA atrial switch	60	Metoprolol XL carvedilol	4 months	Beta-blockade vs. no treatment	*Positive*: NYHA after start beta-blockade (within group)

References	Design	Population	*n*	Intervention	Duration	Comparison	Outcome
Khairy [56]	Multicentre retrospective cohort study	TGA atrial switch	37	Beta-blockers	3 years	Beta-blockade vs. no treatment	Lack of beta-blockers predicts appropriate shocks in patients with AICD
Dos [27]	RCT, double blind	TGA atrial switch	26	Eplerenone	12 months	Placebo	*Negative*: RV mass and function *Trend* towards reduction in collagen turnover biomarkers)

RCT randomised controlled trial, *TGA* transposition of the great arteries, *TR* tricuspid valve regurgitation, *RV* right ventricle, *LV* left ventricle, *QoL* quality of life, *NYHA* New York Heart Association functional class, *AICD* Automated Implantable Cardioverter-Defibrillator

In *symptomatic* patients, diuretics can be used to control fluid status; beta-blockers and rate-limiting calcium channel blockers might help to slow heart rate and prolong ventricular filling [6].

11.7 Other Medical Interventions in the Heart Failure Population

The role of ivabradine in patients with HF and congenital heart disease has not been investigated, but one could presume similar indications as in patients with heart failure due to acquired heart disease, especially in case of left ventricular dysfunction [6]. When using hydralazine and isosorbide dinitrate, the effect on systemic vascular resistance and possible increase in right-to-left shunting should be taken into account.

Lastly, the iron suppletion has been shown to improve functional capacity and quality of life and reduces the number of HF hospitalisations in patients with HF due to acquired heart disease [50]. In patients with adult congenital heart disease, iron deficiency is frequent and has shown to impair prognosis [51, 52]. Furthermore, iron supplementation has shown to improve exercise capacity and quality of life in patients with cyanotic congenital heart disease [53]. Although no trials with iron therapy in patients with congenital heart disease and HF have been done, prevention and substitution of iron deficiency sound reasonable.

Conclusion

Despite major gaps in the evidence for drug therapy in patients with ACHD and HF, both the American Heart Association and the European Society of Cardiology have made an attempt to rationalise therapy in this complex patient population [6, 8]. As a rule of thumb, in case of failure of the systemic left ventricle, guidelines of 'classical' HF can be extrapolated and possible effects on afterload reduction on right-to-left shunting taken into account. In case of right ventricular failure (systemic or sub-pulmonary) or in case of a functionally single ventricle, evidence is even more limited, and recommendations are mainly based on physiological reasoning and expert opinion. In every patient, possible adverse events of drug therapy should always be weighted relative to the possible benefit.

References

1. Tutarel O, Kempny A, Alonso-Gonzalez R, Jabbour R, Li W, Uebing A, Dimopoulos K, Swan L, Gatzoulis MA, Diller GP. Congenital heart disease beyond the age of 60: emergence of a new population with high resource utilization, high morbidity, and high mortality. Eur Heart J. 2014;35:725–32.
2. Verheugt CL, Uiterwaal CS, van der Velde ET, Meijboom FJ, Pieper PG, van Dijk AP, Vliegen HW, Grobbee DE, Mulder BJ. Mortality in adult congenital heart disease. Eur Heart J. 2010;31:1220–9.

3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-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, Members ATF. 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. 2016;37:2129–200.
4. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, Committees P-HIa. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371:993–1004.
5. Bolger AP, Sharma R, Li W, Leenarts M, Kalra PR, Kemp M, Coats AJ, Anker SD, Gatzoulis MA. Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease. Circulation. 2002;106:92–9.
6. Budts W, Roos-Hesselink J, Rädle-Hurst T, Eicken A, McDonagh TA, Lambrinou E, Crespo-Leiro MG, Walker F, Frogoudaki AA. Treatment of heart failure in adult congenital heart disease: a position paper of the Working Group of Grown-Up Congenital Heart Disease and the Heart Failure Association of the European Society of Cardiology. Eur Heart J. 2016;37:1419–27.
7. Ohuchi H, Takasugi H, Ohashi H, Okada Y, Yamada O, Ono Y, Yagihara T, Echigo S. Stratification of pediatric heart failure on the basis of neurohormonal and cardiac autonomic nervous activities in patients with congenital heart disease. Circulation. 2003;108:2368–76.
8. Stout KK, Broberg CS, Book WM, Cecchin F, Chen JM, Dimopoulos K, Everitt MD, Gatzoulis M, Harris L, Hsu DT, Kuvin JT, Law Y, Martin CM, Murphy AM, Ross HJ, Singh G, Spray TL, American Heart Association Council on Clinical Cardiology CuoFGaTB, and Council on Cardiovascular Radiology and Imaging. Chronic heart failure in congenital heart disease: a scientific statement from the American Heart Association. Circulation. 2016;133:770–801.
9. Moltzer E, Mattace Raso FU, Karamermer Y, Boersma E, Webb GD, Simoons ML, Danser AH, van den Meiracker AH, Roos-Hesselink JW. Comparison of Candesartan versus Metoprolol for treatment of systemic hypertension after repaired aortic coarctation. Am J Cardiol. 2010;105:217–22.
10. Jentzer JC, DeWald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. J Am Coll Cardiol. 2010;56:1527–34.
11. Cuypers JA, Eindhoven JA, Slager MA, Opić P, Utens EM, Helbing WA, Witsenburg M, van den Bosch AE, Ouhlous M, van Domburg RT, Rizopoulos D, Meijboom FJ, Bogers AJ, Roos-Hesselink JW. The natural and unnatural history of the Mustard procedure: long-term outcome up to 40 years. Eur Heart J. 2014;35:1666–74.
12. Dobson R, Danton M, Nicola W, Hamish W. The natural and unnatural history of the systemic right ventricle in adult survivors. J Thorac Cardiovasc Surg. 2013;145:1493–501. discussion 1501–3
13. Winter MM, Bouma BJ, van Dijk AP, Groenink M, Nieuwkerk PT, van der Plas MN, Sieswerda GT, Konings TC, Mulder BJ. Relation of physical activity, cardiac function, exercise capacity, and quality of life in patients with a systemic right ventricle. Am J Cardiol. 2008;102:1258–62.
14. Winter MM, Scherptong RW, Kumar S, Bouma BJ, Tulevski II, Tops LF, Roest AA, Vliegen HW, de Roos A, Groenink M, Mulder BJ. Ventricular response to stress predicts outcome in adult patients with a systemic right ventricle. Am Heart J. 2010;160:870–6.
15. Book WM, Hott BJ, McConnell M. B-type natriuretic peptide levels in adults with congenital heart disease and right ventricular failure. Am J Cardiol. 2005;95:545–6.
16. Koch AM, Zink S, Singer H. B-type natriuretic peptide in patients with systemic right ventricle. Cardiology. 2008;110:1–7.
17. Chow PC, Cheung EW, Chong CY, Lun KS, Yung TC, Wong KT, Chau AK, Cheung YF. Brain natriuretic peptide as a biomarker of systemic right ventricular function in patients with transposition of great arteries after atrial switch operation. Int J Cardiol. 2008;127:192–7.
18. Dore A, Houde C, Chan KL, Ducharme A, Khairy P, Juneau M, Marcotte F, Mercier LA. Angiotensin receptor blockade and exercise capacity in adults with systemic right

ventricles: a multicenter, randomized, placebo-controlled clinical trial. Circulation. 2005;112:2411–6.
19. van der Bom T, Winter MM, Bouma BJ, Groenink M, Vliegen HW, Pieper PG, van Dijk AP, Sieswerda GT, Roos-Hesselink JW, Zwinderman AH, Mulder BJ. Effect of valsartan on systemic right ventricular function: a double-blind, randomized, placebo-controlled pilot trial. Circulation. 2013;127:322–30.
20. Doughan AR, McConnell ME, Book WM. Effect of beta blockers (carvedilol or metoprolol XL) in patients with transposition of great arteries and dysfunction of the systemic right ventricle. Am J Cardiol. 2007;99:704–6.
21. Robinson B, Heise CT, Moore JW, Anella J, Sokoloski M, Eshaghpour E. Afterload reduction therapy in patients following intraatrial baffle operation for transposition of the great arteries. Pediatr Cardiol. 2002;23:618–23.
22. Therrien J, Provost Y, Harrison J, Connelly M, Kaemmerer H, Webb GD. Effect of angiotensin receptor blockade on systemic right ventricular function and size: a small, randomized, placebo-controlled study. Int J Cardiol. 2008;129:187–92.
23. Hechter SJ, Fredriksen PM, Liu P, Veldtman G, Merchant N, Freeman M, Therrien J, Benson L, Siu S, Webb G. Angiotensin-converting enzyme inhibitors in adults after the Mustard procedure. Am J Cardiol. 2001;87:660–3. A11
24. Lester SJ, McElhinney DB, Viloria E, Reddy GP, Ryan E, Tworetzky W, Schiller NB, Foster E. Effects of losartan in patients with a systemically functioning morphologic right ventricle after atrial repair of transposition of the great arteries. Am J Cardiol. 2001;88:1314–6.
25. Giardini A, Lovato L, Donti A, Formigari R, Gargiulo G, Picchio FM, Fattori R. A pilot study on the effects of carvedilol on right ventricular remodelling and exercise tolerance in patients with systemic right ventricle. Int J Cardiol. 2007;114:241–6.
26. Josephson CB, Howlett JG, Jackson SD, Finley J, Kells CM. A case series of systemic right ventricular dysfunction post atrial switch for simple D-transposition of the great arteries: the impact of beta-blockade. Can J Cardiol. 2006;22:769–72.
27. Dos L, Pujadas S, Estruch M, Mas A, Ferreira-González I, Pijuan A, Serra R, Ordóñez-Llanos J, Subirana M, Pons-Lladó G, Marsal JR, García-Dorado D, Casaldàliga J. Eplerenone in systemic right ventricle: double blind randomized clinical trial. The evedes study. Int J Cardiol. 2013;168:5167–73.
28. Tutarel O, Meyer GP, Bertram H, Wessel A, Schieffer B, Westhoff-Bleck M. Safety and efficiency of chronic ACE inhibition in symptomatic heart failure patients with a systemic right ventricle. Int J Cardiol. 2012;154:14–6.
29. Oosterhof T, van Straten A, Vliegen HW, Meijboom FJ, van Dijk AP, Spijkerboer AM, Bouma BJ, Zwinderman AH, Hazekamp MG, de Roos A, Mulder BJ. Preoperative thresholds for pulmonary valve replacement in patients with corrected tetralogy of Fallot using cardiovascular magnetic resonance. Circulation. 2007;116:545–51.
30. 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, Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of C, Association for European Paediatric C and Guidelines ESCCfP. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J. 2010;31:2915–57.
31. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, del Nido P, Fasules JW, Graham TP, Hijazi ZM, Hunt SA, King ME, Landzberg MJ, Miner PD, Radford MJ, Walsh EP, Webb GD, Smith SC, Jacobs AK, Adams CD, Anderson JL, Antman EM, Buller CE, Creager MA, Ettinger SM, Halperin JL, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Page RL, Riegel B, Tarkington LG, Yancy CW, American College of C, American Heart Association Task Force on Practice G, American Society of E, Heart Rhythm S, International Society for Adult Congenital Heart D, Society for Cardiovascular Angiography and I and Society of Thoracic S. 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). Developed in collaboration with the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;52:e143–263.
32. Helbing WA, Niezen RA, Le Cessie S, van der Geest RJ, Ottenkamp J, de Roos A. Right ventricular diastolic function in children with pulmonary regurgitation after repair of tetralogy of Fallot: volumetric evaluation by magnetic resonance velocity mapping. J Am Coll Cardiol. 1996;28:1827–35.
33. Babu-Narayan SV, Uebing A, Davlouros PA, Kemp M, Davidson S, Dimopoulos K, Bayne S, Pennell DJ, Gibson DG, Flather M, Kilner PJ, Li W, Gatzoulis MA. Randomised trial of ramipril in repaired tetralogy of Fallot and pulmonary regurgitation: the APPROPRIATE study (Ace inhibitors for Potential PRevention Of the deleterious effects of Pulmonary Regurgitation In Adults with repaired TEtralogy of Fallot). Int J Cardiol. 2012;154:299–305.
34. Norozi K, Bahlmann J, Raab B, Alpers V, Arnhold JO, Kuehne T, Klimes K, Zoege M, Geyer S, Wessel A, Buchhorn R. A prospective, randomized, double-blind, placebo controlled trial of beta-blockade in patients who have undergone surgical correction of tetralogy of Fallot. Cardiol Young. 2007;17:372–9.
35. 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, 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 GY, Orfanos SE, Park MH, Piepoli MF, Ponikowski P, Revel MP, Rigau D, Rosenkranz S, Völler H, Luis Zamorano J. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37:67–119.
36. Mahle WT, Wang A, Quyyumi AA, McConnell ME, Book WM. Impact of spironolactone on endothelial function in patients with single ventricle heart. Congenit Heart Dis. 2009;4:12–6.
37. Ringel RE, Peddy SB. Effect of high-dose spironolactone on protein-losing enteropathy in patients with Fontan palliation of complex congenital heart disease. Am J Cardiol. 2003;91:1031–2. A9
38. Giardini A, Balducci A, Specchia S, Gargiulo G, Bonvicini M, Picchio FM. Effect of sildenafil on haemodynamic response to exercise and exercise capacity in Fontan patients. Eur Heart J. 2008;29:1681–7.
39. Van De Bruaene A, La Gerche A, Claessen G, De Meester P, Devroe S, Gillijns H, Bogaert J, Claus P, Heidbuchel H, Gewillig M, Budts W. Sildenafil improves exercise hemodynamics in Fontan patients. Circ Cardiovasc Imaging. 2014;7:265–73.
40. Goldberg DJ, French B, Szwast AL, McBride MG, Marino BS, Mirarchi N, Hanna BD, Wernovsky G, Paridon SM, Rychik J. Impact of sildenafil on echocardiographic indices of myocardial performance after the Fontan operation. Pediatr Cardiol. 2012;33:689–96.
41. Shabanian R, Shahbaznejad L, Razaghian A, Kiani A, Rahimzadeh M, Seifirad S, Kocharian A, Gilani JS, Navabi MA. Sildenafil and ventriculo-arterial coupling in Fontan-palliated patients: a noninvasive echocardiographic assessment. Pediatr Cardiol. 2013;34:129–34.
42. Ovaert C, Thijs D, Dewolf D, Ottenkamp J, Dessy H, Moons P, Gewillig M, Mertens L. The effect of bosentan in patients with a failing Fontan circulation. Cardiol Young. 2009;19:331–9.
43. Schuuring MJ, Vis JC, van Dijk AP, van Melle JP, Vliegen HW, Pieper PG, Sieswerda GT, de Bruin-Bon RH, Mulder BJ, Bouma BJ. Impact of bosentan on exercise capacity in adults after the Fontan procedure: a randomized controlled trial. Eur J Heart Fail. 2013;15:690–8.

44. Anderson PA, Breitbart RE, McCrindle BW, Sleeper LA, Atz AM, Hsu DT, Lu M, Margossian R, Williams RV. The Fontan patient: inconsistencies in medication therapy across seven pediatric heart network centers. Pediatr Cardiol. 2010;31:1219–28.
45. 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, Investigators PHN. Enalapril in infants with single ventricle: results of a multicenter randomized trial. Circulation. 2010;122:333–40.
46. Vonder Muhll I, Liu P, Webb G. Applying standard therapies to new targets: the use of ACE inhibitors and B-blockers for heart failure in adults with congenital heart disease. Int J Cardiol. 2004;97(Suppl 1):25–33.
47. Kouatli AA, Garcia JA, Zellers TM, Weinstein EM, Mahony L. Enalapril does not enhance exercise capacity in patients after Fontan procedure. Circulation. 1997;96:1507–12.
48. Ishibashi N, Park IS, Waragai T, Yoshikawa T, Murakami Y, Mori K, Mimori S, Ando M, Takahashi Y, Doi S, Mizutani S, Nakanishi T. Effect of carvedilol on heart failure in patients with a functionally univentricular heart. Circ J. 2011;75:1394–9.
49. Lee KJ, Yoo SJ, Holtby H, Grant B, Mroczek D, Wong D, Grosse-Wortmann L, Benson LN, Chaturvedi RR. Acute effects of the ACE inhibitor enalaprilat on the pulmonary, cerebral and systemic blood flow and resistance after the bidirectional cavopulmonary connection. Heart. 2011;97:1343–8.
50. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, McDonagh T, Parkhomenko A, Tavazzi L, Levesque V, Mori C, Roubert B, Filippatos G, Ruschitzka F, Anker SD, Investigators C-H. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. Eur Heart J. 2015;36:657–68.
51. Van De Bruaene A, Delcroix M, Pasquet A, De Backer J, De Pauw M, Naeije R, Vachiéry JL, Paelinck B, Morissens M, Budts W. Iron deficiency is associated with adverse outcome in Eisenmenger patients. Eur Heart J. 2011;32:2790–9.
52. Mascitelli L, Pezzetta F, Goldstein MR. Reduced body iron stores and atherosclerosis in patients with cyanotic congenital heart disease. Int J Cardiol. 2011;146:117.
53. Tay EL, Peset A, Papaphylactou M, Inuzuka R, Alonso-Gonzalez R, Giannakoulas G, Tzifa A, Goletto S, Broberg C, Dimopoulos K, Gatzoulis MA. 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. 2011;151:307–12.
54. Shaddy RE, Boucek MM, Hsu DT, Boucek RJ, Canter CE, Mahony L, Ross RD, Pahl E, Blume ED, Dodd DA, Rosenthal DN, Burr J, LaSalle B, Holubkov R, Lukas MA, Tani LY, Group PCS. Carvedilol for children and adolescents with heart failure: a randomized controlled trial. JAMA. 2007;298:1171–9.
55. Bouallal R, Godart F, Francart C, Richard A, Foucher-Hossein C, Lions C. Interest of β-blockers in patients with right ventricular systemic dysfunction. Cardiol Young. 2010;20:615–9.
56. Khairy P, Harris L, Landzberg MJ, Fernandes SM, Barlow A, Mercier LA, Viswanathan S, Chetaille P, Gordon E, Dore A, Cecchin F. Sudden death and defibrillators in transposition of the great arteries with intra-atrial baffles: a multicenter study. Circ Arrhythm Electrophysiol. 2008;1:250–7.

Arrhythmia and Devices

12

Ilaria Cazzoli and Sabine Ernst

12.1 Introduction

Arrhythmia and heart failure (HF) are the most frequent complications throughout the long-term follow-up of ACHD patients. They often coexist [1] and represent the commonest causes of morbidity and mortality in this population [2, 3]. Whilst after surgical interventions patients often experience relatively uneventful childhood courses, arrhythmias emerge in adulthood with a burden which increases significantly with age.

The relationship between arrhythmias and HF in CHD is complex without a clear separation of cause and effect. Many CHD conditions have associated conduction system abnormalities or are predisposed to arrhythmias because of haemodynamic factors both before and after surgical palliation or repair, with artificial material, incision lines and scars creating a unique arrhythmogenic substrate for each individual patient [4]. Progressive pump failure and arrhythmias are the main cause of death in the ACHD cohort with HF. Over half of patients admitted with HF will also have arrhythmias, whose management is a crucial component of treatment [5, 6].

Non-surgical therapeutic options available to treat arrhythmias in CHD patients include medical therapy, ablative therapy and device therapy, either alone or in combination. Treating arrhythmias in ACHD patients with HF may result in improving

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both the prognosis and the New York Heart Association (NYHA) functional class but presents many challenges to the electrophysiology (EP) specialist. A thorough understanding of the patient's anatomy and haemodynamics (native and after surgery) is essential as is a highly specialized multidisciplinary team and a sophisticated invasive and noninvasive multimodality approach when planning and performing the EP procedures [7].

This chapter will review the specific considerations for atrial and ventricular arrhythmias in patients presenting with HF in the context of ACHD.

12.2 Pathophysiology

The full spectrum of brady- and tachyarrhythmias is encountered in the CHD population. Factors that precipitate rhythm abnormalities can be roughly divided into those that are present at birth and those that evolve over time [8]. Intrinsic myocardial structural and functional abnormalities (e.g. accessory pathways) can lead to arrhythmias and HF even after the removal of the original anatomic substrate. Increased cardiac mass, chamber distension, hypertrophy and fibrosis all have a primary role [9, 10].

Arrhythmogenesis involves a close interplay between CHD and HF, with many reasons predisposing CHD patients to arrhythmias and causing or worsening HF by impairing the cardiorespiratory function. This is mediated through reduced filling times, systolic and diastolic dysfunction and elevated filling pressures, among others. Incessant or recurrent tachyarrhythmias can precipitate HF as well as sinus node dysfunction, rhythm irregularities and loss of the atrioventricular (AV) synchrony especially in the presence of abnormal pressure and volume loads [11]. This is particularly accentuated in CHD patients with fragile physiologies, such as those with cyanosis, systemic right ventricles or univentricular hearts [12, 13]. On the other hand, HF results over time in structural and electrical remodelling changes that might trigger susceptibility to arrhythmias through the dysregulation of a variety of membrane transport processes and ion channels function.

Accessory AV connections may play an important role in the onset of arrhythmias and HF, particularly in complex CHD such as Ebstein's anomaly. In fact, in about a third of these patients, AV re-entrant tachycardia and multiple accessory pathways can be present [14]. An Ebsteinoid malformation of the tricuspid valve can be commonly observed in congenitally corrected transposition of the great arteries (ccTGA). However, these can also be observed in several other conditions with an abnormal AV junction (heterotaxy syndromes, AV septal defects, univentricular hearts) or apparently without any discontinuation of the AV grove (ventricular septal defects, secundum atrial septal defects, left-sided obstructive lesions and tetralogy of Fallot—TOF) [15]. A type of accessory AV connection unique to the CHD population is the Mönckeberg sling consisting of two distinct AV nodes each with a discrete His bundle and a connecting fibre between these two systems [1, 16, 17]. It results in an anatomic substrate for re-entrant tachycardias, which

can reduce cardiac output and worsen a pre-existing HF or provoke sudden death in patients with compromised circulations.

12.3 Atrial Arrhythmia

Supraventricular (SV) arrhythmias occur in about 15% of unselected ACHD patients. The frequency is highest after Fontan palliation and after atrial switch operation, followed by ASD closure and repaired TOF [18]. Their prevalence increases with age, and >50% of adult patients with complex CHD develop atrial arrhythmias by the age of 65 years [19]. Arrhythmia mechanisms vary according to the underlying anatomic defect and technique of surgical repair; however SV arrhythmias are associated with a nearly 50% increase in mortality and a double risk of stroke and congestive HF if compared with the general population. Furthermore, they represent the leading cause of emergency admissions [20, 21].

The most common SV arrhythmia mechanism in ACHD patients involves a macroreentrant circuit within the atria, defined as intra- or interatrial re-entrant tachycardia (IART) [12] around surgical scars or patches (i.e. at the bypass cannulation site or atriotomies) in combination with natural anatomical barriers (crista terminalis, valve orifices and the superior and inferior caval orifices) [22]. The term IART is commonly used to distinguish this SV tachycardia (SVT) from the typical variety of cavo-tricuspid isthmus (CTI) atrial flutter that occurs in structurally normal hearts (Fig. 12.1). Multiple IART pathways can coexist, with varying circuits that are partly depending on the anatomic defect and type of surgical repair [23].

IART usually has a slower atrial rate (150–250 bpm), which may favour 1:1 conduction that can lead to haemodynamic instability and hypotension or cardiac arrest in patients with ACHD and HF [24]. The majority of IART circuits are located within the right atrium (RA), but left-sided circuits occur in patients who have undergone left-sided interventions. Predisposing conditions include Mustard or Senning baffles for d-TGA (~30%) [25, 26], atrial or AV septal defects [27], tetralogy of Fallot (up to one third) [28] and Fontan patients mainly with atrio-pulmonary connections (up to 50–60%) or lateral tunnels (20–30%) [29–31]. Other risk factors for IART include concomitant sinus node dysfunction (tachy-brady syndrome) and older age at the time of heart surgery.

Although less frequent, non-automatic focal atrial tachycardias (FATs) do occur, accounting for ~10–15% of all atrial tachycardias (ATs). They are characterized by electrical activation originating from a small circumscribed region from which it expand centrifugally, with no wavefront circulation around a fixed or functional obstacle and a widely varying cycle length. In ACHD patients the majority of FAT foci are within the right atrium, and differentiation between FAT and IART can be difficult if relying only on the 12-lead electrocardiogram (ECG).

Atrial fibrillation (AF) is frequently associated with ventricular dysfunction and decompensated HF, and its prevalence among ACHD patients is significantly higher than in the general adult population with also an earlier age of onset. The incidence of AF increases with age and CHD complexity, especially in those cases

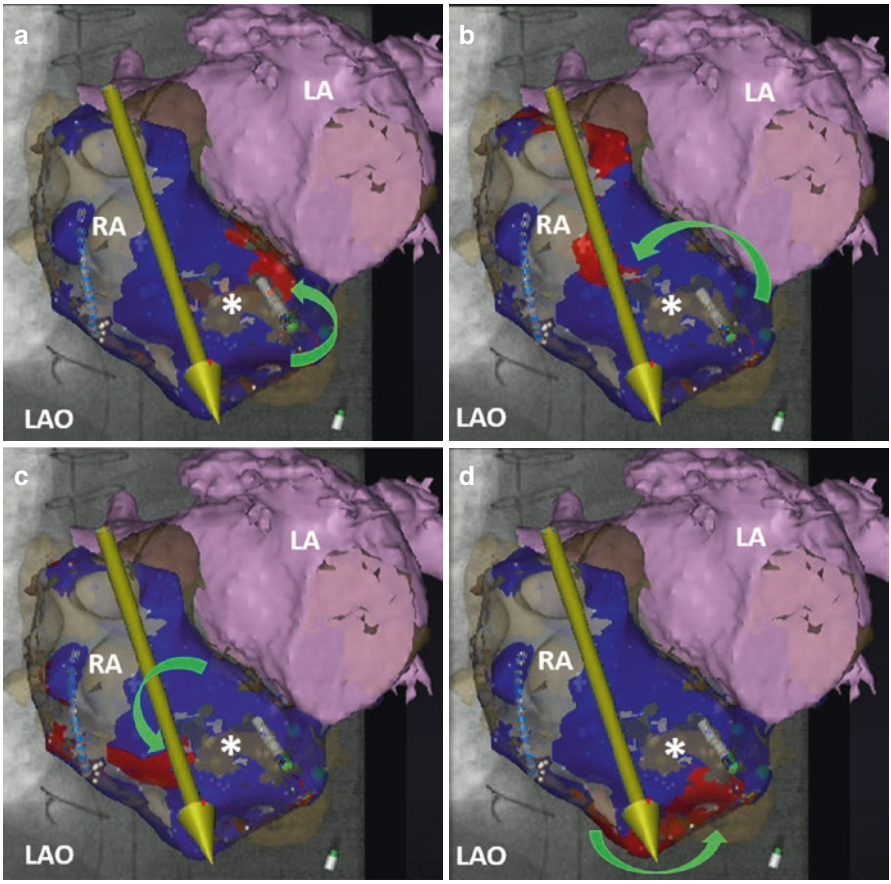

Fig. 12.1 (**a**–**d**) Typical electroanatomical map of an IART with counterclockwise activation (green arrow) around scar tissue (asterisk) in propagation mode (red wavefront on blue 3D reconstruction) merged with a fluoroscopic acquisition (Odyssey, Stereotaxis Inc.) in left anterior oblique projection (LAO). *LA* left atrium, *RA* right atrium. Yellow vector depicts the direction of the magnetic field

of marked left atrial dilatation such as atrial septal defects, left-sided valve disease and dysfunction of the systemic ventricle [32]. In TOF patients it surpasses the incidence of IARTs over the age of 55 years [33]. In ACHD patients referred for Fontan conversion, it stands for nearly half of cases, although the real incidence remains unknown commonly due to patients' scarcity of symptoms until the occurrence of HF. However, we believe that especially patients with previous atrial tachycardia (both IART and FAT) should undergo vigorous regular rhythm surveillance with ambulatory monitoring. Additionally, ACHD patients with AF frequently have a previous history of IART. In the acquired heart disease adult population, AF may be related to atrial size, atrial myocardial fibrosis from pressure/volume loading and scarring related to surgery and alterations in tissue

refractoriness and/or automaticity [34]. As a consequence of the setting of a rapid ventricular response, haemodynamic instability can occur in patients with HF.

As IART may be amenable to catheter ablation, referral for EP assessment should be considered rather earlier than after deterioration into AF, which at present has lower chance of successful ablation therapy.

Regardless whether atrial arrhythmia or HF is primarily responsible for clinical decompensation, treatment of both conditions is critical. Optimization of fluid status and ventricular function is necessary for antiarrhythmic therapy to be effective. Conversely, elimination of atrial arrhythmias contributes to reverse the haemodynamic and clinical manifestations of HF in ACHD patients. Nevertheless, their treatment remains challenging, and clinical experience shows that pharmacological treatment is of limited efficacy and may be poorly tolerated. Although a recent retrospective study showed that direct current cardioversion (DCCV) applied to terminate rapid SV tachycardias has similar outcomes within the CHD and non-CHD population in terms of arrhythmia termination and recurrences (except for patients with Fontan palliation) [35], percutaneous catheter ablation holds great premise with regard to definitive and potentially curative treatment.

12.4 General Considerations for Trans-catheter Ablation of SV Tachycardia

Adult CHD patients may present a complex and variable anatomy within the same group of cardiac anomaly. In some of these subgroups, venous access will be limited. The success of a trans-catheter ablation relies on many factors, such as a thorough understanding of the underlying anatomy and likely arrhythmogenic mechanism, the surgical history as well as the availability of an electrophysiologist specifically trained in ACHD EP and an experienced multidisciplinary team (e.g. nurses, anaesthetist, cardiac surgeon). The optimal team increases the procedural success rate and helps identify any insurmountable obstacles that may lead to a suboptimal outcome.

Meticulous planning of procedures is essential. Over the years, the development and progressive improvement of 2D and 3D imaging modalities such as echocardiography, computed tomography (CT) or cardiac magnetic resonance (CMR) applied to the reconstruction of the individual anatomy have provided important assistance in the EP laboratory (Fig. 12.2). They have been demonstrated to be essential for planning of optimal access routes (e.g. retrograde through a hemiazygos continuation or through a known baffle leak) [36, 37] and clarifying anatomical variations as well as choosing the most appropriate tool (e.g. large curves, long guiding sheaths or remote magnetic navigation). The late gadolinium enhancement CMR may show regions of scar and fibrosis [38], likely origin of low voltage potentials and possibly sites of previous ablations [39].

Intra-procedural imaging by intracardiac or trans-oesophageal echocardiography may facilitate mapping and identification of relevant cardiac structures or artificial

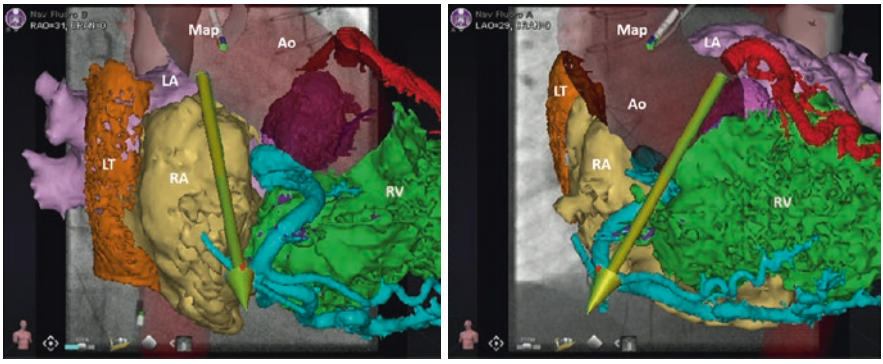

Fig. 12.2 Ablation of an atrial tachycardia in a patient with functional univentricular heart who underwent lateral tunnel (*LT*) total cavo-pulmonary connection (TCPC) with surgical patch closure of the tricuspid valve. Access to the right atrium (*RA*, target chamber) is performed retrogradely via the aorta using remote magnetic navigation (Stereotaxis). The mapping catheter (*Map*) is guided remotely by directing the magnetic vector on the display (yellow/green arrow). The patient's unique anatomy is precisely depicted by 3D image reconstruction (in this particular case from contrast CT scan) and superimposed on the fluoroscopy images in right anterior oblique (RAO 30°, left panel) and LAO (30°, right panel). Simultaneous visualization of the coronary arteries (left coronary artery *in red* and right coronary artery *in blue*) permits a safer approach during radiofrequency ablation. *Ao* aorta, *LA* left atrium, *RV* right ventricle

obstacles (e.g. prosthetic valves) and may be used for safe guidance of trans-patch and trans-baffle puncture [40, 41].

3D electroanatomical mapping (EAM) to facilitate ablation procedures has been successfully used in ACHD patients [42–45] and is by now a standard in their care. Activation mapping, either with non-contact techniques, can be performed to identify the focal source and the sequence of activation (mainly but not solely in presence of a stable cycle AT). Moreover, further features have been developed and now integrate in EAM systems, such as contact force sensing and high-density mapping using multiple electrode catheters (differentiating between a target site for ablation and a scar), with the result of significantly reducing the total fluoroscopy exposure [46].

Nonetheless, when an arrhythmia presents as infrequent, irregular or unstable, which is not rare in ACHD patients, it becomes "non-mappable" using a sequential approach such as CARTO or RHYTHMIA (the most used mapping systems), since the activation pattern constantly changes. To overcome these "obstacles", a noninvasive multi-electrode ECG mapping system (such as ECVUE; CardioInsight Technologies Inc., OH, USA) was introduced, which combines the 3D reconstruction of the cardiac anatomy from computed tomography scans with the simultaneous recording of the cardiac activation from 252 surface ECG electrograms. This not only allows mapping of multiple arrhythmias in a limited frame time, with consequent reduced radiation exposure, but also is particularly suitable for ACHD patients who may have multiple pathways or arrhythmias that are poorly tolerated during an EP procedure. Encouraging preliminary results have been obtained when used together with magnetic navigation technologies [7].

12.4.1 Considerations for Ablation Lesion Formation

Other issues to consider when performing ablation are the shear thickness of a volume-overloaded and scarred myocardium, together with the altered haemodynamic conditions (e.g. increased/reduced blood flow) and subsequent contact force, which may affect the procedural success even when the arrhythmic circuit is well identified and addressed. The recent introduction of "irrigated" and larger tip catheters and contact force monitoring has allowed an increased lesion depth and width, contributing to some improvements in outcome, although not completely free of intra-procedural problems [47].

12.4.2 Remote Magnetic Navigation

Robotic techniques for ablation such as remote-controlled magnetic navigation are a field of major interest in CHD [48]. It permits not only the dramatic reduction in exposure time even to (close to) zero fluoroscopy but can particularly overcome navigation difficulties in CHD patients providing improved stability and manoeuvrability to the catheter. This reduces the need for trans-baffle or transhepatic access in all patients, besides those with metallic valves which would "block" a retrograde approach [43, 49]. In addition, it allows superimposition of pre-acquired 3D images and depiction of the ablation catheter in real time on the displays [37] (Fig. 12.3).

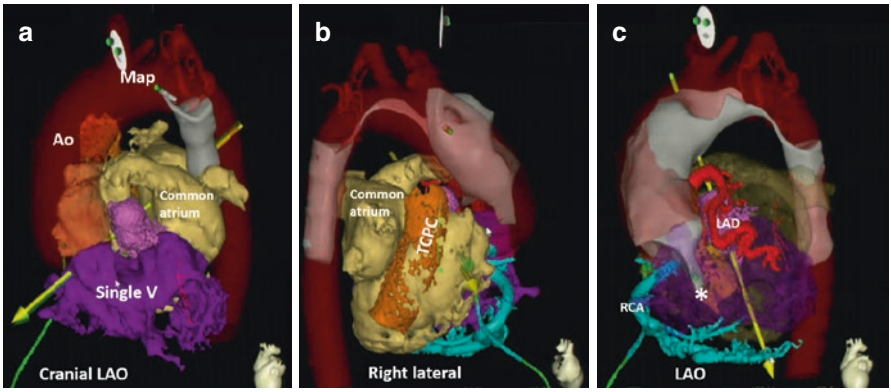

Fig. 12.3 Real-time visualization of the mapping catheter (Map) during retrograde approach using remote magnetic navigation. Fast anatomical mapping (FAM, *in grey in the picture*) of the aorta allows merging and superimposition of 3D pre-acquired (from CT or MR scan) reconstructions with the contact map in a stepwise fashion in order to guide the operator during the procedure. Please note the distance of the FAM to the aorta (Ao) descending in **a**, which is adapted in **b** and **c** to fit the full aortic arch. The *yellow arrow* depicts the direction of the magnetic field that the magnetic Map catheter will align parallel to, thereby allowing remote navigation of the catheter tip. The forward and backward motion is a mechanical motion via the CardioDrive (Stereotaxis Inc.). Note that the catheter has just passed the open aortic valve in panel **c** (asterisk)

12.4.3 Trans-catheter Ablation

Among the atrial arrhythmias (IART, focal tachycardia and AF), IART represents the major indication for arrhythmia ablation in CHD. This may be first-line management [50] or indicated in case of failure of drug therapy or in haemodynamically instable patients. Thanks to the combination of integrated 3D mapping and enhanced lesion creation, data about AT ablation, mainly represented by IART ablation outcomes, have improved over the years. The acute success rate for IART ablation rose from ~60% more than a decade ago to 80–85% nowadays [40, 42, 43, 51–54]. Outcomes among different groups are difficult to compare, being dependent on the patient population (complexity of underlying CHD and therefore arrhythmic circuit/circuits), experience of both centres and operators and definition of "procedural success" on the basis of solely intra-procedural termination or complete non-inducibility of the arrhythmia at the end of the procedure. Besides acute termination, the real challenge especially in HF patients is prevention of recurrences. The AT recurrence rates after radiofrequency ablation are quite high, rising to 20–45% in the short-term follow-up.

Atrial arrhythmias are prevalent in about 60% of patients with an AP Fontan. IART accounts for approximately 75% of SVTs and FATs for about 15%. In patients with Fontan palliation, recurrence rates can reach 85% despite the achievement of a complete ablation success, with a mean rate of 50% within 4–5 years [54]. In these cases the activation mechanism may differ from the previous ablated arrhythmia when using conventional manual RF ablation techniques. Additionally, in patients with Fontan circulation multiple IART circuits can be encountered at various sites due to progressive RA enlargement, requiring often more than an ablation procedure with access to the RA through a pre-existing fenestration, trans-baffle puncture or by retrograde access [49]. Circuits could also, but rarely, be localized in the lower atrial aspect with a pericaval re-entry.

Atrial fibrillation may develop as well over the time in Fontan patients with the progression of pump failure, which is usually poorly tolerated. In case of ineffective conservative management with antiarrhythmic drugs or cardioversion, ablation of AF needs to be considered, either trans-catheter or surgical using the Cox-type maze procedure, before and after surgical Fontan conversion to total cavo-pulmonary connection (TCPC) in those cases where this is appropriate [55]. Despite the high rate of AT recurrence in this cohort, arrhythmia burden and quality of life can be substantially improved [44]. Trans-catheter ablation of AT usually leads to an improvement of ventricular function, symptoms and therefore NYHA functional class [56].

Another group of CHD patients predisposed to multiple arrhythmic circuits and premature development of HF are those with systemic RV, for example, transposition of the great arteries (TGA), post atrial switch (Senning or Mustard operation) or ccTGA. During their life span, about 10% will experience atrial arrhythmias (mainly CTI-dependent flutter and IART) along with deterioration of the systemic ventricular function and systemic atrioventricular valve regurgitation [57, 58]. Success rate of ablation is lower in this population, due to the

typical presence of multiple circuits and accessory pathways. Most circuits are located in the pulmonary venous atrium. Importantly, in more than 80% of patients, the CTI cannot be achieved via a systemic route but requires either a retrograde trans-aortic access, a trans-baffle puncture or access through a baffle leak [37]. The approach is challenging even for experienced electrophysiology physicians and requires the use of the newest available technologies, such as magnetic navigation in combination with 3D electroanatomical mapping (as seen in Figs. 12.2 and 12.3). Still, despite a high acute success rate, the recurrence rate for IART is about 30%, however with excellent long-term results after a second ablation [59].

12.5 Ventricular Arrhythmia in ACHD

Ventricular arrhythmias, such as ventricular tachycardia (VT) or fibrillation, are not uncommon in the CHD population, representing the leading cause of sudden cardiac death (SCD). The subtypes of CHD at greatest risk of SCD include those conditions with a systemic morphologic RV, TOF, left-sided obstructive lesions and Eisenmenger syndrome [60]. In Fontan patients VTs have been described, however with a lower incidence than SV arrhythmias. In a multicentre case-control study by Koyak et al., clinical variables associated with SCD were SVT, moderate to severe systemic ventricular dysfunction, moderate to severe subpulmonary ventricular dysfunction, increased QRS duration and QT dispersion [61], regardless of the complexity of the underlying CHD. Patients at highest risk for VT are those who have undergone a ventriculotomy or a patching of a ventricular septal defect (VSD) in which a macroreentrant circuit develops close to the site of surgical scar, as for TOF repair [62]. Alternatively, VT can present in the context of long-standing haemodynamic ventricular myocardial stress, as in patients with dilated or hypertrophic cardiomyopathy and advanced dysfunction (e.g. chronic aortic valve disease or failing systemic RV after Mustard or Senning operation).

Not surprisingly, the prevalence of VTs in the ACHD-HF subgroup is therefore increased than in the whole CHD population, as myocardial scarring and wall stretching secondary to chronic volume and pressure loads, previous cardiac surgery and intrinsic myocardial disease determine the substrate and expose to triggers for VTs. The progress of HF is reflected by structural and functional remodelling and results in hypertrophy, ischemia and heterogeneous fibrosis. The underlying cellular alteration is expressed by depolarization abnormalities and repolarization dispersion leading to increased ventricular arrhythmia vulnerability [63]. As for ACHD patients presenting with atrial arrhythmias, a thorough clinical assessment and a careful ambulatory follow-up are therefore indicated, inclusive of imaging studies and functional investigations in order to assess patients' anatomy and haemodynamics, along with any change in functional capacity over the time. Interventions to correct the underlying problem can be performed when appropriate, although even after "corrective" surgery or interventional procedures, the late onset of ventricular arrhythmias may be unpredictable.

Most of data available concerning VT in ACHD involve patients with repaired TOF, where the incidence of VT in surgically repaired patients is 11.9% [64], whereas the prevalence ranges between 3% and 14% in several large series, with a risk of SCD estimated at 2% for a decade of follow-up [65]. Within the TOF cohort, the onset of VT has been related to right atrial area increase and right ventricular outflow tract length [66]. Tetralogy of Fallot patients are as well the only CHD population for which programmed ventricular stimulation has demonstrated to provide diagnostic and prognostic value in risk stratifying with regard to SCD [67].

The progressive effects of volume overload, cyanosis, low voltage areas in the atrialized RV and HF play a primary role in initiating VT in patients with Ebstein's anomaly, together with fast reciprocating conduction through the multiple accessory AV pathways commonly observed in these patients. Furthermore, Anderson and Lie described long ago aneurysms of the true RV resembling arrhythmogenic right ventricular cardiomyopathy [68].

The typical mechanism for VT in CHD is sustained by a macroreentry, involving narrow conduction corridors (isthmuses) defined by area of surgical scars and natural conduction barriers (e.g. the edge of a valve annulus) [69], although other causes cannot be excluded. Antiarrhythmic drugs are not generally considered first-line therapy for ventricular arrhythmias in ACHD with HF, although they can decrease the recurrence of events. Trans-catheter ablation is proven to be feasible with good initial results, although the experience is still limited and this therapeutic option needs often to be considered as complementary to the implantation of a defibrillator device (implantable cardioverter defibrillator, ICD), as recommended by 2013 guidelines [70]. Complexity of the anatomy, myocardial hypertrophy, broad isthmuses, haemodynamic instability or non-inducibility of the ventricular arrhythmia may account for ablation failure in 50% of cases and for a 40% recurrence rate [71, 72]. Several mapping strategies have been described, including activation sequential contact analysis, entrainment manoeuvres, pace mapping and 3D registration also with magnetic navigation and simultaneous non-contact mapping. In 2007, Zeppenfield et al. described the use of mapping in identifying four main isthmuses of low voltage responsible for re-entrant VTs in TOF patients, either whilst in sinus rhythm or haemodynamically unstable [69]. In doing so they demonstrated how areas of slow conduction, as those observed in remodelled ventricles presenting with fibrosis and hypertrophy, may provide the link between impaired haemodynamics and VT onset and explain the low rate of catheter ablation success on the basis of a lack of transmurality from endocardial approach, addressed now by the introduction of new cool-tip ablation catheters (Fig. 12.4). Although VTs are represented occasionally by focal arrhythmias, multiple foci could be encountered in a single patient, thereby complicating an ablation approach. Since in majority of cases these VTs are fast and haemodynamically poorly tolerated, a useful tool could be an approach using a simultaneous mapping system such as the ECVUE, as already discussed for SVT ablation [7].

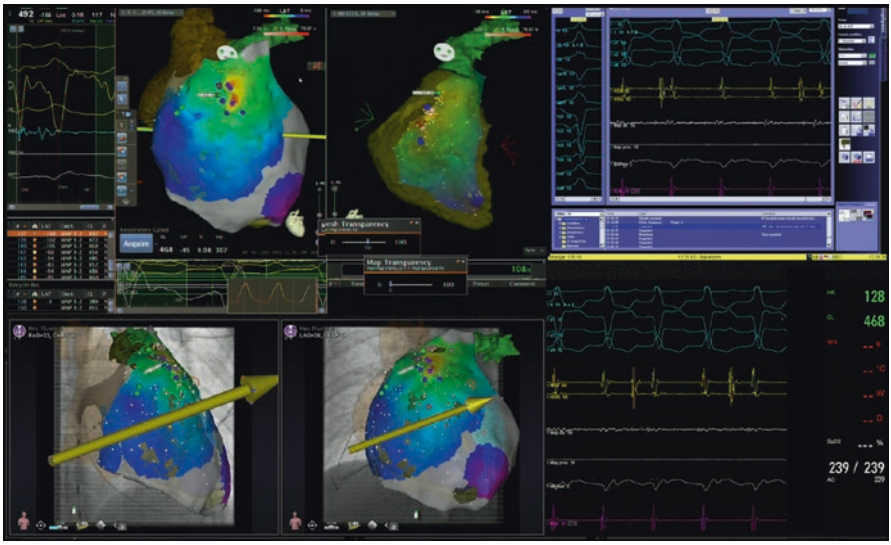

Fig. 12.4 Ablation of VT in a patient with TOF. Catheter FAM allows concomitant collection of a local activation time map (see colour-coded map on the 3D image, left panels). Surface electrocardiograms and endocardial signals (right panels) are simultaneously showed on the screen and registered. Detection of mid-diastolic potentials during ongoing tachycardia or late potentials during SR and best paced match are techniques that allow identification of the site of origin of a given ventricular arrhythmia and subsequent successful ablation

12.6 Devices for CHF in ACHD

12.6.1 General Considerations for Device Therapy

Tachyarrhythmias are not the only rhythm abnormalities that may be observed in CHD patients. Structurally abnormal hearts may be predisposed to bradycardia consequent to absence, displacement or dysfunction of sinus or AV nodes (at birth like in left atrial isomerism or evolving with age). Sometimes it is associated with AV block, as seen in ccTGA, AV septal defects and some types of univentricular hearts. Bradycardia itself, with or without AV or inter-ventricular dyssynchrony, can determine a reduction of cardiac output resulting in HF, especially in patients with fragile physiologies. Additionally, surgical interventions may cause heart block in 1–3% of cases [73] and damage to the sinus node secondary to perfusion interruptions secondary to cannulation for cardiopulmonary bypass or creation of baffles (e.g. Mustard and Senning procedure), Glenn shunts, Fontan palliation and sinus venosus atrial septal defect repairs. Due to the increased expectancy of life, some CHD patients will require permanent pacemakers (PPMs), ICDs or cardiac resynchronization therapy (CRT) with or without defibrillation function, with the likely need of multiple re-interventions and follow-up over a lifetime. A pacemaker

is recommended for isolated sinus node dysfunction in adults with CHD if there are clinical symptoms related to bradycardia or loss of AV synchrony, exercise intolerance secondary to chronotropic incompetence or bradyarrhythmia-related adverse haemodynamic effects documented by noninvasive or invasive testing [50]. The relation between abnormal conduction and HF gives explanation to the onset of tachyarrhythmias in the context of ventricular bradycardia, so that the device therapy in ACHD patient with HF should not be considered as the only option. A multimodality approach is hence recommended, combining drugs, device implantation and trans-catheter or surgical ablation.

12.6.2 Lead Placement

The primary consideration regarding device therapy relates to lead placement, which must take into account abnormal anatomy, limited venous access and the risk of thromboembolic complications. Trans-venous access in CHD is often difficult or even impossible especially after surgical repair (Fig. 12.5). A clear example is provided by patients after Fontan operation, where the lack of access goes with the risk of thrombus formation on the atrial lead (e.g. in the presence of residual intracardiac shunts) which is only partly ameliorated by anticoagulation therapy. Despite the possibility of atrial lead placement, access to the ventricle, if advancing a pacing lead into a ventricular branch of the coronary sinus is not feasible, may be impossible (e.g. in most Fontan and TCPC circulations) [74]. In these cases a hybrid approach or a total epicardial system placement (requiring surgical assistance) can be performed with good long-term outcomes observed for modern steroid-eluting bipolar epicardial leads [75]. Mustard and Senning patients might also present a challenge. The venous route to the atrium and the ventricle may be hindered by

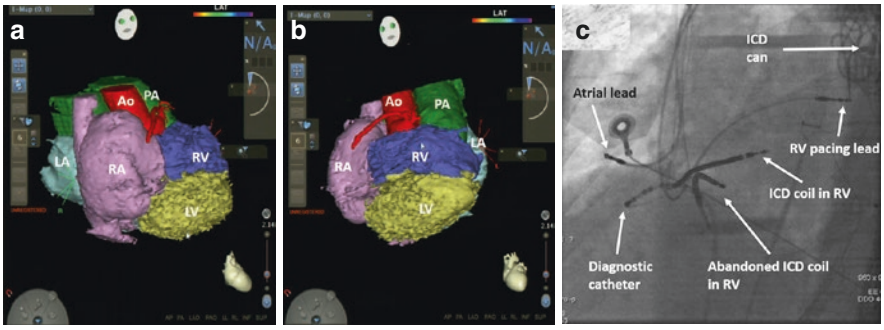

Fig. 12.5 Ablation in a patient with "hamburger" or "criss-cross" heart (the two ventricles are rotated and horizontally oriented with the right on top of the left ventricle, panel **a** and **b**). The fluoroscopic acquisition (anteroposterior projection, panel **c**) shows the presence of a device with multiple trans-venous pacing and defibrillator leads through the right superior vena cava, which may represent an adjunctive "obstacle" to the EP procedure and may risk to be dislocated or damaged. *LA* left atrium, *RA* right atrium, *LV* left ventricle, *RV* right ventricle, *Ao* aorta, *PA* pulmonary artery

baffle obstructions, stenosis and leaks, which may necessitate closure with transcutaneous closure devices or stenting before the implantation. If such a leak or other intracardiac shunts cannot be closed, epicardial lead implantation should be considered to limit the risk of thromboembolic complications. Alternatively, the patient needs to be anticoagulated permanently accepting an increased risk of embolism and stroke. Lead fixation can be problematic, since it requires the physician to accurately understand the patient's anatomy and surgical history in order to avoid areas of patches, scars and sites too close to the phrenic nerve.

12.6.3 Pacing Devices

The most recent recommendations for pacing in CHD patients are summarized in a consensus paper [50]. However, guidelines are always somewhat limited, since there is limited data available from retrospective and non-randomized studies, often extrapolated from children populations, with furthermore heterogeneity within the group of CHD patients. Reasons for pacing can be congenital complete heart block, as well as congenital sinoatrial or AV nodal dysfunction; however more often the cause is iatrogenic following palliative or corrective surgery. The risk of onset of atrial tachyarrhythmias deteriorating the haemodynamics in HF patients may require, apart from considering catheter ablation prior to implantation, the additional need of anti-tachycardia pacemaker therapies (ATP) when programming the device. This is a quite successful tool in patients with a single circuit of relatively slow IART. However, slow IARTs also have a good chance of successful catheter ablation, such that ablation should at least be considered as ATP also carries the risk of AF induction by burst pacing.

12.6.4 Considerations for Choice of Permanent Device Implantation

The choice between implanting a trans-venous or an epicardial system relies on patient's specific characteristics, such as complexity of the underlying CHD condition, body size and necessity of surgical interventions, which may justify contextual epicardial lead positioning, with lower incidence of complications as those related to thromboembolic events or trans-venous lead extraction. On the other hand, lead failure rates and increased pacing thresholds need to be taken into account, as they may reduce system longevity and expose patients to multiple re-interventions over the time. A retrospective study of 287 CHD patients conducted by Silvetti et al. showed a significant survival benefit at 10-year follow-up when trans-venous leads were implanted [76]. As with endocardial lead positioning, pacing site selection for epicardial leads is important and related to long-term outcome. So far, the only data concerning this are provided by a non-randomized retrospective trial performed by Janousek et al. in children with structurally normal heart, which demonstrated benefit to placement of an epicardial ventricular lead in the left ventricle apex or mid-lateral wall [77].

12.6.5 Implantable Cardioverter Defibrillators

Nowadays there is quite a robust literature describing the risk of SCD within the CHD population. SCD of presumed arrhythmic aetiology is the most common cause of mortality in ACHD patients, with a 100-fold increased risk when comparing with age-matched controls [3, 60], often happening in the third or fourth decade of life [78]. The resulting indications for ICD implantation are to be considered in class I level of evidence B after a cardiac arrest or sustained spontaneous VT (secondary prevention), where no reversible cause is identified [50].

The most common CHD diagnosis among defibrillators recipients is TOF, followed by d-TGA and aortic stenosis. With regard to primary prevention in complex CHD, evidence is limited, with the most detailed data relating to the TOF population. Over the past decade, the greatest progress in risk stratification for primary prevention has identified in this cohort several risk factors including QRS ≥180 ms, the rate of change of QRS duration, older age at repair and presence of outflow tract patch [64]. Considering instead shock therapy, a raised left ventricular end diastolic pressure, pulmonary artery pressure and right ventricle systolic pressure are the strongest predictors of appropriate shock therapy [79], together with inducible VT at the electrophysiology study [67]. However, symptomatic non-sustained VTs are the most important prognostic indicator [80].

Outside the TOF population, the indications are less well delineated, as reflected by a lower appropriate shock rate in the overall ACHD population. In TGA patients after Mustard or Senning procedure, suggested factors associated with SCD include severe systemic ventricle dysfunction and history of atrial tachyarrhythmias [24, 81]. Moreover, inducible VT or VF at the EP study does not seem to predict clinical events. For patients with univentricular heart and a Fontan palliation, no recommendation for ICD implantation exists. Theoretically, conventional non-CHD indication could be applicable in ACHD with biventricular circulation [50], but cut-off values defining systemic RV dysfunction may likely be higher than the "universally" accepted 35% as for the left ventricle (LV). The largest multicentre study regarding ICD therapy in CHD is the review of 443 patients performed in 2008 by Berul et al. where a rate of 18% appropriate shocks versus 20% inappropriate shocks (mostly on fast stable cycle atrial arrhythmias or lead failure) was observed [82]. Younger age at implantation and physically active lifestyle were suggested to be associated with a higher rate of inappropriate shock therapy. Additionally, in the younger CHD population, the psychosocial impact of receiving an ICD implanted should not be underestimated [83]. Considerations about technical difficulties at implantation match with those for PPMs, although the larger size of defibrillator coil may represent an adjunctive challenge, especially when considering a route through a stenosed superior vena cava or baffle. ICD implantation in CHD (but no PPM implantation) was seen to be associated with an increased rate of implant-related complications in terms of mechanical complications, repeat procedures and device infections [84].

Interestingly, a multicentre study including an extensive ACHD cohort correlated the risk of SCD with the presence of QRS complex fragmentation at the 12-lead

ECG [85]. However, as a sole risk marker, its prognostic value is too limited to indicate ICD implantation but requires rather combination with other clinical parameters such as impaired systemic ventricular function, HF symptoms and wide QRS complex.

ICD therapy is not recommended in ACHD patients with advanced pulmonary vascular disease (e.g. Eisenmenger syndrome), drug refractory NYHA class IV who are not candidate for heart transplantation (HT), significant psychiatric illness, incessant VT/VF or a life expectancy inferior to 1 year [86].

12.6.6 Resynchronization Therapy

Cardiac resynchronization therapy is a well-established effective treatment for adult patients with left ventricular (LV) failure and can result in improved cardiac function, LV reverse remodelling, decreased rate of hospitalizations for HF, improved quality of life and reduced overall mortality if response is positive [87–89]. Among ACHD patients, issues specific to this unique population result in substantial difficulties in identifying suitable candidates for CRT. Derivation of selection criteria from the trials conducted in the non-CHD population may not be appropriate nor straightforward. For example, in contrast to non-CHD adults with HF and left bundle branch block (LBBB), right ventricular conduction delay and right bundle branch block (RBBB) are the most common situations in ACHD cohorts. Moreover, the systemic ventricle can be the RV, being therefore more prone to early dysfunction and dyssynchrony. In the univentricular heart, "biventricular" pacing is impossible, but multisite pacing (of the same ventricle) may be feasible [90]. Morphologic RV differences in fibre orientation, pumping mechanism and AV valve regurgitation may modulate physiologic and neurohormonal responses to dysfunction, asynchrony and dyssynchrony.

Another important aspect to be taken into account is that the value of the NYHA functional class as a selection criterion for CRT in ACHD-HF patients who have had a lifelong adaptation to CHD. Exercised capacity is commonly depressed in ACHD patients, who also report symptoms of HF less frequently. For this reason objective parameters to assess functional capacity are recommended, such as peak VO2, whose reduction is associated with higher rate of hospitalization and death [91].

Most of the studies available on CRT are retrospective [92–95] or case reports with a very limited follow-up; hence, the impact of CRT on long-term morbidity and mortality in ACHD patient is unknown. Preliminary experiences are, however, promising despite the absence of consensus on techniques to quantify mechanical dyssynchrony.

In general, CRT can be recommended in ACHD patients with NYHA class II–IV symptoms, impaired systemic ventricular ejection function, systemic ventricular dilatation and prolonged QRS duration. Moreover upgrading to CRT should be considered in CHD patients with systemic LV and permanent RV pacing resulting in LV dyssynchrony or dysfunction [96]. Identifying responders and nonresponders is a crucial point. However, results of CRT in failing systemic LV have been observed

more promising than in patients with failing systemic RV. The smaller benefit of CRT in this group may be attributed to suboptimal myocardial fibre arrangement and abnormal ventricular contraction patterns as well as decreased myocardial perfusion reserve, possibly resulting in subendocardial ischemia [6].

The effect of biventricular CRT was analysed by Thambo et al. in adults with TOF and RV dysfunction, showing at 6 months improvement in exercise tolerance, NYHA functional class, LV ejection fraction as well as ventricular synchrony, so that despite the increased level of difficulty at implantation a biventricular system may be suggested when considering CRT, rather than a single site RV pacing [97]. Resynchronization has been shown to be achieved by multisite pacing in the failing single ventricle, with acute post-operative improvement in echocardiographic indices of dyssynchrony, systolic blood pressure and QRS duration [95]. Whichever pacing strategy the EP physician decides to adopt, complexity of the underlying anatomy may represent an important challenge in finding adequate access for effective pacing, requiring in some cases an epicardial approach with the help of the surgical team.

12.7 Heart Transplant in ACHD with HF

According to the 2014 guidelines for HT in ACHD, patients with CHD account for about 3% of adult transplants in the USA and approximately 10% of the indications in patients ranging between 18 and 30 years [98]. Despite the worse short-term outcome in ACHD compared to non-ACHD patients, long-term outcome is improved. Nevertheless, ACHD patients have longer waitlist time and increased waiting list mortality despite younger age and fewer comorbidities.

Patients with chronic Fontan failure are of particular concern, and reduced exercise tolerance below a threshold of about 45% of predicted values predicts hospitalizations and poor outcome [99]. In this situation, aggressive catheter ablation of atrial or ventricular arrhythmias, plus or minus device therapies, may be able to improve functional status, impact on prognosis and stabilize the patient waiting for transplantation.

12.8 Summary

Heart failure and arrhythmias are integrally linked in this population. The treatment of each needs to be proactive and aggressive to prevent further deterioration and optimize outcomes. Catheter ablation of atrial or ventricular arrhythmias is a useful adjuvant therapy in individuals with fragile physiologies and ventricular disease. The presence of an experienced team, along with the use of the newest available techniques such as 3D image integration, advanced EAM (either simultaneous or sequential) and magnetic navigation (if available), contributes to achieve the highest success rate. Implantable devices play a fundamental role in ACHD HF with ICDs being the only effective therapy to prevent sudden death. In all situations if performing an ablation or implanting a device, careful planning with a multidisciplinary team is essential.

References

1. Walsh EP, Cecchin F. Arrhythmias in adult patients with congenital heart disease. Circulation. 2007;115(4):534–45.
2. Zomer AC, Vaartjes I, Uiterwaal CS, van der Velde ET, van den Merkhof LF, Baur LH, et al. Circumstances of death in adult congenital heart disease. Int J Cardiol. 2012;154(2):168–72.
3. Oechslin EN, Harrison DA, Connelly MS, Webb GD, Siu SC. Mode of death in adults with congenital heart disease. Am J Cardiol. 2000;86(10):1111–6.
4. Ho SY, Anderson RH. Conduction tissue in congenital heart surgery. World J Surg. 1985;9(4):550–67.
5. Zomer AC, Vaartjes I, van der Velde ET, de Jong HM, Konings TC, Wagenaar LJ, et al. Heart failure admissions in adults with congenital heart disease: risk factors and prognosis. Int J Cardiol. 2013;168(3):2487–93.
6. Motonaga KS, Khairy P, Dubin AM. Electrophysiologic therapeutics in heart failure in adult congenital heart disease. Heart Fail Clin. 2014;10(1):69–89.
7. Ernst S, Saenen J, Rydman R, Gomez F, Roy K, Mantziari L, et al. Utility of noninvasive arrhythmia mapping in patients with adult congenital heart disease. Cardiac Electrophysiol Clin. 2015;7(1):117–23.
8. Chubb H, Williams SE, Wright M, Rosenthal E, O'Neill M. Tachyarrhythmias and catheter ablation in adult congenital heart disease. Expert Rev Cardiovasc Ther. 2014;12(6):751–70.
9. Garrey WE. The nature of fibrillary contraction of the heart: Its relation to tissue mass and form. Am J Phys. 1914;33:397–414.
10. Ueda A, Adachi I, McCarthy KP, Li W, Ho SY, Uemura H. Substrates of atrial arrhythmias: histological insights from patients with congenital heart disease. Int J Cardiol. 2013;168(3):2481–6.
11. Escudero C, Khairy P, Sanatani S. Electrophysiologic considerations in congenital heart disease and their relationship to heart failure. Can J Cardiol. 2013;29(7):821–9.
12. Walsh EP. Interventional electrophysiology in patients with congenital heart disease. Circulation. 2007;115(25):3224–34.
13. Abadir S, Khairy P. Electrophysiology and adult congenital heart disease: advances and options. Prog Cardiovasc Dis. 2011;53(4):281–92.
14. Hebe J. Ebstein's anomaly in adults. Arrhythmias: diagnosis and therapeutic approach. Thorac Cardiovasc Surg. 2000;48(4):214–9.
15. Bar-Cohen Y, Khairy P, Morwood J, Alexander ME, Cecchin F, Berul CI. Inaccuracy of Wolff-Parkinson-white accessory pathway localization algorithms in children and patients with congenital heart defects. J Cardiovasc Electrophysiol. 2006;17(7):712–6.
16. Epstein MR, Saul JP, Weindling SN, Triedman JK, Walsh EP. Atrioventricular reciprocating tachycardia involving twin atrioventricular nodes in patients with complex congenital heart disease. J Cardiovasc Electrophysiol. 2001;12(6):671–9.
17. Suman-Horduna I, Babu-Narayan SV, Ueda A, Mantziari L, Gujic M, Marchese P, et al. Magnetic navigation in adults with atrial isomerism (heterotaxy syndrome) and supraventricular arrhythmias. Europace. 2013;15(6):877–85.
18. van der Velde ET, Vriend JW, Mannens MM, Uiterwaal CS, Brand R, Mulder BJ. CONCOR, an initiative towards a national registry and DNA-bank of patients with congenital heart disease in the Netherlands: rationale, design, and first results. Eur J Epidemiol. 2005;20(6):549–57.
19. Bouchardy J, Therrien J, Pilote L, Ionescu-Ittu R, Martucci G, Bottega N, et al. Atrial arrhythmias in adults with congenital heart disease. Circulation. 2009;120(17):1679–86.
20. Kaemmerer H, Bauer U, Pensl U, Oechslin E, Gravenhorst V, Franke A, et al. Management of emergencies in adults with congenital cardiac disease. Am J Cardiol. 2008;101(4):521–5.
21. Verheugt CL, Uiterwaal CS, van der Velde ET, Meijboom FJ, Pieper PG, Sieswerda GT, et al. The emerging burden of hospital admissions of adults with congenital heart disease. Heart. 2010;96(11):872–8.

22. Triedman JK, Alexander ME, Berul CI, Bevilacqua LM, Walsh EP. Electroanatomic mapping of entrained and exit zones in patients with repaired congenital heart disease and intra-atrial reentrant tachycardia. Circulation. 2001;103(16):2060–5.
23. Collins KK, Love BA, Walsh EP, Saul JP, Epstein MR, Triedman JK. Location of acutely successful radiofrequency catheter ablation of intraatrial reentrant tachycardia in patients with congenital heart disease. Am J Cardiol. 2000;86(9):969–74.
24. Khairy P, Harris L, Landzberg MJ, Fernandes SM, Barlow A, Mercier LA, et al. Sudden death and defibrillators in transposition of the great arteries with intra-atrial baffles: a multicenter study. Circ Arrhythm Electrophysiol. 2008;1(4):250–7.
25. Flinn CJ, Wolff GS, Dick M 2nd, Campbell RM, Borkat G, Casta A, et al. Cardiac rhythm after the Mustard operation for complete transposition of the great arteries. N Engl J Med. 1984;310(25):1635–8.
26. Khairy P, Landzberg MJ, Lambert J, O'Donnell CP. Long-term outcomes after the atrial switch for surgical correction of transposition: a meta-analysis comparing the Mustard and Senning procedures. Cardiol Young. 2004;14(3):284–92.
27. Li W, Somerville J. Atrial flutter in grown-up congenital heart (GUCH) patients. Clinical characteristics of affected population. Int J Cardiol. 2000;75(2-3):129–37. discussion 38–9
28. Roos-Hesselink J, Perlroth MG, McGhie J, Spitaels S. Atrial arrhythmias in adults after repair of tetralogy of Fallot. Correlations with clinical, exercise, and echocardiographic findings. Circulation. 1995;91(8):2214–9.
29. Bartz PJ, Driscoll DJ, Dearani JA, Puga FJ, Danielson GK, O'Leary PW, et al. Early and late results of the modified fontan operation for heterotaxy syndrome 30 years of experience in 142 patients. J Am Coll Cardiol. 2006;48(11):2301–5.
30. Nurnberg JH, Ovroutski S, Alexi-Meskishvili V, Ewert P, Hetzer R, Lange PE. New onset arrhythmias after the extracardiac conduit Fontan operation compared with the intraatrial lateral tunnel procedure: early and midterm results. Ann Thorac Surg. 2004;78(6):1979–88. discussion 88
31. Wong T, Davlouros PA, Li W, Millington-Sanders C, Francis DP, Gatzoulis MA. Mechanoelectrical interaction late after Fontan operation: relation between P-wave duration and dispersion, right atrial size, and atrial arrhythmias. Circulation. 2004;109(19):2319–25.
32. Kirsh JA, Walsh EP, Triedman JK. Prevalence of and risk factors for atrial fibrillation and intra-atrial reentrant tachycardia among patients with congenital heart disease. Am J Cardiol. 2002;90(3):338–40.
33. Khairy P, Aboulhosn J, Gurvitz MZ, Opotowsky AR, Mongeon FP, Kay J, et al. Arrhythmia burden in adults with surgically repaired tetralogy of Fallot: a multi-institutional study. Circulation. 2010;122(9):868–75.
34. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. J Am Coll Cardiol. 2011;57(11):e101–98.
35. Egbe AC, Asirvatham SJ, Connolly HM, Kapa S, Desimone CV, Vaidya VR, et al. Outcomes of direct current cardioversion in adults with congenital heart disease. Am J Cardiol. 2017;119(9):1468–72.
36. Ernst S, Chun JK, Koektuerk B, Kuck KH. Magnetic navigation and catheter ablation of right atrial ectopic tachycardia in the presence of a hemi-azygos continuation: a magnetic navigation case using 3D electroanatomical mapping. J Cardiovasc Electrophysiol. 2009;20(1):99–102.
37. Ernst S, Babu-Narayan SV, Keegan J, Horduna I, Lyne J, Till J, et al. Remote-controlled magnetic navigation and ablation with 3D image integration as an alternative approach in patients with intra-atrial baffle anatomy. Circ Arrhythm Electrophysiol. 2012;5(1):131–9.
38. Broberg C, Meadows AK. Advances in imaging: the impact on the care of the adult with congenital heart disease. Prog Cardiovasc Dis. 2011;53(4):293–304.

39. Harrison JL, Jensen HK, Peel SA, Chiribiri A, Grondal AK, Bloch LO, et al. Cardiac magnetic resonance and electroanatomical mapping of acute and chronic atrial ablation injury: a histological validation study. Eur Heart J. 2014;35(22):1486–95.
40. Peichl P, Kautzner J, Gebauer R. Ablation of atrial tachycardias after correction of complex congenital heart diseases: utility of intracardiac echocardiography. Europace. 2009;11(1):48–53.
41. El-Said HG, Ing FF, Grifka RG, Nihill MR, Morris C, Getty-Houswright D, et al. 18-year experience with transseptal procedures through baffles, conduits, and other intra-atrial patches. Catheter Cardiovasc Interv. 2000;50(4):434–9. discussion 40
42. de Groot NM, Atary JZ, Blom NA, Schalij MJ. Long-term outcome after ablative therapy of postoperative atrial tachyarrhythmia in patients with congenital heart disease and characteristics of atrial tachyarrhythmia recurrences. Circ Arrhythm Electrophysiol. 2010;3(2):148–54.
43. Ueda A, Suman-Horduna I, Mantziari L, Gujic M, Marchese P, Ho SY, et al. Contemporary outcomes of supraventricular tachycardia ablation in congenital heart disease: a single-center experience in 116 patients. Circ Arrhythm Electrophysiol. 2013;6(3):606–13.
44. Triedman JK, Alexander ME, Love BA, Collins KK, Berul CI, Bevilacqua LM, et al. Influence of patient factors and ablative technologies on outcomes of radiofrequency ablation of intra-atrial re-entrant tachycardia in patients with congenital heart disease. J Am Coll Cardiol. 2002;39(11):1827–35.
45. de Groot NM, Zeppenfeld K, Wijffels MC, Chan WK, Blom NA, Van der Wall EE, et al. Ablation of focal atrial arrhythmia in patients with congenital heart defects after surgery: role of circumscribed areas with heterogeneous conduction. Heart Rhythm. 2006;3(5):526–35.
46. Ector J, De Buck S, Adams J, Dymarkowski S, Bogaert J, Maes F, et al. Cardiac three-dimensional magnetic resonance imaging and fluoroscopy merging: a new approach for electroanatomic mapping to assist catheter ablation. Circulation. 2005;112(24):3769–76.
47. Everett TH, Lee KW, Wilson EE, Guerra JM, Varosy PD, Olgin JE. Safety profiles and lesion size of different radiofrequency ablation technologies: a comparison of large tip, open and closed irrigation catheters. J Cardiovasc Electrophysiol. 2009;20(3):325–35.
48. Ernst S. Robotic approach to catheter ablation. Curr Opin Cardiol. 2008;23(1):28–31.
49. Ueda A, Horduna I, Rubens M, Ernst S. Reaching the ventricular aspect of the inferior isthmus in a Fontan patient using magnetic navigation. Heart Rhythm. 2013;10(7):1094–5.
50. Khairy P, Van Hare GF, Balaji S, Berul CI, Cecchin F, Cohen MI, et al. PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult Congenital Heart Disease: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology (ACC), the American Heart Association (AHA), the European Heart Rhythm Association (EHRA), the Canadian Heart Rhythm Society (CHRS), and the International Society for Adult Congenital Heart Disease (ISACHD). Heart Rhythm. 2014;11(10):e102–65.
51. Triedman JK, DeLucca JM, Alexander ME, Berul CI, Cecchin F, Walsh EP. Prospective trial of electroanatomically guided, irrigated catheter ablation of atrial tachycardia in patients with congenital heart disease. Heart Rhythm. 2005;2(7):700–5.
52. Correa R, Sherwin ED, Kovach J, Mah DY, Alexander ME, Cecchin F, et al. Mechanism and ablation of arrhythmia following total cavopulmonary connection. Circ Arrhythm Electrophysiol. 2015;8(2):318–25.
53. Correa R, Walsh EP, Alexander ME, Mah DY, Cecchin F, Abrams DJ, et al. Transbaffle mapping and ablation for atrial tachycardias after mustard, senning, or Fontan operations. J Am Heart Assoc. 2013;2(5):e000325.
54. Yap SC, Harris L, Silversides CK, Downar E, Chauhan VS. Outcome of intra-atrial re-entrant tachycardia catheter ablation in adults with congenital heart disease: negative impact of age and complex atrial surgery. J Am Coll Cardiol. 2010;56(19):1589–96.
55. Ernst S, Pedersen M, Uebing A, Suman-Horduna I, Mantziari L, Li W, et al. Successful ablation of two right atrial tachycardias on either side of the lateral tunnel patch in a patient with

double inlet left ventricle and total cavopulmonary connection: two sites and two mechanisms. Global Cardiol Sci Pract. 2013;2013(2):198–202.
56. Agnoletti G, Borghi A, Vignati G, Crupi GC. Fontan conversion to total cavopulmonary connection and arrhythmia ablation: clinical and functional results. Heart. 2003;89(2):193–8.
57. Gatzoulis MA, Walters J, McLaughlin PR, Merchant N, Webb GD, Liu P. Late arrhythmia in adults with the mustard procedure for transposition of great arteries: a surrogate marker for right ventricular dysfunction? Heart. 2000;84(4):409–15.
58. Dobson R, Danton M, Nicola W, Hamish W. The natural and unnatural history of the systemic right ventricle in adult survivors. J Thorac Cardiovasc Surg. 2013;145(6):1493–501. discussion 501–3
59. Wu J, Deisenhofer I, Ammar S, Fichtner S, Reents T, Zhu P, et al. Acute and long-term outcome after catheter ablation of supraventricular tachycardia in patients after the Mustard or Senning operation for D-transposition of the great arteries. Europace. 2013;15(6):886–91.
60. Silka MJ, Hardy BG, Menashe VD, Morris CD. A population-based prospective evaluation of risk of sudden cardiac death after operation for common congenital heart defects. J Am Coll Cardiol. 1998;32(1):245–51.
61. Koyak Z, Harris L, de Groot JR, Silversides CK, Oechslin EN, Bouma BJ, et al. Sudden cardiac death in adult congenital heart disease. Circulation. 2012;126(16):1944–54.
62. Harrison DA, Harris L, Siu SC, MacLoghlin CJ, Connelly MS, Webb GD, et al. Sustained ventricular tachycardia in adult patients late after repair of tetralogy of Fallot. J Am Coll Cardiol. 1997;30(5):1368–73.
63. Shiga T, Kasanuki H. Drug therapy for ventricular tachyarrhythmia in heart failure. Circ J. 2007;71(Suppl A):A90–6.
64. Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. Lancet (Lond, England). 2000;356(9234):975–81.
65. Murphy JG, Gersh BJ, Mair DD, Fuster V, McGoon MD, Ilstrup DM, et al. Long-term outcome in patients undergoing surgical repair of tetralogy of Fallot. N Engl J Med. 1993;329(9):593–9.
66. Bonello B, Kempny A, Uebing A, Li W, Kilner PJ, Diller GP, et al. Right atrial area and right ventricular outflow tract akinetic length predict sustained tachyarrhythmia in repaired tetralogy of Fallot. Int J Cardiol. 2013;168(4):3280–6.
67. Khairy P, Landzberg MJ, Gatzoulis MA, Lucron H, Lambert J, Marcon F, et al. Value of programmed ventricular stimulation after tetralogy of fallot repair: a multicenter study. Circulation. 2004;109(16):1994–2000.
68. Anderson KR, Lie JT. Pathologic anatomy of Ebstein's anomaly of the heart revisited. Am J Cardiol. 1978;41(4):739–45.
69. Zeppenfeld K, Schalij MJ, Bartelings MM, Tedrow UB, Koplan BA, Soejima K, et al. Catheter ablation of ventricular tachycardia after repair of congenital heart disease: electroanatomic identification of the critical right ventricular isthmus. Circulation. 2007;116(20):2241–52.
70. Russo AM, Stainback RF, Bailey SR, Epstein AE, Heidenreich PA, Jessup M, et al. ACCF/HRS/AHA/ASE/HFSA/SCAI/SCCT/SCMR 2013 appropriate use criteria for implantable cardioverter-defibrillators and cardiac resynchronization therapy: a report of the American College of Cardiology Foundation appropriate use criteria task force, Heart Rhythm Society, American Heart Association, American Society of Echocardiography, Heart Failure Society of America, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. Heart Rhythm. 2013;10(4):e11–58.
71. Furushima H, Chinushi M, Sugiura H, Komura S, Tanabe Y, Watanabe H, et al. Ventricular tachycardia late after repair of congenital heart disease: efficacy of combination therapy with radiofrequency catheter ablation and class III antiarrhythmic agents and long-term outcome. J Electrocardiol. 2006;39(2):219–24.
72. Morwood JG, Triedman JK, Berul CI, Khairy P, Alexander ME, Cecchin F, et al. Radiofrequency catheter ablation of ventricular tachycardia in children and young adults with congenital heart disease. Heart Rhythm. 2004;1(3):301–8.

73. Gross GJ, Chiu CC, Hamilton RM, Kirsh JA, Stephenson EA. Natural history of postoperative heart block in congenital heart disease: implications for pacing intervention. Heart Rhythm. 2006;3(5):601–4.
74. Hansky B, Blanz U, Peuster M, Gueldner H, Sandica E, Crespo-Martinez E, et al. Endocardial pacing after Fontan-type procedures. Pacing Clin Electrophysiol. 2005;28(2):140–8.
75. Paech C, Kostelka M, Dahnert I, Flosdorff P, Riede FT, Gebauer RA. Performance of steroid eluting bipolar epicardial leads in pediatric and congenital heart disease patients: 15 years of single center experience. J Cardiothorac Surg. 2014;9:84.
76. Silvetti MS, Drago F, Di Carlo D, Placidi S, Brancaccio G, Carotti A. Cardiac pacing in paediatric patients with congenital heart defects: transvenous or epicardial? Europace. 2013;15(9):1280–6.
77. Janousek J, van Geldorp IE, Krupickova S, Rosenthal E, Nugent K, Tomaske M, et al. Permanent cardiac pacing in children: choosing the optimal pacing site: a multicenter study. Circulation. 2013;127(5):613–23.
78. Khairy P, Fernandes SM, Mayer JE Jr, Triedman JK, Walsh EP, Lock JE, et al. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. Circulation. 2008;117(1):85–92.
79. Khairy P, Harris L, Landzberg MJ, Viswanathan S, Barlow A, Gatzoulis MA, et al. Implantable cardioverter-defibrillators in tetralogy of Fallot. Circulation. 2008;117(3):363–70.
80. Koyak Z, de Groot JR, Bouma BJ, Van Gelder IC, Budts W, Zwinderman AH, et al. Symptomatic but not asymptomatic non-sustained ventricular tachycardia is associated with appropriate implantable cardioverter therapy in tetralogy of Fallot. Int J Cardiol. 2013;167(4):1532–5.
81. Kammeraad JA, van Deurzen CH, Sreeram N, Bink-Boelkens MT, Ottenkamp J, Helbing WA, et al. Predictors of sudden cardiac death after Mustard or Senning repair for transposition of the great arteries. J Am Coll Cardiol. 2004;44(5):1095–102.
82. Berul CI, Van Hare GF, Kertesz NJ, Dubin AM, Cecchin F, Collins KK, et al. Results of a multicenter retrospective implantable cardioverter-defibrillator registry of pediatric and congenital heart disease patients. J Am Coll Cardiol. 2008;51(17):1685–91.
83. DeMaso DR, Lauretti A, Spieth L, van der Feen JR, Jay KS, Gauvreau K, et al. Psychosocial factors and quality of life in children and adolescents with implantable cardioverter-defibrillators. Am J Cardiol. 2004;93(5):582–7.
84. Hayward RM, Dewland TA, Moyers B, Vittinghoff E, Tanel RE, Marcus GM, et al. Device complications in adult congenital heart disease. Heart Rhythm. 2015;12(2):338–44.
85. Vehmeijer JT, Koyak Z, Bokma JP, Budts W, Harris L, Mulder BJ, et al. Sudden cardiac death in adults with congenital heart disease: does QRS-complex fragmentation discriminate in structurally abnormal hearts? Europace. 2017. https://doi.org/10.1093/europace/eux044.
86. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;51(21):e1–62.
87. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med. 2002;346(24):1845–53.
88. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med. 2001;344(12):873–80.
89. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005;352(15):1539–49.
90. Khairy P, Fournier A, Thibault B, Dubuc M, Therien J, Vobecky SJ. Cardiac resynchronization therapy in congenital heart disease. Int J Cardiol. 2006;109(2):160–8.

91. Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, et al. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. Circulation. 2005;112(6):828–35.
92. Dubin AM, Janousek J, Rhee E, Strieper MJ, Cecchin F, Law IH, et al. Resynchronization therapy in pediatric and congenital heart disease patients: an international multicenter study. J Am Coll Cardiol. 2005;46(12):2277–83.
93. Cecchin F, Frangini PA, Brown DW, Fynn-Thompson F, Alexander ME, Triedman JK, et al. Cardiac resynchronization therapy (and multisite pacing) in pediatrics and congenital heart disease: five years experience in a single institution. J Cardiovasc Electrophysiol. 2009;20(1):58–65.
94. Janousek J, Gebauer RA. Cardiac resynchronization therapy in pediatric and congenital heart disease. Pacing Clin Electrophysiol. 2008;31(Suppl 1):S21–3.
95. Zimmerman FJ, Starr JP, Koenig PR, Smith P, Hijazi ZM, Bacha EA. Acute hemodynamic benefit of multisite ventricular pacing after congenital heart surgery. Ann Thorac Surg. 2003;75(6):1775–80.
96. Budts W, Roos-Hesselink J, Radle-Hurst T, Eicken A, McDonagh TA, Lambrinou E, et al. Treatment of heart failure in adult congenital heart disease: a position paper of the Working Group of Grown-Up Congenital Heart Disease and the Heart Failure Association of the European Society of Cardiology. Eur Heart J. 2016;37(18):1419–27.
97. Thambo JB, De Guillebon M, Xhaet O, Dos Santos P, Roubertie F, Labrousse L, et al. Biventricular pacing in patients with Tetralogy of Fallot: non-invasive epicardial mapping and clinical impact. Int J Cardiol. 2013;163(2):170–4.
98. Stewart GC, Mayer JE Jr. Heart transplantation in adults with congenital heart disease. Heart Fail Clin. 2014;10(1):207–18.
99. Mondesert B, Marcotte F, Mongeon FP, Dore A, Mercier LA, Ibrahim R, et al. Fontan circulation: success or failure? Can J Cardiol. 2013;29(7):811–20.

13 Transplantation and Mechanical Circulatory Support in Adult Congenital Heart Disease-Related Advanced Heart Failure

Jonathan N. Menachem and Luke J. Burchill

13.1 Introduction

As transplant centers become more familiar with heart transplantation (HTx) in adult congenital heart disease (ACHD) patients, short- and long-term outcomes have improved. Long-term survival conditional on 1-year survival is now better for ACHD patients undergoing HTX than for non-ACHD patients [1]. Despite the perception that the risks associated with HTx are often too high, many ACHD patients have acceptable risk profiles, and all can benefit from review in an advanced heart failure (HF) program. This chapter is dedicated to breaking down barriers to advanced HF care for patients with ACHD-related HF. This chapter has six sections:

- Timing of referral for HTx assessment
- Risks and contraindications to HTx
- Wait-list outcomes and opportunities for decreasing wait-list mortality
- HTx outcomes
- Alternatives to transplantation
- Peri-/postoperative management

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13.2 Timing of Referral for HTx Assessment

Predicting progression from stable to advanced and/or decompensated HF in ACHD-related HF is challenging, even more so than in acquired HF. Declining NYHA class, progressive ventricular dysfunction, elevated serum BNP [2, 3], reduced peak oxygen uptake (VO_2 max), low BMI [4], hyponatremia [5], anemia [6], renal dysfunction [7], elevated troponin [8], pulmonary hypertension (PH), and arrhythmias [9] have each been associated with increased ACHD mortality. More important than any single variable is the overall clinical picture. In particular, the emergence of clinical features of advanced HF portends adverse health outcomes (summarized in Table 13.1). Emphasized here is a history of repeated HF hospitalizations or emergency room visits, escalating diuretic dose, deteriorating kidney function, unexplained weight loss, and intolerance to ACE inhibitors or beta-blockers. Early referral to a is recommended for all ACHD patients with features of advanced HF. Advanced HF review is also recommended in those with idiosyncratic complications suggesting increased short-term mortality risk such as protein-losing enteropathy (PLE) in Fontan patients [10, 11].

An advanced HF service comprises an interdisciplinary team with expertise and formal training in advanced HF treatment strategies. Early referral does not equate to early listing for HTx. Nor does it imply transfer of care from the ACHD to the acquired HF team. Instead, the purpose of early assessment is to facilitate collaboration between the ACHD and HF programs and to afford the team sufficient time to understand each patient's anatomy, hemodynamics, and clinical course. The team should include clinicians with both traditional and advanced HF expertise but also ACHD clinicians. In addition to discussing advanced HF strategies, the team should assess each patient's understanding of mortality risk with and without treatment and advanced care preferences including resuscitation. Research into care preferences show most ACHD patients prefer to discuss life expectancy and advanced directives before their condition becomes life-threatening [12].

Table 13.1 Clinical features of advanced HF

Repeated (≥2) hospitalizations or emergency department for HF in the past year
Progressive deterioration in renal function (rising urea or creatinine)
Weight loss without other causes[a] (i.e., cardiac cachexia)
Intolerance to ACE inhibitors due to hypotension and/or worsening renal function
Intolerance to beta-blockers due to worsening HF or hypotension
Frequent hypotension with systolic BP <90 mmHg
Persistent dyspnea with dressing or bathing requiring rest
Inability to walk one block on the level ground due to dyspnea or fatigue
Escalating and/or high diuretic dose requirements (furosemide equivalent dose >160 mg/D and/or supplemental metolazone use)
Progressive hyponatremia with serum sodium <133 mEq/L
Frequent arrhythmia and/or ICD shocks
Fontan patients with diarrhea or coughing of casts leading to a diagnosis of protein-losing enteropathy or plastic bronchitis

Adapted from Russell et al. Congestive Heart Failure. 2008;14:316-21

[a]In Fontan patients consider also protein-losing enteropathy as an alternative cause of cachexia

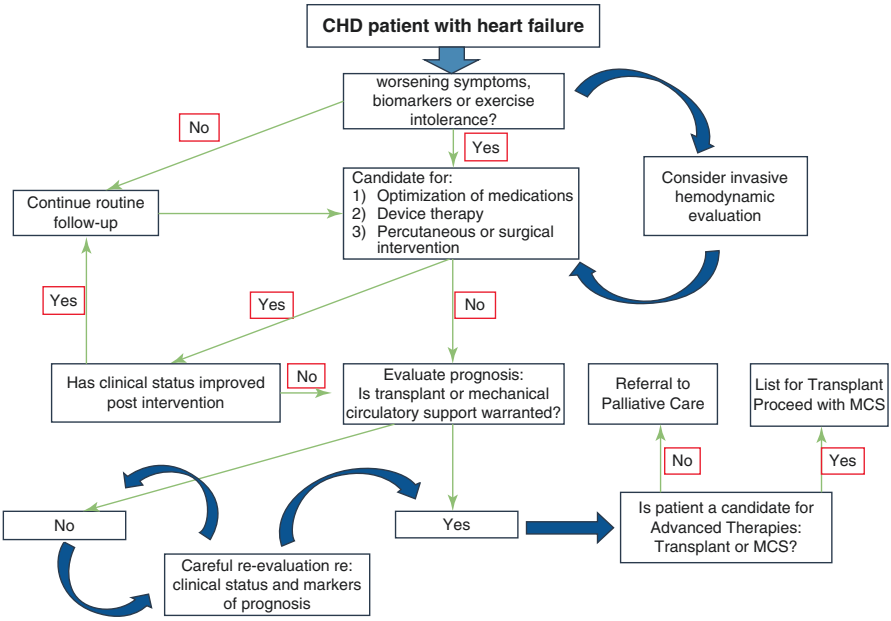

Fig. 13.1 Approach to advanced HF assessment in ACHD. MCS indicates mechanical circulatory support. Illustration used with permission and taken from Ross Circulation 2016

Figure 13.1 provides a stepwise approach to evaluation and treatment of ACHD patients with advanced HF [13]. Worsening symptoms, biomarkers, or exercise intolerance prompts review of medications and candidacy for percutaneous/surgical intervention and device therapies. Multimodality cardiac imaging (echocardiogram, cardiac MRI, cardiac CT, and/or vascular ultrasound) provides a detailed assessment of anatomy and hemodynamics. In addition to quantifying ventricular dimensions and function, attention is paid to the position of the heart and coronary vessels in relation to the sternum, arterial and venous connections, peripheral vascular access, and collateral vessels. Invasive hemodynamic evaluation by a CHD specialist is recommended for ACHD patients with newly diagnosed HF. In addition to guiding medical HF therapy, hemodynamic assessment identifies residual lesions contributing to HF pathophysiology. Advanced therapies (HTx and mechanical circulatory support) should be considered in any ACHD patient who is not responding to medical or device therapy or in whom repeat cardiac surgery is deemed too high risk or unlikely to reset the clinical course. Indications for HTx are summarized in Table 13.2.

13.3 Risks and Contraindications to HTx

Contraindications to HTx in ACHD patients are based on ISHLT guidelines [14] while also taking into account ACHD-related issues. ACHD-related factors such as complex anatomy, the presence of multiple congenital anomalies, or neurocognitive impairment

Table 13.2 Indications for heart transplantation in ACHD

Indications for heart transplantation in ACHD
Stage D HF refractory to medical therapy which will not benefit significantly from surgical, interventional, or electrophysiological intervention
ACHD patients with associated near sudden death or life-threatening arrhythmias refractory to all therapeutic modalities
Patients with stage C HF associated with reactive pulmonary hypertension and a potential risk of developing fixed, irreversible elevation of pulmonary vascular resistance that could preclude isolated orthotopic heart transplantation in the future
Fontan patients with protein-losing enteropathy ± plastic bronchitis refractory to medical therapy
Progressive cyanosis leading to functional decline not amenable to surgery- or catheter-based intervention

Table adapted from Ross et al. Circulation 2016

rarely serve as absolute contraindications in isolation. More frequently it is these issues in combination that lead to determination of excessive risk although risk thresholds vary significantly by transplant and ACHD center volume and expertise. Over time thresholds of risk in ACHD patients are being challenged. A good example is a history of multiple sternotomies which despite being associated with increased HTx risk can generally be managed with anticipatory measures (i.e., peripheral cannulation and bypass, careful dissection of adhesions) [15]. Absolute, relative, and ACHD-related contraindications are summarized in Table 13.3. For this review we have chosen to focus on three issues of major concern—liver disease, PH, and sensitization.

13.3.1 Liver Disease

Liver disease is common in ACHD patients due to the high prevalence of right heart disease, passive liver congestion and hepatitis C [16]. Fontan patients are at especially high risk due to systemic venous hypertension, hepatic congestion, and low cardiac output leading to cirrhosis and, in some patients, hepatocellular carcinoma [17]. Whether Fontan patients should undergo isolated heart versus combined heart-liver transplantation continues to be hotly debated with the current approach to assessment and treatment varying across transplant centers. The Hospital of the University of Pennsylvania reported outcomes in eight Fontan patients who underwent combined heart-liver transplantation for biopsy-proven advanced fibrosis or cirrhosis; 100% survival was achieved at 30 days and 1 year [18]. It has been postulated that the addition of liver transplant reduces bleeding risk in Fontan patients [19]. In addition, there is increasing evidence that cardiac cellular and antibody-mediated rejection are less frequent after combined heart-liver transplant [20] [21]. Despite these potential advantages, it remains unclear whether combined heart-liver transplant should be recommended in all Fontan patients. A recent UNOS study reported equivalent survival in CHD patients undergoing isolated heart versus combined heart-liver transplantation [15].

The model for end-stage liver disease excluding international normalized ratio (MELD-XI) score may be helpful for stratifying risk. A MELD-XI score

Table 13.3 Risk factors and contraindications to heart transplant in ACHD patients

Absolute contraindications
Systemic illness with life expectancy <2 years despite heart transplant including:
Active or recent solid organ or blood malignancy within 5 years
AIDS with frequent opportunistic infections
Active systemic lupus erythematosus, sarcoid, or amyloidosis with multisystem involvement
Irreversible renal or hepatic dysfunction in patients considered only for heart transplant
Significant obstructive pulmonary disease (FEV1 <1.0)
Fixed pulmonary hypertension
Pulmonary artery systolic pressure >60 mmHg
Mean transpulmonary gradient >15 mmHg
Pulmonary vascular resistance >6 Wood units
Relative contraindications
Age >70 years[a]
Active infection
Active peptic ulcer disease
Severe diabetes with poor glycemic control (HBA1c >7.5%) and/or end-organ damage (neuropathy, nephropathy, retinopathy)
Severe peripheral vascular or cerebrovascular disease not amenable to surgical or percutaneous therapy
Morbid obesity (body mass index >35 g/m^2) or cachexia (BMI <18 g/m^2)
Estimated glomerular filtration rate <40 mL/min/1.73 m^2
Bilirubin >2.5 mg/dL, serum transaminases >3×, INR >1.5 off warfarin
Irreversible neurological or neuromuscular disorder
Psychosocial instability limiting adherence after transplant
Active smoker or drug use within 6 months
Heparin-induced thrombocytopenia within 100 days
ACHD related
Complex anatomy combined with additional contraindication as listed above[b]
Multiple severe congenital anomalies (rare)
Severe metabolic disease (rare)
Neurocognitive impairment limiting adherence after transplant

[a]Carefully selected patients > 70 years of age may be considered for transplantation
[b]Complex anatomy alone is not a contraindication to heart transplantation. However, the combination of complex anatomy with additional risk factors is associated with increased mortality after heart transplantation. Adapted from Mancini D, Lietz K. Selection of cardiac transplantation candidates in 2010. Circulation 2010; 122:174

>18 has been associated with increased ACHD recipient mortality after HTx [22]. A second study reported significantly lower survival after HTx in Fontan patients when more than one of the following findings was identified: elevated MELD-XI, MELD-XI >19, EF <20%, moderate or severe AV valve regurgitation, Fontan pressure >16.5 mmHg, and need for dialysis and ECMO support [23]. Validation of these risk scores in larger patient populations will be important before these criteria, and cutoffs for liver disease can be integrated into transplant selection criteria.

Based on the existing data, a case-by-case approach is recommended with combined heart-liver transplant being an important consideration in those with high-risk features as described but particularly once cirrhosis is confirmed on liver biopsy.

13.3.2 Pulmonary Hypertension

Assessment of PH in ACHD patients is made more challenging by the presence of complex anatomy, passive pulmonary blood flow, imbalanced flow to the right and left lung, and alternative sources of pulmonary blood flow in the form of collateral vessels. Based upon current ISHLT HTx guidelines, a transpulmonary gradient (TPG) <15 mmHg and pulmonary vascular resistance (PVR) <3 Wood units are considered acceptable for HTx [14]. Vasodilator challenge should be undertaken if PH is confirmed at catheterization. Inotropes and diuretics are important in patients with pulmonary venous HT arising secondary to a failing systemic ventricle. Reversible PH has been associated with good outcomes after isolated HTx [24, 25] despite an increased risk of donor right HF during the first 30 days after HTx [26].

Although PVR and TPG are commonly used to differentiate HF patients with pulmonary vascular disease from those with passive PH, elevations in TPG and PVR do not always reflect precapillary PH. As such more sensitive measures of PH continue to be sought. An elevated diastolic pulmonary artery pressure-to-pulmonary capillary wedge pressure gradient (DPG) has been proposed as a better indicator of pulmonary vascular remodeling. However, in a study of over 5800 patients with PH, there was no difference in post-HTx survival in those with high versus low DPG indicating a limited prognostic role for this measure [27]. Others have shown the hemodynamic response to nitroprusside at the time of right heart catheterization to be useful for differentiating risk in PH patients with non-ACHD-related HF. Short-term mortality was significantly higher in patients with fixed PVR above 2.5 Wood units and those whose PVR could be reduced but only at the expense of systemic hypotension (SBP <85 mmHg) [28]. These findings are more applicable to patients with biventricular anatomy and are as yet unproven in ACHD.

Overall, these studies underscore the fact that reliance on one static measure to characterize PH type and severity prior to HTx is inadequate and that serial monitoring, provocative maneuvers, and integration of several indices are important at the time of ACHD HTx assessment.

13.3.3 Sensitization

Sensitization, the process by which preformed antibodies to human leukocyte antigens (HLA) are developed, remains an important barrier to HTx. Patients with panel reactive antibodies (PRA) greater than 10% are considered sensitized. Sensitization risk factors include prior blood transfusions, pregnancies, homografts, tissue allografts, and mechanical circulatory support [29]. HTx recipients with high degrees of sensitization have increased wait-list times and are at a higher risk of posttransplant rejection, cardiac transplant vasculopathy, graft failure, and mortality [30–33]. Treatment options for sensitization include plasmapheresis/intravenous immunoglobulin/rituximab (pre-/posttransplant) and thymoglobulin (posttransplant) (IVIg). By decreasing circulating antibodies, desensitization can

allow patients to undergo HTx with a negative prospective donor-specific crossmatch. Surprisingly, equivalent 5-year survival has been reported in sensitized patients undergoing HTx with and without prior desensitization [34]. These findings suggest desensitization increases the chance of sensitized patients proceeding to HTx with a negative crossmatch but without clear evidence for improved long-term survival.

13.4 Wait-List Outcomes and Opportunities for Decreasing Wait-List Mortality

The decision to proceed with listing for HTx is based on an estimated 1-year survival of less than 80%. Estimating survival in ACHD HF patients is challenging since patients are younger and often appear compensated despite significant circulatory dysfunction and end-organ disease. In a multicenter study of 45 ACHD patients undergoing HTx evaluation between 2000 and 2012, 13 were deemed too high risk, 6 because of liver cirrhosis, and 1 due to irreversible pulmonary HT. Five were considered too well [35]. As observed elsewhere [18], those declined were more likely to have single-ventricle physiology. No difference in survival was observed between those listed versus not listed for HTx. Among patients who underwent HTx, 1-year survival was 85% with four ACHD deaths occurring within 30 days of HTx. Of the 13 patients not listed due to high risk, 5 (38%) died secondary to progressive HF. Of the five patients considered too well for HTx, one died from a hemorrhagic stroke, and the other four continued to be managed medically without need for HTx. In reviewing these outcomes, it is clear that morbidity and mortality are high in ACHD HF patients, both with and without HTx.

Once listed, ACHD patients spend longer on the HTx wait list [36, 37]. Wait-list times in ACHD recipients are increased for several reasons including being listed at lower urgency, being more highly sensitized, and the need for non-lung donors to enable vascular reconstruction in some recipients [37]. Since 1996, the number of ACHD patients listed status 2 has remained constant, whereas for non-ACHD patients, this percentage has fallen likely due to a relative increase in the number of non-ACHD patients being upgraded to status 1 [38]. Changes in the organ allocation policies, including a provision that patients with a ventricular assist device (VAD) be listed as status 1B, have influenced this shift. VAD patients also receive 30 days of discriminatory 1A time as well as 1A status for VAD complications leaving ACHD patients, many of whom do not require or qualify for mechanical circulatory support, at a significant disadvantage.

Wait-list mortality of 10% in ACHD patients is comparable to others listed for HTx although ACHD patients are significantly more likely to die secondary to cardiac causes, most commonly sudden cardiac death [37]. Highlighting a need for improved arrhythmia risk stratification and treatment, ACHD patients are less likely to be protected with an implantable cardiac defibrillator while on the HTx wait list (44% of ACHD patients listed for transplantation have an ICD vs. 75% of non-ACHD patients; $p < 0.001$) [37].

13.5 HTx Outcomes

ACHD patients comprise approximately 3% of the total HTX population, although this number is growing rapidly with a 40% increase in ACHD HTx over the last two decades [36, 39]. Multicenter registries provide a broad overview of ACHD outcomes after HTx (Table 13.4). Single center studies report outcomes by congenital subtype and therefore enable comparison between ACHD subgroups and transplant center [18, 40–47].

ACHD is an independent predictor of increased mortality with a two- to threefold increase in the relative risk of 1-year posttransplant mortality [30, 36, 48]. Of the ACHD subgroups, evaluated mortality is highest in the Fontan population with posttransplant mortality of 25–30% [41, 44–46]. The main causes of increased mortality in Fontan recipients are primary graft failure (reflecting longer ischemic times), early rejection (due to sensitization), and the combined effect of comorbid disease (hypoalbuminemia, immune dysfunction, liver disease, coagulopathy, renal dysfunction, and occult PH).

Technical complications are important with death secondary to bleeding and other surgical factors accounting for 10% of ACHD HTx recipient deaths vs. 4% of others ($p < 0.0001$) [1]. Ischemic times are significantly longer due to the need for reconstructive surgery, required in up to 75% of CHD patients undergoing HTx [49]. Bleeding risks are especially high in patients with single-ventricle anatomy following reconstruction of the aortic arch, vena cavae, or pulmonary arteries and those with dense sternal adhesions from previous sternotomies [50]. For these reasons congenital surgical expertise at the time of HTx in CHD recipients is essential. Excellent outcomes have been reported with congenital heart and adult HTx surgeons working in collaboration, not only at the time of surgery but also in the assessment and planning stages [18, 40]. Current guidelines recommend all ACHD patients undergo transplantation in high-volume centers with combined expertise in congenital heart disease and HTx [14].

A survival paradox exists among ACHD recipients whose high early mortality is balanced by better long-term survival. Compared to other HF subgroups, ACHD patients who survive the early period after HTx have better long-term survival due to lower infection and malignancy-related mortality as well as decreased incidence of coronary allograft vasculopathy. Lower rates of infection and malignancy are likely due to ACHD patient's younger age and a more robust immune system but with a converse increased risk of graft failure and rejection. The clinical implication of this finding is that immunosuppression protocols need to be carefully adjusted in ACHD recipients to maintain the balance between the competing risks of rejection, infection, and malignancy.

With appropriate risk stratification, patient selection, planning, and team-based care, ACHD patients can successfully undergo transplantation in high-volume

Table 13.4 Multicenter studies evaluating heart transplant outcomes in patients with congenital heart disease

Author (year)	Registry and age group	Major findings
Shah (2016)	UNOS >18 years	Graft dysfunction, cardiovascular, and multiple organ failure are the top three causes of death in ACHD HTx recipients. The graft dysfunction rate is significantly higher in ACHD ($p = 0.03$). Postoperative hemorrhage as a cause of death was higher in ACHD HTx (2% vs. 0.5%, $p < 0.01$) A 30-day mortality has improved in the current era (2010–2014) to 6.8% from 14.3% in the early era (2000–2004), $p < 0.0001$)
Burchill (2014)	ISHLT >18 years	Early death due to technical reasons is higher among ACHD HTx recipients vs. controls (10% vs. 4%, $p < 0.0001$) ACHD HTx recipients who survive the first 30 days after HTx have superior long-term survival vs. controls ($p < 0.0001$) which is in part due to lower infection ($p < 0.0001$) and malignancy-related ($p < 0.01$) mortality
Davies (2011)	UNOS >18 years	Early HTx mortality higher in ACHD HTx recipients vs. others (18.9% vs. 9.6%, $p = XX$) MCS was not associated with improved survival in ACHD patients awaiting HTx
Karamlou (2010)	UNOS >18 years	HTx in ACHD patients increased by 41% between 1990 and 2008 ACHD is an independent risk factor for death and pre-transplantation
Patel (2009)	UNOS >17 years	Early HTx mortality higher in ACHD patients vs. others (16% vs. 6%, $p = XX$) ACHD HTx recipients are more likely to die from primary graft and MOF ($p=$) ACHD HTx recipients have longer wait-list time ($p=$) ACHD HTx recipients have higher PVR ($p=$)
Lamour (2009)	Pediatric Heart Transplant Study, Cardiac Transplant Registry Database; infants, children, and adults combined	Survival after HTx lower in Fontan vs. non-Fontan congenital heart disease patients ($p=$) Predictors of death in ACHD HTx recipients; older age, older donors, longer ischemic time, Fontan
Bernstein (2006)	Pediatric Heart Transplant Study; Fontan patients age <17 years	Survival in Fontan children after HTx 76% at 1 year and 68% at 5 years Protein-losing enteropathy resolved in all who survived >30 days after HTx Cause of death in Fontan children undergoing HTx: infection (30%), graft failure (17%), rejection (13%), sudden death (13%), and coronary allograft vasculopathy (9%)

(continued)

Table 13.4 (continued)

Author (year)	Registry and age group	Major findings
Doumouras (2016)[a]	Meta-analysis	Meta-analysis of 12 studies including 2007 patients with congenital heart disease A 30-day mortality significantly higher in CHD versus non-CHD patients (RR 2.33, 95% CI 1.80–3.03). A 30-day mortality risk was significantly higher in Fontan/Glenn CHD patients than others with congenital heart disease

ACHD adult congenital heart disease, *HTx* heart transplantation, *ISHLT* International Society of Heart and Lung Transplantation, *MCS* mechanical circulatory support, *MOF* multi-organ failure, *UNOS* United Network for Organ Sharing, *PVR* pulmonary vascular resistance
[a]In press, *Journal of Heart and Lung Transplantation* 2016

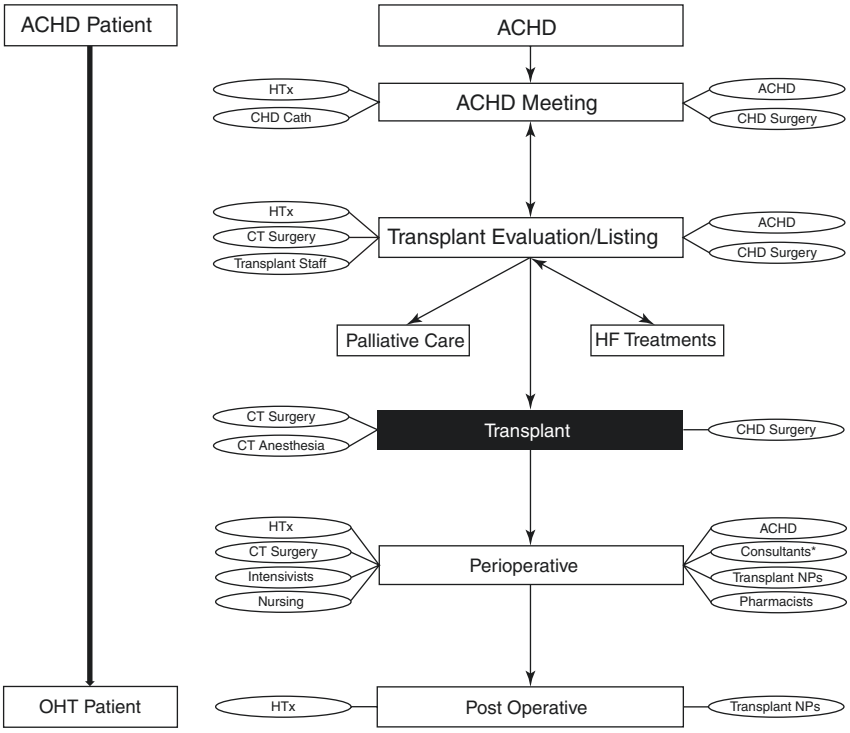

Fig. 13.2 An interdisciplinary team providing subspecialist expertise at the time of ACHD patient evaluation/listing, HTx, and perioperative and postoperative care is recommended

centers with combined expertise in congenital heart disease and HTx [14]. An interdisciplinary team providing subspecialist expertise at the time of ACHD patient evaluation/listing, HTx, and perioperative and postoperative care is recommended [18] (Fig. 13.2).

13.6 Alternatives to Transplantation

13.6.1 Mechanical Circulatory Support

A recent analysis of the INTERMACS data demonstrated that VAD use is limited overall in the ACHD population [51]. ACHD patients frequently require alternative positioning and surgical implantation techniques that vary by anatomy and device (Fig. 13.3) [52–56].

Outcomes in ACHD patients with biventricular anatomy supported by LVAD alone are equivalent to non-ACHD HF patients [51]. However, for those requiring biventricular assist device or total artificial heart, outcomes are poor with low short-term survival and a high incidence of stroke and thromboembolic complications [55]. For most ACHD patients, VAD is used as a bridge to HTx (rather than destination therapy) although little is known about outcomes after HTx in this population. For non-ACHD HF patients bridged to HTx with a VAD, 60-day survival is significantly lower [57]. Future research into outcomes in ACHD patients being bridged to HTx on VADs is important given the potential for higher early mortality related to complex anatomy, multiple sternal reentries, dense scarring, longer ischemic times, and higher sensitization [58].

Mechanical support has been used in patients with a systemic right ventricle (RV) [52, 59] to support the failing RV and to reverse pulmonary (venous) HT. Practical considerations in Mustard/Senning patients include the integrity of the

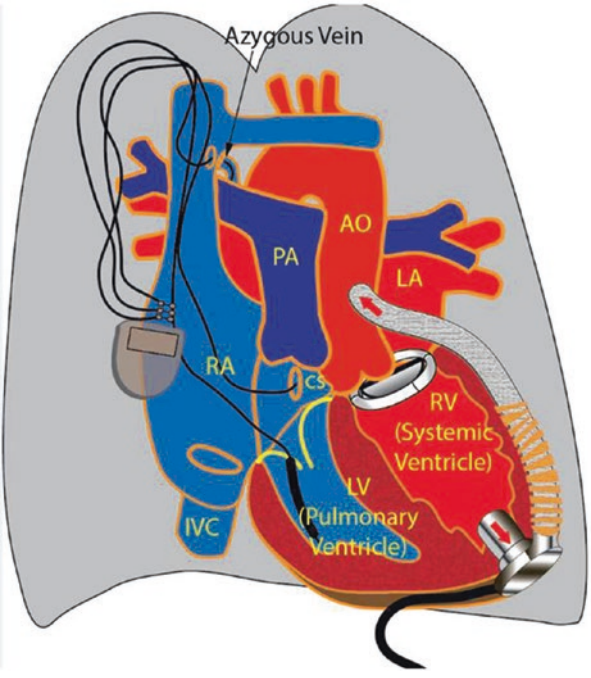

Fig. 13.3 Illustration detailing the orientation of VAD placement and the direction of blood flow in a patient with congenitally corrected transposition of the great arteries. *AO* aorta, *CS* coronary sinus, *IVC* inferior vena cava, *LA* left atrium, *LV* left ventricle, *PA* pulmonary artery, *RA* right atrium, *RV* right ventricle. Illustration used with permission and taken from Menachem Congenital Heart Disease 2015

atrial baffles which must be assessed prior to RVAD implant. Baffle stenosis interferes with VAD flow and may contribute to persistent PH in the case of pulmonary baffle stenosis. Baffle leaks increase the risk of thromboembolism, cyanosis, and ventricular volume overload. Preemptive treatment of arrhythmia substrate should also be considered prior to VAD implant given the impact of uncontrolled atrial and ventricular arrhythmias on VAD flows and ventricular function. There is a perception that the subpulmonic LV is less prone to failing after systemic RV implantation [52]. However, failure of the subpulmonic LV is not uncommon and requires preemptive planning at the time of RVAD implant. For those not responding to inotropes and volume removal with ultrafiltration/dialysis, temporary LVAD support may be needed.

13.6.2 Extracorporeal Membrane Oxygenation (ECMO)

Extracorporeal membrane oxygenation (ECMO) is arguably the most commonly used mechanical support platform for ACHD patients. Most commonly ECMO is used to support ACHD patients who develop acute HF in the postoperative period [60] witnessed as failure to wean from cardiopulmonary bypass. Among 77 CHD patients undergoing HTx between 1988 and 2014, postoperative ECMO was required in 14 patients [61]. Eleven of these patients were placed on ECMO in the operating room due to failure to wean from cardiopulmonary bypass. The remaining three were placed on ECMO within 48 h of surgery due to low cardiac output. Of these 14 patients, 7 died in the hospital. In addition to highlighting poor outcomes with ECMO support, these findings emphasize the importance of ACHD patient selection for cardiac surgeries. ACHD HF patients with significantly reduced ventricular systolic function are especially high risk for acute HF, and candidacy for "exit strategies" (i.e., ECMO transitioning to VAD as a bridge to HTx) is important to consider before surgery is undertaken.

13.6.3 Palliative Care

Palliative care improves quality of life, anxiety, depression, and spiritual well-being in patients with HF [62]. Increasingly, advanced HF teams incorporate palliative care specialists with expertise in symptom management and end-of-life therapies in the care of all patients with HF requiring advanced therapies. Palliative care can be offered in addition to advanced HF therapies or as the mainstay of treatment in those with contraindications to transplant and mechanical circulatory support.

13.7 Peri-/Postoperative Management

The perioperative period has been described as the "Achilles' heel" for transplantation in ACHD patients [48]. In an evaluation of UNOS from 2000 to 2014, graft and cardiovascular dysfunction were found to be the top two reasons for early mortality

and were most likely due to the elevated PVR, allosensitization, and longer donor ischemic times. The management of PH in the perioperative setting is paramount to a successful outcome. Following congenital heart surgery, the incidence of perioperative pulmonary hypertensive crisis is in the range of 2–5% [63]. Pulmonary vasoconstriction leads to right HF and systemic hypotension. Treatment options include inhaled nitric oxide, prostacyclins, endothelin receptor antagonists, phosphodiesterase inhibitors, inotropes, and pressors.

Conclusion

Both HF and ACHD are rapidly growing subspecialties of cardiology, but it is only relatively recently that ACHD HF is being recognized as complication requiring particular expertise. As the number of ACHD patients grows, there will be a shortage of appropriately trained providers to care for them. Over time, advanced fellowships will need to collaborate to adequately train both specialties to handle the vast number of patients with ACHD-related HF [64].

In conclusion, HTx is an effective treatment strategy for selected ACHD patients with end-stage cardiac disease. Diagnosis and treatment of ACHD-related HF rely heavily on the art rather than science of medical practice. A number of opportunities for improving outcomes in patients are identified including:

(1) Earlier collaboration with advanced HF teams
(2) Mitigation of risk through team-based evaluation
(3) Recognition that liver disease, PH, and sensitization play important roles in the risk profile of patients
(4) Assessment of sudden cardiac death risk while awaiting transplantation
(5) Multicenter studies to better define guidelines for transplant
(6) Expert surgical planning involving congenital and transplant surgeons to reduce ischemic time and bleeding risk
(7) Tailored immunosuppression protocols in the posttransplant period
(8) Identification of centers of excellence specializing in transplant ACHD patients
(9) The use of VAD as a bridge to HTX
(10) Palliative care as a vital component of care irrespective of the decision to proceed with HTx or not

References

1. Burchill LJ. Heart transplantation in adult congenital heart disease. Heart. 2016;102:1871–7.
2. Baggen VJ, van den Bosch AE, Eindhoven JA, Schut AW, Cuypers JA, Witsenburg M, de Waart M, van Schaik RH, Zijlstra F, Boersma E, Roos-Hesselink JW. Prognostic value of N-terminal Pro-B-type natriuretic peptide, troponin-T, and growth-differentiation factor 15 in adult congenital heart disease. Circulation. 2017;135:264–79.
3. Giannakoulas G, Dimopoulos K, Bolger AP, Tay EL, Inuzuka R, Bedard E, Davos C, Swan L, Gatzoulis MA. Usefulness of natriuretic peptide levels to predict mortality in adults with congenital heart disease. Am J Cardiol. 2010;105:869–73.

4. Brida M, Dimopoulos K, Kempny A, Liodakis E, Alonso-Gonzalez R, Swan L, Uebing A, Baumgartner H, Gatzoulis MA, Diller GP. Body mass index in adult congenital heart disease. Heart. 2017;103:1250–7.
5. Dimopoulos K, Diller GP, Petraco R, Koltsida E, Giannakoulas G, Tay EL, Best N, Piepoli MF, Francis DP, Poole-Wilson PA, Gatzoulis MA. Hyponatraemia: a strong predictor of mortality in adults with congenital heart disease. Eur Heart J. 2010;31:595–601.
6. Dimopoulos K, Diller GP, Giannakoulas G, Petraco R, Chamaidi A, Karaoli E, Mullen M, Swan L, Piepoli MF, Poole-Wilson PA, Francis DP, Gatzoulis MA. Anemia in adults with congenital heart disease relates to adverse outcome. J Am Coll Cardiol. 2009;54:2093–100.
7. Dimopoulos K, Diller GP, Koltsida E, Pijuan-Domenech A, Papadopoulou SA, Babu-Narayan SV, Salukhe TV, Piepoli MF, Poole-Wilson PA, Best N, Francis DP, Gatzoulis MA. Prevalence, predictors, and prognostic value of renal dysfunction in adults with congenital heart disease. Circulation. 2008;117:2320–8.
8. Schuuring MJ, van Riel AC, Vis JC, Duffels MG, van Straalen JP, Boekholdt SM, Tijssen JG, Mulder BJ, Bouma BJ. High-sensitivity troponin T is associated with poor outcome in adults with pulmonary arterial hypertension due to congenital heart disease. Congenit Heart Dis. 2013;8:520–6.
9. Rodriguez FH 3rd, Moodie DS, Parekh DR, Franklin WJ, Morales DL, Zafar F, Adams GJ, Friedman RA, Rossano JW. Outcomes of heart failure-related hospitalization in adults with congenital heart disease in the United States. Congenit Heart Dis. 2013;8:513–9.
10. John AS, Johnson JA, Khan M, Driscoll DJ, Warnes CA, Cetta F. Clinical outcomes and improved survival in patients with protein-losing enteropathy after the Fontan operation. J Am Coll Cardiol. 2014;64:54–62.
11. Mertens L, Hagler DJ, Sauer U, Somerville J, Gewillig M. Protein-losing enteropathy after the Fontan operation: an international multicenter study. PLE study group. J Thorac Cardiovasc Surg. 1998;115:1063–73.
12. Tobler D, Greutmann M, Colman JM, Greutmann-Yantiri M, Librach LS, Kovacs AH. End-of-life care in hospitalized adults with complex congenital heart disease: care delayed, care denied. Palliat Med. 2012;26:72–9.
13. Ross HJ, Law Y, Book WM, Broberg CS, Burchill L, Cecchin F, Chen JM, Delgado D, Dimopoulos K, Everitt MD, Gatzoulis M, Harris L, Hsu DT, Kuvin JT, Martin CM, Murphy AM, Singh G, Spray TL, Stout KK. American Heart Association Adults With Congenital Heart Disease Committee of the Council on Clinical C, Council on Cardiovascular Disease in the Young tCoCR, Intervention, the Council on Functional G and Translational B. Transplantation and mechanical circulatory support in congenital heart disease: a scientific statement From the American Heart Association. Circulation. 2016;133:802–20.
14. Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, Danziger-Isakov L, Kirklin JK, Kirk R, Kushwaha SS, Lund LH, Potena L, Ross HJ, Taylor DO, Verschuuren EA, Zuckermann A. International Society for Heart Lung Transplantation Infectious Diseases P, Heart F and Transplantation C. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. J Heart Lung Transplant. 2016;35:1–23.
15. Bradley EA, Pinyoluksana KO, Moore-Clingenpeel M, Miao Y, Daniels C. Isolated heart transplant and combined heart-liver transplant in adult congenital heart disease patients: insights from the united network of organ sharing. Int J Cardiol. 2017;228:790–5.
16. Wang A, Book WM, McConnell M, Lyle T, Rodby K, Mahle WT. Prevalence of hepatitis C infection in adult patients who underwent congenital heart surgery prior to screening in 1992. Am J Cardiol. 2007;100:1307–9.
17. Josephus Jitta D, Wagenaar LJ, Mulder BJ, Guichelaar M, Bouman D, van Melle JP. Three cases of hepatocellular carcinoma in Fontan patients: review of the literature and suggestions for hepatic screening. Int J Cardiol. 2016;206:21–6.
18. Menachem JN, Golbus JR, Molina M, Mazurek JA, Hornsby N, Atluri P, Fuller S, Birati EY, Kim YY, Goldberg LR, Wald JW. Successful cardiac transplantation outcomes in patients with adult congenital heart disease. Heart. 2017. https://doi.org/10.1136/heartjnl-2016-310933.

19. Greenway SC, Crossland DS, Hudson M, Martin SR, Myers RP, Prieur T, Hasan A, Kirk R. Fontan-associated liver disease: implications for heart transplantation. J Heart Lung Transplant. 2016;35:26–33.
20. Reich HJ, Awad M, Ruzza A, De Robertis MA, Ramzy D, Nissen N, Colquhoun S, Esmailian F, Trento A, Kobashigawa J, Czer LS. Combined heart and liver transplantation: the Cedars-Sinai experience. Transplant Proc. 2015;47:2722–6.
21. Padegimas A, Molina M, Korwin A, Birati E, Kamoun M. Successful long-term outcomes in combined heart-liver transplants across pre-formed high levels of donor-specific antibodies in highly sensitized patients. J Heart Lung Transplant. 2016;35:1382–4.
22. Lewis M, Ginns J, Schulze C, Lippel M, Chai P, Bacha E, Mancini D, Rosenbaum M, Farr M. Outcomes of adult patients with congenital heart disease after heart transplantation: impact of disease type, previous thoracic surgeries, and bystander organ dysfunction. J Card Fail. 2015;22:578–82.
23. Berg CJ, Bauer BS, Hageman A, Aboulhosn JA, Reardon LC. Mortality Risk Stratification in Fontan Patients Who Underwent Heart Transplantation. Am J Cardiol. 2017;119:1675–9.
24. Drakos SG, Kfoury AG, Gilbert EM, Horne BD, Long JW, Stringham JC, Campbell BA, Renlund DG. Effect of reversible pulmonary hypertension on outcomes after heart transplantation. J Heart Lung Transplant. 2007;26:319–23.
25. Goland S, Czer LS, Kass RM, De Robertis MA, Mirocha J, Coleman B, Capelli C, Raissi S, Cheng W, Fontana G, Trento A. Pre-existing pulmonary hypertension in patients with end-stage heart failure: impact on clinical outcome and hemodynamic follow-up after orthotopic heart transplantation. J Heart Lung Transplant. 2007;26:312–8.
26. Klotz S, Wenzelburger F, Stypmann J, Welp H, Drees G, Schmid C, Scheld HH. Reversible pulmonary hypertension in heart transplant candidates: to transplant or not to transplant. Ann Thorac Surg. 2006;82:1770–3.
27. Tedford RJ, Beaty CA, Mathai SC, Kolb TM, Damico R, Hassoun PM, Leary PJ, Kass DA, Shah AS. Prognostic value of the pre-transplant diastolic pulmonary artery pressure-to-pulmonary capillary wedge pressure gradient in cardiac transplant recipients with pulmonary hypertension. J Heart Lung Transplant. 2014;33:289–97.
28. Costard-Jackle A, Fowler MB. Influence of preoperative pulmonary artery pressure on mortality after heart transplantation: testing of potential reversibility of pulmonary hypertension with nitroprusside is useful in defining a high risk group. J Am Coll Cardiol. 1992;19:48–54.
29. Geft D, Kobashigawa J. Current concepts for sensitized patients before transplantation. Curr Opin Organ Transplant. 2017;22:236–41.
30. Patel ND, Weiss ES, Allen JG, Russell SD, Shah AS, Vricella LA, Conte JV. Heart transplantation for adults with congenital heart disease: analysis of the United network for organ sharing database. Ann Thorac Surg. 2009;88:814–21. discussion 821–2
31. Kaczmarek I, Deutsch MA, Kauke T, Beiras-Fernandez A, Schmoeckel M, Vicol C, Sodian R, Reichart B, Spannagl M, Ueberfuhr P, Donor-specific HLA. alloantibodies: long-term impact on cardiac allograft vasculopathy and mortality after heart transplant. Exp Clin Transplant. 2008;6:229–35.
32. Kobashigawa J, Mehra M, West L, Kerman R, George J, Rose M, Zeevi A, Reinsmoen N, Patel J, Reed EF, Consensus Conference P. Report from a consensus conference on the sensitized patient awaiting heart transplantation. J Heart Lung Transplant. 2009;28:213–25.
33. Nwakanma LU, Williams JA, Weiss ES, Russell SD, Baumgartner WA, Conte JV. Influence of pretransplant panel-reactive antibody on outcomes in 8,160 heart transplant recipients in recent era. Ann Thorac Surg. 2007;84:1556–62. discussion 1562–3
34. Kobashigawa J, Crespo-Leiro MG, Ensminger SM, Reichenspurner H, Angelini A, Berry G, Burke M, Czer L, Hiemann N, Kfoury AG, Mancini D, Mohacsi P, Patel J, Pereira N, Platt JL, Reed EF, Reinsmoen N, Rodriguez ER, Rose ML, Russell SD, Starling R, Suciu-Foca N, Tallaj J, Taylor DO, Van Bakel A, West L, Zeevi A, Zuckermann A, Consensus Conference P. Report from a consensus conference on antibody-mediated rejection in heart transplantation. J Heart Lung Transplant. 2011;30:252–69.

35. Boucek D, Yetman AT, Yeung E, Miyamoto SD, Stehlik J, Kfoury AG, Kaza AK, Weng C, Everitt MD. Survival based on patient selection for heart transplant in adults with congenital heart disease: a multi-institutional study. Int J Cardiol. 2014;172:e89–90.
36. Davies RR, Russo MJ, Yang J, Quaegebeur JM, Mosca RS, Chen JM. Listing and transplanting adults with congenital heart disease. Circulation. 2011;123:759–67.
37. Everitt MD, Donaldson AE, Stehlik J, Kaza AK, Budge D, Alharethi R, Bullock EA, Kfoury AG, Yetman AT. Would access to device therapies improve transplant outcomes for adults with congenital heart disease? Analysis of the United Network for Organ Sharing (UNOS). J Heart Lung Transplant. 2011;30:395–401.
38. Gelow JM, Song HK, Weiss JB, Mudd JO, Broberg CS. Organ allocation in adults with congenital heart disease listed for heart transplant: impact of ventricular assist devices. J Heart Lung Transplant. 2013;32:1059–64.
39. Burchill LJ, Edwards LB, Dipchand AI, Stehlik J, Ross HJ. Impact of adult congenital heart disease on survival and mortality after heart transplantation. J Heart Lung Transplant. 2014;33:1157–63.
40. Mori M, Vega D, Book W, Kogon BE. Heart transplantation in adults with congenital heart disease: 100% survival with operations performed by a surgeon specializing in congenital heart disease in an adult hospital. Ann Thorac Surg. 2015;99:2173–8.
41. Chen JM, Davies RR, Mital SR, Mercando ML, Addonizio LJ, Pinney SP, Hsu DT, Lamour JM, Quaegebeur JM, Mosca RS. Trends and outcomes in transplantation for complex congenital heart disease: 1984 to 2004. Ann Thorac Surg. 2004;78:1352–61. discussion 1352–61
42. Coskun O, Coskun T, El-Arousy M, Parsa MA, Reiss N, Blanz U, Von Knyphausen E, Sandica E, Schulz U, Knobl H, Tenderich G, Bairaktaris A, Kececioglu D, Korfer R. Heart transplantation in adults with congenital heart disease: experience with 15 patients. ASAIO J. 2007;53:103–6.
43. Greutmann M, Pretre R, Furrer L, Bauersfeld U, Turina M, Noll G, Luescher TF, Trindade PT. Heart transplantation in adolescent and adult patients with congenital heart disease: a case-control study. Transplant Proc. 2009;41:3821–6.
44. Irving C, Parry G, O'Sullivan J, Dark JH, Kirk R, Crossland DS, Chaudhari M, Griselli M, Hamilton JR, Hasan A. Cardiac transplantation in adults with congenital heart disease. Heart. 2010;96:1217–22.
45. Izquierdo MT, Almenar L, Martinez-Dolz L, Moro J, Aguero J, Sanchez-Lazaro I, Cano O, Ortiz V, Sanchez R, Salvador A. Mortality after heart transplantation in adults with congenital heart disease: a single-center experience. Transplant Proc. 2007;39:2357–9.
46. Jayakumar KA, Addonizio LJ, Kichuk-Chrisant MR, Galantowicz ME, Lamour JM, Quaegebeur JM, Hsu DT. Cardiac transplantation after the Fontan or Glenn procedure. J Am Coll Cardiol. 2004;44:2065–72.
47. Seddio F, Gorislavets N, Iacovoni A, Cugola D, Fontana A, Galletti L, Terzi A, Ferrazzi P. Is heart transplantation for complex congenital heart disease a good option? A 25-year single centre experience. Eur J Cardiothoracic Surg. 2013;43:605–11. discussion 611
48. Shah DK, Deo SV, Althouse AD, Teuteberg JJ, Park SJ, Kormos RL, Burkhart HM, Morell VO. Perioperative mortality is the Achilles heel for cardiac transplantation in adults with congenital heart disease: evidence from analysis of the UNOS registry. J Card Surg. 2016;31:755–64.
49. Lamour JM, Addonizio LJ, Galantowicz ME, Quaegebeur JM, Mancini DM, Kichuk MR, Beniaminovitz A, Michler RE, Weinberg A, Hsu DT. Outcome after orthotopic cardiac transplantation in adults with congenital heart disease. Circulation. 1999;100:II200–5.
50. Doumouras BS, Alba AC, Foroutan F, Burchill LJ, Dipchand AI, Ross HJ. Outcomes in adult congenital heart disease patients undergoing heart transplantation: a systematic review and meta-analysis. J Heart Lung Transplant. 2016;35:1337–47.
51. VanderPluym CJ, Cedars A, Eghtesady P, Maxwell BG, Gelow JM, Burchill LJ, Maltais S, Koehl DA, Cantor RS, Blume ED. Outcomes following implantation of mechanical circulatory support in adults with congenital heart disease: an analysis of the Interagency Registry

for Mechanically Assisted Circulatory Support (INTERMACS). J Heart Lung Transplant. 2017;37:88–99.
52. Schweiger M, Falk V, Biry M, Hubler M, Wilhelm MJ. Biventricular failure in dextro-transposition of the great arteries corrected with the Mustard procedure: VAD support of the systemic ventricle is enough. Int J Artif Organs. 2015;38:233–5.
53. Maly J, Netuka I, Besik J, Dorazilova Z, Pirk J, Szarszoi O. Bridge to transplantation with long-term mechanical assist device in adults after the Mustard procedure. J Heart Lung Transplant. 2015;34:1177–81.
54. Peng E, O'Sullivan JJ, Griselli M, Roysam C, Crossland D, Chaudhari M, Wrightson N, Butt T, Parry G, MacGowan GA, Schueler S, Hasan A. Durable ventricular assist device support for failing systemic morphologic right ventricle: early results. Ann Thorac Surg. 2014;98:2122–9.
55. Poh CL, Chiletti R, Zannino D, Brizard C, Konstantinov IE, Horton S, Millar J, d'Udekem Y. Ventricular assist device support in patients with single ventricles: the Melbourne experience dagger. Interact Cardiovasc Thorac Surg. 2017;25:310–6.
56. Stokes MB, Saxena P, McGiffin DC, Marasco S, Leet AS, Bergin P. Successful bridge to orthotopic cardiac transplantation with implantation of a HeartWare HVAD in management of systemic right ventricular failure in a patient with transposition of the great arteries and previous atrial switch procedure. Heart Lung Circ. 2016;25:e69–71.
57. Awad M, Czer LS, De Robertis MA, Mirocha J, Ruzza A, Rafiei M, Reich H, Trento A, Moriguchi J, Kobashigawa J, Esmailian F, Arabia F, Ramzy D. Adult heart transplantation following ventricular assist device implantation: early and late outcomes. Transplant Proc. 2016;48:158–66.
58. Ko BS, Drakos S, Kfoury AG, Hurst D, Stoddard GJ, Willis CA, Delgado JC, Hammond EH, Gilbert EM, Alharethi R, Revelo MP, Nativi-Nicolau J, Reid BB, McKellar SH, Wever-Pinzon O, Miller DV, Eckels DD, Fang JC, Selzman CH, Stehlik J, Utah Transplant Affiliated Hospitals Cardiac Transplant P. Immunologic effects of continuous-flow left ventricular assist devices before and after heart transplant. J Heart Lung Transplant. 2016;35:1024–30.
59. Menachem JN, Swaminathan AC, Bashore TM, Ward CC, Rogers JG, Milano CA, Patel CB. Initial experience of left ventricular assist device support for adult patients with transposition of the great vessels. Congenit Heart Dis. 2015;10:382–6.
60. Clark JB, Pauliks LB, Myers JL, Undar A. Mechanical circulatory support for end-stage heart failure in repaired and palliated congenital heart disease. Curr Cardiol Rev. 2011;7:102–9.
61. Shi WY, Saxena P, Yong MS, Marasco SF, McGiffin DC, Shipp A, Weintraub RG, d'Udekem Y, Brizard CP, Konstantinov IE. Increasing complexity of heart transplantation in patients with congenital heart disease. Semin Thorac Cardiovasc Surg. 2016;28:487–97.
62. Rogers JG, Patel CB, Mentz RJ, Granger BB, Steinhauser KE, Fiuzat M, Adams PA, Speck A, Johnson KS, Krishnamoorthy A, Yang H, Anstrom KJ, Dodson GC, Taylor DH Jr, Kirchner JL, Mark DB, O'Connor CM, Tulsky JA. Palliative care in heart failure: the PAL-HF randomized, controlled clinical trial. J Am Coll Cardiol. 2017;70:331–41.
63. Brunner N, de Jesus Perez VA, Richter A, Haddad F, Denault A, Rojas V, Yuan K, Orcholski M, Liao X. Perioperative pharmacological management of pulmonary hypertensive crisis during congenital heart surgery. Pulm Circ. 2014;4:10–24.
64. Menachem JN. Advanced heart failure in the ACHD population: finding the fellows' role in a growing field. J Am Coll Cardiol. 2017;69:1986–9.

Holistic Care and Palliation

14

Matthias Greutmann, Gudrun Theile, and Daniel Tobler

14.1 Introduction

Adults with congenital heart disease comprise a rapidly growing cohort of complex patients in adult cardiology [1, 2]. There is no doubt that many of these adult survivors are at high risk of developing (heart) failure, as many surgical repair procedures are rather palliative in nature and by no means curative [3, 4]. Although a lot of efforts are made to improve survival and to find novel treatment concepts for these patients, we have to accept that for many patients, no viable treatment options will be available and many will be at high risk of dying from their disease as young and middle-aged adults [5]. Although our ability to 'cure' these patients may be limited, our ability to support our patients with non-strictly 'medical' measures is substantial and may have an important impact on patients' quality of life and a self-determined and dignified end of life [6, 7]. Hence in this chapter, we will focus on measures of patient support, advance care planning and end-of-life care.

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14.2 The Concept of Comprehensive Care

Case vignette 1: A 17-year-old male patient is attending for his first outpatient visit in the ACHD clinic accompanied by his mother. He was born with hypoplastic left heart syndrome and underwent staged Norwood palliation. After Fontan completion, he had a relatively uncomplicated clinical course but is known to have significant neo-aortic root dilatation of 5.2 cm, moderate neo-aortic regurgitation and moderately impaired systolic function of the right single ventricle. He was diagnosed with attention deficit disorder at the age of 13 years and struggled with his performance throughout school time. He never had a deepened discussion about his underlying heart condition, potential long-term complications and counselling regarding physical activity. The patient and his mother report that they are very glad that the patient finally found a post for apprenticeship training as a construction worker, which will start next week and includes heavy physical work.

The above-mentioned case vignette illustrates that successful care for patients with congenital heart disease includes a variety of non-medical issues that play an important role for the overall well-being of patients. This includes, for example, counselling about appropriate choices for professions. If such discussions are neglected, patients may get involved in activities that may inflict their long-term prognosis.

Important aspects that need to be included into routine clinical practice are (1) the anticipation of the general future disease trajectory and possible complications, (2) an appreciation of medical and non-medical measures that may interfere with optimal outcomes and (3) appropriate education and information of affected patients and families. Only careful, comprehensive and repeated information about their medical condition and about potential long-term outcomes, along with careful, non-directive counselling, will enable patients to informed decision-making throughout their lives. This informed decision-making is not only relevant for medical issues, such as reoperation or re-intervention, but reaches far beyond, including decision-making, for example, regarding the choice of a profession or about family planning.

This led to the evolution of the concept of comprehensive care that was adapted from care in patients with chronic heart failure and is illustrated in Fig. 14.1 [6, 8].

The concept of comprehensive care combines cardiac care, supportive care and measures of palliative care adjusted and matched to the individual patient's stage of disease and circumstances of living. The different categories of care are by no means exclusive or sequential but rather complement each other in every stage of cardiac disease, as illustrated in Fig. 14.1. More often than not, borders between supportive, palliative and cardiac care are blurred or may go hand in hand. For example, instituting or maintaining diuretic therapy in patients with end-stage heart failure may be the most effective measure to relieve the symptom of breathlessness and may well be combined with initiation of opioid therapy.

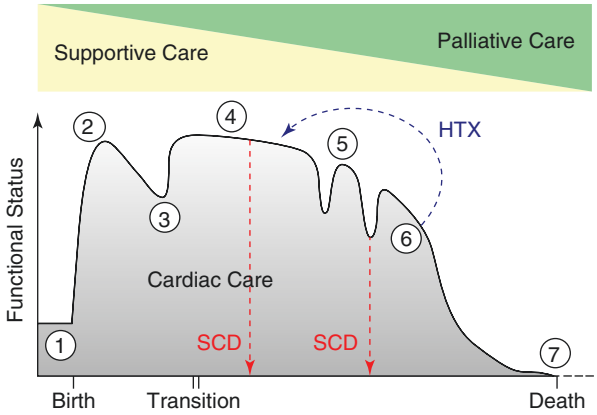

Fig. 14.1 Illustration of the comprehensive care model with stages of disease in patients with congenital heart disease (Modified from Greutmann and Tobler et al. with permission) [8]. Disease stages in congenital heart disease covering the entire lifespan (*x*-axis). The *y*-axis depicts the functional status along the different disease stages. Numbers 1–7 represent the several stages of comprehensive care in patients with congenital heart disease: (1) parental prenatal support, (2) initial surgical repair/palliation, (3) re-interventions during childhood or adolescence, (4) plateau of variable lengths in adulthood, (5) variable adverse cardiac events and functional decline with variable slope, intermittent exacerbations that respond to rescue efforts and/or adult re-interventions or procedures, (6) refractory symptoms and limited function and (7) end-of-life care including bereavement care. Dotted line with arrowhead represents possible occurrence of sudden cardiac death events. *SCD* sudden cardiac death, *CHD* congenital heart disease, *HTX* heart transplantation

14.3 Important Aspects of Supportive Care

A 48-year-old female patient was born with complex pulmonary atresia and hypoplastic left lung, palliated with a Waterston shunt in infancy. At the age of 29 years, when she contemplated child adoption, she was told that her life expectancy was estimated at around 50 years. She later divorced and was then living alone, working full-time as an accountant. Exercise capacity had gradually declined over the past several years, and the patient complained of increasing fatigue and a feeling of exhaustion after her 8 h workdays. This led to social isolation as the patient was no longer able to attend any social activities after work. She frequently called in for emergent outpatient clinic visits for non-specific muscle pains, headaches and dizziness accompanied by anxiety. She complained of increasing struggles being home alone for fear of not being able to call the emergency services in case of medical complications.

A full workup did not reveal any target for further palliative surgery or intervention nor for specific medical therapy. Psychiatric assessment confirmed reactive anxiety disorder. A number of measures were initiated to support the patient. This included enrolment in an outpatient cardiac rehab programme. On completion of the programme, peak aerobic capacity remained unchanged, the patient, however, felt much more confident in her physical capacity and the diffuse muscle pains had completely resolved. She was encouraged her to apply for disability pension, which was granted and allowed the patient to reduce her workload to half-days. This led to a markedly improved stamina and increased her ability for participation in social activities. At last, the patient was encouraged to attend meetings of the patient self-support organization. The contact with other patients was extremely helpful and relieving, and the patient even incurred an active role organizing meetings within the patient organization.

This case vignette illustrates the many facets of supportive care and the wide range of people and services that may be involved in providing supportive care. While some aspects of supportive care, for example, recommendations about recreational sports, travelling or healthy lifestyle behaviours, have already been integrated in routine care at many centres, studies have shown that other aspects, such as discussions about prognosis, advance care planning or end-of-life care, are still often neglected [9–11]. Figure 14.2 illustrates the many players and tasks that supportive care involves in adolescents and adults with congenital heart disease. These aspects of care go far beyond pure medical care and often require out of the box

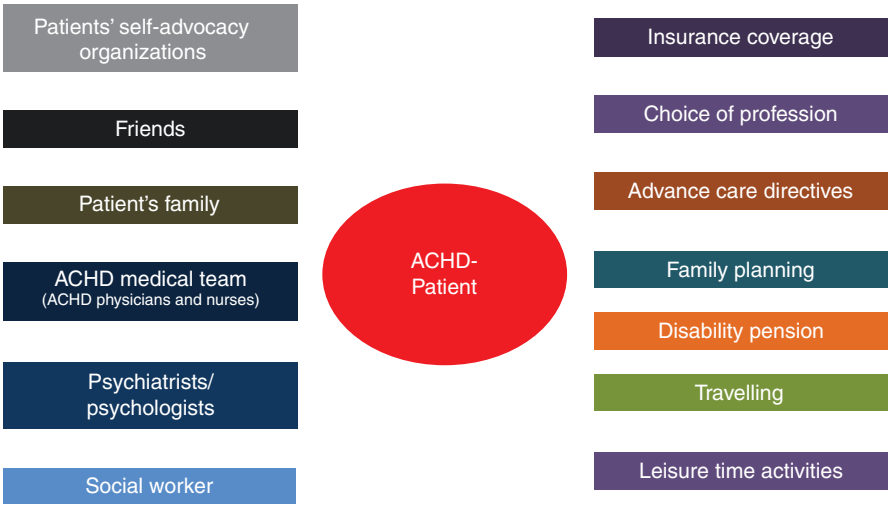

Fig. 14.2 Network and tasks of supportive care in adult congenital heart disease

thinking. Nonetheless, these aspects of care may have an important impact on the patient's quality of life, and it may be important to invest in developing comprehensive care networks in the future. Peer support by other affected patients is particularly important and underdeveloped source of support.

14.4 Important Aspects of Palliative Care

After reparative surgery in infancy, most patients, even those with complex congenital heart defects, experience a relatively stable disease course during childhood and adolescence. Long-term complications and the life-shortening nature of the underlying heart condition are often not discussed during paediatric visits and may thus leave patients and families with the erroneous concept of 'cure' or 'total correction' [12]. Questions about long-term complications or longevity often surface in adult life, when first complications occur or when important life decisions have to be made, such as career planning, insurance issues and family planning [13]. The following part of the chapter will discuss aspects of advance care planning and principles of palliative care in adults with congenital heart disease.

14.4.1 Advance Care Planning: Hope for the Best Yet Prepare for the Worst

The goal of advance care planning is to guide medical teams and family members about future care, should a patient become incapable to speak for him- or herself. It enhances patients' autonomy and self-determination in important aspects such as end-of-life care. It may prevent overly aggressive or futile treatment at the end of life, for which adults with congenital heart disease are at particularly high risk.

There are many available resources to support the creation of an advance directives document (e.g. https://agingwithdignity.org and http://advancecareplanning.ca). Such documents allow expressing important personal wishes, views and values about life and dying in a formalized way. As an important part of advance care planning, patients are encouraged to identify a substitute or 'proxy' decision-maker that may be approached by the medical team to assist with decision-making, once difficult treatment decisions must be made and the patient is unable to communicate. Adult congenital heart disease physicians play an important role in supporting patients in the completion of advance directives.

Although recommended by guidelines, studies have shown that early completion of advance directives is rather the exemption than the rule and there is lot of room for improvement in this aspect in routine clinical care [9, 11]. In our opinion, encouraging advance care planning is one of the most important tasks regarding end-of-life care during medically stable phases in adults with congenital heart disease, and discussions about advance care planning should be integrated in routine clinical care, either by adult congenital heart disease physicians or specialist nurses. Discussions about advance care planning may allow exploring patients' readiness and interest to

learn more about the nature of their heart disease, the variations in disease trajectories, potential long-term complications and anticipated life expectancy. Adult congenital heart disease physicians often have a very close patient-doctor relationship evolving over years, or even decades that represents both an opportunity and an obligation to explore patients' readiness and wishes for more deepened discussions about their heart condition and longer-term health expectations [8, 14]. These discussions should not be regarded as a single event but rather an ongoing process along the journey we follow with our patients. Patients' views and preferences may change over time as does their readiness to discuss such sensitive issues. Advance directives documents, once completed, should be made readily available at any time, and it may be wise to flag such documents in the patient's chart.

Practical recommendations for effective communication about advance care planning or end-of-life issues are outlined in Table 14.1, reprinted with permission

Table 14.1 The ask-tell-ask cycle (with permission from Kovacs et al. [14])

Ask	*Ask what patients currently understand about their CHD and what they would like to know*	• Tell me what you understand about your congenital heart disease, and what you expect? • What have other doctors or nurses told you about what to expect down the road? • What would you like to know about your health? • How would you like decisions to be made about your health care? • What have you told your family or other doctors you want when the time comes that your heart or breathing stops? • What worries do you have?
Tell	*Provide information that is requested by the patients or is important to communicate to them*	• You asked about how long I think you will live. Based upon how your health is doing now, we would expect that you have several months/a few years/a few decades. Of course, this kind of thing is not easy to predict and some patients live shorter and some live longer than we expect. • When your heart or breathing stops, we can either try to revive you or allow you to die naturally. • I am afraid we have reached a phase in your illness in which you will near the end of life. • We are at a turning point in your heart disease, and there are choices about which road to take. • I try to talk with all patients about what they would like to happen when they become very ill or near death. These might not be easy things to discuss, but it is very important that we know your preferences for end-of-life care and who you want to make your decisions about your health if you become unable to do so. Talking about this now will help your family if ever they need to make decisions on your behalf.
Ask	*Confirm an understanding of what was said and provide an opportunity for patients to ask follow-up questions*	• It is important that I explain things clearly to you. Please tell me what you understood. • What questions do you have?

from Kovacs et al. [14]. When talking with patients about their prognosis, it must be emphasized that an exact estimation of life expectancy is never possible and the best we can provide is a general range of expected length of life for patients with a similar condition (e.g. weeks, months, years or decades) based on published literature and one's personal experience. The limited evidence base of estimations about prognosis should be openly acknowledged.

14.4.2 Principles of Palliative Care in End-Stage Heart Failure

Care for patients with end-stage heart failure and care of the dying patient require teamwork that involves many subspecialties, including palliative care specialists. Although many concepts can be adopted from care for patients with heart failure from acquired heart disease, several aspects are unique to adults with congenital heart disease [7].

- Adults with congenital heart disease typically die from their heart disease at a younger age than adults with acquired heart disease. This can be particularly difficult and distressing for patients, families and healthcare providers [15]. This also appears to lead to an elevated risk of receiving overly aggressive or futile treatment before death ensues [10].
- The focus of care for patients with CHD has traditionally been advances in life-prolonging measures and interventions. The transition of care towards principles of palliative care, rather than life-prolonging care, represents a major shift and may cause cardiologists to avoid 'do not resuscitate' discussions or other anticipatory planning despite futility of aggressive treatment.
- In contrast to heart failure from acquired heart disease, in which risk models have been developed to predict timing of death, such reliable tools and scores do not exist for adults with congenital heart disease, and prognostication remains difficult [16, 17].
- The socio-professional situation of CHD patients is often very different from that of older adults and elderly patients followed in heart failure clinics. For younger and middle-aged adults with CHD, a decline in functional status may interrupt careers long before retirement age and may occur within complex family systems. Financial difficulties and lack of appropriate insurance in many countries may add to the distress of dying.

Adult congenital heart disease physicians are tasked with the responsibility to develop dedicated multidisciplinary teams within our programmes to address the special and specific needs of patients. The introduction of palliative care should occur early and concurrently with continued specialized medical care as appropriate. It should be seen as a helpful adjunct rather that as an alternative to ongoing conventional medical care. The concurrent and timely approach will enhance the acceptance of palliative care concepts that have the ability to improve quality of life, especially in the end stage of disease (for an overview on principles of opioid

therapy, see Box 14.1). It is important to involve patients' families, who have supported their loved ones for decades. After a patient's death, condolence by a telephone call or a condolence card is important. The offer of an appointment a few weeks after the patient's death offering the opportunity to discuss remaining open questions or simply to talk to people, who knew the deceased well, often gives a great relief to families and is well appreciated. This may be particularly important when a death occurred unexpectedly [14]. The demise of such a patient may thus be traumatic for the medical team as well. Professionals should thus acknowledge emotional reactions of team members and try to provide opportunities to discuss the death of our patients within the team to improve coping with such situations [14].

Box 14.1 Principles of Opioid Therapy for Symptom Management (Dyspnoea, Pain) in End-Stage Disease

Principles of opioid administration and titration

- Start low, increase slow.
- Broad range of available routes of administration: oral, subcutaneous, intravenous, transdermal, rarely intramuscular or rectal application.
- In opioid naive patients, short-lasting preparations are recommended. Titrate to effective dose, and then change to long-lasting preparations.
- In patients with dyspnoea, frequent boluses may be more effective than long-lasting preparations or continuous infusion. Remember to administer non-medical support: fresh air, ventilation, comfortable position and calmness of supporting personnel.
- In patients with pain, after initial titration, long-lasting preparations are preferred. Never forget to prescribe additional short-lasting preparation for acute pain crises (a sixth of daily dosage per bolus, maximally once per hour).
- Transdermal application is not recommended in cachectic patients.
- In case of renal insufficiency, remember to avoid morphine (due to accumulation of active metabolites); buprenorphine is preferred; fentanyl and hydromorphone are possible alternatives. In patients on dialysis, fentanyl and methadone are viable choices.

Management of side effects

- Always inform patients about potential and frequent side effects: Nausea, drowsiness and tiredness are transient; constipation will stay! Thus, always prescribe pre-emptively laxatives.
- Nausea: Metoclopramide is first choice (less QT prolonging than other antiemetics and additionally propulsive).

- Constipation: At least use a substance to increase faecal bulk and, if necessary, add stimulants. Avoid osmotic laxatives (especially lactulose causes relevant flatulence/aerogastrocolia). Enemas and suppositories are second choice. In refractory constipation caused by opioids, naloxone or methylnaltrexone may be tried.
- Don't forget opioids may also cause urinary retention.
- Pruritus due to mast cell activation: Switch to another opioid.
- Hallucination: Switch opioid preparation before administering antipsychotics. Review co-medication for potential other triggers for hallucination. Consider terminal delirium as a differential diagnosis.

References

1. Marelli AJ, Ionescu-Ittu R, Mackie AS, Guo L, Dendukuri N, Kaouache M. Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. Circulation. 2014;130(9):749–56.
2. Padrutt M, Bracher I, Bonassin F, Santos Lopes B, Gruner C, Stampfli SF, et al. Impact of growing cohorts of adults with con-genital heart disease on clinical workload: a 20-year experience at a tertiary care centre. Swiss Med Wkly. 2017;147:w14443.
3. Greutmann M, Tobler D. Changing epidemiology and mortality in adult congenital heart disease: looking into the future. Futur Cardiol. 2012;8(2):171–7.
4. Diller GP, Kempny A, Alonso-Gonzalez R, Swan L, Uebing A, Li W, et al. Survival prospects and circumstances of death in contemporary adult congenital heart disease patients under follow-up at a large tertiary care centre. Circulation. 2015;132(22):2118–25.
5. Greutmann M, Tobler D, Kovacs AH, Greutmann-Yantiri M, Haile SR, Held L, et al. Increasing mortality burden among adults with complex congenital heart disease. Congenit Heart Dis. 2015;10(2):117–27.
6. Goodlin SJ. Palliative care in congestive heart failure. J Am Coll Cardiol. 2009;54(5):386–96.
7. Tobler D, de Stoutz N, Greutmann M. Supportive and palliative care for adults dying from congenital heart defect. Curr Opin Support Palliat Care. 2011;5(3):291–6.
8. Greutmann M, Tobler D, Colman JM, Greutmann-Yantiri M, Librach SL, Kovacs AH. Facilitators of and barriers to advance care planning in adult congenital heart disease. Congenit Heart Dis. 2013;8(4):281–8.
9. Tobler D, Greutmann M, Colman JM, Greutmann-Yantiri M, Librach LS, Kovacs AH. End-of-life in adults with congenital heart disease: a call for early communication. Int J Cardiol. 2012;155(3):383–7.
10. Tobler D, Greutmann M, Colman JM, Greutmann-Yantiri M, Librach LS, Kovacs AH. End-of-life care in hospitalized adults with complex congenital heart disease: care delayed, care denied. Palliat Med. 2012;26(1):72–9.
11. Tobler D, Greutmann M, Colman JM, Greutmann-Yantiri M, Librach SL, Kovacs AH. Knowledge of and preference for advance care planning by adults with congenital heart disease. Am J Cardiol. 2012;109(12):1797–800.
12. Stark J. Do we really correct congenital heart defects? J Thorac Cardiovasc Surg. 1989;97(1):1–9.
13. Kovacs AH, Silversides C, Saidi A, Sears SF. The role of the psychologist in adult congenital heart disease. Cardiol Clin. 2006;24(4):607–18. vi

14. Kovacs AH, Landzberg MJ, Goodlin SJ. Advance care planning and end-of-life management of adult patients with congenital heart disease. World J Pediatr Congenit Heart Surg. 2013;4(1):62–9.
15. Badger JM. Factors that enable or complicate end-of-life transitions in critical care. Am J Crit Care. 2005;14(6):513–21.
16. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. JAMA. 2003;290(19):2581–7.
17. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation. 2006;113(11):1424–33.

Future Research

15

Konstantinos Dimopoulos and Alessia David

Acronyms

ACE	Angiotensin-converting enzyme
CHD	Congenital heart disease
PAH	Pulmonary arterial hypertension
PAH-CHD	Pulmonary arterial hypertension related to congenital heart disease
SNPs	Single nucleotide polymorphisms
TCPC	Total cavopulmonary connection

15.1 Introduction

As heart failure (HF) is becoming ever more common in congenital heart disease (CHD), there is increasing need for studies to support clinical practice. Indeed, current practice in non-congenital heart failure is largely evidence-based, supported by randomized trials [1]. Unfortunately, this is not the case in CHD, and practice is often based on soft evidence from cohort studies and expert consensus, resulting in significant variation between centres in terms of management and use of medication and devices. Most current practice guidelines (American Heart Association and European Society of Cardiology) are evidence level C (very limited populations are

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evaluated, consensus of opinion of the experts and case studies), and a minority are level B (limited population is evaluated or single randomized or non-randomized studies) [2, 3]. Randomized controlled trials have been attempted, but most have failed to prove a benefit from medical therapies [4–6] often due to study design, sample size and the large heterogeneity of the CHD population. Extrapolating from studies performed in non-congenital patients may appear reasonable in certain conditions but is not without risks and remains controversial [7].

A general lack of funding has also limited research in CHD, compared to other types of cardiovascular disease. Despite CHD being the most common inborn condition, significantly more common than, for example, pulmonary arterial hypertension and other orphan conditions, which have received the attention of industry and funding bodies, large international multicentre randomized trials have not been funded in CHD. As the CHD population ages, long-term complications become more common, and the need for evidence to guide practice will become stronger. It is, thus, increasingly important that efforts are made to support research in addressing the most important clinical dilemmas in CHD, which include heart failure.

Gurvitz et al. recently produced a consensus statement of the National Heart, Lung, and Blood Institute (NHLBI) and Adult Congenital Heart Association [8] on emerging research directions for adult CHD patients (Table 15.1). They identified heart failure, vascular disease, multisystem complications and "foundation gaps" as high-priority research topics. This chapter provides an overview of some of the areas of need and potential future research in CHD and more specifically heart failure related to CHD.

15.2 The Mechanisms of Heart Failure in CHD

The first step in understanding how heart failure and exercise intolerance in CHD should be managed is by examining the underlying mechanisms responsible for its development and identifying the most common modifiable causes [9]. These

Table 15.1 Emerging research directions in adult congenital heart disease according to a report from a NHLBI/ACHA Working Group [8]

Research area of need
Heart failure
– In tetralogy of Fallot
– Transplantation and mechanical circulatory support
– Sudden cardiac death
Vascular disease
– Outcomes in coarctation of the aorta
Multisystem complications
– Multisystem involvement in single-ventricle disease
– Cognitive and psychiatric outcomes
– Pregnancy
Other gaps
– Epidemiological understanding of the CHD population
– Biological mechanistic and translational work
– Multidisciplinary approach

mechanisms, which are described in the preceding chapters, are potential targets for treatment. Common cardiac causes can be classified into those leading to ventricular dysfunction or chronotropic incompetence [10]. A growing area of concern in the ACHD HF field is that of HF with preserved ejection fraction. This is becoming increasingly recognized and is extremely difficult to manage [11, 12]. Even in acquired HF, the understanding of HF driven by anything other than isolated impaired LV systolic dysfunction is limited. Finally, chronotropic incompetence is common and is an under-investigated component of effort intolerance and HF [13]. Non-cardiac causes of exercise intolerance and heart failure also warrant further research [14–16].

15.3 Overview of CHD Research

Future research should aim at improving our understanding of the pathophysiology of HF related to CHD and in developing new strategies for its optimal management. Moreover, ways of delaying or preventing its development should be sought. This will include developing a better understanding of the interplay of CHD, ageing and the components of acquired heart disease risk. Finally, in the years to come, genetics are likely to inform and direct clinical management, both in terms of prevention and treatment.

15.3.1 Collaborative Research in CHD

In view of the heterogeneity of mechanisms behind HF in CHD, significant expertise is required to identify targets for treatment within specific populations. CHD is heterogeneous, even within individual conditions, not least due to differences in surgical approaches over previous decades and the variety of long-term sequelae. Heterogeneity increases variance and makes identification of the effect of an intervention less likely, unless a large sample size can be achieved.

The only way to overcome this problem is to establish worldwide research networks that promote collaborative studies. One of the most remarkable collaboration studies in CHD was published by Ohye et al. on the Norwood procedure [17]. Over 500 patients with hypoplastic left heart syndrome were enrolled from 15 centres and randomized to a Norwood procedure with either a B-T shunt or RV-to-PA conduit, demonstrating the superiority of the RV-to-PA conduit, at least in the short term. Another such example was the international study from Kempny et al. where a large number of adult CHD and PAH centres came together to study prognostication in Eisenmenger syndrome. Over 1000 patients with this rare condition were included. The large sample size and significant event rate enabled the authors to assess a large number of potential predictors of outcome and to generate powerful multivariate models [18].

Collaboration at such a scale is not easy. There are ethical and legal issues around sharing data, including confidentiality, consent and storing of personal data.

Collaboration requires resources, uniform definitions and strict protocols for data collection. Registries should be designed with specific hypotheses in mind and both derivation and validation cohorts identified when producing prediction models. CHD registries should also linked to biobanks of biological and genetic samples. Such registries can be used to guide the design and power calculation of future intervention and genetic studies.

Finally, CHD research needs to be multidisciplinary. Pregnancy, arrhythmia, anaesthesia and transplantation are all rich grounds for collaborative research with colleagues from other disciplines.

The following sections provide a brief overview of major areas of research in CHD.

15.3.2 Risk Stratification Strategies in Heart Failure

Identifying risk factors for clinically relevant outcomes, including HF and death, is the first step to early diagnosis and prevention. A significant number of papers have been published on predictors of outcome in adult CHD as a whole and within major CHD groups. For example, much is known on predictors of death (and/or malignant tachycardias) in patients with tetralogy of Fallot, and risk stratification models have been proposed, and are often used in clinical practice [2, 19]. Clinical parameters related to the risk of death have also been published for patients with Eisenmenger syndrome. Unfortunately, to date, no validated risk score has been published in adult CHD, and doubts remain on the wider clinical applicability of published risk parameters and scores. Derivation and validation of risk scores are likely to only be achieved within large, carefully designed international registries.

15.3.3 Pharmacotherapy

Neurohormonal activation is well described in CHD, but despite several attempts, there are no large randomized trials of pharmacotherapy that use hard endpoints (e.g. mortality) in CHD (see Chap. 11) [20–22]. Large, carefully designed studies, with enough follow-up time (or event driven) to allow for adequate powering, are urgently needed to explore the role of afterload reduction, beta blockade and novel strategies, such as angiotensin receptor-neprilysin inhibition or sinus-node inhibition in ventricular dysfunction [23, 24].

Anticoagulation is commonly used in patients with CHD. However, in many conditions, the prescription of anticoagulation remains inconsistent and controversial (e.g. in Fontan patients). Given that therapy is likely to be lifelong and that many of these patients have an increased bleeding risk, further evidence of efficacy, or harm, would be highly beneficial. Moreover, the limitations of anticoagulation with vitamin K antagonists (e.g. warfarin) are well recognized. There is, thus, urgent need for international collaboration studies examining indications for

anticoagulation and the role of novel anticoagulants. (Note: An international registry supported by the International Society for Adult CHD is currently under way assessing the efficacy and safety of non-vitamin K anticoagulants [25].)

15.3.4 Non-pharmacologic Management

Exercise and physical training can produce significant health benefits, and indeed, all components of cardiac rehabilitation should be addressed in patients with CHD and heart failure [26]. There are few but promising studies on exercise and rehabilitation in CHD, but guidelines and consensus statements on exercise prescription are currently supported by very little evidence [27–30]. Therefore, studies of structured exercise training and life modification are required, with a focus on long-term, home-based programmes, with remote telemonitoring using modern technology [31].

15.4 Research in Specific Types of CHD

15.4.1 Univentricular Hearts

Heart failure is a common finding in the population of palliated univentricular circulation patients. Research hypotheses in this area include afterload reduction and beta blockade for the impaired systemic ventricle and the use of pulmonary vasodilators to reduce pulmonary vascular resistance when there is Fontan failure or protein losing enteropathy. Other non-HF questions include the management of liver complications and the optimal care of those contemplating pregnancy.

With successes in surgery over the last two decades, an increasing number of patients with hypoplastic left heart syndrome are reaching ACHD services. This population is at significant risk of heart failure and premature death [32]. Urgent work is required to understand how to optimize the management of this emerging population, including medical treatment and the timing of referral for transplantation.

15.4.2 Pulmonary Hypertension

Eisenmenger syndrome, the extreme end of the spectrum of pulmonary arterial hypertension in CHD, has received most of the attention, and is the type of pulmonary arterial hypertension related to CHD (PAH-CHD) with the most evidence [33, 34]. However, other forms of PAH-CHD require attention. A small proportion of patients develops PAH after timely repair of a septal defect (or PAH persists after repair). Little is still known, however, on the criteria that should be used to decide on the operability of patients with raised pulmonary vascular disease, with poor

correlation between histology, haemodynamics and long-term outcome [16, 35–37]. Further studies are needed in the form of well-designed registries to identify reliable clinical criteria for operability and the role of pulmonary vasodilators to optimize outcome, including the treat-and-repair approach and fenestrated/valved techniques for septal defect closure [38, 39].

15.5 Interventional Procedures and Devices

Transcatheter approaches are now routinely used as first line in the repair of atrial and ventricular septal defects, as well as redo pulmonary valve replacement. However, they have a limited role in terms of the types of defects they can be used to treat. Transcatheter aortic valve replacement is still currently used only in patients who cannot undergo surgery, while transcatheter pulmonary valve replacement is currently offered to patients with a previous pulmonary valve prostheses or conduit. Research is ongoing to develop devices that are safer and can be used in a larger spectrum of patients with CHD. A percutaneous pulmonary valve that can be implanted in a native right ventricular outflow tract in patients with tetralogy of Fallot has been developed, but needs further long-term evaluation as do some of the newer valve repair devices. Hybrid approaches, involving collaboration between interventionalists and surgeons, may be of particular value in the high-risk HF patient, and ongoing research is needed to assess their safety, efficacy and long-term outcome [40].

New invasive haemodynamic monitoring devices are now available to remotely monitor pulmonary pressures and detect early decompensation. The role of such devices in ACHD is another interesting avenue for investigation [41].

Ventricular dyssynchrony significantly affects cardiac function and is present in patients with CHD-related HF. Randomized trials of resynchronization are lacking, especially in patients with a systemic right ventricle and those with a complete right bundle branch block [42, 43]. The role of novel resynchronization strategies warrants further exploration.

Other acquired HF devices are finding their way into the ACHD field. These include the use of atrial septal defect devices. Atrial septostomy is recommended in advanced pulmonary hypertension with the purpose of “offloading” the right ventricle and increasing cardiac output [44]. Atrial septostomy has also been advocated for patients with left-sided heart failure, as a means of reducing left atrial pressure and improving exercise capacity [45]. In non-congenital HF and preserved ejection fraction, implantation of an interatrial shunt device (IASD, Corvia Medical, MA, USA) reduced left atrial pressure during exercise and improved 6 min walk distance [46, 47]. Another smaller study demonstrated the safety of atrial septal fenestration in patients with reduced ejection fraction [48].

Baroreceptor stimulator devices are aimed at targeting sympathetic activation in HF and regulating cardiovascular activity. Preliminary data are promising, and a large study in acquired heart failure is ongoing [49, 50]. Phrenic nerve stimulation using an implantable device has shown to reduce the severity of central sleep apnoea, which is common in ACHD HF, up to 12 months post implantation [51, 52].

15.6 Tissue Engineering

Progressive deterioration of prosthetic valves and conduits is one of the most common causes of re-intervention and heart failure in ACHD, and tissue prostheses still have a relatively limited longevity, especially in the young. Tissue engineering involves the development of functional replacements for damaged tissues and organs, by producing engineered tissues using pluripotent or embryonic stem cells. Scaffolds should have mechanical properties similar to the tissue of interest and be integrated into the tissue or replaced by natural extracellular matrix. Scaffold tissue can also be generated and used as a cardiac patch. Animal models show promising results [53]. Valve leaflets require regional variation in cell types and material properties, which can be achieved by using decellularized valves or 3D bioprinting [54].

Tissue engineering can also produce models of disease in vitro to assess drug responses. This is achieved by integrating tissue engineering, microfluidics and advanced sensing methods. Microphysiological systems are already available for the heart and blood vessels, using a combination of primary human cells and stem cells. Future research should focus on technology to promote cell differentiation and the production of engineered tissues, either in vitro or as a substrate guiding cell repopulation and differentiation [55].

15.7 Transplantation

Transplantation remains challenging in CHD, with ongoing questions regarding optimal timing of referral and patient selection [56]. The role of mechanical circulatory support is also still limited in this population.

International registries of patients with advanced heart failure who are potential candidates for transplantation (not just those assessed or listed) should be established to identify the adequate timing for transplant assessment. Further research is required in the development of assist devices that can be applied to CHD patients, both for the left and the right ventricle (in the subpulmonary or systemic circulation). Randomized trials are also required to identify the optimal inotropic and vasodilator protocols to improve the longevity of those who are on the waiting list. Again, implantable haemodynamic monitors may prove useful in this setting.

15.8 The Role of Genetics and Developmental Biology

In ACHD, genetic testing has focused on identifying genetic/chromosomal abnormalities responsible for the occurrence of the congenital defect, even though the aetiology of the vast majority of cases of CHD remains unknown [57]. Mutations in different genes that can result in identical cardiac malformations suggest a high interdependency between molecules involved in heart development, while the spectrum of malformations that can arise from identical gene mutations suggests an interaction between genes, environment and cardiac biomechanics.

The understanding of the genetics of HF is constantly evolving [58]. At present, in those with familial forms of HF, the genetic cause is known in only half of patients. Large ongoing sequencing projects, such as 100K Genomes Project in the UK, are likely to greatly aid the discovery of novel genetic defects responsible for such conditions. Next-generation sequencing technologies now sequence not just the entire DNA coding region (exome) but also the whole genome at a fast and relatively non-expensive manner. Sequencing projects are now producing vast amounts of data, and the challenge is the interpretation of these data, in order to identify actionable genetic variants that can be used to stratify patients and offer treatment tailored to their genetic background (personalized medicine). Over the last decade, several in silico tools have been developed to identify and prioritize genetic variants occurring in coding regions causing amino acid substitutions and, hence, protein modifications. However, our limited knowledge of the function of the non-coding region and the mechanisms regulating gene expression has made the identification of novel pathogenetic mechanisms underlying CHD and HF difficult. Epigenetic mechanisms that affect gene expression, such as DNA methylation and histone modification, are thought to be involved in the development of heart failure and are an exciting new line of research [59].

There is still a poor understanding of the genotype-phenotype relationship in ACHD HF. For example, it remains unclear why in some patients a systemic right ventricle fails earlier than others. A background genetic predisposition is thought to contribute to the significant differences in response to similar haemodynamic insults and may identify those more prone to develop HF [16]. Developmental genetic studies have identified a large number of pathways involved in cardiac embryology [60]. Mutations that lead to a structural defect are expected to potentially affect the composition of the myocardium, promoting ventricular dysfunction and heart failure. Recent examples of this are included in Chap. 2, such as mutations in beta-myosin heavy chain MYHA7 linked to noncompaction and Ebstein anomaly [61].

There is increasing evidence that an individual's genetic background can influence the risk of developing heart failure, as well as their outcome. However, to date, genome-wide association studies in non-CHD heart failure have only been able to identify few single nucleotide polymorphisms (SNPs), which appear to increase the risk of developing heart failure [62]. Identification of such SNPs will require collaborative studies among several major centres, to collect large and well-characterized cohorts of CHD patients. Gene therapies may also hold promise in patients with monogenic diseases.

15.9 Big Data from Administrative and Other Sources

The recent "big data revolution" is likely to have a significant impact in CHD. Many countries have large national datasets linking hospitalizations, family practitioner data and national statistics on births and death. While such datasets are not designed with specific research hypotheses in mind and may focus on certain aspects of clinical care, they contain a wealth of information on rare conditions or complications.

To achieve this, a combination of clinical expertise and in-depth understanding of such databases and the ethical, statistical and other methodological issues around their use is important. Advanced knowledge in statistics and computing are essential, including natural language processing and machine learning. Last but not least, storage and computing power are important for working with large data that are several gigabytes long.

15.10 Patient Involvement

Research participants are nowadays active partners in the entire research process, from concept and design to reporting and dissemination of results. Research hypotheses should be developed ensuring that outcomes matter to the individuals living with the condition, through shared goals, respect and co-learning [63]. Researchers should be trained to recognize the value of these "patient research partners". Partnership with patient groups and associations is instrumental in raising awareness about research and supporting recruitment, especially in relatively rare conditions.

Patient-reported outcome measures (PROMs) are essential endpoints in clinical trials [64]. International variations in PROMs have been reported in CHD [65]. As PROMs have only recently been introduced in certain areas of clinical practice, further research is urgently needed to understand how best to utilize them to make clinical work more effective, without becoming a burden to the patient or healthcare workers. Relevant validated outcome measures and effective communication technologies need to be developed to promote patient-centred clinical practice and for the identification of research priorities that are relevant to the patients' experience.

Conclusion

Despite enormous progress in our understanding and management of CHD, there is urgent need for further research in this area. National and international collaborations and a multidisciplinary approach to CHD research appear to be the way forward, integrating advances in technology and bioinformatics/genetics with the aim of achieving an evidence-based, holistic approach to CHD that improves the patients' longevity and quality of life.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 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. 2016;37(27):2129–200.
2. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease. J Am Coll Cardiol. 2008;52(23):e143–263.

3. Baumgartner H, Bonhoeffer P, De Groot NMS, de Haan F, Deanfield JE, Galie N, et al. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J. 2010;31(23):2915–57.
4. van der BT, Winter MM, Bouma BJ, Groenink M, Vliegen HW, Pieper PG, et al. Effect of valsartan on systemic right ventricular function a double-blind, randomized, placebo-controlled pilot trial. Circulation. 2013;127(3):322–30.
5. Robinson B, Heise CT, Moore JW, Anella J, Sokoloski M, Eshaghpour E. Afterload reduction therapy in patients following intraatrial baffle operation for transposition of the great arteries. Pediatr Cardiol. 2002;23(6):618–23.
6. Therrien J, Provost Y, Harrison J, Connelly M, Kaemmerer H, Webb GD. Effect of angiotensin receptor blockade on systemic right ventricular function and size: a small, randomized, placebo-controlled study. Int J Cardiol. 2008;129(2):187–92.
7. Dimopoulos K. Trials and tribulations in adult congenital heart disease. Int J Cardiol. 2008;129(2):160–2.
8. Gurvitz M, Burns KM, Brindis R, Broberg CS, Daniels CJ, Fuller SMPN, et al. Emerging research directions in adult congenital heart disease: a report from a National Heart, Lung, and Blood Institute/Adult Congenital Heart Association Working Group. J Am Coll Cardiol. 2016;67(16):1956–64.
9. Dimopoulos K, Alonso-Gonzalez R, D'Alto M. Heart failure, exercise intolerance, and physical training. In: Diagnosis and management of adult congenital heart disease [Internet]. 3rd ed. 2017 [cited 2017 Mar 27]. https://www.elsevier.com/books/diagnosis-and-management-of-adult-congenital-heart-disease/unknown/978-0-7020-6929-1.
10. Stout KK, Broberg CS, Book WM, Cecchin F, Chen JM, Dimopoulos K, et al. Chronic heart failure in congenital heart disease: a scientific statement from the American Heart Association. Circulation. 2016;133(8):770–801.
11. Tutarel O, Kempny A, Alonso-Gonzalez R, Jabbour R, Li W, Uebing A, et al. Congenital heart disease beyond the age of 60: emergence of a new population with high resource utilization, high morbidity, and high mortality. Eur Heart J. 2014;35(11):725–32.
12. Gatzoulis MA, Clark AL, Cullen S, Newman CG, Redington AN. Right ventricular diastolic function 15 to 35 years after repair of tetralogy of Fallot. Restrictive physiology predicts superior exercise performance. Circulation. 1995;91(6):1775–81.
13. Diller G-P, Dimopoulos K, Okonko D, Uebing A, Broberg CS, Babu-Narayan S, et al. Heart rate response during exercise predicts survival in adults with congenital heart disease. J Am Coll Cardiol. 2006;48(6):1250–6.
14. Alonso-Gonzalez R, Borgia F, Diller G-P, Inuzuka R, Kempny A, Martinez-Naharro A, et al. Abnormal lung function in adults with congenital heart disease: prevalence, relation to cardiac anatomy, and association with survival. Circulation. 2013;127(8):882–90.
15. Dimopoulos K, Diller G-P, Giannakoulas G, Petraco R, Chamaidi A, Karaoli E, et al. Anemia in adults with congenital heart disease relates to adverse outcome. J Am Coll Cardiol. 2009;54(22):2093–100.
16. Dimopoulos K, Wort SJ, Gatzoulis MA. Pulmonary hypertension related to congenital heart disease: a call for action. Eur Heart J. 2014;35(11):691–700.
17. Ohye RG, Sleeper LA, Mahony L, Newburger JW, Pearson GD, Lu M, et al. Comparison of shunt types in the Norwood procedure for single-ventricle lesions. N Engl J Med. 2010;362(21):1980–92.
18. Kempny A, Hjortshøj CS, Gu H, Li W, Opotowsky AR, Landzberg MJ, et al. Predictors of death in contemporary adult patients with Eisenmenger syndrome: a multicenter study. Circulation. 2017;135(15):1432–40.
19. Khairy P, Harris L, Landzberg MJ, Viswanathan S, Barlow A, Gatzoulis MA, et al. Implantable cardioverter-defibrillators in tetralogy of Fallot. Circulation. 2008;117(3):363–70.
20. Giannakoulas G, Dimopoulos K, Bolger AP, Tay EL, Inuzuka R, Bedard E, et al. Usefulness of natriuretic peptide levels to predict mortality in adults with congenital heart disease. Am J Cardiol. 2010;105(6):869–73.

21. Sharma R, Bolger AP, Li W, Davlouros PA, Volk H-D, Poole-Wilson PA, et al. Elevated circulating levels of inflammatory cytokines and bacterial endotoxin in adults with congenital heart disease. Am J Cardiol. 2003;92(2):188–93.
22. Bolger AP, Sharma R, Li W, Leenarts M, Kalra PR, Kemp M, et al. Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease. Circulation. 2002;106(1):92–9.
23. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993–1004.
24. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010;376(9744):875–85.
25. NOTE registrylISACHD [Internet]. [cited 2017 Dec 3]. http://www.isachd.org/content/note-registry.
26. The British Association for Cardiovascular Prevention and Rehabilitation. The BACPR standards and core components for cardiovascular disease prevention and rehabilitation [Internet]. 2017 [cited 2016 Sep 23]. http://www.bacpr.com/pages/page_box_contents.asp?pageid=791.
27. Dua JS, Cooper AR, Fox KR, Graham Stuart A. Exercise training in adults with congenital heart disease: feasibility and benefits. Int J Cardiol. 2010;138(2):196–205.
28. Duppen N, Kapusta L, de Rijke YB, Snoeren M, Kuipers IM, Koopman LP, et al. The effect of exercise training on cardiac remodelling in children and young adults with corrected tetralogy of Fallot or Fontan circulation: a randomized controlled trial. Int J Cardiol. 2015;179:97–104.
29. Becker-Grünig T, Klose H, Ehlken N, Lichtblau M, Nagel C, Fischer C, et al. Efficacy of exercise training in pulmonary arterial hypertension associated with congenital heart disease. Int J Cardiol. 2013;168(1):375–81.
30. van der Bom T, Winter MM, Knaake JL, Cervi E, de Vries LSC, Balducci A, et al. Long-term benefits of exercise training in patients with a systemic right ventricle. Int J Cardiol. 2015;179:105–11.
31. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2016;37(29):2315–81.
32. Lewis M, Rosenbaum M. The miracle baby grows up: hypoplastic left heart syndrome in the adult. Curr Cardiol Rep. 2017;19(8):74.
33. Galiè N, Beghetti M, Gatzoulis MA, Granton J, Berger RMF, Lauer A, et al. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. Circulation. 2006;114(1):48–54.
34. Galie N, Landzberg M, Beghetti M, Berger RM, Efficace M, Gesang S, et al. Evaluation of macitentan in patients with Eisenmenger syndrome: results from the randomised controlled MAESTRO study. Eur Heart J [Internet]. 2017 Aug 1 [cited 2017 Dec 3];38(suppl_1). https://academic.oup.com/eurheartj/article/38/suppl_1/ehx493.P5462/4086822.
35. Balzer DT, Kort HW, Day RW, Corneli HM, Kovalchin JP, Cannon BC, et al. Inhaled nitric oxide as a preoperative test (INOP test I): the INOP test study group. Circulation. 2002;106(12 Suppl 1):I76–81.
36. Frescura C, Thiene G, Giulia Gagliardi M, Mazzucco A, Pellegrino PA, Daliento L, et al. Is lung biopsy useful for surgical decision making in congenital heart disease? Eur J Cardiothorac Surg. 1991;5(3):118–22. discussion 122–3
37. Wagenvoort CA. Morphological substrate for the reversibility and irreversibility of pulmonary hypertension. Eur Heart J. 1988;9(Suppl J):7–12.
38. Novick WM, Sandoval N, Lazorhysynets VV, Castillo V, Baskevitch A, Mo X, et al. Flap valve double patch closure of ventricular septal defects in children with increased pulmonary vascular resistance. Ann Thorac Surg. 2005;79(1):21–8.
39. Dimopoulos K, Peset A, Gatzoulis MA. Evaluating operability in adults with congenital heart disease and the role of pretreatment with targeted pulmonary arterial hypertension therapy. Int J Cardiol. 2008;129(2):163–71.

40. Perera AH, Rudarakanchana N, Hamady M, Kashef E, Mireskandari M, Uebing A, et al. New-generation stent grafts for endovascular management of thoracic pseudoaneurysms after aortic coarctation repair. J Vasc Surg. 2014;60(2):330–6.
41. Benza R, Correa-jaque P, Franco V, Doyle M, White JA, Ginn G, et al. Abstract 19282: safety and utility of the CardioMEMs device in pulmonary arterial hypertension. Circulation. 2016;134(Suppl 1):A19282.
42. Janoušek J, Gebauer RA, Abdul-Khaliq H, Turner M, Kornyei L, Grollmuß O, et al. Cardiac resynchronisation therapy in paediatric and congenital heart disease: differential effects in various anatomical and functional substrates. Heart. 2009;95(14):1165–71.
43. Janousek J, Tomek V, Chaloupecký VA, Reich O, Gebauer RA, Kautzner J, et al. Cardiac resynchronization therapy: a novel adjunct to the treatment and prevention of systemic right ventricular failure. J Am Coll Cardiol. 2004;44(9):1927–31.
44. Authors/Task Force Members, Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, et al. ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2015;36(41):2793–867.
45. Lutembacher R. De la sténose mitrale avec communication interauriculaire. Arch Mal Coeur. 1916;9:237–60.
46. Hasenfuß G, Hayward C, Burkhoff D, Silvestry FE, McKenzie S, Gustafsson F, et al. A transcatheter intracardiac shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF): a multicentre, open-label, single-arm, phase 1 trial. Lancet Lond Engl. 2016;387(10025):1298–304.
47. Kaye DM, Hasenfuß G, Neuzil P, Post MC, Doughty R, Trochu J-N, et al. One-year outcomes after transcatheter insertion of an interatrial shunt device for the management of heart failure with preserved ejection fraction. Circ Heart Fail. 2016;9(12):pii: e003662.
48. Trigo MD, Bergeron S, Bernier M, Amat-Santos IJ, Puri R, Campelo-Parada F, et al. Unidirectional left-to-right interatrial shunting for treatment of patients with heart failure with reduced ejection fraction: a safety and proof-of-principle cohort study. Lancet. 2016;387(10025):1290–7.
49. Abraham WT, Zile MR, Weaver FA, Butter C, Ducharme A, Halbach M, et al. Baroreflex activation therapy for the treatment of heart failure with a reduced ejection fraction. JACC Heart Fail. 2015;3(6):487–96.
50. Barostim therapy for heart failure—full text view. ClinicalTrials.gov [Internet]. [cited 2017 Dec 3]. https://clinicaltrials.gov/ct2/show/NCT02627196.
51. Costanzo MR, Ponikowski P, Javaheri S, Augostini R, Goldberg L, Holcomb R, et al. Transvenous neurostimulation for central sleep apnoea: a randomised controlled trial. Lancet Lond Engl. 2016;388(10048):974–82.
52. Jagielski D, Ponikowski P, Augostini R, Kolodziej A, Khayat R, Abraham WT. Transvenous stimulation of the phrenic nerve for the treatment of central sleep apnoea: 12 months' experience with the remedē® System. Eur J Heart Fail. 2016;18(11):1386–93.
53. Weber B, Dijkman PE, Scherman J, Sanders B, Emmert MY, Grünenfelder J, et al. Off-the-shelf human decellularized tissue-engineered heart valves in a non-human primate model. Biomaterials. 2013;34(30):7269–80.
54. Duan B, Kapetanovic E, Hockaday LA, Butcher JT. Three-dimensional printed trileaflet valve conduits using biological hydrogels and human valve interstitial cells. Acta Biomater. 2014;10(5):1836–46.
55. Truskey GA. Advancing cardiovascular tissue engineering. F1000Research [Internet]. 2016 May 31 [cited 2017 Nov 27];5. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4890312/.
56. Ross HJ, Law Y, Book WM, Broberg CS, Burchill L, Cecchin F, et al. Transplantation and mechanical circulatory support in congenital heart disease a scientific statement from the American Heart Association. Circulation. 2016;133(8):802–20.

57. Fahed AC, Gelb BD, Seidman JG, Seidman CE. Genetics of congenital heart disease: the glass half empty. Circ Res. 2013;112(4):707–20.
58. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, et al. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2008 Jan;29(2):270–6.
59. Yang J, Xu W-W, Hu S-J. Heart failure: advanced development in genetics and epigenetics. Biomed Res Int. 2015;2015:352734.
60. Preuss C, Andelfinger G. Genetics of heart failure in congenital heart disease. Can J Cardiol. 2013;29(7):803–10.
61. Postma AV, van Engelen K, van de Meerakker J, Rahman T, Probst S, Baars MJH, et al. Mutations in the sarcomere gene MYH7 in Ebstein anomaly. Circ Cardiovasc Genet. 2011 Feb;4(1):43–50.
62. Lopes LR, Elliott PM. Genetics of heart failure. Biochim Biophys Acta. 2013;1832(12):2451–61.
63. Kirwan JR, de Wit M, Frank L, Haywood KL, Salek S, Brace-McDonnell S, et al. Emerging guidelines for patient engagement in research. Value Health. 2017;20(3):481–6.
64. Nelson EC, Eftimovska E, Lind C, Hager A, Wasson JH, Lindblad S. Patient reported outcome measures in practice. BMJ. 2015;350:g7818.
65. Moons P, Kovacs AH, Luyckx K, Thomet C, Budts W, Enomoto J, et al. Patient-reported outcomes in adults with congenital heart disease: inter-country variation, standard of living and healthcare system factors. Int J Cardiol. 2017;251:34–41.