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Review

Heart Failure in Adult Congenital Heart Disease: From Advanced Therapies to End-of-Life Care

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ABSTRACT

There is mounting recognition that some of the most urgent problems of adult congenital heart disease (ACHD) are the prevention, diagnosis, and management of heart failure (HF). Recent expert consensus and position statements not only emphasize a specific and pressing need to tackle HF in ACHD (ACHD-HF) but also highlight the difficulty of doing so given a current sparsity of data. Some of the challenges will be addressed by this review. The authors are from 3 different centres; each centre has an established subspeciality ACHD-HF clinic and is able to provide heart transplant, multiorgan transplant, and mechanical support for patients with ACHD. Appropriate care of this complex population requires multidisciplinary ACHD-HF teams evaluate all possible treatment options. The risks and benefits of nontransplant ACHD surgery, percutaneous structural and electrophysiological intervention, and ongoing conservative management must be considered alongside those of transplant strategies. In our approach, advanced

RÉSUMÉ

Il est de plus en plus admis que la prévention, le diagnostic et la prise en charge de l'insuffisance cardiaque (IC) font partie des problèmes les plus urgents dans le traitement de la cardiopathie congénitale chez l'adulte (CPCA). Les consensus d'experts et les énoncés de position formulés récemment font ressortir la nécessité particulière et urgente de s'attaquer à l'IC dans la CPCA (IC-CPCA), mais aussi la difficulté que pose cette tâche étant donné le peu de données dont on dispose. L'article expose certains des défis à relever. Les auteurs sont rattachés à trois centres différents, chacun doté d'une clinique spécialisée dans l'IC-CPCA et offrant des services de greffe cardiaque, de greffe multiorgane et de soutien artificiel aux patients atteints de CPCA. Pour que les patients de cette population complexe puissent recevoir des soins adéquats, des équipes multidisciplinaires spécialisées dans l'IC-CPCA doivent évaluer toutes les options thérapeutiques possibles. Les risques et les avantages associés à une intervention chirurgicale autre

Advances in care during the earliest years of life have transformed the epidemiology of congenital heart disease (CHD), and expansion of the adult CHD (ACHD) population is expected to continue until the middle of this century in both North America and Europe.[1,2] Unfortunately, complications can develop in mid and late adult life, especially in those with complex lesions, and it is important to recognize that some ACHD subgroups have a much more worrying mortality profile than others. Although life expectancy for simple CHD approaches that of the general population, patients with more complex disease face a substantial risk of premature death, with contemporary studies reporting a median age of death between 30 and 40 years in ACHD patients under follow up.[3-5] Given that the biggest population upsurge has been in the number of patients below 40s living with complex CHD,[4,6] this is a pressing concern. Although sudden cardiac death remains important, in recent years, heart failure (HF) has become the leading cause of ACHD mortality and it kills those with complex disease earliest.[3-5,7,8] It is also the source of significant morbidity and a frequent cause of hospitalization.[9] HF in ACHD (ACHD-HF) is a weighty burden, not only on patients and their families, but also on health care systems and resource allocation[9,10] (Fig. 1).

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care planning and palliative care coexist with the consideration of advanced therapies. An ethos of shared decision making, guided by the patient's values and preferences, strengthens clinical care, but requires investment of time as well as skilled communication. In this review, we aim to offer practical real-world advice for managing these patients, supported by scientific data where it exists.

qu'une greffe, à une intervention percutanée visant à effectuer un remodelage structurel et électrophysiologique et à une prise en charge prudente soutenue doivent être envisagés en parallèle avec ceux d'une greffe. En vertu de notre approche, la planification préalable des soins avancés et les soins palliatifs sont tout aussi importants que la prise en considération des traitements avancés. Une culture axée sur la prise de décision partagée, qui tient compte des valeurs et des préférences du patient, rehausse les soins cliniques, mais exige plus de temps ainsi qu'une communication efficace. Nous tentons ici de formuler des conseils pratiques et réalistes pour la prise en charge de ces patients, en nous fondant dans la mesure du possible sur des données scientifiques.

Preventative measures, treatment strategies, and criteria for advanced therapies are well established and well founded for HF in the general population,[11] and there is a natural enthusiasm to pursue the same approaches in ACHD. Unfortunately, equivalent benefits have not been observed in ACHD-HF, and ACHD-HF position statements caution against blanket extrapolation of standard HF management guidelines.[12,13] Although this may, in part, be due to underpowered trials with limited follow-up, more dominant reasons are likely related to the heterogeneity of the ACHD population and differences in the pathophysiology of ACHD-HF when compared with that of a failing subaortic left ventricle (LV) in a congenitally normal heart.[14-17] Given the paucity of evidence-based medical therapy, it may be that for many patients with ACHD-HF, advanced therapies are the only means to reduce mortality.

Recognizing Who Is Most at Risk

At every stage (prevention, management, timely onwards referral, transplant listing) and in every setting (family physician or cardiologist's office, emergency department, ACHD centre, HF program), optimal ACHD-HF care requires an understanding of which patients are most at risk. Risk assessment involves identifying the patients with ACHD most likely to develop HF and, later, those who are the most vulnerable to progression and death. We usually encounter ACHD-HF in one of the following 4 circumstances:

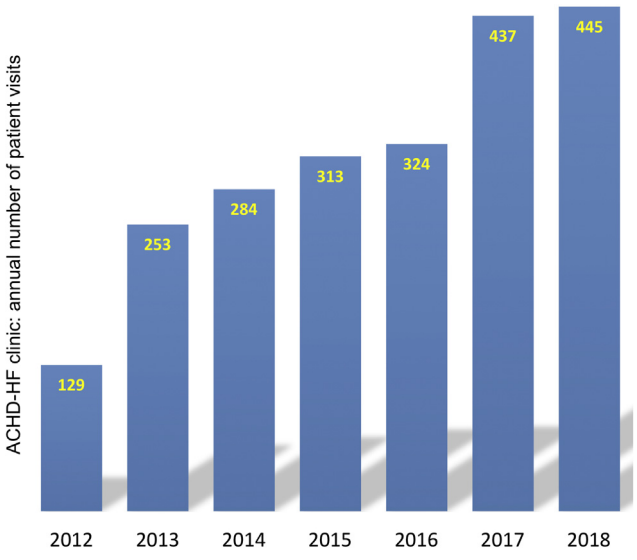

Figure 1. Growth of Toronto's Peter Munk Cardiac Centre heart failure in adult congenital heart disease (ACHD-HF) clinic, 2012-2018.

1. HF as the sequelae of a gradually declining cardiovascular system

Most often ACHD-HF is a fairly predictable late complication caused by a slowly progressive pathophysiology primarily related to the underlying diagnosis and its residual haemodynamic and electrical disturbances. Patients with failing Fontan operations, palliated single ventricles, a biventricular circulation with subaortic right ventricle (2V-RV), Ebstein anomaly, and Eisenmenger syndrome are the most vulnerable.[4,5,14] Although these diagnoses have the worst survival curves, other, more common lesions, such as repaired tetralogy of Fallot (TOF), are also well represented in ACHD-HF and transplant cohorts.[14,18-23] Collectively, these are the patients most frequently referred to our ACHD-HF clinics (Fig. 2) for assessment for cardiac transplantation.[22] It is something of a misnomer to say that Fontan patients die of HF. Very few develop isolated systolic or diastolic ventricular dysfunction. In most cases, death occurs in the setting of multisystem failure, also called Fontan failure.[24,25] However, because appropriately timed heart transplant can restore health to many failing Fontan patients and because most studies report HF as a cause of Fontan death, in this review, we will use the term HF rather than Fontan failure.

2. HF secondary to infective endocarditis

Infective endocarditis (IE) is an ACHD-HF scenario where the risk of rapid mortality or serious morbidity can be extremely high. The highest risk patients with ACHD are those with prosthetic valves and/or valve-containing conduits, which elevate the risk of IE more than 5-fold.[26] The significant challenges of IE and the benefit of multidisciplinary IE teams to manage these patients are well described.[27,28] The treatment of IE causing HF in patients with ACHD often requires high-risk surgery. Ideally, these patients should be operated on by CHD surgeons and the team should develop a perioperative plan for support strategies and reasonable limits for care. This includes discussing the potential options for mechanical support, in particular extracorporeal membrane oxygenation (ECMO). In some cases, when redo cardiac surgery to remove infected material and address haemodynamic abnormalities is especially high risk, it is reasonable to

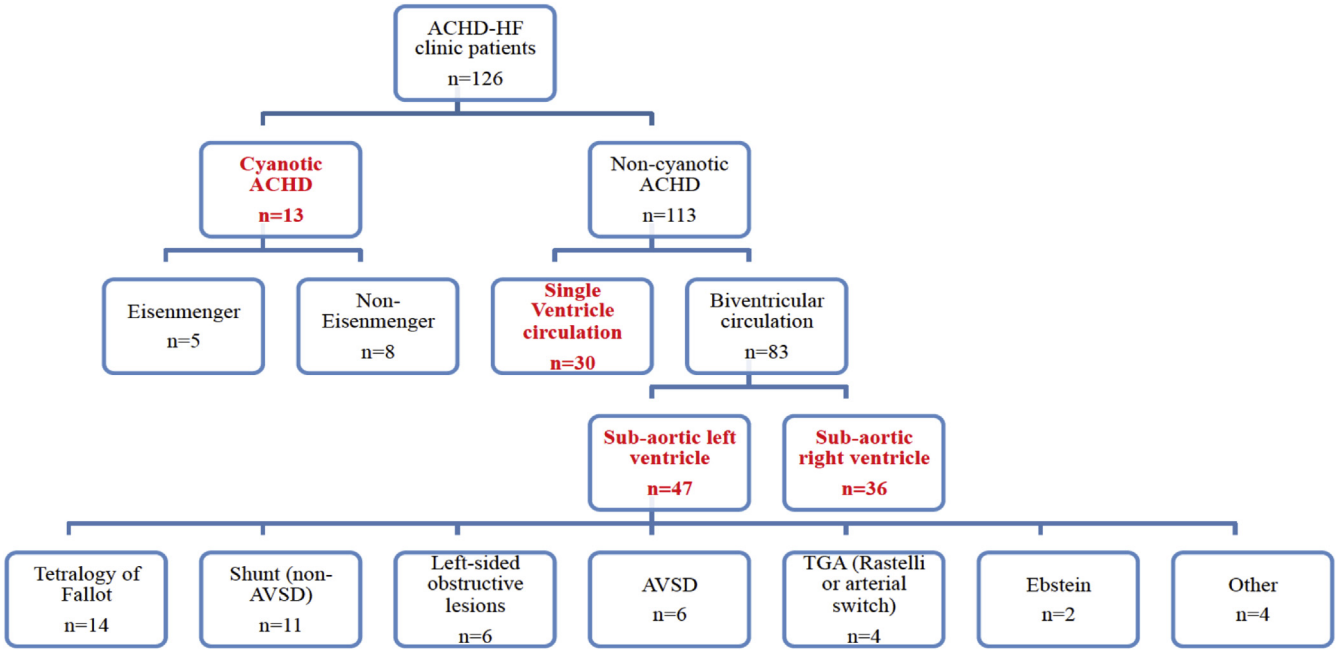

Figure 2. Diagnoses of patients referred to Toronto's Peter Munk Cardiac Centre heart failure in adult congenital heart disease (ACHD-HF) clinic, 2012-2015. AVSD, atrio-ventricular septal defect; TGA, transposition of the great arteries. Reproduced from Van De Brauene et al.[14] with permission from Elsevier.

consider transplant as an alternative option if the patient can be temporized medically.

3. HF secondary to atrial tachyarrhythmia

Atrial tachyarrhythmia has been termed a "call to arms" for ACHD caregivers[29] and inextricably linked to ACHD-HF. More than a quarter of ACHD-HF admissions are associated with either new onset or acute recurrence of atrial tachyarrhythmia.[30] In ACHD, atrial tachyarrhythmia is a strong predictor of subsequent mortality, and like HF, the risk is highest in patients with severe ACHD.[31] Atrial tachyarrhythmia may herald progression of a chronic ACHD-HF syndrome and often acutely triggers or worsens ventricular dysfunction.[31] In some, restoration and maintenance of sinus rhythm will have lasting improvement on ventricular function, but atrial tachyarrhythmia, particularly in complex patients, should trigger a search for modifiable haemodynamics issues and heightened ongoing vigilance.[32,33] Management of recurrent atrial tachyarrhythmia in patients with a right-atrial to pulmonary artery (PA) or Bjork Fontan circulation prompts the discussion of Fontan conversion surgery with the dialogue including consideration of transplant.[34]

4. HF in patients who have become lost to specialist follow-up

It is the antitheses of aspirations for ACHD care that we increasingly encounter patients who present with HF having been lost to specialist follow-up. These patients with repaired CHD have residual cardiac abnormalities that, were they under regular specialist review, would have been dealt with electively and much more safely at an earlier time point.[35,36] Although additional triggers such as noncardiac illness or arrhythmia may play a role, the fundamental problem is one of untreated residual haemodynamic disturbance. In this situation, patients usually present to emergency departments in local hospitals with no in-house ACHD team. Sometimes, because patients are relatively young, able to compensate, unsure of their cardiac history, or because the health care team is unfamiliar with CHD, the gravity of the situation goes unrecognized. Management of ACHD-HF in this situation may require high-risk, emergent surgical or percutaneous intervention. Some patients only become aware at this time that their CHD is not "cured," but also that in mid-adult life, seemingly without warning, they are facing decisions involving their own mortality. Such cases emphasize the importance of improving general medical awareness of ACHD, streamlining referral pathways, and refining processes of transition to adult care.

Case 1

A boy born with transposition of the great arteries (TGA) underwent an arterial switch procedure and ventricular septal defect closure at the age of 2 weeks. There were no concerns at his last paediatric visit aged 17 years, and his echocardiogram showed normal function with mild aortic regurgitation. He had no contact with any health provider until, when aged 38 years, he presented to his local emergency department with a 2-month history of HF symptoms. His serum brain-type natriuretic peptide (BNP) was elevated at 1340 pg/mL. Echocardiography and computer tomography showed a 7-cm neo-aortic root aneurysm, severe aortic regurgitation, and severe LV dysfunction (Fig. 3). After extensive discussion with the patient and his family and a multidisciplinary discussion about options for support, he underwent a Bentall aortic root replacement. In view of his tenuous cardiovascular status and proximity of the PA to the sternum, bypass and cooling were initiated from the

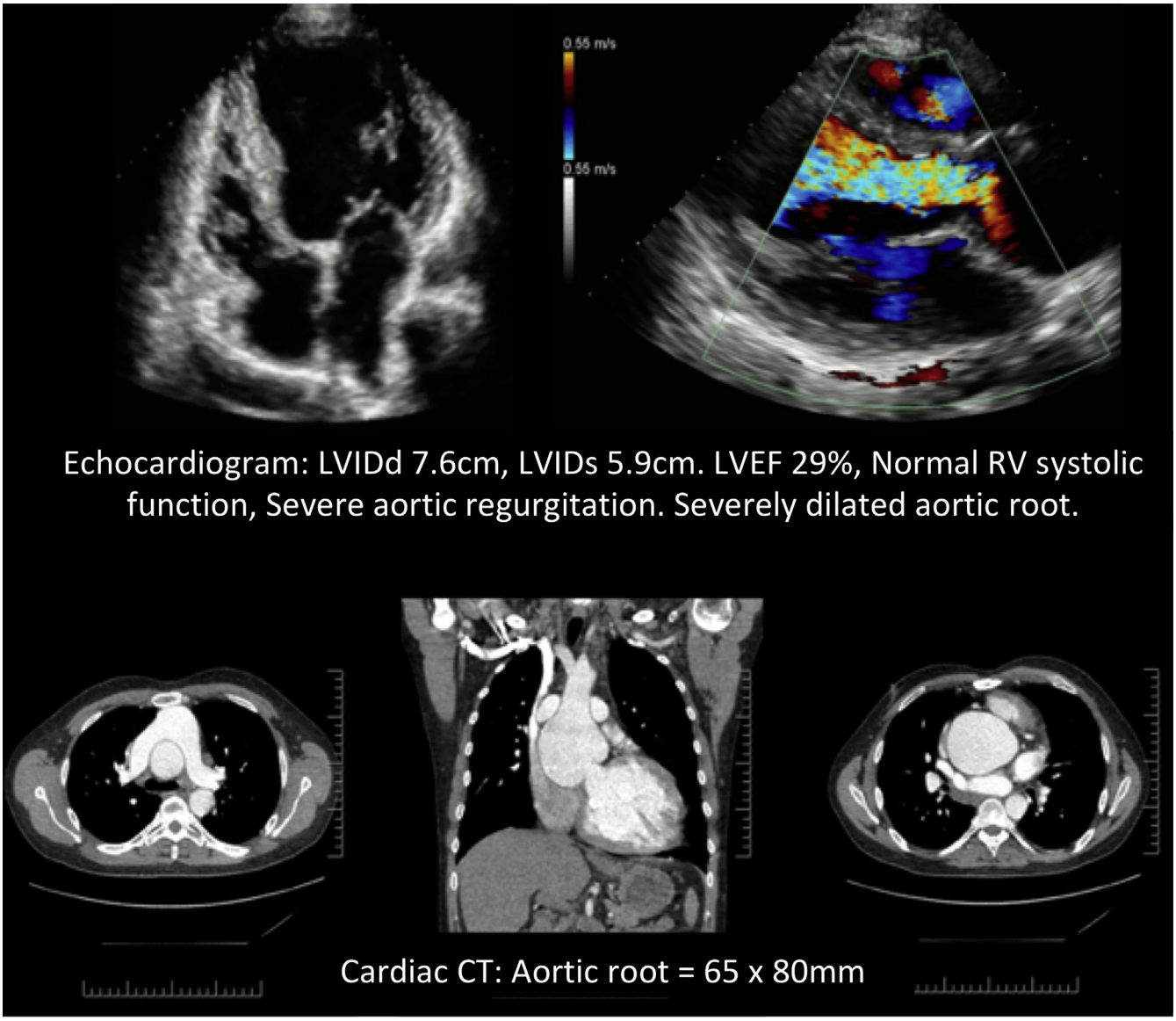

Figure 3. Imaging assessment of case study 1. CT, computed tomography; LVEF, left ventricular ejection fraction; LVID, left ventricular internal dimension; RV, right ventricle.

groin before sternal re-entry. After a prolonged bypass time, he was weaned with stable ventricular function, but oxygenation was poor, with an acute respiratory distress syndrome picture, presumably in part related to a history of smoking. He was supported with veno arterial ECMO for 3 days and remained in the cardiovascular surgical intensive care unit for 3 weeks. During this time, he required a transvenous pacemaker with implantable cardioverter-defibrillator (ICD) implantation for complete heart block and as primary prevention. Six months after his surgery he returned to work. Two years after surgery, he remains asymptomatic with an left ventricular ejection fraction of 45% and normal BNP.

Advanced Care Planning and End-of-Life Care

Advanced care planning should begin long before the clinical manifestations of ACHD-HF, and it was a deliberate choice to position this section, immediately after that on identification of risk. Empowering patients with ACHD to participate as partners in maintaining their health, with management decisions and also in political advocacy for the specialty, will improve all aspects of care. Although patients with ACHD-HF often recall a childhood awareness of a potentially life-threatening diagnosis, they typically do not remember having had specific conversations about that with their parents or care providers.[37] Some feel vulnerable during adult health care interactions, because they lack the information needed to understand their acute situation and make medical management choices.[37] Beyond the potential psychosocial benefits of helping young people to understand their diagnoses and potential health trajectories, there may be practical advantages of discussing ACHD-HF with at-risk patients from late childhood onwards. For instance, it is important to understand that becoming obese, smoking, or taking drugs will not only aggravate cardiac

vulnerability but may also limit the options for eventual transplant. It is relevant that women who might predictably end up on a transplant track are aware that pregnancies (including incomplete pregnancies) are important human leucocyte antigen-sensitizing events.[38]

Once confronted with an ACHD-HF diagnosis, the process and style of communication should permit an understanding of the situation, coming to terms, reflection on values, sharing of goals, and elucidation of preferences. In essence this is the definition of advanced care planning.[39] In ACHD a diagnosis of HF is a notable risk factor for death and it changes the physicians' expectations of clinical course. It is only appropriate that this information be shared with the patient. Deferral to do so may delay reaching a decision about how the patient wants his or her care to progress and ultimately reduce the options available. In a Canadian study, the average age of patients in Ontario's subspecialty HF clinics was 72 ± 13 years,[40] which contrasts with 38 ± 13 years for patients in Toronto's ACHD-HF clinic,[14] and 32 years (interquartile range, 23-41 years) was the average age of patients with ACHD assessed for transplant at the Freeman Hospital, United Kingdom.[23] The relative youth of patients with ACHD-HF, their potentially poor prognosis,[14] and the well-recognized neurocognitive impacts of CHD[41] predict psychosocial needs that are different to those of the general HF population. For example, many patients with ACHD-HF are often very concerned about who will provide for their young children and/or elderly parents if their health declines or they die. Establishing preferences for limits of care, identifying substitute decision makers and financial planning are important whether the ongoing plan is conservative management, high-risk intervention, or transplant. In these difficult situations, the best approach is to provide trustworthy information, acknowledge unknowns, consider what your team can realistically offer, whether ACHD centres can offer more, and take great account of what matters to patients and their families. It is a complex and dynamic process, requiring ongoing communication, sometimes with more than 1 health care professional. Elwyn et al.[42,43] proposed a practical, easy-to-remember, 3-talk model to help clinicians to tackle shared decision making in routine clinical practice. A modified version can be a useful framework for talking with patients with ACHD-HF about the various options for ongoing management, building in an extra step to clarify that the patient and care provider structure their conversations from a similar understanding of the patient's heart defect and previous surgeries (Fig. 4). Close collaboration with palliative care, local practitioners, and homecare services can be highly beneficial. However, for patients with ACHD, whose care since birth has been closely linked to a congenital cardiac team, it can be difficult, and is sometimes inappropriate, to transition to another group of care providers as end-of-life approaches. Care at this point must be individualized, and ACHD-HF providers should develop skills to navigate the process.

Who Should Be Referred for Consideration of Advanced Therapy?

Patients with ACHD-HF at a significant risk of death in the next 2 to 3 years or in danger of becoming "untransplantable" should be referred for consideration of advanced therapies. When ACHD-HF is the sequelae of a gradually declining cardiovascular system, identifying this time point remains an enormous challenge. Quite marked haemodynamic abnormalities and ventricular dysfunction can exist for decades without clinical symptoms or signs and disease progression difficult to spot. If in doubt, it is important to remember that patients with advanced comorbidities, too unwell or with end-stage haemodynamics, have the poorest survival of all patients with ACHD referred for transplant assessment, whereas in contrast, there is little to be lost from early referral.[23] Vulnerability to ACHD-HF, timing of referral for advanced therapies, and initiating conversations about preferences and goals are intertwined concepts and the focus and emphasis of ACHD care shifts with time (Fig. 5).

As in general adult HF, New York Heart Association functional class, hyponatremia, natriuretic peptides (BNP or NT-proBNP), peak VO_2, and subaortic ventricular function have predictive value in ACHD, particularly when considering the entire ACHD population (Table 1). On the other hand, some have less discriminatory power to identify risk in the subset of patients with ACHD already recognized to be failing (Table 1). In the analysis of patients followed in Toronto's ACHD-HF clinic, neither subaortic ejection fraction nor peak VO_2 was associated with death/transplant or ventricular assist device (VAD) and BNP seemed to be a clearer predictor of adverse outcome in patients with a failing biventricular circulation than it was in patients with a failing Fontan circulation or cyanotic heart disease.[14] Haemodynamic parameters obtained during cardiac catheterization reflect the underlying pathophysiology, and repeated measurements can be useful as part of the assessment of disease progression or management response. Elevated mean PA and wedge pressure are clear markers of adverse outcome in those with a 2V-RV circulation[44] and possibly in other patients with ACHD-HF.[14] In patients with a 2V-RV, the absence of pulmonary hypertension (defined as a mean PA pressure $\geq$25 mm Hg) and normal BNP seems to identify a subgroup at much lower risk in the short term.[44] Risk factors rarely exist in isolation from the underlying diagnosis or from each other, and as yet, none establishes which patients have the most to gain from advanced HF therapies and least to lose. There seems a realistic possibility that machine learning algorithms will help with this conundrum, and it is exciting that there are perhaps answers on the horizon.[45]

Invasive Nontransplant Strategies to Improve Haemodynamics and Heart Function

ACHD surgical/interventional centres regularly carry out procedures to improve survival, alleviate symptoms, and improve long-term outcomes. Transplant and general adult HF teams and ACHD cardiologists from nonsurgical centres are unlikely to be so familiar with these options. In patients with developing or established ACHD-HF, these "conventional" nontransplant options are higher risk than usual but remain as possibilities to explore. In general, it is more likely that a nontransplant surgical or percutaneous option exists for patients with a biventricular circulation,[46] but Fontan pathway revision and conversion strategies can provide relief for some types of Fontan failure. When evaluating such options, the team must balance concerns about further chest wall incisions and human leucocyte antigen sensitization

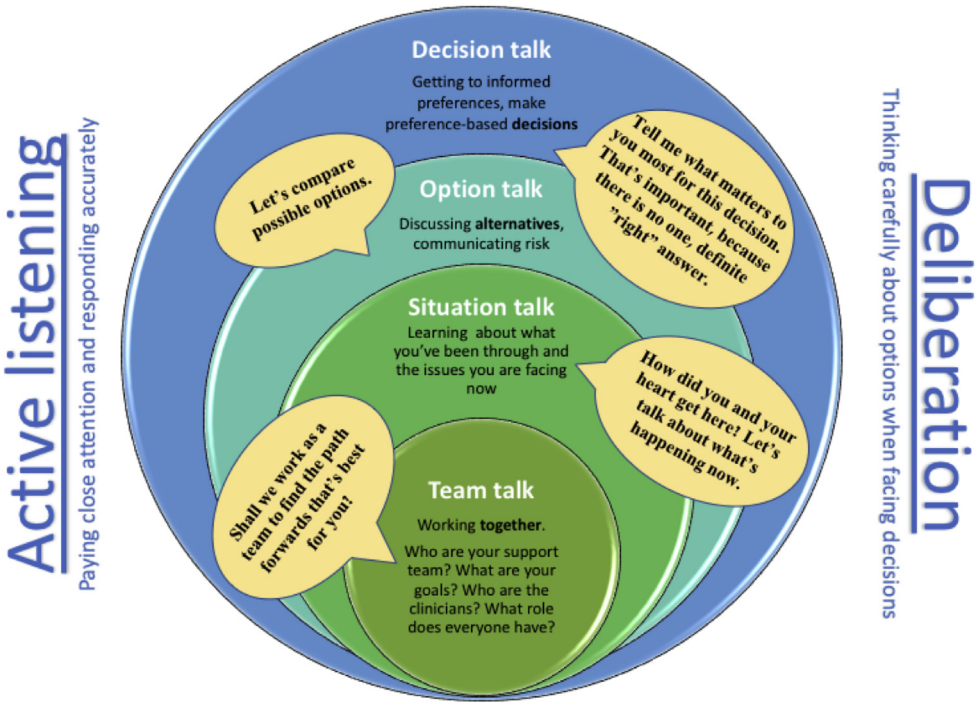

Figure 4. A 4-talk, layered multistage communication process for shared decision making in heart failure in adult congenital heart disease. Adapted from Elwyn et al.[43] with permission from BMJ Publishing Group Ltd.

against potential for improvement in overall status and the durability of that improvement, given that these patients may ultimately progress to transplant. This is particularly the case for Fontan patients where the scale of Fontan revision surgery is similar to transplant,[47] which will remain the destination for most.[48] Decisions about very high-risk conventional options should be made in ACHD centres with the potential to offer the backup of ECMO, mechanical support, and transplant. The following cases illustrate patients who might have been accepted for transplant were ACHD cardiologists not closely involved in the transplant assessment process and thus able to suggest alternative nontransplant strategies.

Case 2

An 18-year-old woman was referred for consideration of heart transplant. She had undergone staged palliation to extracardiac Fontan completion for an initial diagnosis of right atrial isomerism, bilateral superior caval veins with left superior caval vein to coronary sinus, mitral atresia and hypoplastic LV, atrial and ventricular septal defects, and double outlet RV. There was a 2-year history of increasing symptoms of shortness of breath on exertion, lethargy, and ascites. Cardiac magnetic resonance imaging (MRI) showed that RV end diastolic volume was 152 mL/m^2, with an right ventricular ejection fraction of 52% and severe tricuspid regurgitation (Fig. 6). There was no anatomical obstruction to her Fontan pathway. Fontan pressure was 24 mm Hg and resting oxygen saturations were 90% to 95%. There was no history of arrhythmia. It was felt that heart transplant was the best strategy and the assessment process was started. For optimization and to improve symptoms she commenced diuretics and home milrinone. On reassessment, Fontan pressures had reduced to 15 mm Hg. After lengthy discussion within the multidisciplinary team and with the patient and her family, she underwent surgical replacement of the tricuspid valve with 33-mm St Jude Medical prosthesis; the right atrium was reduced in size and unipolar pacing leads were placed onto the apex of the ventricle in case they might later be needed. Three days after the surgery, she developed complete heart block and required an urgent epicardial pacemaker that was facilitated by having the leads already placed. She made an excellent recovery and was able to enrol at university. Two years later she remains well with no cardiac symptoms.

Case 3

A 49-year-old woman with left atrial isomerism and repaired TOF was referred for consideration of heart-lung transplant. She had previously undergone a Waterston shunt, TOF repair, and revision of her RV outflow tract including pulmonary valve replacement and placement of 2 stents in her right PA—a total of 4 previous median sternotomies. At age 45 years, she received an ICD after an episode of ventricular tachycardia, complicated by multiorgan failure, during which time she required renal dialysis for several weeks. In the year before referral to the transplant team, she had been hospitalized for atrial fibrillation and severe right HF. Her BNP during one of those admissions was >4000 pg/L. She had been started on sildenafil due for pulmonary hypertension noted on an echo and on cardiac catheter. She was seen by the ACHD-HF clinic as part of a transplant assessment and admitted for a period of intravenous diuresis and repeat cardiac catheterization and MRI. The ACHD group felt that most of her RV hypertension was due to RVOT obstruction, pulmonary regurgitation, and residual

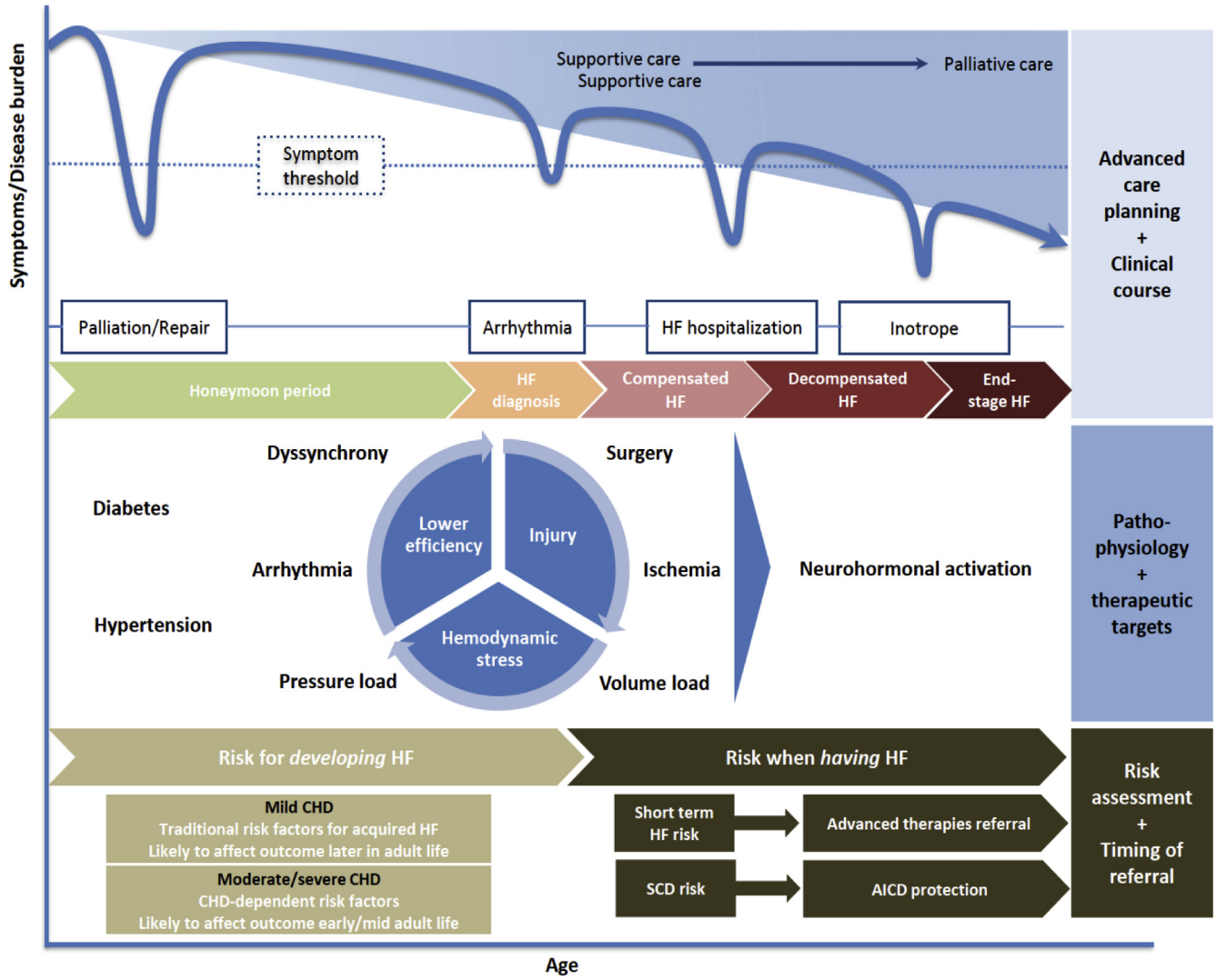

Figure 5. Lifetime health trajectory and shifts in health care focus in patients with congenital heart disease (CHD). AICD, automated implantable cardioverter-defibrillator; HF, heart failure; SCD, sudden cardiac death.

right PA stenosis, which would be amenable to percutaneous pulmonary valve replacement and stenting. A good result was achieved without complication, and her clinical status, renal function, and biventricular function were improved. Two years later she remains largely asymptomatic, sildenafil has been stopped, and she no longer requires diuretics.

Durable VADs

Use of mechanical support technology in patients with ACHD-HF is expanding, although numbers remain tiny compared with left VAD (LVAD) use in the general population. ACHD accounted for 126 of 16,182 VAD implants in the Intermacs registry between 2006 and 2016.[49] Survival and transplant rates in patients with ACHD VAD are lower than those in propensity-matched patients without ACHD VAD (survival 72% vs 84%, transplant 20% vs 34% at 1 year).[50] Survival for patients with ACHD transplanted from VAD is similar to non-VAD ACHD transplant survival.[49-51]

VAD in Patients With a Biventricular Circulation and Subaortic LV

Some patients with ACHD with a biventricular circulation and subaortic LV circulation and primary LV failure are suitable for LVAD in the same way as their acquired heart disease counterparts. However, they are likely to have undergone previous sternotomies and may also have left-sided mechanical valves or residual intracardiac shunts that need special consideration. Other patients with a biventricular circulation and subaortic LV have a pathophysiology in which LV dysfunction is primarily driven by right-sided CHD (eg, patients with repaired TOF or Ebstein anomaly). In acquired HF, RV failure at the time of LVAD insertion is a poor prognostic marker and LVAD alone may be insufficient for these patients with ACHD-HF.[52,53] In these circumstances, a temporary right VAD can be considered to support the early postoperative period, although weaning this may prove difficult. Long-term options for isolated subpulmonary RV failure remain limited.[54,55] It may seem that the most realistic VAD solution for some patients with ACHD-HF would be either

Table 1. Red flags that should prompt referral for evaluation by an ACHD-HF team for advanced therapies

Red flag	Implications		References
Heart failure hospitalization(s)	In-hospital mortality: approximately 7%. After first ACHD-HF hospitalization (registry/population data): 1-y mortality approximately 25%, 5-y mortality approximately 45%, median survival approximately 6.5 y. Within 18 mo of ACHD-HF admission (transplant centre data): dead = 20%, readmitted with HF = 18%, transplanted = 11%. 90% of deaths due to cardiovascular cause; majority from HF progression		9,90,91
Hypoalbuminaemia	Entire ACHD cohort: predictive of death	ACHD-HF cohort: not predictive of death, transplant, or VAD. Is a risk factor for death on heart transplant wait list	14,92,93
Atrial arrhythmia	Entire ACHD cohort: HR for HF 2.6 (CI, 2.4-2.9), HR for death 1.5 (CI, 1.4-1.6)	ACHD-HF cohort: HR for death, transplant or VAD 1.7 (CI, 0.8-3.4)	14,31
Symptoms	Entire ACHD cohort: HR for death 8.7 (CI, 5.26-14.35) in NYHA class III vs NYHA I	ACHD-HF cohort: presence of symptoms (NYHA class II, III, or IV) vs absence of symptoms (NYHA class I) discriminative of death, transplant, or VAD	14,94
Impaired cardiopulmonary exercise capacity	Entire ACHD cohort: peak VO_2, $VE:CO_2$ slope, and heart rate reserve predictive of death in mid-term	ACHD-HF cohort: not found to be predictive of death, transplant, or VAD	14,95
Hyponatremia	Even mild (< 136 mmol/L) hyponatremia is an important predictor of death, in both cohorts		14,96
Elevated BNP or NT-ProBNP	Important predictors of death, in both cohorts. Serial measurements may be very useful in those with elevated baseline measurements. Normal values reassuring in terms of mid-term outcome. Less predictive in single ventricle patients		14,97,98
Anaemia	An important predictor of death in the entire cohort of patients with ACHD, < 120 mg/dL in females, < 130 mg/dL in males		99
Patients with a 2V-RV: pulmonary hypertension	Important risk factor for death, transplant, or VAD in the short term. Without treatment can limit options for heart-only transplant		14,44
Fontan patients: severe FALD, worsening PLE	Increases the perioperative risks of heart transplant, can be insidious, and may ultimately limit transplant options		25,68-71
HLA-sensitized patients	Substantially longer wait for a suitable donor organ, risk of deterioration/death on wait list, therefore should prompt earlier referral than otherwise		80,100
Noncardiac comorbidities (eg, hepatitis, diabetes, renal dysfunction, obesity, smoking, drug abuse)	Refer early for discussion of long-term outcomes and transplant options. This may permit time to address/optimize modifiable risk factors		65,93

2V-RV, biventricular circulation with subaortic right ventricle; ACHD, adult congenital heart disease; ACHD-HF, heart failure in adult congenital heart disease; BNP, brain-type natriuretic peptide; CI, confidence interval; FALD, Fontan-associated liver disease; HF, heart failure; HLA, human leucocyte antigen; HR, hazard ratio; NT-ProBNP, N-type pro hormone B-typr naturetic peptide; NYHA, New York Heart Association; PLE, protein losing enteropathy; VAD, ventricular assist device.

biventricular assist (BiVAD) or a total artificial heart (TAH). Unfortunately, improvements in survival with isolated LVADs have not yet been duplicated with biventricular support devices.[56] The need for BiVAD or TAH is currently associated with significantly worse survival than systemic VAD only in ACHD.[50]

VAD in Patients With a 2V-RV

Today, patients with failing 2V-RV circulations are one of the larger subgroups of ACHD-HF (Figs. 2 and 7). The majority of these patients have undergone previous atrial baffle procedures for TGA, and a sizable minority have congenitally corrected TGA. Although the experience of subaortic VAD in patients with a 2V-RV is still evolving, survival is comparable with or exceeds that of VAD in acquired heart disease and is effective for similar indications (bridge-to-transplant, bridge-to-decision, bridge-to-candidacy).[57,58] Patients with 2V-RV circulations are in particular at risk of developing pulmonary hypertension.[44] As with patients with acquired heart disease, reducing subaortic RV end diastolic pressure with a VAD is effective at reducing PA pressures in some patients to levels acceptable for heart transplant, with those with persistent elevation of pulmonary vascular resistance continued on VAD as destination therapy or considered for combined heart-lung transplant.[44,57]

Successful outcomes for VAD in patients with a 2V-RV require careful preoperative planning. Patients with TGA who have undergone venous return redirection may have developed baffle obstruction and/or residual shunts.[59] These along with multiple sternotomies, technical problems related to the orientation of the great vessels, the position of the heart within the chest, and the heavy trabeculations of the RV all pose challenges.[60] Percutaneous intervention to relieve baffle stenoses and/or leaks is an integral part of pre-VAD planning. Many patients with congenitally corrected TGA have had previous surgery to physiologically correct their circulation and may have residua that need addressing at the time of VAD, for instance, replacement of a stenosed LV-PA conduit. In all patients with a 2V-RV, careful consideration is given as to whether or not to replace a regurgitant tricuspid valve (subaortic atrial-ventricular valve), which may ensure maximal reduction of pulmonary venous pressure after VAD insertion. There is a low threshold to replace a regurgitant aortic valve, because aortic regurgitation increases after VAD insertion reducing the effectiveness of the VAD due to the resultant circular shunt.[58,60] Similarly, an accurate assessment of the subpulmonary LV function is vital. Exacerbation of

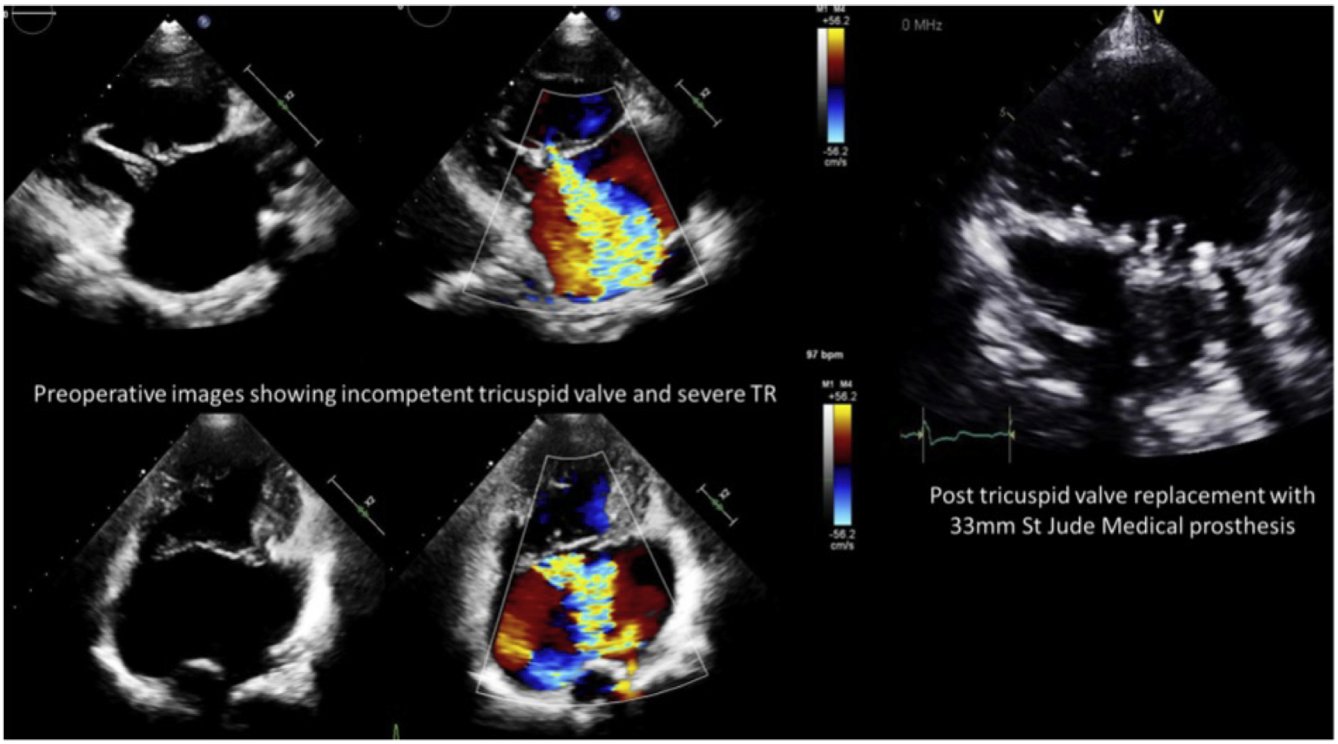

Figure 6. Echocardiographic images of case 2 pre- and post-tricuspid valve replacement. TR, tricuspid regurgitation.

subpulmonary LV failure can occur after VAD implant, and temporary support with a subpulmonary VAD or prolonged inotrope administration may be required.

Case 4

A 31-year-old with the Senning procedure for TGA and subcutaneous ICD was referred for heart-lung transplant assessment in view of New York Heart Association functional class III-IV symptoms and very poor subaortic RV function. The cardiac catheter showed a PA pressure of 80/30 mean 40 mm Hg, a PA wedge of 20 mm Hg, and a transpulmonary gradient of 20 mm Hg. The patient underwent HeartWare insertion and tissue tricuspid valve replacement for severe tricuspid regurgitation (Fig. 8). Eight months later, his symptoms and haemodynamics had improved; the PA pressure was 36/14 mean 22 mm Hg, PA wedge 10 mm Hg (transpulmonary gradient 12), allowing him to be listed for heart transplant. However, with improvement in symptoms, the patient declined listing at that time. His haemodynamics remained stable for almost 2 years after device insertion, but ultimately, he was listed for transplant because of a recurrent drive line infection. There were no concerns about tricuspid valve function.

VAD in Fontan Patients

The technical and physiological challenges of VAD in patients with ACHD are most apparent in the Fontan population. Although ventricular dysfunction can be a component and sometimes the cause of Fontan failure, the majority of patients have Fontan failure as opposed to primary pump failure. Case series and case reports have shown the effectiveness of subaortic VAD for the subgroup with primary ventricular dysfunction, and although the total number of reported implants remains low (17 of 126 ACHD Fontan VADs reported to INTERMACS 2006-2015), the reported survival is equivalent to VAD in biventricular circulation ACHD patients, although presumably with highly selected cases.[49,50,61] Use of TAH and BiVAD in Fontan patients, including the need to create a subpulmonary venous collection chamber for the right-sided are being considered, however, worldwide experience is limited.[54] Recovery from the effects of cardiopulmonary bypass and the implant surgery are major considerations, as is the addition of a further sternotomy and exposure to additional blood products. Also, there is likely to be significant procedure-related mortality particularly from bowel and liver ischemia. Part of the solution may come from less invasive VADs for the pulmonary side of the circulation instituted sooner in the patient's course which remain at the developmental stage.[62-64]

Transplant

Notwithstanding the issue of donor availability, orthotopic heart transplant is an effective treatment for cardiac failure from all causes.[65] Centres offering ACHD heart transplant are assessing and transplanting increasing numbers of patients, with particular growth in referrals of patients with single ventricle physiology[23] (Fig. 7). In Canada (excluding Quebec), between 2008 and 2017, a diagnosis of CHD was given for 11% of heart transplants in those aged 18 to 34 years and 6% of those aged 35 to 59 years.[66] As of 2018, the International Society for Heart and Lung Transplantation registry dataset included 1-year survival outcomes for heart transplants in 2498 patients with ACHD and 105,478 patients transplanted for other diagnoses.[65] In this large

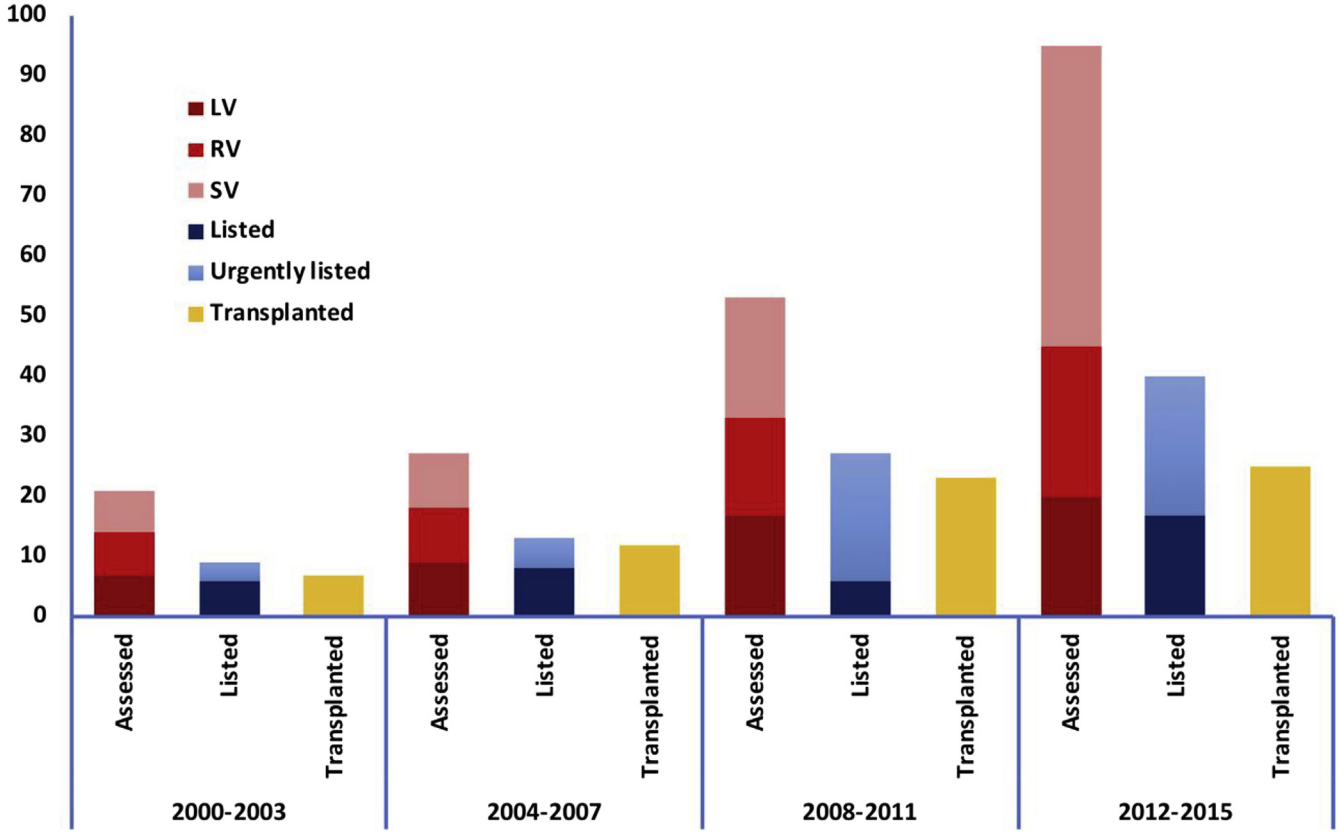

Figure 7. Trends in adult congenital heart disease heart transplant assessments and transplants over time at the Freeman Hospital, Newcastle upon Tyne, United Kingdom. LV, left ventricle; RV, right ventricle; SV, single ventricle. Reproduced from Crossland et al.[23] with permission from BMJ Publishing Group Ltd.

dataset, with a 1-year survival of 77%, the outcome for ACHD heart transplant is significantly worse than that for ischemic cardiomyopathy (ICM) 82% or non-ICM (NICM) 84%; it is similar to that for valvular cardiomyopathy 77% and better than that for retransplant 69%.[65] Long-term outcomes for adults transplanted for a diagnosis of ACHD are excellent, the best of all diagnostic groups beyond 8 years. Median post-transplant survival by diagnosis is currently: ACHD = 15 years, NICM = 12 years, valvular cardiomyopathy = 11.2 years, ICM = 9.7 years, and retransplant = 6.6 years, and patients with ACHD surviving the first year after heart transplant have a median survival of 20 years.[65] These registry data contain much important information but lack granularity. For example, there are no data as to whether the number of ACHD transplants a centre performs affects outcome and all diagnoses are pooled under the CHD heading with no data on outcomes by individual lesions. A systematic review and meta-analysis of publications until 2013 again showed increased early mortality in ACHD compared with non-ACHD heart transplant recipients, but in this study, although 30-day post-transplant mortality was higher in patients with ACHD, there was no disparity at 1 or 5 years and by 10 years, survival was better in the ACHD population.[67] This meta-analysis suggested that much of the early mortality burden was borne by single ventricle patients.[67] A study of patients with ACHD referred for heart transplant assessment at the Freeman Hospital, United Kingdom, between 2000 and 2016 provides outcomes for the 67 patients with ACHD who underwent transplant in that centre.[23] Overall post-transplant survival was 85% at 30 days, 80% at 1 year, and 76% at 5 and 10 years, which is similar to the outcomes for non-ACHD dilated cardiomyopathy patients in the International Society for Heart and Lung Transplantation dataset.[23] In this study, single ventricle outcomes were equivalent to recipients transplanted for biventricular ACHD.[23]

The technical challenges of ACHD transplant can be daunting (Fig. 9), and in all assessments, a careful pretransplant understanding of the anatomy is mandatory, including the position and orientation of the great arteries, the adequacy of the PAs, and the systemic and pulmonary venous return. This ensures anatomical eligibility for transplant and allows surgical planning of the anastomoses (including PA reconstruction) and the potential need for larger sections of systemic vessels to be taken with the graft organ. Previous sternotomies and thoracotomies lead to extensive adhesions, and the cardiac structures may be adherent to the sternum. Relative locations of vascular structures to the sternum should be assessed by cross-sectional imaging to plan a safe approach, with femoral bypass often required before opening the chest. An accurate assessment of pulmonary vascular resistance can be complex, particularly in patients with multiple sources of pulmonary blood flow. Cardiac MRI measurement of pulmonary vein flow with contemporaneous cardiac

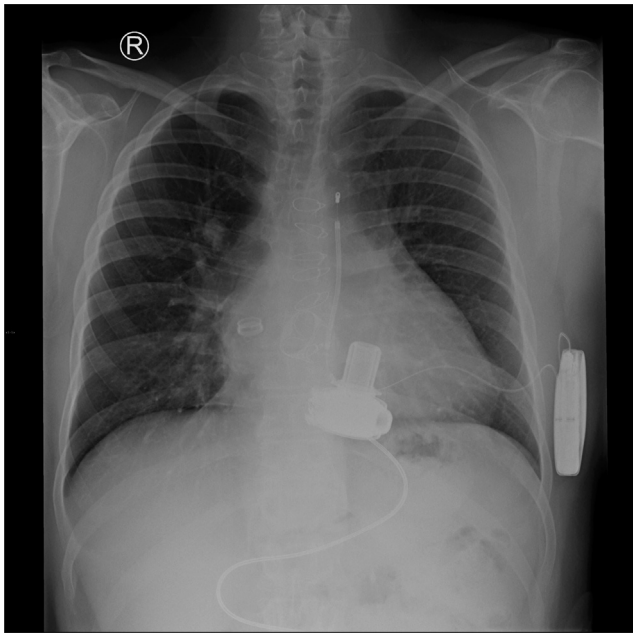

Figure 8. Chest radiograph of case 4 after HeartWare insertion and tissue tricuspid valve replacement. Note the previously placed subcutaneous implantable cardioverter-defibrillator.

catheter—measured PA pressures is often required. Embolization of aortopulmonary collaterals to reduce pulmonary venous return on cardiopulmonary bypass may be part of preparation for transplant listing.[68] Many patients will have had multiple previous arterial and venous cannulas, and vascular accesses can be limited. All patients undergo comprehensive pretransplant vascular imaging to plan potential bypass cannulation in the event that peripheral bypass or ECMO is required and to develop a comprehensive plan for venous access throughout the transplant process. Some patients have extensive antibody formation related to pregnancy, homografts, and previous blood transfusion. As with non-CHD transplant, a detailed review of comorbidities is a vital part of the assessment. This is not limited to respiratory, renal, and hepatic status but also the potential impact of neurologic events, chromosomal abnormalities, and behavioural and psychological factors that can all be significant in the context of CHD. Frequently transplant centres, in particular those offering transplant for complex CHD, are geographically distant from the patient being assessed. This can lead to challenges for these young adults and their families with the burden of travel for the assessment and the need to be away from home for often-long periods of time during the wait for a donor organ and the recovery after transplant. The change of team from the referral centre to the transplant centre and establishing trust with the new team can also be disrupting for patients at the time of complex discussion and difficult decisions. The assessment process includes counselling and educating patients with regard to these areas and ensuring that they are given the help and information needed to make the major commitment required. The possibilities of death on the waiting list, loss of transplant eligibility due to deterioration, and post-transplant mortality also need open discussion.

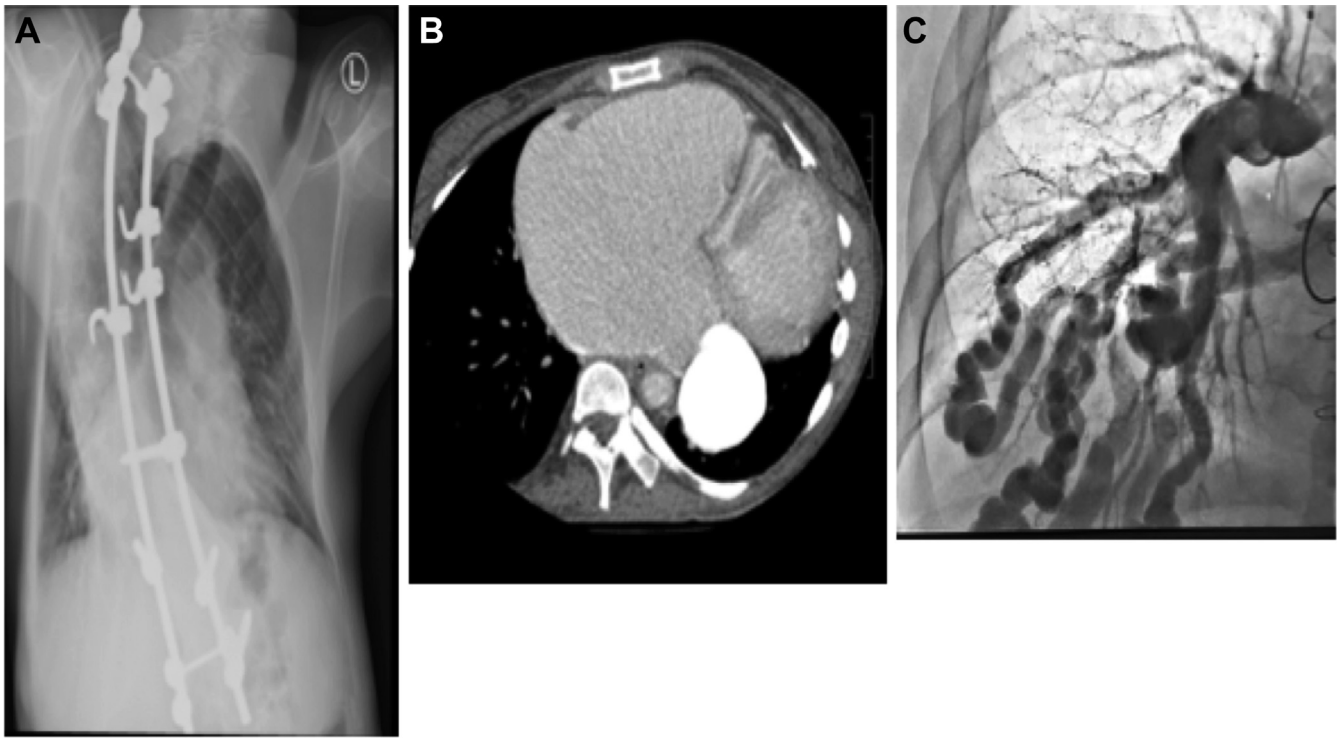

Figure 9. Some of the technical challenges encountered when considering transplant in adult congenital heart disease. (**A**) Patient with a highly abnormal chest wall and thorax shape due to previous surgeries, scoliosis, and overall small body size. (**B**) Patient with right atrial to pulmonary artery Fontan circulation, massively dilated right atrium in close proximity to sternum making sternal re-entry very high risk. (**C**) Patient with massive pulmonary artery to pulmonary vein malformation.

Transplant for Fontan Patients

Specific considerations are required for Fontan patients. Those with preserved ventricular function represent a particularly high-risk group,[69] presumably because such patients have worse overall Fontan failure and end organ involvement. Detailed anatomical assessment, proactive embolization of collaterals, increasing the donor/recipient weight range ratio and active monitoring for and treatment of post-transplant vasoplegia have together been suggested as significant factors in the improved survival for paediatric Fontan heart transplant.[67]

Fontan-associated liver disease (FALD) is a significant factor implicated in early post-transplant mortality. ACHD-HF and transplant teams must have a close collaboration with hepatology and liver transplant groups to decide on the suitability for heart-only transplant or to consider combined heart-liver transplant. A degree of cirrhosis is ubiquitous in Fontan patients and its presence is not a contraindication to heart transplant.[69-71] However, extensive cirrhosis, a low liver volume, and portal hypertension are considered markers of significant FALD.[70] Although a variety of imaging techniques and tissue biopsy can be used to assess the degree of liver involvement, there is no consensus, which provides the best estimate as to whether the liver will cope with the perioperative demands of heart transplant. The development of hepatocellular carcinoma is well recognized in Fontan patients and must be actively excluded before listing for heart-only transplant.[72] The development of protein losing enteropathy can cause significant symptoms for Fontan patients with marked ascites, oedema, and intolerable stool frequency. Refractory protein losing enteropathy is a risk factor for mortality in Fontan patients, and its presence even without other symptoms is an indication to consider cardiac transplant with a reported survival of 92% at 1 month and 83% at 1 year and resolution of symptoms in those who are transplanted successfully.[73]

Waiting List, Donor, and Perioperative Transplant Strategies to Improve Early Survival

The risk of developing of additional comorbidity on the waiting list necessitates regular specialist outpatient review to ensure that transplant eligibility is maintained, and all information is current when a graft becomes available. In Canada, where geographical distances can be huge, patients with ACHD-HF may sometimes be asked to relocate to the city of the ACHD transplant centre while they wait for a suitable donor. Sometimes candidates, in particular Fontan patients, are kept as in-patients on intravenous inotropes and diuretics to optimize cardiac output and end-organ reserve.

Specific strategies to reduce perioperative transplant mortality must be individualized within different centres, countries, and health care systems, but there are some general considerations. In our teams, marginal donors and distances that will substantially prolong ischemic times are avoided; surgery is carried out by highly experienced CHD surgeons, in conjunction with cardiac anaesthesiologists experienced in ACHD surgery. Preparation for and induction of anaesthesia occurs well before arrival of the donor heart. We anticipate long dissection times and plan the donor and recipient operation times to minimize pressure of time urgency and use extreme caution during chest re-entry. Dissection of the groin before opening the sternum is often performed, to permit rapid institution of femoral bypass in case of injury, and we aim for enough time to achieve haemostasis before the donor organ arrives. All reconstructive work (including arch reconstructions under deep hypothermic circulatory arrest) is undertaken before the donor organ being taken off ice. The warm ischemic time is one of the most important determinants of acute graft failure, and every effort is made to keep it to a minimum. Separation from cardiopulmonary bypass is slow and cautious, using intracardiac direct atrial lines for accurate monitoring and ensuring haemostasis to limit the need for re-exploration. Haemodialysis lines are placed intraoperatively in many cases in anticipation of the need for early dialysis.

Postoperatively, the emphasis is on early extubation and weaning of vasoconstrictors. Every effort is made to avoid ongoing sedation to permit intubation and the resultant effects of opiate and sedative medication on cardiac output, liver function, and potential delirium. Spontaneous ventilation in an extubated patient often breaks this vicious cycle. If unsuccessful (intubation beyond 48 hours), planning a tracheostomy in order to be able to wake the patient while remaining on a ventilator may be required. As for all heart transplant recipients, RV preservation is crucial. This is often more challenging in patients with ACHD not least due to the prolonged bypass time, volume of blood products, unmasking of elevated pulmonary resistance (either capillary vascular resistance or arterial anatomy), and acidosis related to perioperative haemodynamic instability.[74]

The introduction of *ex vivo* organ care systems is a significant recent technological advance. These portable perfusion systems are designed to maintain organs in a warm, functioning state outside of the body for prolonged periods of time. Among other things, this can increase the viability time of the heart without ischemic injury. The advantages to extending the donor pool as a whole by increasing potential to use marginal donors as well as donations after cardiac death are readily apparent. Organ care systems can mitigate the risks of the long cold ischemic times inherent to transfer across vast geographical areas and allow complete flexibility regarding the timing of graft anastomosis that, as earlier described, has unique benefits for ACHD. These systems have not yet been used for ACHD transplants in Canada, although they have in the United Kingdom (Fig. 10).

Listing Status and ACHD Transplant in the Wider Context

In most national organ donation structures, complications related to mechanical support, short-term devices, inotrope requirement, and ventilation all increase the urgency at which patients can be listed and therefore the probability of receiving a donor organ.[75-77] A large proportion of patients with ACHD are either not suitable or have no survival benefit from these therapies that would elevate their listing status.[78,79] The listing criteria for patients in Canada give some recognition to this and include potentially beneficial prioritization for sensitized patients,[75,80] and changes in the United States and United Kingdom may partially address the issue. Patients with

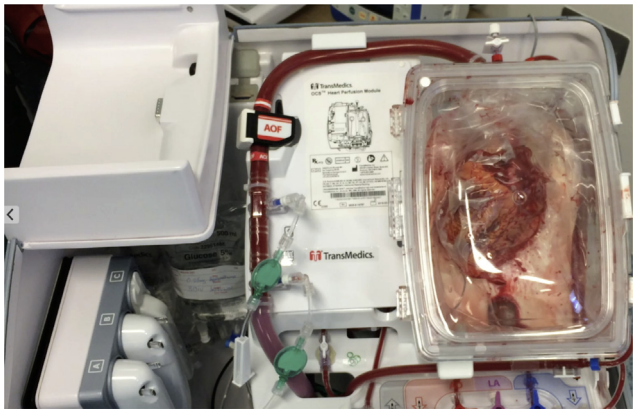

Figure 10. Photograph of the TransMedics in use for an adult congenital heart disease transplant. The heart is directly cannulated at the donor site and the heart warm perfused via the dedicated system housed within the system.

ACHD, in particular Fontan patients, show a gradual decline that does not affect their listing status but does impact on their transparent eligibility, and progression of FALD and other comorbidity in these patients during the wait for a donor organ potentially leads to a higher risk from the transplant or removal from the waiting list; further changes to listing criteria should be considered.[79] More data are required to define survival benefit of cardiac transplantation in ACHD and establish the point at which listing should take place before some of these issues can be resolved. With the already overburdened wait list and the predicted increase in the number of patients with ACHD who will require transplant, donor organ availability remains the main limitation of transplant as a treatment strategy.[81]

Multiorgan Transplant

Death on all thoracic and abdominal organ transplant waiting lists is compounded for patients waiting for more than 1 organ from a single donor. There are also complex issues surrounding justification for dual organ transplant. Nevertheless, there are an increasing number of patients with ACHD who, if the transplant option is to be a real possibility, need to be considered for multiorgan transplant.

Heart-Liver Transplant

The extensive liver assessment and close collaboration between ACHD transplant and hepatology teams in assessing Fontan patients' suitability for heart transplant naturally raises the option of combined heart-liver transplant for those whose FALD is thought to be too extensive[82] (Fig. 11). Registry data suggest that heart-liver transplant survival is comparable with heart transplant in patients with ACHD and combined heart-liver for Fontan transplants is also used.[22,82] Defining when heart-liver transplant should be offered to Fontan patients remains difficult, and the answer varies between centres, depending on local expertise, experience, and risk tolerance. Although heart-liver transplant is an option for selected

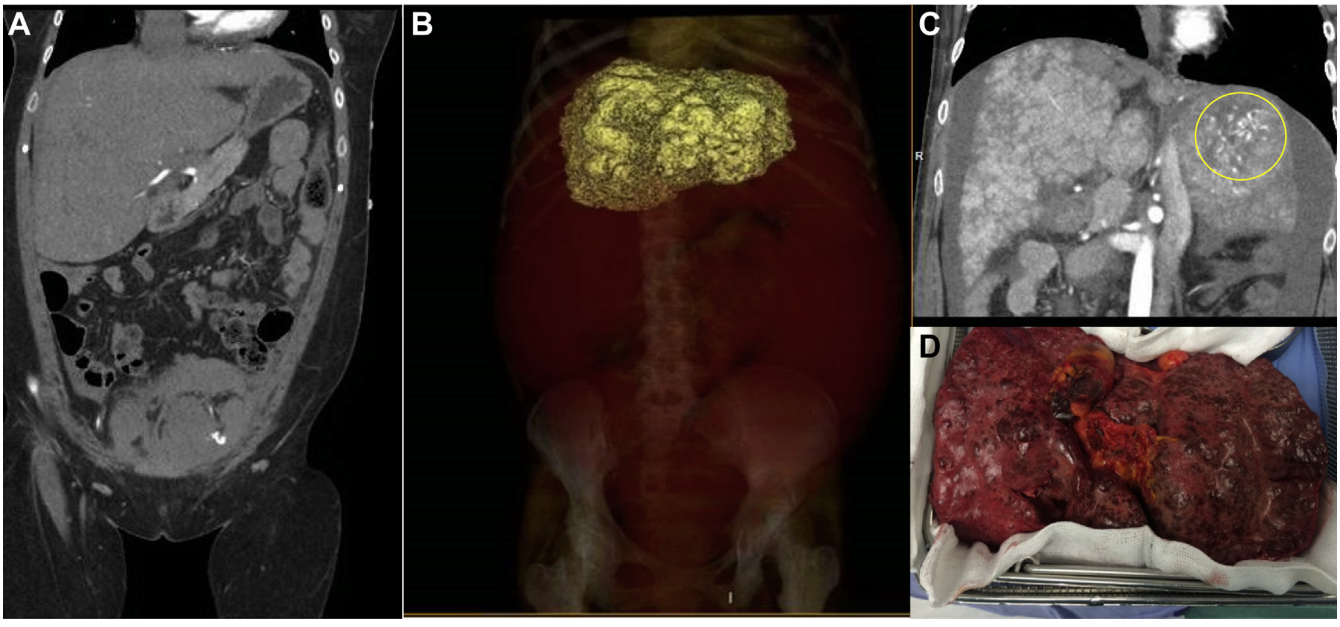

Figure 11. Examples of the Fontan-associated liver disease in patients referred to our heart failure (HF) in adult congenital heart disease clinics for consideration of advanced therapies. Some of the liver problems we have encountered in adults with failing Fontan circulations referred for consideration of advanced heart failure therapies. (**A**) Computed tomography (CT) showing hepatomegaly in patient referred for consideration of heart transplant. (**B**) CT showing small, shrunken, nodular liver, and massive ascites (**coloured red**) in right atrium to pulmonary artery Fontan patient originally referred for atrial arrhythmia ablation (unrecognized severe Fontan failure). (**C**) CT showing recurrent hepatocellular carcinoma (**yellow circle**) post ablation in RA-PA Fontan patient. (**D**) Explanted cirrhotic, nodular shrunken liver in a patient undergoing combined heart-liver transplant. (**D**) Modified from Duong et al.[101] under license by Creative Commons (CC BY-NC-ND 4.0).

patients, its use as a solution for the large numbers of Fontan patients graduating to ACHD clinics is unlikely to be realistic.

Heart-Lung Transplant

Patients with ACHD with small or absent true pulmonary arteries or irreversible pulmonary hypertension, including Eisemenger syndrome, can be considered for heart-lung transplant. Between 2012 and 2017, a total of 31 patients were listed for heart-lung transplant in Canada, and there were only 10 such transplants over the same time period.[66] Registry data show a 5-year survival after heart-lung transplant of 45%, which is substantially less than the survival for heart transplant alone.[65] Based on these survival data, it is reasonable to weigh the potential to markedly improve quality of life over any certainty of lengthening life when considering heart-lung transplant in patients with ACHD. Some Eisenmenger's patients with good ventricular function, such as those with an atrial or ventricular septal defect, can be listed for lung transplant and intracardiac repair, instead of a heart-lung transplant to increase the likelihood transplant and long-term survival.[83] The assessment of patients with ACHD referred for heart-lung transplant should begin with an ACHD-HF team, who can first consider nontransplant strategies. For patients with no other options, who wish to proceed with listing for heart-lung transplant, counselling during the long wait is essential. Despite the limitations, some patients have considerable improvement in symptoms and quality of life after heart-lung or lung transplant.[84]

Heart-Kidney Transplant

It is often difficult to determine the extent to which renal failure in ACHD-HF is potentially reversible due to ongoing low cardiac output and renal perfusion pressure or is established irreversible renal failure. Perioperative dialysis is more common after ACHD heart transplant than after heart transplant in the noncongenital population, and the authors have experience of return of urine output and adequate renal function after 3 months of anuria after ACHD heart transplant.[19,85,86] For those patients in whom adequate renal function is not restored, consideration is given to listing for sequential heart-kidney transplant. This is preferred to combined heart-kidney (from a single donor) at many institutions (including the authors').

Developing the Unit, Building the Team, and Establishing Regional/National Strategies

Which units should deliver advanced ACHD-HF care is dependent on many factors including local expertise, the population in need, regional referral patterns, the level of service currently provided (particularly existing transplant and mechanical support programmes), and financial considerations. All paediatric and ACHD cardiologists have a role to play in helping at-risk patients understand their situation, participate in decision making, and attend for regular follow-up, as well as in monitoring patients for signs of decline. The majority of CHD centres have cardiologists with focused areas of expertise, and extending this to ACHD-HF is a natural and necessary step. Establishment of dedicated HF clinics has been shown to improve survival in acquired HF and, although similar data do not exist for ACHD-HF, our experience suggests this to be the case. It seems sensible to concentrate on expertise and experience for patients with ACHD-HF both in terms of clinical care and developing cohorts to advance research. Larger volume heart transplant centres, carrying out 20 or more transplants a year, have better survival than small volume units.[65] Similarly, patients with CHD transplanted within high- and medium-volume units do better than those in low-volume centres.[87,88] ACHD surgery and VAD and transplant for acquired heart disease on the same site would seem to be prerequisite starting points for the development of an advanced ACHD-HF service and linked experience of CHD transplant in children is very important. Developing a model requires collaboration within and between programmes (ACHD, Cardiac Surgery, Heart transplant, Liver transplant, Anaesthesia, and Critical Care) to remove potential barriers, communicate honestly, accept knowledge limitations, and build trustful relationships. Teams developed in this way have shown increased access of patients with ACHD to advanced HF options, stepwise improvement in the ACHD transplant mortality, and the ability to extend mechanical support to the CHD population.[19,23,69,89]

Conclusions

Seventy years of pioneering care have given rise to a growing population of young and middle-aged patients with ACHD living with and dying from HF. The frustrating limitations of medical therapy present our specialty with yet another challenge and lead to the exploration of advanced options. The creation of subspecialty ACHD-HF teams within a wider network of ACHD care seems to be crucial. Increased clinical awareness, earlier referral, and better organization would enable more patients with ACHD-HF to benefit from current successful strategies. Looking to tomorrow, our specialty (and society) needs to embrace its responsibility to these patients, engage in technological advances, and improve advocacy at every level.

Disclosures

The authors have no conflicts of interest to disclose.

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