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Transplant and mechanical circulatory support in patients with adult congenital heart disease

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Abstract

Advances in surgery and pediatric care over the past decades have achieved improved survival for children born with congenital heart disease (CHD) and have produced a large, growing population of patients with adult congenital heart disease (ACHD). Heart failure has emerged as the leading cause of death and a major cause of morbidity among the ACHD population, while as little evidence supports the efficacy of guideline-directed medical therapies in this population. It is increasingly important that clinicians caring for these patients understand how to utilize mechanical circulatory support (MCS) in ACHD. In this review, we summarize the data on transplantation and MCS in the ACHD–heart failure population and provide a framework for how ACHD patients may benefit from advanced heart failure therapies like transplantation and MCS.

Keywords

Adult congenital heart disease; Fontan; UNOS; Heart transplantation; Mechanical circulatory support; LVAD

Introduction

Advances in surgery and pediatric care over the past decades have achieved improved survival for children born with congenital heart disease (CHD) and have produced a large, growing population of patients with adult congenital heart disease (ACHD). Clinically significant ACHD prevalence is estimated at 0.3% of the adult population or 1.4 million people in the USA [1, 2]. Over 90% of children born with CHD are expected to survive to adulthood. Even if considering only those with the most complex disease, expected survival is still over 50% [3]. Unfortunately, survival of patients with ACHD is considerably lower than the general population [4].

Heart failure has emerged as the leading cause of death and a major cause of morbidity among the ACHD population, accounting for between a quarter and one half of deaths [4–6]. Annual hospitalizations from ACHD-related heart failure (ACHD-HF) have risen 91% between 1998 and 2011, over four times the rate of growth of non-ACHD heart failure

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hospitalizations [7]. Treatment options for ACHD-HF remain limited, as little evidence supports the efficacy of guideline-directed medical therapies in this population [8]. As a result, appropriate utilization of heart transplantation (HT) and especially mechanical circulatory support (MCS) are of increasing importance to the ACHD-HF population.

While ACHD patients received increasing numbers of transplantations throughout the 2000s, a similar increase was not seen in durable MCS use for ACHD-HF compared to the general advanced heart failure population [7, 9, 10]. Despite increases in ACHD-HF HT, congenital patients have continued to experience lower listing status, longer wait times, and worse waitlist outcomes compared to other causes of transplant listing [11, 12]. Since 2018, there has been a major overhaul in the UNOS HT allocation criteria with movement from a 3-tier system to a 6-tier system. While data on the impact of these changes are still being collected, it is critical that clinicians who care for ACHD and ACHD-HF populations have a thorough understanding of these changes. Additionally, it is increasingly important that clinicians caring for these populations understand how to utilize MCS in ACHD. In this review, we summarize the data on HT and MCS in the ACHD-HF population and provide a framework for how ACHD patients may benefit from these advanced heart failure therapies.

Defining ACHD-HF and determining when to consider advanced heart failure therapies

Understanding the unique challenges associated with HT and MCS in the ACHD population requires an appreciation of the unique aspects of ACHD-HF. While heart failure is consistently reported as the leading cause of death in ACHD populations, comprising one quarter to one half of deaths in recently published cohorts, its distribution and expression within the population are heterogeneous [4-6]. Because of this diversity of presentation and prognosis, there is no universally accepted definition of ACHD-HF. A detailed discussion of the mechanisms and complexities of ACHD-HF can be found in the scientific statement released by the AHA in 2016 [8]. Patients with simple lesions and normal repaired anatomy have low rates of heart failure; these patients often have more straightforward expressions of left ventricular systolic dysfunction, which responds to guideline-directed medical therapy [4-6]. Those with more complex heart disease, however, may develop symptoms of advanced heart failure with higher systemic ventricular ejection fractions, making them less likely to benefit from medical therapies [13]. Left-sided obstructive lesions in fetal life and childhood can contribute to persistent diastolic dysfunction even after their surgical resolution. Impaired subpulmonic right ventricular function and reserve are common within the ACHD population and correlate with poor outcomes, but are difficult to identify on standard cardiac imaging and functional testing [14]. Patients with a morphologically right systemic ventricle, such as congenitally corrected transposition, have not been shown to derive functional or mortality benefit from guideline-directed medical therapy and have a particularly rapid decline after the onset of clinical heart failure [13, 15].

Use of BNP, LVEF, peak VO₂, and risk scoring systems, while somewhat helpful in ACHD-HF, appear to have reduced prognostic value compared with general heart failure population and are not equally applicable across all forms of ACHD [8, 13]. In a case series from

Vanderbilt, 11 out of 12 consecutive ACHD transplant patients who received preoperative cardiopulmonary exercise testing had a peak VO₂ over 14 ml/kg/min, above the cutoff for advanced heart failure therapies like HT or MCS, demonstrating the limitations of the advanced heart failure guidelines on exercise testing when applied to ACHD-HF [16]. At the same time, many confounding and potentially modifiable factors can lead to symptoms suggestive of advanced heart failure. Restrictive lung disease, related to postsurgical chest wall changes or abnormal lung development, is common in the ACHD population and significantly contributes to exercise intolerance [17, 18]. Chronotropic incompetence and heart block frequently coincide with many defects and surgical corrections [19]. Severe valvar disease, nonvalvar stenoses (such as subaortic stenosis or re-coarctation of a repaired aorta), acquired shunts (such as dehiscence of intraventricular patch material), or acquired artero-pulmonary collaterals, can potentially be addressed surgically or interventionally and may contribute to heart failure symptoms. Thus, it is important to identify patients with ACHD-HF early and to evaluate them thoroughly and expediently at a comprehensive ACHD center with referrals to pulmonologists, electrophysiologists, or other specialists when appropriate.

While it is reasonable to attempt initiation of guideline-directed medical therapy for heart failure in those patients with depressed systolic function of the systemic ventricle, this should be done with the knowledge that its efficacy is largely unproven and that it should not delay consideration of advanced therapies. Current expert consensus holds that there are insufficient data to make blanket recommendations as to when ACHD-HF patients should be referred for advanced therapy evaluation [20]. The AHA's scientific statement on HT and MCS in ACHD provides a framework for indications of when to consider advanced therapies and reasonable tests and biomarkers that may aid in prognosis [21].

Of those ACHD-HF patients who are evaluated for advanced therapies, limited data are available to assess how many patients currently proceed to listing for HT or MCS. Recently published series of ACHD-HF patients referred for HT evaluation from the UK and Italy reported listing rates of 45% and 43%, respectively, while 21% in the UK series and 57% in the Italian series were deemed too high risk to list [22, 23]. The variation in the proportion of patients determined to be too ill to list likely reflects variation in institutional culture, capabilities, and timing of referrals, but the large portion of patients in both series who could not proceed to listing demonstrates the need to better optimize timing of referrals. In the absence of universal guidelines, it is most important for the clinician to be familiar with institutional policies and resources regarding advanced therapies for ACHD-HF and to connect ACHD-HF patients to the institutional evaluation process expediently.

Among the many congenital malformations that can lead to ACHD-HF, those that leave the patient with only a single ventricle functionally capable of handling the full cardiac output require more detailed discussion in this review. For such patients, first-line treatment is generally surgical palliation leading to a Fontan physiology. The majority of adults with a single functional ventricle, therefore, have undergone Fontan palliation where systemic venous flow is redirected to the pulmonary arteries without a subpulmonic ventricle. An average of 1062 Fontan operations are performed per year in the USA [24]. Twenty-year transplant-free survival after the Fontan operation has continuously improved and now

approaches 80%. However, this is driven almost entirely by improved perioperative mortality, without gains in life expectancy among those who survive the perioperative period [25, 26]. Heart failure causes between a third and one half of the deaths reported in the adult Fontan population [4, 5, 27]. Thus, clinicians can anticipate that in the near future, approximately 400 new adult Fontan patients annually may benefit from advanced therapy evaluations in the USA alone. Their care will be a defining challenge for this generation's ACHD and heart failure physicians. Therefore, it is valuable to discuss the unique challenges that arise in connecting this population with advanced therapies.

Fontan patients can express heart failure very differently from the biventricular population. While they may develop ventricular systolic failure and depressed cardiac output, those with univentricular hearts and Fontan palliation may develop elevated venous pressures and symptoms of advanced heart failure without abnormal ventricular systolic function or reduced cardiac output [28, 29]. In fact, those who develop elevated Fontan pressures in the setting of a cardiac index above 2.5–3.0 l/min/m² have been shown to have markedly worse mortality [28, 30]. Likewise, Fontan patients with preserved ventricular systolic function undergoing isolated HT have historically experienced dismal outcomes, with 40–60% 30-day mortality [31, 32]. This counterintuitive result may be explained by the increased presence of liver disease, protein losing enteropathy, and arteriovenous collaterals, all common complications of Fontan physiology. Lower ventricular afterload and increase measured cardiac output, combined with severe pulmonary vascular disease, are known to drive elevation in Fontan pressures [33]. Symptomatic heart failure in the Fontan patient carries a much worse prognosis than in the biventricular population, where hospitalization for Fontan failure is associated with 8% in-hospital mortality—four times higher than an admission for biventricular ACHD-HF [29]. In addition to more typical symptoms of heart failure, adult patients with a failing Fontan may primarily present with protein-losing enteropathy, a highly morbid condition which is a guideline-supported indication for transplant listing [20]. Fontan-associated liver disease (FALD) driven by chronic congestion is also a major cause of mortality in the Fontan population, and its progression may identify patients who are no longer tolerating the Fontan physiology. Unfortunately, there is no optimal strategy for monitoring the progression of FALD, with significant limitations of most noninvasive testing strategies and a lack of data correlating test results with outcomes in the Fontan population. Adult Fontan patients require careful monitoring for changes in symptoms or markers of hepatic function combined with a low threshold to perform invasive testing. Considering the high morbidity and mortality of adult Fontan patients, once symptomatic, a plan for potential referral to advanced therapies should be developed as early as possible so as to not delay care once they show signs of disease progression.

Transplantation in ACHD-HF

Transplantation listing and waitlist outcomes

ACHD-HF patients listed for HT are on average younger, with lower rates of obesity, smoking, renal disease, and diabetes compared to those listed for other indications [11, 12, 34]. Despite this, ACHD-HF patients have tended to fare worse while listed for HT. Patients listed for HT due to ACHD have historically been more likely to list at low priority

compared to other indications, and spend a longer time on the waitlist [12, 34]. They have also been shown to be less likely to receive HT, even in comparison to other listees of the same allocation tier, and face higher mortality while awaiting HT. [12, 34] The excess in mortality appears particularly marked when comparing those listed at Status 1A (highest priority in the 2006–2018 heart transplant allocation system), with 24% of ACHD-HF patients listed 1A delisting due to death or clinical worsening at 180 days compared to 17% of 1A non-ACHD patients [11].

Numerous medical factors contribute to the lower listing priority, longer wait times, and poorer waitlist outcomes. ACHD-HF patients have very frequently undergone prior cardiac surgeries requiring blood transfusions or cadaveric allografts; this contributes to higher rates of allo-sensitization among those listed for HT. [35, 36] Additionally, prior surgeries or underlying congenital disease have often affected the anatomy and quality of the systemic vasculature and pulmonary arteries to accept a surgical anastomosis at the time of HT, potentially requiring complex reconstruction and use of the donor's pulmonary arteries as homograft material [37]. These factors conspire to limit the pool of acceptable donors, as well as the number of transplant centers with the necessary expertise. Further complicating matters, there are a large number of sudden cardiac deaths on the HT waitlist in the ACHD population driven by low utilization of implanted defibrillators [12, 34]. From 2004 to 2014, only 47% of listed ACHD patients had an ICD compared to over 75% of patients listed for ischemic or nonischemic cardiomyopathy [12]. This is likely driven by the lack of evidence-based criteria for utilization of ICDs in patients with congenital anatomies known to have increased risk of sudden death with preserved LV ejection fraction, combined with the increased technical complexity of placing devices in ACHD patients.

Lower rates of durable MCS in the ACHD population have historically contributed to lower listing status, prolonging waitlist time since MCS use has historically conferred higher prioritization on the waitlist. A recently published review of the Scientific Registry of Transplant Recipients (SRTR) database between 2004 and 2014 found that only 3% of ACHD patients listed for HT had durable LVADs; this compared to 18% respectively for nonischemic cardiomyopathy (NICM) patients and 20% for ischemic cardiomyopathy (ICM) patients [12]. Given the role of MCS within the allocation criteria, it is clear how this lower utilization may contribute to a lower listing status. Whether or not MCS improves waitlist outcomes for ACHD-HF patients as it does for other forms of heart failure is unclear. ACHD patients with MCS appear to experience longer waitlist times despite higher average listing status, and otherwise equivalent waitlist outcomes compared to ACHD patients without MCS [38]. Another recently published analysis of SRTR data found that when compared to ACHD patients awaiting HT without MCS, those with MCS had either unchanged (if listed 1A) or worsened (if 1B) rates of delisting due to death or worsening; patients without ACHD who received MCS had improved (if 1A) or unchanged (if 1B) listing outcomes [39]. Recently published data from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) suggest that ACHD patients tend to be sicker at the time of implant, and these data also show that ACHD patients with durable MCS are still less likely to receive HT at 1 year than non-ACHD patients (20.1% vs 33.7%) [40]. This may reflect the higher barriers in current practice to MCS initiation in ACHD, with patients more frequently receiving MCS as a bailout therapy. Given the

complex vascular and thoracic anatomies of many ACHD patients and considering the dearth of data proving benefit of MCS in the ACHD population, it is not surprising that clinicians might be reluctant to expose their ACHD patients to the known risks of devices until it is felt they have no other options. With the continued and heightened emphasis on MCS in the new UNOS allocation criteria, determining if and how the utilization of MCS in the ACHD-HF population can be appropriately expanded remains an important problem.

Elevated pulmonary vascular resistance (PVR), a known contraindication to HT, is another significant medical factor complicating transplant eligibility and outcomes in ACHD-HF patients. A PVR over 4 WU (i.e., above the generally utilized HT eligibility cutoff) is present in 44% to 62% of ACHD patients listed for HT. [11, 36] Elevated PVR may be more common in patients listed for HT for ACHD compared to other indications [36, 41]. Additionally, it can be difficult to accurately diagnose and treat elevated PVR in certain complex physiologies in which venovenous shunting, nonpulsatile flow, unequal distribution of flow within the pulmonary beds, and developmental abnormalities limited to a single lung or lung segment can all lead to standard measurements from the cath lab not reflecting the true total PVR. ACHD patients listed for HT are thus less likely to receive inotropes or a durable LVAD, which are guideline-recommended decongestive therapies capable of resolving reversible PVR elevations in the end-stage heart failure population [11, 41]. Elevated PVR at time of HT confers a risk of acute right heart failure of the graft and may drive more stringent selection of donor organs. For example, several groups have reported the use of donor organ oversizing intending to mitigate this risk in their complex ACHD patients, an approach which further limits the prospective donor pool [31, 42]. Evaluation of UNOS data through 2006 by Patel and colleagues found elevated preoperative PVR in transplanted ACHD patients to be a risk factor for 30-day mortality [36]. A more recent evaluation of the UNOS data through 2014 by Krishnamurthy et al. found elevated PVR to be a risk factor for death while awaiting HT but did not identify a statistically significant link to longer waitlist time or post-transplant mortality [43]. Notably, there are a lack of data elucidating how frequently the presence of elevated PVR in the ACHD population prevents listing altogether.

Post-transplantation outcomes

A decade of data have consistently shown a survival curve in ACHD HT that underscores both its challenge and its promise: perioperative and 1-year survival is worse than other populations, but 10- and 15-year survival is superior when compared to other indications adult HT (see Table 1) [36, 44-47]. This is driven by a heavy excess in perioperative mortality among ACHD transplants, followed by superior conditional survival among those who reach 1 year [46]. Preoperative factors that have been associated with excess short-term mortality in the ACHD population include prior sternotomies and elevated preoperative pulmonary vascular resistance. Prolonged ischemic time, perioperative hemorrhage, stroke, acute graft failure, and renal injury occur more frequently in ACHD transplants and also drive their poor acute outcomes [36, 44, 46] These factors are linked to the fact that HT in the ACHD population is a more complex surgery often requiring prolonged sternal re-entry and lysis of adhesions, alternate bypass cannulation strategies, and complex vascular reconstruction, all of which contribute to longer surgical, bypass, and ischemic times [44,

46]. Given the improved childhood survival among complex CHD patients, there has been a reported temporal trend towards even longer bypass and ischemic times in the modern era of ACHD transplantation [48].

Patients surviving the perioperative period go on to enjoy better long-term outcomes than the average heart transplant recipient. Meta analyses have identified lower rates of malignancy and infection within the post-transplant ACHD population, although few specific causes have been shown to definitively drive the improved long-term outcomes [44, 45].

Interestingly, despite the higher rates of allosensitization among ACHD patients, increased rates of antibody mediated rejection and coronary artery vasculopathy have not been reported among ACHD transplant recipients, and in fact, trends towards less rejection have been suggested [44, 45]. Aftercare of the ACHD transplant patient who survives the perioperative period is not substantially different from other transplant recipients. Because of their younger average age, however, ACHD transplant recipients do face increased likelihood of re-transplantation. This is associated with significantly increased short and long-term mortality compared to first time HT. [45, 46]

With so much of the morbidity and mortality of HT in ACHD arising from the complexity and duration of the surgery and aftercare, it is not surprising that center volume has a significant impact upon survival. Patients transplanted at high-volume ACHD transplant centers have significantly superior survival of 91% at 30 days and 84% at 1 year, compared to 83% and 75% survival at low-volume centers [49]. Those centers that have published case series achieving high perioperative survival emphasize the need for specialized ACHD expertise among the preoperative medical care team, cardiac anesthesiologist, and surgeon, as well as strong multidisciplinary support and involvement. Expertise in multimodality cardiac imaging is also important, as CT and MRI are vital tools to fully elucidate anatomy and allow surgeons to plan sternal entry, cannulation strategies, and to determine the need for vascular reconstruction [37]. Extensive staff experience managing postoperative mechanical support and prolonged critical illness is also identified as a factor for success, given the extended recovery many patients face [50, 51]. For centers with separate children's and adult hospitals and transplantation programs, this may pose a unique logistical challenge, as the teams most comfortable with the management of congenital heart disease and those most comfortable with the aftercare of a critically ill adult may not be based out of the same institution.

Challenges of transplantation in ACHD-HF

Transplantation in patients with the Fontan circulation

Adult Fontan patients present complex challenges in HT. They have universally undergone prior sternotomies and have had prior exposure to blood transfusion or allograft material. Their complex anatomies require reconstruction of the pulmonary arteries and venae cava, factors associated with prolonged ischemic times, sensitization, and surgical bleeding at time of HT. [35-37] Some degree of comorbid pulmonary vascular and hepatic disease is universal. Appropriate listing, donor selection, and aftercare for these patients require complex evaluation and optimization.

Although significant pulmonary vascular disease is present in the majority of failing Fontans, nonpulsatile flow and highly heterogeneous resistance across the pulmonary capillary beds make accurate calculation of PVR from catheterization difficult, with pre-transplantation measurements often correlating poorly with post-transplantation pulmonary pressures and resistances [52]. As a result, centers that report success with adult Fontan transplants have generally developed strategies that incorporate strict avoidance of undersized donor grafts and prolonged post-transplant support with inhaled pulmonary vasodilators [31, 42, 53]. In addition to obstructive pulmonary vascular disease, patients with Fontan physiology commonly develop pulmonary arteriovenous malformations, venovenous collaterals, and arteriovenous collaterals that increase the risk of bleeding during surgery, obfuscate hemodynamics, and can lead to high output failure after HT. Identifying and embolizing collaterals prior to transplant may lead to better surgical outcomes [53].

Chronic hepatic congestion results in the presence of some degree of Fontan-associated liver disease (FALD) in all adult Fontan patients. However, this may vary from mild radiographic and laboratory abnormalities to advanced cirrhosis, synthetic dysfunction, or hepatocellular carcinoma. The effects of FALD on HT outcomes are heterogeneous within the small body of literature that reports on adult Fontan transplants [54]. Even when early cirrhosis is present, good outcomes from isolated HT remain feasible [54-56]. As liver failure becomes more advanced, multiorgan transplantation should be considered. Combined heart-liver transplant may provide noninferior or even superior outcomes compared to HT, related to improved synthetic function and the induced immune tolerance seen after liver transplantation [57, 58]. Decisions to list single-ventricle adults for combined heart-liver transplantation or heart-only transplantation are dependent on institutional experience, culture, and expert opinion. Hepatic imaging, biopsy, and risk scoring systems such as the VAST score or MELD-XI score can help guide decision-making [50, 54, 55].

Protein-losing enteropathy (PLE) is a complication of the Fontan circulation in which the development or recruitment of abnormal lymphatic channels from chronic hepatic congestion allows protein-rich lymphatic fluid losses into the gastrointestinal tract [59]. It carries a high morbidity and mortality, and a large majority of cases resolve after HT, making it an accepted indication for transplant evaluation. PLE patients face additional challenges in organ transplantation even beyond the general single ventricle population. PLE causes hypoalbuminemia, immune deficiency related to loss of immune globulins, and an increased risk of both thrombosis and hemorrhage due to loss of clotting factors. Each of these has been associated with poor outcomes in listing and HT. [11, 44] Patients who develop PLE generally have a preserved LV function and cardiac output with elevated Fontan pressures, historically factors that have predicted worse outcomes after HT. [28-32] The immunoglobulin loss from PLE may also obscure immune sensitization. A recent multicenter pediatric study found that 44% of patients transplanted for PLE developed donor-specific antibodies and 31% experienced clinically significant antibody-mediated rejection, despite only 25% having a panel reactive antibody screen over 10% at the time of HT. [60] In spite of these challenges, it is not clear that PLE patients have worse outcomes in the modern era. While data in adults is scant, recent multicenter pediatric trials did not demonstrate worse HT outcomes in PLE patients compared to single ventricle patients transplanted without PLE and did not find a correlation between PLE severity or duration

and HT outcomes [60, 61]. A retrospective analysis of transplanted Fontan patients seen at the Mayo Clinic identified 12 adults with PLE who were transplanted with survival at 1 year and 5 years of 75% and 67%, respectively [56]. University of California Los Angeles and the University of Pennsylvania have reported performing HT on a combined 7 adults with Fontan-associated PLE without any early mortalities [50, 55].

As a result of these many factors, Fontan patients have historically represented a population with particularly high mortality during listing and after HT. In fact, some studies suggest that the Fontan population drives the bulk of the excess risk observed when ACHD transplants are compared as a group to non-ACHD transplants [44, 62]. More recent data suggest that surgical outcomes are improving in the modern era and that adult Fontan patients, when transplanted at centers of expertise, can have outcomes similar to the rest of the ACHD population, with 1-year survival exceeding 90% [50, 53, 55]. As with HT in ACHD generally, success in the adult single ventricle patient relies heavily on the availability and coordination of a wide variety of expertise between multiple clinical disciplines at every stage in the patient's care.

Multiorgan transplantation

The ACHD population is disproportionately represented in multiorgan heart transplant, with 4.7% of multiorgan heart transplantation recipients carrying a CHD indication compared with 3.1% of isolated HT. [47] This overrepresentation is driven by heart–liver and heart–lung transplantations. Given the small number of multiorgan transplantations performed, data to guide decision-making in the ACHD population are extremely limited.

ACHD patients, predominantly with advanced FALD, comprise 22% of patients listed for and 20% of patients receiving a heart–liver [57, 58]. Heart–liver transplantation remains a rare procedure, however, with only 320 documented in the UNOS database from 1987 through 2014, compared to over 100,000 total heart transplants in the same period [57]. Annual incidence has been slowly increasing, having risen from fewer than 10 up to 20–25 per year over the last two decades [63]. Published outcomes in ACHD heart–liver transplantation are quite good, with reported 1-, 5-, and 10-year survivals of 86%, 83%, and 83% [58]. Small series of heart–liver in ACHD patients with 100% 1-year survival have been reported by Stanford (9 patients), University of Pennsylvania (7 patients), University of California at Los Angeles (5 patients), and Cleveland Clinic Foundation (2 patients) [55, 64–66]. These favorable short-term outcomes likely reflect the highly specialized nature of the procedure, with small numbers of carefully selected patients undergoing heart–liver transplantation at a small number of centers. The good long-term outcomes are potentially related to the observed decrease in rejection that occurs in heart–liver, possibly related to the immunologic function of the liver [58].

ACHD with associated pulmonary hypertension (PH) accounts for over 50% of combined heart–lung transplantations [67]. Heart–lung transplantation, like heart–liver, is rare with only about 4000 having been performed since 1987. Unlike heart–liver, the utilization of heart–lung transplantation has been continuously decreasing from a peak of over 200 in 1990 to around 50 per year in the modern era [67]. This is likely reflective of improved medical therapies for PH, improved techniques for surgically palliating congenital heart disease,

improved management of PH in heart transplantation, and the additional surgical risk of heart-lung transplantation. Unlike heart–liver, heart–lung transplantation outcomes do not compare favorably to isolated HT, with almost 25% perioperative mortality and a median survival of under 6 years [67]. This also does not compare favorably to medical therapy: the mortality rate in Eisenmenger syndrome patients treated with pulmonary vasodilators appears to be under 5% per year [68]. Heart–lung transplantation should therefore be reserved for only those patients unable to tolerate or not benefitting from pulmonary vasodilator therapy.

2018 heart transplantation allocation changes and implications for ACHD

In October 2018, UNOS changed the adult HT allocation system, with significant implications to the listing of patients with ACHD. Under the old allocation system, three priority statuses existed, 1A, 1B, and 2, which considered the patient's ability to discharge from the hospital and their current level of inotropic or mechanical support. This system did not seem to accurately capture the degree of illness of the ACHD-HF population, producing longer wait times and inferior listing outcomes. This was also reflected in the listing practices at ACHD transplantation centers: ACHD patients disproportionately relied on exception requests to achieve higher listing statuses, comprising 14% of all 1A and 1B status exception requests [69]. The University of Pennsylvania reported utilizing exemption requests in over 50% of their ACHD patients [50]. The new UNOS criteria include revisions that seek to help list ACHD patients in a manner that more accurately reflects their level of risk but has also maintained aspects that are likely to continue to disadvantage the ACHD population.

The new allocation system has 6 statuses (see Table 2) and sequential geographic zones centered around the location of the donor: the Donor Service Area (DSA), Zone A, which extends to 1000 miles from the DSA, and Zone B, which is between 1000 and 1500 miles from the DSA. Allocation is by geography and urgency status. Hearts are first offered to patients listed Statuses 1 and 2 in Zone A, then to Status 3 patients in the DSA, then to Statuses 1 and 2 patients in zone B, then to Status 4 patients in the DSA.

The most obviously relevant change to the ACHD population is that patients with ACHD-HF are listed at Status 4, giving them equivalent priority to most noncongenital patients with stable LVAD or outpatient inotropic support. This prioritizes them over the majority of stable noncongenital transplant listees, who list at Status 6. Unlike stable LVAD patients, however, unsupported ACHD patients do not have discretionary time to temporarily increase their status to 3. Higher priority statuses require patients to receive high-dose inotropes or mechanical circulatory support and to meet certain hemodynamic criteria demonstrating cardiogenic shock or severe congestion. As has already been shown, ACHD patients are historically less likely to meet these criteria. Acknowledging this, UNOS has outlined recommendations for specific exemptions, which should be granted if requested in the congenital population (see Table 3). These exceptions are likely to be of particular benefit to the Fontan population.

Given how recently the new allocation system has been instituted, it will likely be at least another year before sufficient data are available to draw conclusions regarding how it has altered ACHD outcomes. However, early data raise some cause for concern. As of January 2019, UNOS data shows 1592 patients were listed for transplant at Status 4, representing 62% of the actively listed patients. However, between the October 2018 introduction of the new system and January of 2019, only 105 hearts, comprising 19% of donor organs, were allocated to Status 4 patients. Half of the transplanted hearts during this time were allocated to patients listed Status 1 or 2, with 28% going to patients listed Status 3. This distribution is driven by the geographic allocation changes under the new system—Status 4 patients receive offers of local hearts only after the organs have been offered to Status 1 and 2 patients up to 1500 miles from the DSA and local Status 3 patients. For Status 1 and 2 patients, who are universally critically ill, this is encouraging news. However, this shows the challenges that ACHD patients still face on the transplant list, and underscores how judicious utilization of exemption requests and mechanical circulatory support are likely to remain critical to achieving good outcomes for listed ACHD patients.

Mechanical circulatory support in ACHD

Overview of durable MCS in ACHD

Advancements in MCS, especially the development of effective implantable left ventricular assist devices (LVADs), have revolutionized the management of advanced heart failure. Over 2000 LVADs are now implanted annually, with almost half as destination therapy [70]. In 2017, 50% of HT recipients had an LVAD at the time of transplant [47]. In contrast, MCS use in the ACHD-HF population has lagged. Only 0.8% of patients in the INTERMACS database were ACHD as of 2015 [71]. There are likely multiple reasons for these differences. Commercially available devices were designed for use in anatomical left ventricles that are dilated and experiencing advanced systolic failure. Not all modes of failure in the ACHD population might benefit from such support, and those that do frequently require novel surgical techniques to accommodate their anatomy. As a clinician, it is difficult to justify exposing a patient to the risks of MCS surgery without confidence in its benefit. Very little outcomes data are available to help determine whether ACHD-HF patients can derive similar benefits. Nonetheless, as the ACHD-HF population swells, it is clear that a need exists, and a body of literature is starting to develop.

Two in-depth analyses of ACHD patients in the INTERMACS database were published in 2018, providing some of the first insights beyond case reports and series into the use and outcomes of durable MCS in ACHD [40, 71]. Only 128 ACHD patients in the INTERMACS database received MCS as of 2015, compared to over 16,000 non-ACHD patients. While ACHD patients had worse mortality after MCS than non-ACHD patients, this difference was driven by a higher proportion (21% vs 7%) of ACHD patients receiving biventricular assist devices (BiVADs) or total artificial hearts (TAH). This subset was disproportionately INTERMACS class 1 or 2 at time of implant and had markedly poorer outcomes [71]. Excess mortality among ACHD patients was also seen to occur primarily within the first 5 months of transplant, with similar outcomes thereafter [40]. When comparing only LVADs between ACHD and non-ACHD, there was no difference in mortality despite higher rates of

hepatic and renal dysfunction, arrhythmias, and infection in the ACHD group. ACHD patients had significantly less bleeding. MCS was also used much less frequently as a destination therapy in ACHD patients, with only 16% of implants performed with this intent [71]. Functional and quality of life measures improved equally in ACHD and non-ACHD patients after MCS [40]. As noted previously, MCS as a bridge to transplant in ACHD had poorer outcomes compared to non-ACHD, with lower 1-year transplant rates and increased risk of delisting due to worsening or death [39, 40]. Overall, the INTERMACS data show that MCS remains in its infancy but has significant promise. The majority of excess mortality appears to be in the perioperative period, and the history of surgery in CHD would suggest this can be improved with growing experience. Outcomes in MCS in the general population have improved over time as clinical practice has trended toward implanting in more stable patients earlier in their disease course; as clinicians become more comfortable with the management of MCS in the ACHD population, hopefully similar trends will emerge [70].

Beyond these reviews of the INTERMACS data, published clinical experience of MCS in ACHD is limited to case reports, series, and a systematic review of published series. From these observations and data, we can appreciate some of the major technical challenges that must be addressed in advancing the use of MCS in complex ACHD (see Table 4).

Mechanical support of the systemic right ventricle with a subpulmonic left ventricle

The current era of ACHD-HF has seen a glut of patients with a failing systemic right ventricle, as the last generation of atrial-switch repaired patients with dextro-transposition of the great arteries (dTGA) enter their fourth and fifth decades of life [48]. Patients with a failing systemic right ventricle do not appear to benefit from traditional guideline-directed medical therapy and have a particularly rapid course after onset of heart failure [13]. They may also develop particularly severe pulmonary hypertension, which makes primary transplant difficult. They are therefore a population of particular interest for durable MCS and comprise the most frequently described anatomy in ACHD MCS cases [72]. The unusual position and anatomy of the systemic right ventricle may create difficulties in obtaining and maintaining stable inflow cannula position and in achieving chest closure without compression of the ventricle. The heavily trabeculated inner surface of the right ventricle and the moderator band, combined with the crescent shape of the decompressed right ventricle, can increase the incidence of suction events and pump thrombus. Published series describe employing surgical techniques such as nonapical cannulation sites, nonstandard pump orientations, and aggressive muscle bundle resections at time of implant to address these problems [72-74]. The desire to avoid repeat sternotomy may drive choice of device, as the Heartware HVAD and Heartmate 3 devices can potentially be implanted via thoracotomy [73, 75]. Innovative approaches to surgical planning have been reported in this population, including 3D printing heart models from CT datasets to evaluate cannula positioning, and even creating 3D CGI models of the patients anatomy from CT data that can be manipulated in a virtual reality environment to find suitable device orientation [76, 77]. At least in the limited published case series, the use of LVADs in the systemic right ventricle has been effective in supporting the systemic circulation and producing significant

reductions in pulmonary pressures and resistances, with many patients successfully bridged to transplant.

Mechanical support of the Fontan patient

If our current era of ACHD-HF is shaped by the last of the dTGA atrial switches, the next will be defined by growing numbers of the adult Fontan-palliated single ventricle patients. Experience of durable MCS in this population is markedly limited; to date, there have only been 17 single ventricle patients in the INTERMACS database [71]. Case studies have been published on successful outcomes using all current commercially available continuous flow devices in Fontan patients with systolic failure of the systemic ventricle [78-81]. A recent series published by the Advanced Cardiac Therapies Improving Outcomes Network (ACTION) has reported low rates of complications with the HeartMate 3 LVAD [82]. These case reports describe improvement in symptoms, function, Fontan pressures, successful bridge-to-transplantation, and in at least one case, the resolution of PLE. Technical considerations included the need for nonstandard cannula placements such as the diaphragmatic surface or even the atrium, as well as the need to run pumps at high speeds to minimize the systemic ventricular filling pressure and promote passive flow across the pulmonary vasculature. Authors of several cases discussed consideration of creating a Fontan fenestration at time of VAD placement to improve venous decongestion in future cases. Despite limited data, it appears that well-selected Fontan patients who develop systolic failure, especially those with hypoplastic left heart syndrome, can benefit from a systemic VAD.

For Fontan patients with preserved ventricular function, support of the pulmonic circulation to relieve congestion is needed. Currently described approaches include the use of the Syncardia TAH for biventricular replacement or the Berlin Heart EXCOR paracorporeal VAD in the subpulmonic position [83-85]. Both options are technically challenging surgeries, and in the case of the Berlin Heart EXCOR, does not allow for hospital discharge. To mechanically support the subpulmonic circulation in the Fontan patient requires takedown of the Fontan and Glenn or Hemifontan, repair of the pulmonary arteries, and creation of a new “atrium” from which the device can pump. To our knowledge, no reports exist of a continuous flow device used to support the subpulmonic circulation in an adult Fontan patient. A single published case report describes the use of HeartWare HVADs in a BiVAD configuration in a previously unpalliated adult patient with double-inlet left ventricle and pulmonary stenosis, achieved by septation of the common atrium and placement of the subpulmonary HVAD into the newly isolated right atrium [86]. A similar anatomy might be achieved in a Fontan patient. However, for the commercially available continuous flow pumps this is also a much different hemodynamic scenario than that for which they were designed. In the low-afterload subpulmonic circulation, current devices are likely to deliver excessive flow even if at minimum speed, increasing incidence of suction events and thrombus risk. This was described in the last case report, which required banding of the outflow cannula. In silico and in vitro modeling suggests that currently available LVADs, when implanted in the subpulmonic position under most hemodynamic conditions, will require either banding or lengthening of the outflow cannula to augment afterload and allow the device to perform within the range of pump speeds for which it is designed [87].

Because of this, at least one group has been working to develop a purpose-built pump designed for the anatomic and hemodynamic demands of the Fontan circulation [88]. Subpulmonic mechanical support of the Fontan patient remains a daunting challenge. However, the potential to decongest the hepatic circulation, arrest progression of FALD, and resolve PLE makes it a potentially transformative technology should it come to fruition.

BiVAD, TAH, and subpulmonic RVAD

The utilization of durable implanted BiVADs, TAH, and isolated RVAD remain rare in the general MCS population, comprising 2.6%, 1.3%, and 0.07% of the patients in the INTERMACs registry [70]. Their use is more common in the ACHD MCS population, with 11% receiving BiVADs, 10% receiving TAH, and 2% receiving isolated RVAD [71]. This increased use in the ACHD population may be driven by increased incidence of right heart failure, as well as the incompatibility of Fontan anatomy with percutaneous RVADs, such as the ProTek DUO and Impella RP, that could be utilized for short- or medium-term inpatient support in biventricular anatomy. Mortality is high in all patients with these forms of MCS but is particularly poor in the ACHD population. These outcomes likely reflect both the limitations of the hardware as well as trends in patient selection.

BiVAD support with two continuous flow VADs is limited by the relatively low sensitivity of existing devices' flow profiles to preload in comparison to afterload, and the lack of existing software or hardware to allow dynamic adaptation of pump speed. This means that changes in flow through one pump are not in a stable equilibrium flow through the other, potentially leading to suction events or venous congestion. The pulsatile design of the Syncardia TAH, relying on two pneumatically operated pumping chambers that fill partially and eject fully with each cycle, ameliorates this issue. However, the TAH has not achieved consistently superior mortality outcomes to BiVAD, although it may be associated with higher rates of discharge on support and lower rates of neurologic events compared to BiVADs [89]. Use of the TAH is limited by the high complexity of its surgical placement and the small number of centers with adequate experience in its management, which has resulted in steadily high in-hospital mortality since its introduction. BiVADs and TAH are therefore both used largely as an option of last resort in attempting to bridge patients to transplant, being performed disproportionately in INTERMACS class 1 patients. This skew towards the most unstable patients, combined with the extreme technical challenges of surgically reconstructing the congenital anatomy to accept such devices, likely drives the especially poor ACHD outcomes [71].

Overall, modest improvements in outcomes might still be anticipated with continued experience in postoperative management and trends towards greater utilization in INTERMACS class 2 patients, but until better technology is developed, BiVAD and TAH in the ACHD population will likely remain an infrequent choice of desperation.

Conclusion

Advanced heart failure is the leading cause of death in ACHD, and it is rapidly growing with the population. ACHD-HF often presents differently from typical heart failure, and hewing too closely to existing transplant guidelines is likely to miss patients with ACHD-HF who

could benefit from advanced therapies. Identification of such patients should be undertaken as soon in their care as feasible. HT has been well established as a beneficial treatment option with good long-term outcomes. As experience improves, perioperative ACHD transplant outcomes are approaching those of the general heart transplant population at high-volume transplant programs. In light of new changes to the UNOS allocation criteria, judicious use of exemption requests and continued improvement in MCS utilization will likely be key to improving waitlist outcomes for ACHD patients. Mechanical circulatory support in ACHD remains a young field, but as more robust outcomes data become available to support its benefit, the use of durable VADs has become an increasingly popular option both for optimizing patients listed for transplant as well as for possible destination therapy. Outcomes in ACHD MCS are likely to improve as perioperative experience increases and as patient selection trends toward less critically ill patients, as it has with the general MCS population.

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Reported survival outcomes after transplant in ACHD as compared to other indications at 30 days, 1, 10, and 15 years. Numbers are percent survival at time point post-surgery. Pairwise comparisons that achieved statistical significance are in italics [36, 44, 45]

Table 1

	<u>30 days</u>		<u>1 year</u>		<u>10 years</u>		<u>15 years</u>	
	ACHD	Others	ACHD	Others	ACHD	Others	ACHD	Others
Patel (2009)	<i>83.9</i>	<i>93.6</i>	79.6	86.2	57.4	50.9		
Burchill (2014)			77	83	57	53	53	37
Doumouras (2016)	<i>82.6</i>	<i>92.6</i>	79.4	84.6	<i>59.3</i>	<i>51</i>		

Table 2

Comparison of prior and current UNOS allocation statuses and criteria. Lower-numbered status tiers receive highest priority when organ offers are made. MCS mechanical circulatory support; LVAD, RVAD, BiVAD left, right, and biventricular assist devices; IABP intraaortic balloon pump; TAH total artificial heart

2006 UNOS allocation statuses	2018 UNOS allocation statuses
1A: Evidence of shock, inpatient, continuous hemodynamic monitoring, plus at least one of the following:	1: Evidence of severe shock, inpatient, plus
• multiple high dose inotropes	• ECMO
• nondischageable MCS	• nondischageable BiVAD
• refractory unstable ventricular arrhythmia	• MCS AND refractory unstable ventricular rhythm
• malfunctioning LVAD	2: Evidence of shock, inpatient, plus
	• nondischageable or percutaneous LVAD, or
	• IABP
	• durable TAH, BiVAD, RVAD, or any VAD in a single ventricle patient
	• refractory unstable ventricular rhythm
1B: Inpatient or outpatient	3: Evidence of shock, plus
• stable LVAD	• inpatient with high dose inotrope or inotropes
• low-dose inotrope dependence	• LVAD with malfunction, infection, clot, or bleeding
	OR
	• LVAD using discretionary 30 days
	4:
	• evidence of low cardiac index on a stable
	• inotrope
	• stable LVAD
	• congenital heart disease
	• other high risk etiologies.
2:	5: Concurrently listed for another organ
• All others	6: All others

Table 3

UNOS has released a working document outlining justified exemption requests for ACHD patients. Centers seeking to list ACHD patients at these high statuses still must submit a formal exemption request, which must be approved by a review committee for the patient to receive the elevated priority status

Recommended exemptions for ACHD patients

Status 1 exemption: Inpatient, plus

- single ventricle anatomy with a surgically implanted VAD, with malfunction, clot, or bleeding

Status 2 exemption: Inpatient, plus

- single ventricle anatomy with high dose or maximally tolerated inotropes (does not need to meet traditional hemodynamic criteria for shock)
- single ventricle anatomy, mechanically ventilated

Status 3 exemption: Inpatient plus

- single ventricle anatomy, and cause of admission is a complication of heart disease
 - biventricular anatomy with high dose or maximally tolerated inotropes (does not need to meet traditional hemodynamic criteria for shock)
 - biventricular anatomy with risk factors that limit ability to place a surgical LVAD (including systemic RV, failing subpulmonic ventricle, heterotaxy, > 1 prior sternotomy)
-

Table 4

Summary of challenges and potential solutions reported by centers that have implanted commercially available VADs in ACHD patients. VAD ventricular assist device

Challenge to VAD utilization in ACHD	Potential solutions
Ventricular anatomy does not allow cannula to be directed from apex towards the AV valve	Utilization of nonapical inflow cannula position such as free wall, diaphragmatic surface, or atrium
Extensive trabeculation and moderator band of a systemic right ventricle	Surgical resection of muscle bundles at time of device implant
Atypical position of heart in chest or altered thoracic anatomy	3D modeling of relevant anatomy from imaging to allow visualization of different device positioning strategies prior to surgery
Multiple prior sternotomies	Utilization of Heartware VAD with placement by thoracotomy
Passive transpulmonary flow, as in the Fontan physiology	Increase device speed until systemic ventricle is fully decompressed to minimize filling pressure