Review Article

Cardiac transplantation in adult congenital heart disease: a narrative review

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Background and Objective: As more children with congenital heart disease survive to adulthood, adult congenital heart disease (ACHD) prevalence will increase (currently ~1 million US patients). Heart failure (HF) accounts for 26–42% of ACHD deaths. The rate of ACHD heart transplantations (ACHD HTx) is also increasing. We describe the ACHD HTx recipient/candidate cohort, analyze ACHD HTx outcomes, identify ACHD HTx specific challenges, and discuss opportunities to better serve more patients with ACHD HF.

Methods: PubMed literature search including articles published from 2010–2023. Reviewed 89 studies, 67 included. Our search focused on the challenges of ACHD HTx and potential solutions.

Key Content and Findings: ACHD HTx recipients are young [median age 35 years, interquartile range (IQR): 24–46 years]. 87–95% of ACHD HTx recipients had prior cardiac surgery. The most common underlying diagnoses include transposition of the great arteries (31%) and Fontan/Glenn circulation (28%). 63% of listed ACHD HTx candidates received a transplant within one year of listing. Post-transplant 1-year survival is 80%, 5-year survival 74%, and 10-year survival 59%. There are 4 unique ACHD HTx challenges: (I) difficulty in assessing pulmonary hypertension, resulting in some centers selecting oversized donor hearts. However, selecting oversized hearts does not improve post-operative mortality and could prolong waitlist time. (II) Increased immunologic sensitization, increasing rejection risk. Desensitization therapy has enabled sensitized HTx recipients to enjoy outcomes similar to non-sensitized recipients. (III) Procedural complexity with ~30% of cases requiring additional surgical reconstruction. Detailed multidisciplinary planning, extensive imaging, and transferring the patient into the operating room early can help manage the complexities and reduce organ ischemic time. (IV) Increased intraoperative bleeding due to patients' surgical histories and circulatory collaterals. Preoperative collateral coil embolization and select utilization of hypothermic circulatory arrest can help reduce bleeding. Additional Fontan specific challenges include extensive great artery repair, liver failure, plastic bronchitis, and protein loss enteropathy. Finally, given limited donor heart availability, mechanical circulatory support is a promising technology for patients with ACHD HF.

Conclusions: The prevalence of ACHD HTx is slowly but steadily increasing. The operational complexity of ACHD HTx can be managed, and the majority of recipients have excellent outcomes (59% 10-year survival).

Keywords: Heart transplant; adult congenital heart disease; adult congenital heart disease (ACHD) heart failure; ACHD heart transplant surgical complexities

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Introduction

The prevalence of adult congenital heart disease (ACHD) is estimated to be 3 per 1,000 adults, corresponding to ~775,000 adults in the US with ACHD (1). Others estimate that there are over 1 million patients with ACHD in the US and ~1.2 million in Europe (2). ~58% of adults with ACHD have mild lesions, while 36% and 5% have moderate and severe lesions, respectively (1).

As more children with congenital heart disease (CHD) live to adulthood, the number of adults with CHD will increase. Among 7,497 Belgian patients born with CHD, the adulthood survival rate increased from 81% for children born from 1970–1974, to 89% for children born from 1990–1992 (P<0.01) (3). The survival improvement was concentrated among the moderate (e.g., tetralogy of Fallot, coarctation of the aorta) and severe (e.g., transposition of the great arteries, univentricular physiology) heart lesion cohorts (3). Analysis of the Quebec universal health coverage database from 2000–2010 found a 55% increase in the number of adults with severe ACHD lesions (95% CI: 51–62%) (4). It is often cited that the birth prevalence of CHD is increasing (5). However, it is more likely that the diagnosis of CHD is improving following the advancement of non-invasive diagnostic tools (e.g., echocardiography, pulse oximetry) (5).

Most patients with mild (e.g., patent foramen ovale) heart lesions, as per the Bethesda Conference heart defect severity categories, have lifespans similar to the general population (6). A Dutch study from 2002–2013 of 14,325 patients with ACHD (91% mild/moderate lesions, 9% severe lesions) found a median lifespan of 84 years and 75 years for patients with mild and moderate ACHD lesions, respectively (7). However, patients with ACHD and severe lesions only had a 53-year life expectancy (7). For example, the median lifespan for patients with Fontan circulation or Eisenmenger syndrome was 28 and 42 years, respectively (6).

Cardiac disease is the leading cause of death in patients with ACHD (6,8). Another Dutch study of 6,933 patients with ACHD, including 197 deaths, determined that 77% of deaths had cardiovascular origin with 26% due to chronic heart failure (HF) (8). A British study of 524 deaths among patients with ACHD found that cardiac disease caused 49% of deaths (42% HF, 7% sudden cardiac death). The next leading cause was pneumonia (10%) (6). Given ACHD's heterogenous nature, it is difficult to diagnose advanced ACHD HF, and there are no established severity criteria (9). When evaluating ACHD HF, it is more important to focus on the entire clinical context, including increased HF hospitalizations, arrhythmias, and diuretic dosing, rather than results from individual tests designed for non-CHD cohorts (10).

Patients with ACHD and advanced HF can be treated with heart transplantation (HTx). More patients with ACHD are being listed for and receiving HTx (11,12). In the UK, from 2009–2014, patients with ACHD comprised 7.2% of the heart-only transplantation registry, a 2-fold increase from 3.5% between 1995–2002 (P<0.01) (11). In the US, patients with ACHD represented 3% of adult HTx from 2009–2017, an increase from 2% in 1992–2003 (13). From 2018-2020, there were ~90 US ACHD heart transplants (ACHD HTx) each year, up 40% from 64 per year in 2010–2018 (12). Of the ~90 annual ACHD HTx recipients, 21 are dual heart-liver-transplant recipients (14).

Given the increasing prevalence of ACHD and ACHD HTx, we conducted a review to describe (I) the profile of patients with ACHD requiring HTx, (II) outcomes of ACHD HTx, (III) unique ACHD HTx challenges and potential solutions, and (IV) future opportunities to better serve more patients with ACHD HF. We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-513/rc).

Methods

We conducted a PubMed search from December 2022 to March 2023. A summary of the search terms used is available in *Table 1*. We also reviewed select articles cited by papers in our original search especially when the referenced article was on a topic of importance for the review (e.g., outcomes for ACHD HTx, organ selection, preoperative coil embolization, and hypothermic circulatory arrest). The review and selection of articles was conducted by all authors. In total, 89 papers were reviewed. We focused our review on articles since 2010 to provide information most

Table 1 Summary of search strategy

Items	Specification
Date of search	December 1, 2022–March 27, 2023
Database utilized	PubMed
Search terms used	"Adult congenital heart disease heart failure"
	"Adult congenital heart disease heart transplantation outcomes"
	"Adult congenital heart disease heart transplantation donor selection"
	"Adult congenital heart disease repair"
	"Adult congenital heart disease transplantation surgical complications"
	"Adult congenital heart disease mechanical circulation support"
	"Adult congenital heart disease pulmonary hypertension"
	"Adult Fontan heart transplantation"
	"Adult single ventricle heart transplant"
	"Adult congenital heart disease anatomical considerations"
	"Hypothermic circulatory arrest for adult heart transplantation"
Timeframe	2010–2023
Inclusion and exclusion criteria	Inclusion criteria: all publications indexed to PubMed including original articles, meta-analyses, reviews, editorials, books, guidelines, case series, and case reports Exclusion criteria: non-English articles
Selection process	Murthy R conducted the initial literature search. All authors conducted additional literature searches, reviewed the papers, and contributed to the final selection of papers

relevant to current and future ACHD HTx cases. Insights from 67 of those papers are included in this review.

Profile of patients with ACHD requiring heart transplants (HTx)

Heart failure (HF) occurs in 40% of patients post-Fontan, 32% of patients with congenitally corrected transposition of the great arteries (TGA), and 22% of patients with a Mustard (i.e., s/p atrial switch operation) TGA repair (2). Given the high rate of HF among these patients, they likely represent a large proportion of ACHD HTx recipients. UK data (n=189) shows that patients with single ventricle anatomy comprise 50% of patient with ACHD listed for HTx from 2010–2014, a nearly 3-fold increase from 18% from 2005–2009 (P=0.04) (11). 87–95% of ACHD HTx recipients underwent a prior cardiac surgery (15-17).

Current multi-center transplant databases (e.g., United Network for Organ Sharing) do not collect data on the underlying diagnoses for ACHD HTx recipients and candidates (11,18). Compiling and aligning data from 8 studies (N=402), we found that the most common diagnoses were: TGA (31% of patients, range 20–61%), Fontan/Glenn (28%, range, 0–58%), non-Fontan/Glenn single ventricle (11%, range, 0–28%), and right heart pathologies including Tetralogy of Fallot (TOF) (12%, range, 0–38%) (*Table 2*) (17,19-25). Further investigation of the underlying diagnoses for ACHD HTx candidates is warranted.

Compared to non-ACHD HTx recipients, ACHD HTx recipients (n=1,159 and n=666) are younger (median age 35–37 *vs.* 56–57), less overweight [body mass index (BMI) >25 kg/m^2 45% *vs.* 66%], less likely to have diabetes (6% *vs.* 26%), and less likely to have smoked (15% *vs.* 37%) (26,27). ACHD HTx recipients also have lower incidences of renal dysfunction (estimated glomerulus filtration rate of <60 mL/min/1.73 m^2 at transplant 23% *vs.* 28%) (27). Conversely, ACHD HTx recipients are more likely to have liver dysfunction (bilirubin >1.2 mg/dL at transplant 29% *vs.* 23%) and immune sensitization (panel reactive antibodies ≥10% 38% *vs.* 29%) (27). Finally, ACHD HTx recipients are less likely to have a ventricular assist device (9–14% *vs.* 37–46%) (26,27).

Table 2 Underlying diagnoses for adult congenital heart disease heart transplant recipients and candidates

Author	Country	Study period	Patients assessed or transplanted	Fontan/ Glenn (% of total)	Other single ventricle (% of total)	Transposition of the great arteries (% of total)	Ebstein anomaly (% of total)	Right heart pathology (e.g., TOF, pulmonary stenosis) (% of total)	Left heart pathology (e.g., aortic stenosis, shone complex) (% of total)	Other (e.g., ASD) (% of total)
Crossland *et al.*, (19)	UK	2000–2016	196	68 (35%)	18 (9%)	61 (31%)	13 (7%)	18 (9%)	11 (6%)	7 (4%)
Cohen *et al.*, (17)	France	1988–2012	97	16 (16%)	27 (28%)	25 (26%)	3 (3%)	13 (13%)	7 (7%)	6 (6%)
de la Rosa *et al.*, (20)	US	2010–2020	29	5 (17%)	–	10 (34%)	1 (3%)	2 (7%)	7 (24%)	4 (14%)
Lo Rito *et al.*, (21)	Italy	2004–2015	21	4 (19%)	–	6 (29%)	1 (5%)	8 (38%)	–	2 (10%)
Menachem *et al.*, (22)	US	2010–2016	20	8 (40%)	–	4 (20%)	1 (5%)	4 (20%)	–	3 (15%)
Heid *et al.*, (23)	US	2013–2020	18	4 (22%)	–	11 (61%)	1 (6%)	–	1 (6%)	1 (6%)
Mori *et al.*, (24)	US	2005–2013	12	7 (58%)	–	5 (42%)	–	–	–	–
Verzelloni *et al.*, (25)	UK	2015–2019	9	–	–	2 (22%)	1 (11%)	3 (33%)	2 (22%)	1 (11%)
Total	–	–	402	112 (28%)	45 (11%)	124 (31%)	21 (5%)	48 (12%)	28 (7%)	24 (6%)

All patients with a history of Fontan or Glenn operations listed as such, regardless of potential additional anatomical anomalies (e.g., TGA). 1 patient from Cohen *et al.*, with a single ventricle, TGA, and non-Fontan circulation listed as other single ventricle. TOF, tetralogy of Fallot; ASD, atrial septal defect; TGA, transposition of the great arteries.

Outcomes of adult congenital heart disease heart transplants (ACHD HTx)

Heart waitlist outcomes: 63% of ACHD HTx candidates receive a transplant within 1-year

Adults with ACHD awaiting transplants have worse waitlist outcomes than patients without ACHD (12,28,29). An analysis of 39,847 US patients (1999–2014), found that potential ACHD HTx recipients (n=1,290) were less likely to be listed as status I when compared to non-ACHD HTx recipients (38% *vs.* 56%, P<0.01) (28). Furthermore, when listed as status I, potential ACHD HTx recipients were more likely to die or be delisted due to worsening health (17.6% *vs.* 14.5%, P=0.04) (28). Among US HTx recipients (2000–2016), ACHD HTx recipients (n=903) spent 70 additional days on the waitlist (unadjusted waitlist time of 253 *vs.* 199 days, P<0.01) (29). Among 204 European patients with ACHD listed for transplant (1999–2015), 23.5% died or were delisted due to deteriorating conditions (30).

In 2018, the US United Network for Organ Sharing (UNOS) updated their heart transplant listing policy (31). The update added an exception enabling patients with ACHD to apply for a status that reflects their medical urgency (31). Following the policy update, listed patients with ACHD (n=255) were more likely to receive a transplant within 1-year of listing (63% from 2018–2020 *vs.* 54% from 2010–2018, P<0.01) (12). There was also a non-statistically significant reduction in 1-year waitlist mortality (7% *vs.* 12%, P=0.3) and delisting (18% *vs.* 22%, P=0.9) (12). Despite the update, patients with ACHD were still less likely to receive a heart transplant than those without ACHD (63% *vs.* 66%, P=0.03) (12).

There are no ACHD specific guidelines to inform donor selection (29,32). Given the young age of ACHD HTx candidates, physicians are potentially inclined to wait for more "perfect" hearts utilizing non-data-driven practices (33). Recent studies by Diamant *et al.*, (N=1,271) and Clark *et al.*, (N=827) demonstrated no survival benefit from utilizing hearts from non-lung donors nor from utilizing oversized donor hearts (32,33). Furthermore, Huntley *et al.*, found that among listed patients with ACHD, waiting for a donor with negative viral serology, no

history of alcohol use disorder, or larger size, was associated with an increase in waitlist time without an increase in post-operative survival (29). Given the risk of death or delisting while waiting for a donor, we would recommend against delaying for a more "perfect" heart (29,33).

Heart transplantation outcomes: 1-, 5-, & 10-year survival of 80%, 74%, & 59% respectively (12,27,34)

Of the ACHD HTx patients fortunate enough to receive a donor heart, the majority live beyond 10 years post-operation. One study (n=22), reported a 66% 15-year survival rate (35). When compared to non-ACHD HTx recipients, those with ACHD have worse perioperative outcomes, similar 1- to 5-year outcomes, and superior long-term outcomes (10+ years) (34). A meta-analysis of ~850 ACHD HTx recipients and ~43,000 non-ACHD HTx recipients found that ACHD HTx recipients have a higher 30-day mortality [17% *vs.* 7%, risk ratio (RR) =2.2, 95% confidence interval (CI): 1.6–2.9] (34). One- and 5-year mortality rates (~20% and ~30% respectively) were similar between the two cohorts and 10-year mortality was lower among ACHD HTx recipients (41% *vs.* 49%, RR =0.75, 95% CI: 0.60–0.95) (34). Another analysis (N=108,034) found that ACHD HTx recipients had higher 1-year-post-transplant mortality compared to non-ACHD-non-ischemic cardiomyopathy recipients [hazard ratio (HR) =1.88, P<0.01] and lower 5-year mortality (HR =0.77, P<0.01) (36). A 2000–2019 analysis of UNOS data (n=1,139) utilizing restricted mean survival time found a higher 1-year survival among the non-ACHD HTx cohort and no difference in long-term (18-year) survival (26). ACHD HTx recipients (n=559) had higher, though non-statistically significant, rates of reoperation (21% *vs.* 11%) and dialysis (22% *vs.* 8%) than those without ACHD (34). The most common causes of ACHD HTx perioperative death are graft failure (41%), multiorgan failure (14%), and infection (13%) (37).

The higher ACHD HTx perioperative mortality may be driven by worse outcomes among single ventricle patients (38). An analysis of 16 ACHD HTx recipients with a single ventricle and prior Fontan or Glenn operations found a 30-day mortality of 44% (7/16) (34). An investigation of 509 ACHD HTx recipients revealed a 23% in-hospital mortality rate among the single ventricle cohort *vs.* 8% among the double ventricle cohort (38). The 8% in-hospital mortality among the ACHD double ventricle cohort is similar to the 7% 30-day mortality for non-ACHD HTx previously discussed (34,38). The challenges of HTx for recipients with Fontan physiology are discussed separately. While 10-year post-transplant outcomes are well-documented, we anticipate that as more data is collected, ACHD HTx recipients will have significantly better outcomes than non-ACHD HTx over longer timeframes (e.g., 20 years post operation).

It is unclear whether outcomes are improving for ACHD HTx patients (12). An Australian analysis of 77 patients with CHD (average age 18 years) found no statistically significant improvement in hospital mortality between 1988–1999 and 2000–2014 (16% *vs.* 10%, P=0.5), potentially due to increased case complexity (39). French analysis of 97 patients with CHD also found no statistically significant improvement in 30-day, 1-year, nor 5-year mortality between 1988–2005 and 2006–2012 (17). Analyzing UNOS data (N=1,161), Riggs *et al.*, found an increase in 1-year (86% *vs.* 78%, P<0.01) and 5-year (74% *vs.* 68%, P<0.01) survival between 2000–2008 to 2009–2018 (27). However, an updated study of UNOS data (n=689), found no improvement between 2010–2018 and 2018–2020 with 1-year survival dropping from 86% to 80% (P=0.8) and 30-day survival increasing from 92% to 94% (P=0.6) (12).

Challenges unique to adult congenital heart disease heart transplants (ACHD HTx)

We identified 7 unique challenges for ACHD HTx, 4 for the entire cohort of ACHD HTx recipients and 3 specific to patients with Fontan/Glenn circulation (30–40% of all ACHD HTx recipients) (19). For the entire ACHD HTx cohort, the challenges are: (I) pulmonary hypertension (PH) assessment and heart sizing (32,40), (II) recipient immune sensitization (41), (III) surgical complexity due to anatomical anomalies and scar tissue from prior surgeries (23), and (IV) increased intraoperative bleeding due to the development of collaterals (*Table 3*) (42,43). The 3 challenges primarily related to ACHD HTx recipients with Fontan/Glenn circulation include: (V) extensive reconstruction of the great arteries (39), (VI) liver failure (14), and (VII) protein loss enteropathy (44).

PH assessment and heart sizing

Among non-ACHD HTx recipients, those with preexisting PH who receive an undersized heart are at increased risk of mortality and graft failure compared to recipients without preexisting PH (32). Given the challenges of assessing PH in patients with ACHD, particularly those with single

Table 3 Challenges and potential solutions for adult congenital heart disease heart transplant

Challenges for ACHD-HTx	Potential solutions
(I) Pulmonary hypertension assessment & heart sizing	Assess each potential ACHD HTx recipient for PH based on their anatomy
	If PH diagnosed consider vasodilator treatment prior to Tx
	Do not extend waitlist time by waiting for an oversized heart
(II) High sensitization among ACHD HTx recipients	When appropriate utilize desensitization therapies including:
	Intravenous immunoglobulins
	Plasmapheresis
	Rituximab
	Bortezomib
(III) Surgical complexity	In-depth preoperative planning with a multidisciplinary team
	Extensive imaging (e.g., catheterization, CT, & magnetic resonance angiography)
	Begin the operation hours before the donor heart is expected to arrive
(IV) Bleeding	Aggressive collateral coil embolization prior to operation
	Utilize an oscillating saw during sternotomy
	Rapid transfusion device and blood on hand
	When needed, hypothermic circulatory arrest

ACHD HTx, adult congenital heart disease heart transplant; PH, pulmonary hypertension; Tx, transplant; CT, computed tomography.

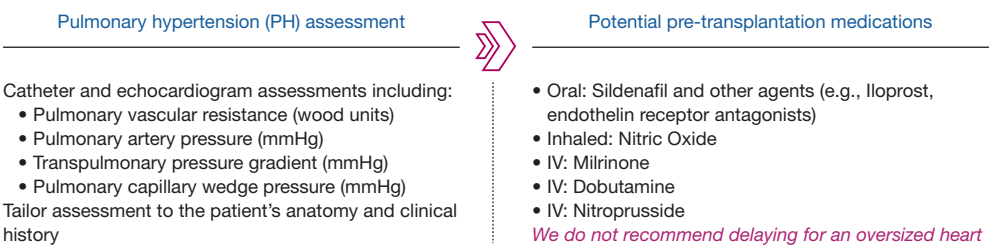

Figure 1 Approach to pulmonary hypertension in adult congenital heart disease heart transplant candidates (10,32,43,45).

ventricle Fontan circulation, some centers intentionally select oversized donor hearts (45). Others do not select oversized donor hearts given the restricted mediastinum space (46).

An analysis of 825 ACHD HTx recipients, including 197 (24%) who received an oversized donor heart, defined as >120% of recipient size, found no benefit in utilizing an oversized heart (32). Furthermore, an analysis of 983 ACHD HTx recipients, 216 of which had pre-transplant PH, defined as a transpulmonary pressure gradient of >12 mmHg, found that PH had no negative impact on survival when compared to the non-PH cohort, 30-day survival hazard ratio 0.51 (95% CI: 0.2–1.1) (40).

PH assessments should be tailored to the unique clinical history of potential ACHD HTx recipients (10). This includes variables such as single *vs.* dual ventricle circulation, one *vs.* two functional lungs in the recipient, pulmonary vein stenosis, and anatomy of the branch pulmonary arteries. If PH is found, vasodilator therapy can be administered to reduce PH and potentially enable transplantation, *Figure 1* (10,43). Some patients required combined heart-lung transplantation (30). Combined heart-lung transplantations are beyond the scope of discussion of this article. Pre-transplant PH is associated with higher post-operative RV dysfunction and mortality (10,47). Severe PH is a relative contraindication to heart transplantation

alone [e.g., pulmonary vascular resistance (PVR) >5 wood units, transpulmonary pressure gradient (TPG) >16–20 mmHg]. Mechanical circulatory support (MCS) can be considered as a bridge to transplant in patients with severe PH (48). Use of a Swan-Ganz catheter can help guide post-operative care. Furthermore, care must be taken to address all pulmonary artery stenosis intra-operatively. This can often be complex, and one may have to deal with old stents.

We do not recommend selecting oversized hearts due to the limited data supporting the practice and the potentially prolonged waitlist time associated with waiting for an oversized heart (49). Pulmonary vasodilatory therapy is often continued post-operatively.

High sensitization among ACHD HTx recipients

Patients with ACHD are often sensitized (i.e., more likely to reject) due to their surgical (e.g., repairs with homograft patch material) and blood transfusion history (41). ACHD HTx recipients are more likely to have a panel of reactive antibodies (PRA) ≥10% than non-ACHD HTx recipients (38% *vs.* 29%, 2009–2018, n=20,238) (27). Historically, allosensitized HTx recipients had inferior outcomes (36). From 2000–2005, patients with a PRA ≥80% had a 79% 1-year survival rate compared to 90% for those with PRA =0% (36).

Advances in the ability to monitor for donor-specific antibody production and improved prevention/treatment medications have eliminated this difference in outcomes (36). From 2012–2017 both cohorts of HTx recipients, PRA ≥80% and PRA =0%, had 90% 1-year survival (36). Among ACHD HTx recipients (n=1,161), the proportion with PRA ≥10% increased from 23% (2000–2008) to 38% (2009–2018) (27).

When appropriate, desensitization therapy should be administered to increase the chances of finding an appropriate donor (46). Potential desensitization treatments include intravenous immunoglobulins, plasmapheresis, rituximab (a monoclonal antibody immunosuppressor causing B-cell depletion), and bortezomib (a proteasome inhibitor often used to treat multiple myeloma) (20,46). The mechanism of action for intravenous immunoglobulins is not well defined but could be related to a reduced burden on circulating antibodies (50). Plasmapheresis mechanically removes antibodies from circulation. Rituximab and bortezomib kill immune cells, thereby preventing them from attacking the donor heart (50).

Surgical complexity

ACHD HTx recipients undergo more complex transplantations than their non-ACHD counterparts. Patients with ACHD HTx have a more extensive surgical history with 87–95% of ACHD patients having had a prior cardiac surgery (15-17). Data from the University of Texas demonstrates that 56% of ACHD HTx recipients (n=18) have a history of 2 or more previous cardiac surgeries (*vs.* 14% among non-ACHD HTx recipients, P<0.01) (23). Healing from prior cardiac surgeries increases scar tissue and mediastinal/sternal adhesions (13). Patients with prior cardiac surgeries also have less available anterior pericardium. Additionally, multiple sternotomies cause a restrictive chest wall and can interfere with post-operative pulmonary mechanics. HTx is an extremely time-sensitive operation, requiring excellent coordination between the donor and recipient surgical teams, careful sternal re-entry, liberal use of peripheral cannulation strategies and extensive pre-operative cross-sectional imaging to help with all the above.

Additional surgical procedures during transplantation are reported in ~30% of ACHD HTx (N=97 and N=37) (17,51). The most common additional surgical corrections include pulmonary artery reconstruction, and aortic arch reconstruction (39,51). In a case series by Mori *et al.*, all 12 ACHD HTx recipients required additional reconstructive procedures during transplantation (24).

Resulting from the increased surgical complexity, perioperative death is higher among ACHD HTx recipients compared to non-ACHD HTx (52,53). Donor organ ischemic time is also higher. Utilizing data from 2009–2018, Riggs *et al.*, found higher ischemic times for ACHD HTx (n=666) recipients than for non-ACHD recipients (3.5 *vs.* 3.1 hours, P<0.01) (27). The findings of Riggs *et al.*, align with aggregated non-US single center data (N=231 ACHD HTx recipients) reporting an aggregate average ischemic time of 3.7 hours (*Table 4*) (17,39,51,54). An additional hour of ischemic time is associated with a 40% increased risk of 1-year mortality (HR =1.4, P<0.01) (27).

Multiple strategies can be utilized to reduce surgical complications and ischemic time. In-depth planning, including cannulation and lesions correction strategies, can improve operative outcomes (49). Multiple imaging modalities can inform the planning process, including cardiac catheterization, computed tomography, and magnetic resonance angiography (31). It is also critical

Table 4 Bypass and organ ischemic time for adult congenital heart disease heart transplant

Author	Country	Study period	Patients	Bypass time (hours)	Organ ischemic time (hours)
Cohen *et al.*, (17)	France	1988–2005	48	3.5	3.2
Cohen *et al.*, (17)	France	2006–2012	49	3.1	3.6
Shi *et al.*, (39)	Australia	1988–1999	38	3.2	3.7
Shi *et al.*, (39)	Australia	2000–2014	39	4.5	4.6
Irving *et al.*, (51)	UK	1988–2009	37	–	3.5
Kinsella *et al.*, (54)	Canada	1988–2017	20	2.7	3.7
Menachem *et al.*, (22)	US	2010–2016	20	–	3.5
de la Rosa *et al.*, (20)	US	2010–2020	19	2.9	3.2
Heid *et al.*, (23)	US	2013–2020	18	3.3	3.3
Mori *et al.*, (24)	US	2005–2013	12	3.5	3.3
Total patients and unweighted averages			300	3.3	3.6

to map all stents, as stent location will influence the cannulation and vessel reconstruction strategies (31). Utilizing a multidisciplinary team, including adult heart transplant and congenital cardiac surgeons, to meticulously plan the operation, one site (N=20) reported a 100% 30-day survival rate (22). One Australian hospital transfers HTx recipients into the operating room at least 4 hours prior to donor heart arrival to minimize ischemic time (39).

Given the immense complexity of ACHD HTx, it is not surprising that high volume HTx centers report improved patient outcomes. A US study from 2000–2015 (N=827) found that ACHD HTx recipients at low volume centers (<14 total HTx per year) had a 75% 1-year survival rate compared to 84% at high volume centers (>38 total HTx per year) (55). Multivariable analysis showed a reduced 1-year mortality (HR =0.6, P=0.02) for ACHD patients receiving a HTx at a high-volume center compared to a low volume center (55). Interestingly, no statistically significant difference was found when comparing patient outcomes by number of ACHD HTx performed (HR =0.66, P=0.07) (55). Potential causes of worse outcomes at low HTx volume centers include less surgical experience with ACHD patients and "failures to rescue" following complications (56).

Intraoperative and perioperative bleeding

Patients with ACHD, particularly those with a history of Fontan/Glenn operations, are more likely to develop arteriovenous and veno-venous collaterals, increasing the risk of intraoperative bleeding (42,43). Hemorrhage is most common upon sternal entry and increases operational complexity and potentially donor ischemic time (46). Often, the neo-aorta is large and adherent to the sternum (57). Bleeding was the cause of death for 2% of US ACHD HTx recipients from 2000–2014 *vs.* 0.5% for non-ACHD HTx recipients (P<0.01) (52). Cohen *et al.*, (N=97) reported that 25% of ACHD HTx recipients required reoperations for bleeding (17).

A potential strategy to reduce bleeding is to coil embolize collaterals pre-operation (42,46). One US pediatric hospital aggressively embolized aorta-pulmonary collaterals prior to transplantation for patients with Fontan circulation. While bleeding rates did not improve after implementing routine aggressive pre-transplant embolization, 1-year survival rates increased (90% *vs.* 63%, P=0.05, N=47) (42). Aorta-pulmonary collaterals also increase volume load on the heart (46). After cardiopulmonary bypass initiation, there can be a tremendous amount of pulmonary venous return with open collaterals. This can cause distension of the donor heart after implantation (58). Additionally, brain perfusion may be affected if the collaterals 'steal' a large proportion of the blood during bypass. Post-operatively, collateral burden can also increase the risk of vasoplegia and prolonged chest tube drainage. The ACHD team at University of California, Los Angeles (UCLA) embolizes arterial-pulmonary collaterals for patients considered for transplant, and then embolizes veno-venous collaterals once the patient is accepted for transplant (46). It is also recommended to leverage an oscillating saw for additional precision during sternotomy (59). Rapid transfusion devices and blood should be readily accessible throughout the operation (46).

When required, hypothermic circulatory arrest (HCA) can also be initiated. A Columbia university study analyzing 928 adult HTx recipients (25 operated with HCA, average temperature of 25 ℃, 903 without HCA) found no increase in 30-day mortality, 1-year mortality, nor postoperative stroke following the use of HCA (59). HCA was utilized following significant operative hemorrhage (9/25, 36%), to aid in mediastinal dissection (7/25, 28%), and to perform distal aortic procedures (9/25, 36%) (59). In high-risk cases, some surgeons expose the patient's femoral vessels in preparation for a potential emergency femoral-femoral cardiopulmonary bypass (60).

Extensive great artery reconstruction among ACHD HTx recipients with Fontan/Glenn circulation

Among ACHD HTx recipients, patients with Fontan/Glenn circulation require even more complex surgeries and have higher rates of perioperative mortality and complications. Analysis of 93 US adult Fontan HTx recipients from 2004–2014 revealed a 26% in-hospital mortality rate compared to 5% for non-Fontan HTx recipients [adjusted odds ratio (aOR) =18, P<0.01] (61). Fontan patients were also more likely to require post-operative ECMO support (16% *vs.* 4%, aOR =5.3, P=0.02) (61). Shi *et al.*, detail a case series including 44 patients with single ventricle hearts undergoing HTx (39). Of these 44 patients, 13 (30%) required pulmonary artery reconstruction and 4 (9%) required aortic arch replacement (39). A mix of Goretex patches, vascular prosthesis, donor tissue, and homografts were utilized (39). Ideally, procurement surgeons will take extended vena cavas, innominate vein, aorta, and pulmonary arteries from the donor when harvesting the heart (46). However, this is not always possible, especially when the heart donor is also a lung donor. It is important to note that an analysis of 1,271 ACHD HTx recipients (859 from non-lung donors) found no survival benefit among the non-lung donor group (33). This is potentially due to the ability of most congenital heart surgeons to expertly reconstruct the pulmonary arteries (46).

While significant expertise and planning is required to successfully transplant a heart for an ACHD HTx recipient with a history of Fontan, a non-lung heart donor may not be required.

Fontan associated liver failure

Fontan circulation lowers cardiac output and increases venous hypertension and hepatic congestion (46). Eventually, the increased hepatic venous pressure and congestion causes liver failure (14). One potential treatment for Fontan associated liver disease (FALD) is combined heart-liver transplantation (16). The number of combined US heart-liver transplants for patients with ACHD rapidly increased from ~4 per year (2010–2015) to 21 in 2019 (14). 2009–2020 1-year survival for patients with ACHD receiving heart-liver transplants (n=74) and heart only transplants (n=817) were similar, 82% *vs.* 86% respectively (P>0.05) (14). A separate analysis by Wong *et al.*, (N=834) analyzing data from 2000-2016 also found no difference in 5-year survival between ACHD HTx recipients (84%) and ACHD heart-liver transplant recipients (86%, P=0.8) (62).

A potential benefit of combined heart-liver transplants is that the transplanted liver may confer immune protection (14). One study found a lower rate of acute organ rejection among the heart-liver (n=74) cohort compared to the heart only (n=817) cohort (6% *vs.* 23%, P<0.01) (14). The lower rate of acute organ rejection among the heart-liver cohort was especially impressive given the higher proportion of sensitized (PRA >25%) patients in the heart-liver cohort (47% *vs.* 31%, P<0.01) (14).

While initial results are promising, the need for combined heart-liver *vs.* heart-only transplantation in patients with FALD is not established (63). A UTSW study including 4 Fontan patients, 3 with hepatic fibrosis and 1 with cardiac cirrhosis, reports excellent outcomes for heart only transplants, including no progression of liver disease (median follow-up 3.7 years) (23). In a review focused on ACHD HTx, Matsuda *et al.*, hypothesized that HTx alone should be able to reverse liver damage in most patients (63). It is important to note that hepatocellular carcinoma can be associated with FALD and may require combined transplantation (45,47).

Fontan associated protein loss enteropathy

Protein loss enteropathy (PLE) is an often fatal disease characterized by the abnormal loss of proteins into the gastrointestinal tract (44). The protein loss results in reduced oncotic blood pressure and significant body edema. In addition, the loss of protein clotting factors increases bleeding (49). The prevalence of PLE in patients following Fontan operations is not well known with estimates ranging from 1% to 11% (44). Fortunately, HTx seems to effectively treat Fontan associated PLE. A study of 52 patients (pediatric and adults) with Fontan associated PLE receiving HTx found that among the 43 patients alive 1-year post-operation (83%

Table 5 Patients with adult congenital heart disease heart failure assessed, listed, and receiving heart transplants

Author	Country	Study period	Patients assessed	Patients listed	Patients transplanted	% of patients assessed transplanted	% of patients listed transplanted
Crossland *et al.*, (19)	UK	2000–2016	196	89	67	34%	75%
Merás *et al.*, (35)	UK	2000–2018	102	38	22	22%	58%
Menachem *et al.*, (22)	US	2010–2016	41	26	20	49%	77%
De La Rosa *et al.*, (20)	US	2010–2020	37	29	19	51%	66%
Lo Rito *et al.*, (21)	Italy	2004–2015	21	9	3	14%	33%
Total patients & unweighted averages			397	191	131	34%	62%

1-year survival), PLE resolved in 42/43 patients (98%) (44).

Open questions for challenges unique to ACHD HTx

While the literature describes multiple challenges unique to ACHD HTx and potential solutions, research is still required to refine these solutions. Open questions include: What is the optimal desensitization therapy? How can we further reduce ACHD HTx organ ischemic time? How best to employ coil embolization to reduce bleeding? Do patients with FALD receiving combined heart-liver transplantations have better outcomes than those receiving heart-only transplantations?

Future opportunity to better serve more patients with ACHD heart failure (HF)–mechanical circulatory support (MCS)

There is a consistent shortage of suitable donor hearts (29). Only 63% of listed ACHD HTx candidates (n=255) receive a HTx (12). Furthermore, less than 40% of evaluated ACHD patients receive a HTx (*Table 5*) (19-22,35). Given the limited availability of donor hearts, durable MCS could help patients with ACHD HF both as a bridge to transplant and, potentially, as a destination therapy (64,65).

MCS is utilized less for patients with ACHD HF than those with non-ACHD HF. An analysis of UK patients listed for HTx (1995–2014, N=3,880) found that 25% of non-ACHD patients received MCS compared to only 10% of patients with ACHD (P=0.01) (11). An analysis of US ACHD HTx recipients (n=689) revealed that the proportion of patients with durable ventricular assist devices (VAD), a type of MCS, decreased from 11% in 2010–2018 to 4% in 2018–2020 (P=0.03) (12). During the same period there was an increase in patients with temporary intra-aortic balloon pumps (3% to 17%, P<0.01), likely driven by updated organ allocation policies preferring patients with intra-aortic balloon pumps (12). Lack of clinical data and clinician familiarity with MCS for patients with ACHD likely contributes to MCS underutilization (43). Another concern is that placement of MCS could potentially result in inferior ACHD HTx outcomes by increasing the HTx surgical complexity (66). However, a study of 12 ACHD HTx recipients who previously had a VAD as a bridge to transplantation found no adverse outcomes 1-year post operation (100% 1-year survival *vs.* 95% for the non-VAD ACHD HTx cohort, P=0.5) (66).

For patients with ACHD (n=126), MCS is primarily used as a bridge to transplant (45%) or a bridge to transplant candidacy (38%) (64). MCS is less likely to be used as a destination therapy for patients with ACHD with compared to patients with non-ACHD HF (16% *vs.* 38%, P<0.01) (64). While not specifically designed for ACHD anatomies, MCS devices have been utilized in a variety of ACHD lesions including Fontan circulation, TGA, TOF, VSD, and congenital valvular disease (48,64-67). 77% of patients with ACHD and MCS devices have left VADs (LVADs) (64). Compared to patients with non-ACHD MCS devices, patients with ACHD MCS devices were more likely to have biventricular assist devices or total artificial hearts (21% *vs.* 7%, P<0.01) (64).

Among patients with ACHD and LVADs (n=97), 1-year post-device-implantation, 62.5% were alive with device in-place, 21% died, and 16.5% received a transplant (64). These outcomes were similar to patients with non-ACHD and LVADs. It is important to note that the type of lesion (e.g., single ventricle) was not associated with inferior outcomes among patients with ACHD and MCS devices (64). Patients with ACHD and MCS devices also have similar improvements in functional capacity and quality of life improvements as their non-ACHD peers (65). LVAD

may also be useful in reducing pulmonary pressure for patients with ACHD and PH (40,43). While outcomes are promising, it is important to note that MCS implantation is a high-risk procedure with a 10% in-hospital mortality rate for patients with ACHD (n=128) (65).

MCS for patients with ACHD is an emerging field (48). Given the shortage of donor hearts and promising initial clinical data, MCS for ACHD HF is a field that warrants further investment. Furthermore, we feel that outcome data for MCS device usage in the ACHD population will improve as clinicians gain experience and continue to refine their practice.

Limitations

The limitations of our review are that we only included articles in English that were indexed to PubMed and published since 2010. Expanding our search strategy to include other languages, databases, and older articles could have resulted in a more comprehensive review.

Conclusions

The most common underlying diagnoses among ACHD HTx patients are transposition of the great arteries and Fontan/Glenn circulation. There are many complexities to ACHD HTx including PH assessment, immunological sensitization, additional surgical reconstructions, intraoperative bleeding, and Fontan specific complications (e.g., liver failure). Despite these challenges, the majority (59%) of ACHD HTx recipients survive beyond 10-year post-operation. Unfortunately, less than 40% of patients with ACHD assessed for transplantation receive a donor heart. Further research is warranted to both improve outcomes for ACHD HTx recipients and to better utilize MCS for patients with ACHD HF.

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Footnote

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