A United Network for Organ Sharing analysis of heart transplantation in adults with congenital heart disease: Outcomes and factors associated with mortality and retransplantation

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Objectives: Heart transplantation in patients with adult congenital heart disease is increasing, yet no large studies have defined how this subgroup differs from other adult recipients. We investigated outcomes and risk factors for mortality and retransplantation among patients with adult congenital heart disease compared with adult recipients.

Methods: A review was performed of 18- to 45-year-old patients undergoing heart transplantation from 1990–2008 reported to the United Network for Organ Sharing database. Trends were compared between 2 eras: era 1 (1990–1998) and era 2 (1999–2008). Multivariable semiparametric hazard models identified factors associated with time-related death and retransplantation.

Results: Of 8496 patients identified, 575 had adult congenital heart disease. The prevalence of heart transplantation among adult recipients decreased by 28% over time (P < .001) and increased among patients with adult congenital heart disease by 41% (P < .001). Induction therapy use was less in patients with adult congenital heart disease (66%) compared with that seen in adult recipients (71%, P = .02). Steroid maintenance was less in patients with adult congenital heart disease (92%) compared with that seen in adult recipients (97%, P < .001). Post–heart transplantation survival among adult recipients improved over time (P = .02) but not among patients with adult congenital heart disease (P = .81). Overall post–heart transplantation mortality (P = .006) and retransplantation (P = .03) were significantly higher for patients with adult congenital heart disease than for adult recipients, mainly because of an early hazard phase. Adult congenital heart disease was a risk factor for both death (P < .001) and retransplantation (P = .04). Any induction therapy and steroid maintenance was associated with improved survival for all recipients (P = .001).

Conclusions: Adult congenital heart disease represent an increasing proportion of heart transplant recipients. Compared with adult recipients, patients with adult congenital heart disease experience higher post–heart transplantation mortality and retransplantation. Immunosuppression differs among patients with adult congenital heart disease and adult recipients. Further studies should investigate whether post–heart transplantation outcomes would be improved by more aggressive induction therapy or judicious steroid tapers. (J Thorac Cardiovasc Surg 2010;140:161-8)
Abbreviations and Acronyms

- ACHD = adult congenital heart disease
- AR = adult recipient
- CHD = congenital heart disease
- HTx = heart transplantation
- RTx = retransplantation
- UNOS = United Network for Organ Sharing

International Society of Heart and Lung Transplantation registry reports,\textsuperscript{1} which include a brief summary of overall outcomes, there are only single-institution reports for posttransplantation outcomes in patients with ACHD. Considering the rapidly increasing population of patients with ACHD, a comparison of posttransplantation management strategies and outcomes to ARs based on cumulative United Network for Organ Sharing (UNOS) experience is timely.

We therefore undertook this study to evaluate current management strategies for ACHD after HTx, to identify determinants associated with mortality and retransplantation (RTx), and to compare these with AR outcomes.

MATERIALS AND METHODS

Patients

Using the UNOS database from 1990–2008, we identified all recipients between the ages of 18 and 45 years undergoing isolated HTx. We chose this age group to capture the vast majority of patients with ACHD and to compose a more homogeneous pool of recipients with more closely approximated demographics and whose outcomes were less likely to be influenced by other medical comorbidities typical of older ARs but rare in patients with ACHD. Patients were grouped into broad diagnostic categories (congenital heart disease, dilated cardiomyopathy, ischemic cardiomyopathy, restrictive cardiomyopathy, and other), as were immunosuppression regimens to simplify analyses (Appendices 1 and 2). Patients without follow-up information ($n = 583$) were excluded.

Statistical Analysis

Overall descriptive statistics were computed. Recipient groups (ARs and patients with ACHD) were compared by using the $\chi^2$ test for categorical variables or the $t$ test for continuous variables. Percentages were calculated by using the number of available data, with missing values indicated. Trends were compared between 2 eras, era 1 (1990–1998) and era 2 (1999–2008), to capture changes in immunosuppression (ie, introduction of newer agent use, including interleukin 2 antagonists, was less prevalent in patients with ACHD (66.5\%) compared with that seen in ARs (71.2\%, $P = .02$). In particular, patients with ACHD were less likely than ARs to receive steroid induction (72.8\% vs 77.6\%, $P = .01$) without a corresponding increase in alternative agents (Figure 1). In general, induction therapy was less prevalent among both groups over time; however, this might represent an underreporting of newer agent use, including interleukin 2 antagonists, within the UNOS database.

Immunosuppression Regimen

Induction therapy. Immunosuppression regimens among groups are shown in Table 1. Overall use of induction therapy with standard agents, including antithymocyte globulin, Muromonab-CD3, and interleukin 2 receptor antagonists, was less prevalent in patients with ACHD (66.5\%) compared with that seen in ARs (71.2\%, $P = .02$). In particular, patients with ACHD were less likely than ARs to receive steroid induction (72.8\% vs 77.6\%, $P = .01$) without a corresponding increase in alternative agents (Figure 1). In general, induction therapy was less prevalent among both groups over time; however, this might represent an underreporting of newer agent use, including interleukin 2 antagonists, within the UNOS database.

Maintenance therapy. Maintenance therapy was similar among patients with ACHD and ARs, except that steroids were less frequently used in patients with ACHD (92.1\%) than in ARs (96.6\%, $P < .001$). Maintenance regimens also changed over time in both groups. Decreased use of steroids in patients with ACHD relative to ARs persisted in both eras (Figure 1). Tacrolimus replaced cyclosporine as the predominant calcineurin inhibitor, and azathioprine was used more frequently for maintenance in patients with ACHD than in ARs (86.8\% vs 72.2\%, $P = .02$).

Mortality and RTx

There were 3208 total deaths during the study period, yielding an overall mortality of 37.8\%. Cause of death was graft failure in 665 patients, cardiovascular failure in 733 patients, infection in 271 patients, malignancy in 156 patients, pulmonary failure in 81 patients, hemorrhage in 65 patients, technical in 8 patients, other in 492 patients, and unknown in 737 patients. Cause of death was similar among both groups, except patients with ACHD had a greater prevalence of death from early hemorrhage ($n = 15 [2.6\%]$) compared with ARs ($n = 76 [1\%], P < .001$), and ARs had a greater prevalence of death from malignancy ($n = 152 [2.1\%]$) compared with patients with ACHD ($n = 4$ (n = 575) were patients with ACHD, and 93.2\% (n = 7921) were ARs. The AR group was comprised of the following diagnostic subgroups: dilated cardiomyopathy, 46.4\% (n = 3939); inoperable coronary artery disease (nondilated ischemic cardiomyopathy), 19.1\% (n = 1624); hypertrophic cardiomyopathy, 2.5\% (n = 215); valvular heart disease, 2.7\% (n = 231); and restrictive cardiomyopathy, 1.9\% (n = 163). Patients with ACHD were younger, had longer ischemic and waitlist times, and were more likely to have preoperative extracorporeal membrane oxygenation support ($P < .05$ for all). In contrast, status 1 prevalence was higher among ARs than patients with ACHD ($P < .001$). Between eras 1 and 2, the frequency of HTx decreased by 28\% in ARs (4033 to 2888, $P < .001$) but increased by 41\% among patients with ACHD (239 to 336, $P < .001$).

RESULTS

Case Mix

Demographics and clinical characteristics of the study patients are shown in Table 1. Of 8496 cases identified, 6.8\%
TABLE 1. Demographic characteristics among study patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with ACHD (n = 575)</th>
<th>ARs (n = 7921)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), mean ± SD</td>
<td>28.3 ± 8.1</td>
<td>35.4 ± 7.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female sex, no. (%)</td>
<td>212 (37)</td>
<td>2476 (31)</td>
<td>.005</td>
</tr>
<tr>
<td>Status 1, no. (%)</td>
<td>355 (62)</td>
<td>5809 (73)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Waitlist time (d), median (range)</td>
<td>114 (0–2245)</td>
<td>74 (0–4318)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ischemic time (h), median (range)</td>
<td>3.8 (1–8.9)</td>
<td>2.9 (0.5–12)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ECMO before transplantation, no. (%)</td>
<td>6 (1)</td>
<td>34 (0.4)</td>
<td>.04</td>
</tr>
<tr>
<td>Immunosuppression regimens, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid induction</td>
<td>385 (72.8)</td>
<td>5268 (77.6)</td>
<td>.01</td>
</tr>
<tr>
<td>OKT3 induction</td>
<td>56 (74.7)</td>
<td>600 (71.2)</td>
<td>.52</td>
</tr>
<tr>
<td>Induction with any agent</td>
<td>358 (66.5)</td>
<td>5191 (71.2)</td>
<td>.02</td>
</tr>
<tr>
<td>Cyclosporine maintenance</td>
<td>119 (99.2)</td>
<td>2074 (98.9)</td>
<td>.36</td>
</tr>
<tr>
<td>Azathioprine maintenance</td>
<td>216 (90.8)</td>
<td>3294 (91.6)</td>
<td>.65</td>
</tr>
<tr>
<td>Steroid maintenance</td>
<td>487 (92.1)</td>
<td>7010 (96.6)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

ACCHD, Adult congenital heart disease; ARs, adult recipients; SD, standard deviation; ECMO, extracorporeal membrane oxygenation; OKT3, Muromonab-CD3.

[0.7%], P = .02). Freedom from death at 1, 10, and 15 years for the entire study population was 86%, 54%, and 38%, respectively (Figure 2), with similar crude mortality between groups (227/575 [39%] vs 2981/7921 [38%], P = .9). Importantly, post-HTx survival among ARs improved over time (era 1: 1- and 5-year survival of 85% and 67%, respectively; era 2: 1- and 5-year survival of 87% and 71%, respectively; P = .02), whereas no era effect was seen among patients with ACHD (era 1: 1- and 5-year survival of 76% and 63%, respectively; era 2: 1- and 5-year survival of 75% and 63%, respectively; P = .81; Figure 3). Kaplan–Meier freedom from death was significantly higher for ARs (1- and 10-year survival of 87% and 55%, respectively) than for patients with ACHD (1- and 10-year survival of 76% and 52%, respectively, P = .003), mainly because of an early hazard phase (Figure 4).

Multivariable factors associated with increased mortality included ACHD (P < .001), younger age (P = .002), status 1 (P = .03), longer ischemic times (P < .001), and female sex (P = .04). Any induction therapy (P = .008) and steroid maintenance therapy (P < .001) were associated with improved survival for all recipients, and there was an important interaction term whereby patients with ACHD gained an additional survival benefit with use of maintenance steroids (P < .001, Table 2).

For the overall cohort, RTx was necessary in 273 (3.5%) patients. There was a higher RTx rate in patients with ACHD (n = 27/575 [4.7%]) than in ARs (n = 266/7921 [3.4%], P = .09). Kaplan–Meier freedom from RTx was greater for ARs (1- and 10-year freedom of 99% and 91%, respectively) than for patients with ACHD (1- and 10-year freedom of 96% and 86%, respectively; P = .04; Figure 5). Multivariable factors associated with an increased risk of RTx included ACHD (P = .03).

**DISCUSSION**

We have shown, using a large administrative database, that mortality and RTx rates are higher after HTx for ACHD than for those with other underlying diagnoses. Although ARs have seen an improvement in these outcomes over time, no era effect could be demonstrated for patients with ACHD, mainly because of the persistent early attrition among patients with ACHD in the first year after transplantation. Importantly, although patients with ACHD are still a small

![FIGURE 1. Immunosuppression trends over time among patients with adult congenital heart disease (ACHD) and adult recipients (ARs). In era 1 patients with ACHD significantly received less aggressive induction than ARs. In era 2, although the induction gap decreased among groups, the prevalence of steroid maintenance was still significantly lower in patients with ACHD compared with those seen in ARs. AI, Any induction with standard agents excluding steroids; SI, steroid induction; SM, steroid maintenance. *P < .05.](image)
overall proportion of the recipient pool (approximately 2%), the incidence of HTx is increasing among patients with ACHD in the recent era compared with ARs, in whom HTx incidence has decreased. Certainly, inherent differences among these groups, such as age, which we found to be a risk factor for mortality, explain some of the variation in post-HTx death and RTx. However, our study is unique in that we have elucidated differences in immunosuppression regimens among patients with ACHD and ARs that could represent modifiable therapeutic targets. Specifically, more aggressive induction therapy and use of steroid maintenance therapy in patients with ACHD could lead to improved outcomes.

Our data agree with the 24th Official Adult Heart Transplant Report by Taylor and colleagues, which showed that an underlying diagnosis of ACHD was a powerful risk factor for 1-year mortality, with a 2- to 3-fold increase in relative risk. Pigula and associates also found in a subanalysis of 8 patients (of 33 undergoing combined cardiopulmonary transplantation) that patients with ACHD had significantly worse survival after HTx than ARs. The influence of underlying diagnosis of ACHD has been negligible in other studies. Lamour and coworkers studied 24 patients older than 18 years with an underlying diagnosis of congenital heart disease (CHD) who underwent HTx at their institution from 1995–1998. These authors found similar 1-year survival (75%) among patients with ACHD to that reported in our present study. However, post-HTx 1-year survival among a control group in their study, which was composed of 33 ARs, was only 79%, and they concluded that outcomes for ARs and patients with ACHD are equivalent. The Mayo Clinic reported excellent outcomes, with 16 patients having CHD, 11 of whom were older than 18 years. Actuarial survival was 86% at 5 years, although, similar to our findings, these authors also noted an early hazard phase for the patients with ACHD after HTx. Importantly, in the Mayo Clinic series patients with CHD received aggressive induction with steroids, OKT3, and azathioprine, and they were maintained on prednisone (0.2 mg/kg) daily. Our data would support that outcomes in patients with ACHD could be improved by administering aggressive induction and continued judicious use of steroids after HTx.

The lack of improved outcomes over time among patients with ACHD, as opposed to ARs, is an important finding in our analysis. The negligible era effect is mainly because of the unmitigated early attrition among patients with ACHD, which can be attributed to challenges within preoperative, postoperative, and intraoperative care. We recognize that our findings might seem contradictory in that induction use and steroid maintenance decreased over time in both groups, yet outcomes improved within ARs. However, it is possible that we have failed to capture increased use of newer induction agents, including interleukin 2 receptor antagonists, which are underreported in our dataset. It is also likely that the early hazard among patients with ACHD is due to more complex perioperative factors that have yet to be elucidated. Selection of patients with ACHD with increased pulmonary vascular resistance for isolated cardiac rather than combined cardiopulmonary transplantation can be challenging. Many single-ventricle recipients with failing Fontan circulation have systemic complications, such as protein-losing enteropathy or systemic arteriovenous or venovenous collaterals, which can complicate intraoperative management and postoperative care. Most recipients with ACHD have also had prior cardiac surgery, and many have complex anatomy, both of which
necessitate longer cardiopulmonary bypass and ischemic times and contribute to postoperative coagulopathy and increased infection risk.\textsuperscript{4,7}

Certain factors that likely contribute to the difference in posttransplantation outcomes among patients with ACHD and ARs, including the precise congenital diagnosis, the prevalence and distribution of recipient comorbidities, and the number of prior cardiac procedures, could not be captured with the current dataset. Further elaboration of the influence of these variables using either the International Society for Heart and Lung Transplantation database or a more complete single-institution database is warranted. However, our data suggest that a potentially modifiable reason underlying the increased risk of death among

FIGURE 3. A, Risk-unadjusted freedom from death for adult recipients stratified by eras demonstrates an improvement in mortality over time, especially within midterm survival. Note the areas of the curves between years 4 and 7 in which the confidence limits do not overlap. Era 1 (1990–1998) is depicted in red, and era 2 (1999–2008) is depicted in blue. Solid circles represent censored patients. Numbers at inset show the number of patients remaining at risk. Dashed lines enclose 95\% confidence intervals. B, Risk-unadjusted freedom from death for patients with adult congenital heart disease was equivalent in both eras. Era 1 (1990–1998) is depicted in red, and era 2 (1999–2008) is depicted in blue. Solid circles represent censored patients. Numbers at inset show the number of patients remaining at risk. Dashed lines enclose 95\% confidence intervals.
patients with ACHD is a difference in postoperative immuno-
suppression. Patients with ACHD were less likely to re-
ceive induction therapy and were less likely to be treated 
with maintenance steroids. The risk of allograft rejection is 
highest in the first several months after transplantation, 
and cytolytic induction therapy, which rapidly depletes 
recipient lymphocytes, might mitigate the risk of acute 
rejection. Patients with ACHD might be at increased risk 
for rejection because of increased levels of lymphocytotoxic 
IgG class antibodies from multiple prior blood transfusions 
or use of homograft implants.4,8,9 Unfortunately, data 
regarding early rejection episodes were available in too few 
patients within the UNOS dataset to allow a meaningful 
analysis, although this will be an important focus for future 
study.

We also found that younger age and longer ischemic time 
were risk factors for death. The 2007 International Society of 
Heart and Lung Transplantation report similarly detailed that 
extremes of age (<20 and >60 years), as well as longer du-
ration of ischemic time, were associated with an increased 
risk of death.1 We anticipated that advanced age would be 
an influential variable and therefore chose a study popula-
tion between 18 and 45 years to reduce this bias. It is unclear 
what underlies the difference in postoperative immuno-
suppression therapy among patients with ACHD and ARs. 
One possibility is that health care providers are reticent to 
administer steroid maintenance in patients with ACHD be-
cause of concerns for late osteoporosis, avascular femoral 
head necrosis, and accelerated coronary vasculopathy. A 
less aggressive approach to induction therapy might simi-
larly belie an unfamiliarity regarding the possible effect of 
newer medications on younger patients. We were not able 
to gather data regarding the specialty (eg, pediatric cardiol-
ogists vs adult cardiologists) of post-HTx providers, but 
prior reports, albeit not specific to HTx recipients, have dem-
onstrated that patients with ACHD fare better when cared for 
within a children’s hospital environment by pediatric spe-
cialists who are more familiar with the complex anatomy 
and physiology of these challenging patients.10,11

Limitations
Our study has several limitations, including all of those 
that apply to any retrospective analysis of prospectively col-
lected data. Missing data regarding important outcomes, in-
cluding early rejection and immunosuppression regimens,

### TABLE 2. Multivariable factors associated with posttransplantation mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter estimate (± SE)</th>
<th>Hazard ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACHD</td>
<td>0.67 ± 0.15</td>
<td>1.96</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Younger age</td>
<td>0.01 ± 0.002</td>
<td>1.01</td>
<td>.003</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.08 ± 0.04</td>
<td>1.10</td>
<td>.03</td>
</tr>
<tr>
<td>Longer ischemic time</td>
<td>0.07 ± 0.02</td>
<td>1.07</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No steroid maintenance</td>
<td>0.78 ± 0.09</td>
<td>2.18</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No induction agent</td>
<td>0.19 ± 0.07</td>
<td>1.22</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Status I</td>
<td>0.09 ± 0.04</td>
<td>1.09</td>
<td>.03</td>
</tr>
<tr>
<td>Interaction term between ACHD</td>
<td>–</td>
<td>0.51</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

SE, Standard error; ACHD, adult congenital heart disease.
especially newer agents introduced in the recent era, might have biased our results. Data regarding panel-reactive antibody levels could be crucial to identifying additional inherent differences among patients with ACHD and ARs but were incompletely captured within the UNOS dataset. More detailed information regarding the precise congenital diagnosis, irrespective of whether death was related to graft rejection, the incidence of chronic rejection, and the prevalence and distribution of comorbidities, would also have contributed substantially to the study but is currently unavailable within our dataset. Finally, an analysis of outcomes based on center volume and provider specialty, data unavailable in the present dataset, would have provided more insight underlying the differences in management among patients with ACHD and ARs.

CONCLUSIONS

Patients with ACHD represent an increasing proportion of HTx recipients. Higher post-HTx mortality and RTx rates among patients with ACHD compared with ARs are persistent over time. Management of immunosuppression differs among patients with ACHD and ARs. Further studies should investigate whether post-HTx outcomes would be improved by more aggressive induction therapy or judicious steroid tapers.

References


APPENDIX 1. UNOS database codes used to define diagnostic groups

ACHD: 1203, 11205, 1206, 1207, 1500, 1501, 1502, 1548, 1549, 1600
Dilated cardiomyopathy: 1000,* 1001, 1002, 1003, 1004, 1005, 1006, 1007†
Nondilated ischemic cardiomyopathy: 1200
Hypertrophic cardiomyopathy: 1201
Valvular heart disease: 1202
Restrictive cardiomyopathy: 1050, 1051, 1052, 1053, 1054, 1099
Failed prior heart transplantation: 1100, 1101, 1102, 1103, 1104, 1105, 1106, 1199


APPENDIX 2. Lexicon for grouping immunosuppression agents

Cyclosporine
- Includes generic cyclosporine, Gengraf, Neoral, Sandimmune, and cyclosporine

MMF
- Includes mycophenolate mofetil and Myfortic

Any induction
- Includes ATG, OKT3, and IL-2 receptor antagonists

MMF, Mycophenolate mofetil; ATG, antithymocyte globulin; OKT3, Muromonab-CD3; IL-2, interleukin 2.