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Review

Early outcomes of cardiac transplantation in adult patients with congenital heart disease and potential strategies for improvement

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ABSTRACT

With significant improvements in the medical and surgical management of patients with congenital heart disease, prognosis has improved substantially in the last several decades. However, many lesions are still associated with the eventual development of progressive heart failure, resulting in an increasing number of adults with congenital heart disease potentially requiring heart transplant. This presents many challenges, ranging from difficulty in determining the appropriate timing of transplant and organ allocation, to technical challenges in the operating room and problems with postoperative anti-rejection medication management. While recent studies have attempted to clarify many of these issues, questions remain.

1. Introduction

1.1. The ACHD Crisis

"We are accursed by our own success…"

The prevalence of congenital heart disease (CHD) in Quebec increased by 11% in children and 57% in adults CHD from 2000 to 2010, such that now adults comprise two thirds of the entire CHD population [1]. Similar trends have probably occurred elsewhere in the developed world. The median age of those alive with severe CHD has also increased, from 11 to 17 years as observed from 1985 to 2000 [2], and further to 25 years of age by 2010. Importantly, adults are becoming increasingly likely to have severe CHD [1]. Previously lethal lesions are now treated, delaying mortality and leaving patients with potentially significant long-term sequelae. Subjects remain at a constant risk of signification cardiac dysfunction. Progression to heart failure can occur after palliative or corrective surgery and is one of the most common causes of death in patients with congenital heart disease. Of all the adults currently on the cardiac transplant waitlist, 3% of them have CHD as their primary indication [3].

Transplantation in adults with CHD presents its own unique technical and medical challenges. Heart failure symptoms in adult congenital heart disease (ACHD) patients are heterogeneous, owing in part to complex physiology and previous corrective surgery, leaving some subjects with single ventricles and others with systemic right ventricles or residual shunts. Up to 84% of patients undergoing transplant for CHD have a history of previous surgery for correction or palliation [4], and most have been exposed to blood products and homograft materials that increase the risk of allosensitization and elevated panel-reactive antibodies. Heightened allosensitization vastly reduces the pool of suitable donors, may require virtual cross-matching, and increases wait-list attrition. Elevated PRAs have been identified in children awaiting transplantation and have been shown to increase perioperative mortality, in addition to wait times and hospital length of stay [5,6]. Additionally, CHD patients often have complex intra and extra cardiac anatomy that may require additional donor tissue (i.e. longer length pulmonary arteries, innominate vein, aorta) and enhances the difficulty of the recipient implant. Finally, elevated pulmonary vascular resistance is, unfortunately, common among the CHD transplant candidates, and this may necessitate concomitant lung transplantation in extreme cases.

Clearly, considering the rapidly increasing population of ACHD patients and the increasing number of ACHD transplant recipients, a review of the challenges that characterize the ACHD recipients, and those strategies that may improve early outcomes, is timely.

2. Strategies that May Impact Early and Mid-term Survival among ACHD

2.1. Immunosuppression Regimens

Outcomes of cardiac transplantation among adults with acquired heart disease have improved over the last several decades, owing to numerous factors including improved pre-operative assessment, donor

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management, peri-operative care and immunosuppression. However, similar gains our group demonstrated that outcomes among patients with ACHD have not kept pace. This discrepancy may provide insight into one potential mechanism to improve ACHD post-transplant survival. We undertook an exploration of the United Network Organ Sharing (UNOS) database, assessing outcomes of all adults who underwent heart transplant between 1990 and 2008 [7]. The study period was divided into two eras to capture important changes in immunosuppression that could bias results (1990–1998, 1999–2008). Interestingly, we found that there were critical differences among the adult-acquired recipients and the ACHD recipients regarding management of perioperative immunosuppression regimens. Specifically, use of induction therapy was less common in ACHD patients than among adult acquired recipients, and steroids were less commonly used in maintenance therapy (92 vs 97%, $p < 0.001$). While crude mortality rates were similar between the two groups, post transplant mortality in non-ACHD patients improved—with no concomitant change in ACHD patient outcomes (one year survival in non-ACHD patients between era 1 and 2 improved from 85 to 87%, while ACHD patient survival stayed stable at 76 and then 75%). Survival was also higher at one year for non-ACHD patients, largely due to early deaths in the ACHD patients (Fig. 1). Importantly, both the use of induction therapy and maintenance steroid use were associated with improved survival. ACHD patients were also more likely to require re-transplantation, which could also be related to less aggressive immunosuppression regimens among this population. The reasons for less aggressive immunosuppression in ACHD patients are unclear, but the greater prevalence of multi organ dysfunction versus non-ACHD HTx transplant recipients—including hepatic and renal—may be of importance. Unfortunately, the UNOS dataset at the time of this study did not allow much granularity with respect to post-transplant immunosuppression complications, but certainly this would be an important future area of investigation.

Other investigators have demonstrated similar findings. A smaller study assessing outcomes of heart transplantation in congenital heart disease patients at a single Italian center considered a number of factors that may influence outcomes. There was no statistically significant difference in survival between those transplanted in 1985–2000 versus those transplanted between 2001 and 2011 ($p = 0.284$) [8]. However, this study included only 85 patients, many of whom were pediatric. The applicability of these findings to other centers is unclear.

3. Impact of Case Mix on ACHD Post-transplant Outcomes

3.1. Single- Versus Two-ventricle Physiology

Reasons for the lack of improvement in era specific survival in ACHD transplant patients relative to non-ACHD transplant recipients remain obscure. Based upon our prior study, one explanatory hypothesis we posited was that there has been an increase in single ventricle recipients in the recent era relative to biventricular recipients, thereby increasing the complexity of the case-mix and mitigating any advances in perioperative care. However, there were several obstacles to the completion of a study investigating case mix among ACHD recipients. First, data such as specific congenital diagnosis are not captured in available large HTx registries (such as the United Network for Organ Sharing or International Society for Heart and Lung Transplantation databases) [7,9,10]. Furthermore, because most HTx registries evaluate time-related survival after censoring for early death, it was unclear whether in-hospital survival has improved in the recent era. Owing to these limitations, the Nationwide Inpatient Sample (NIS) was queried to identify all heart transplant recipients over the age of 14. Detailed information on specific congenital cardiac lesions was also abstracted, and subjects were classified as being either single (unknown one ventricle, tricuspid atresia, unbalanced atrioventricular defect) or two ventricle (atrial septal defect/ventricular septal defect, transposition of the great arteries, double outlet right ventricle). As we anticipated, there were differences among the patient groups. Biventricular patients were older at time of transplant, had more comorbidities, and were more likely to be bridged with implantable mechanical circulatory support. This last point was critical as death among failing Fontan patients may be related to the lack of viable options for mechanical support [11]. Unexpectedly, the proportion of single versus two ventricle patients did not appreciably increase over time, suggesting that evolution in case mix may not be playing a significant role. In 2007 (the last year of the study), for example, single ventricle patients comprise roughly 25% of all ACHD transplant recipients, the same proportion as in 1993 (the first year of the study). When examined by era, single ventricle recipients comprised 36% (51.9 ± 14) of the case-mix in era 1 (162.8 ± 15.1) and 30% (110.9 ± 11.4) of the case-mix in era 2 (346.2 ± 16.2), $P = 0.46$.

However, in-hospital death post transplant was much higher for single ventricle than two ventricle patients (23% vs 8%, $p < 0.001$), a

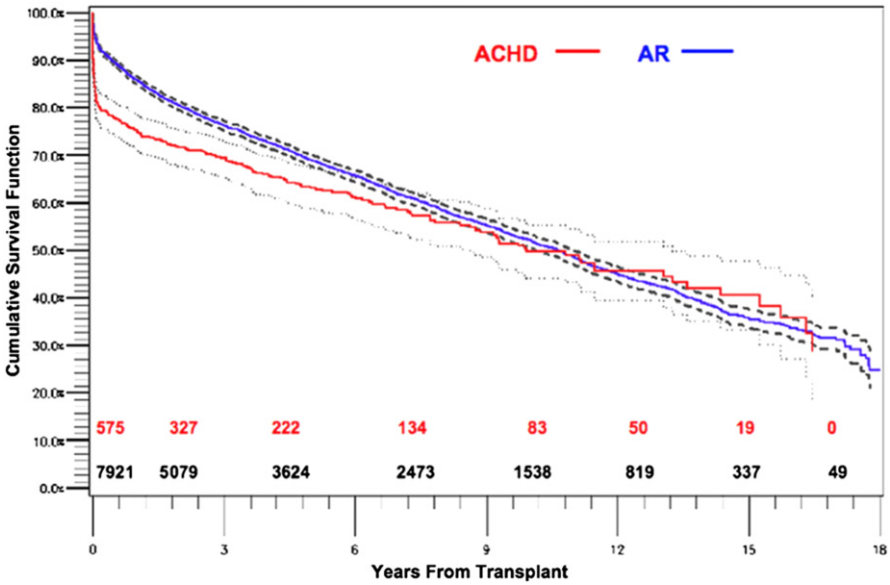

Fig. 1. Freedom from death stratified by underlying diagnosis (Karamlou et al, J Thorac Cardiovasc Surg 2010;140:161–8) [7].