Chapter 14

Cardiac Re-Transplantation: A Growing Indication with Unique Considerations

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Abstract

Cardiac re-transplantation (ReTx) accounts for a small proportion of the patients undergoing heart transplantation every year. However, due to improved patient management following transplant, the number of patients potentially requiring re-transplant is growing. We will review the current epidemiology of ReTx and describe the potential increase in candidates for ReTx. We will also highlight important characteristics of patients undergoing ReTx including co-morbidities and allosensitization. We will summarize single-center and registry data on patient outcomes following ReTx, and discuss patient selection. Finally, we will outline the management of patients following cardiac ReTx as well as alternate therapies and ethical considerations in cardiac ReTx.

Keywords: cardiac Retransplantation, epidemiology, outcomes

1. Introduction

There are over 5000 heart transplants performed annually worldwide. Survival following cardiac transplantation has improved dramatically, with one-year survival approaching 85% with a median survival of 11 years [1]. As a result, many patients are now surviving to develop late complications of cardiac transplantation such as chronic rejection, cardiac allograft vasculopathy (CAV), or late graft failure. Unfortunately, there are few medical therapies that significantly alter the development and progression of these complications, particularly at advanced stages [2, 3]. Cardiac retransplantation (ReTx) offers possible benefit to patients who survive to develop these late complications, particularly those patients who have developed left ventricular systolic dysfunction [4].

The first ReTx was performed in 1974 at Stanford, and the first group of patients was reported in 1977 by Copeland et al., which included 5 patients who underwent ReTx for either CAV or acute graft failure. ReTx currently comprises 3.0% of adult cardiac transplants [3, 5, 6], and a similar proportion of pediatric transplants [7]. While this proportion may seem small, it mirrors the proportion of patients transplanted for congenital heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, and valvulvar cardiomyopathy [5]. Additionally, as more patients survive to develop late complications, the number of patients who are candidates for ReTx will rise. Given this increase, ReTx will potentially outgrow these other indications for cardiac transplant.

2. Epidemiology of cardiac re-transplantation

The number of patients undergoing ReTx has been gradually increasing over time. Between 2000 and 2005, ReTx accounted for 2.9% of all heart transplants [3]. Between January 2009 and June 2015 there were 722 patients who underwent ReTx, which constituted 3.1% of heart transplants. While this seems like a small increase over time, there has been a simultaneous shift towards more rigorous patient selection for ReTx. This shift has been a response to the uniformly poor outcomes when patients undergo ReTx for acute events like primary graft failure. In this context, the median survival of patients undergoing cardiac transplantation has increased from 8.5 years in the era of 1982–1991 to almost 12 years for patients transplanted between 2002 and 2008. Median survival is even longer in young patients, with a median survival of 12.6 years in patients undergoing initial transplant between age 18 and 39, compared to 9.1 years in patients aged 60–69. Patients under age 40 comprise 17% of the adult heart transplant population, but also represent the population most likely to require to eventually require ReTx. There is no reason to believe that there will not be an ongoing trend towards improved survival, potentially increasing the number of patients considered for ReTx.

Most of the data regarding the epidemiology of ReTx is only reflective of patients who successfully undergo ReTx. Therefore, in order to demonstrate the potential increase in candidates for ReTx, we have provided an estimate based on outcomes in current transplant recipients, shown in **Figure 1**. Currently 74% of patients are surviving at least 5 years after their initial transplant date [5]. We will assume that patients who die before this time are not candidates for ReTx given poor outcomes in patients undergoing ReTx for acute graft failure. The proportion of patients who are over age 60 at the time of initial cardiac transplant is 23.8% [5]. For the sake of a conservative estimate, we will assume that these patients are not candidates for ReTx due to advanced age. In patients who die more than 5 years after transplant, CAV accounts for 7–17% of deaths and graft dysfunction accounts for 22–40% of deaths [5]. If all patients under age 60 at initial transplant who eventually die from CAV or graft dysfunction are assessed for ReTx, then 17% of all transplant patients could potentially be ReTx eligible. There are several assumptions built into this estimate. Many patients who are potential ReTx candidates due to CAV will not be eligible due to sudden death [8], or co-morbidities that preclude ReTx. However, if even half of the patients we estimated undergo ReTx this would essentially triple the current rate of ReTx.

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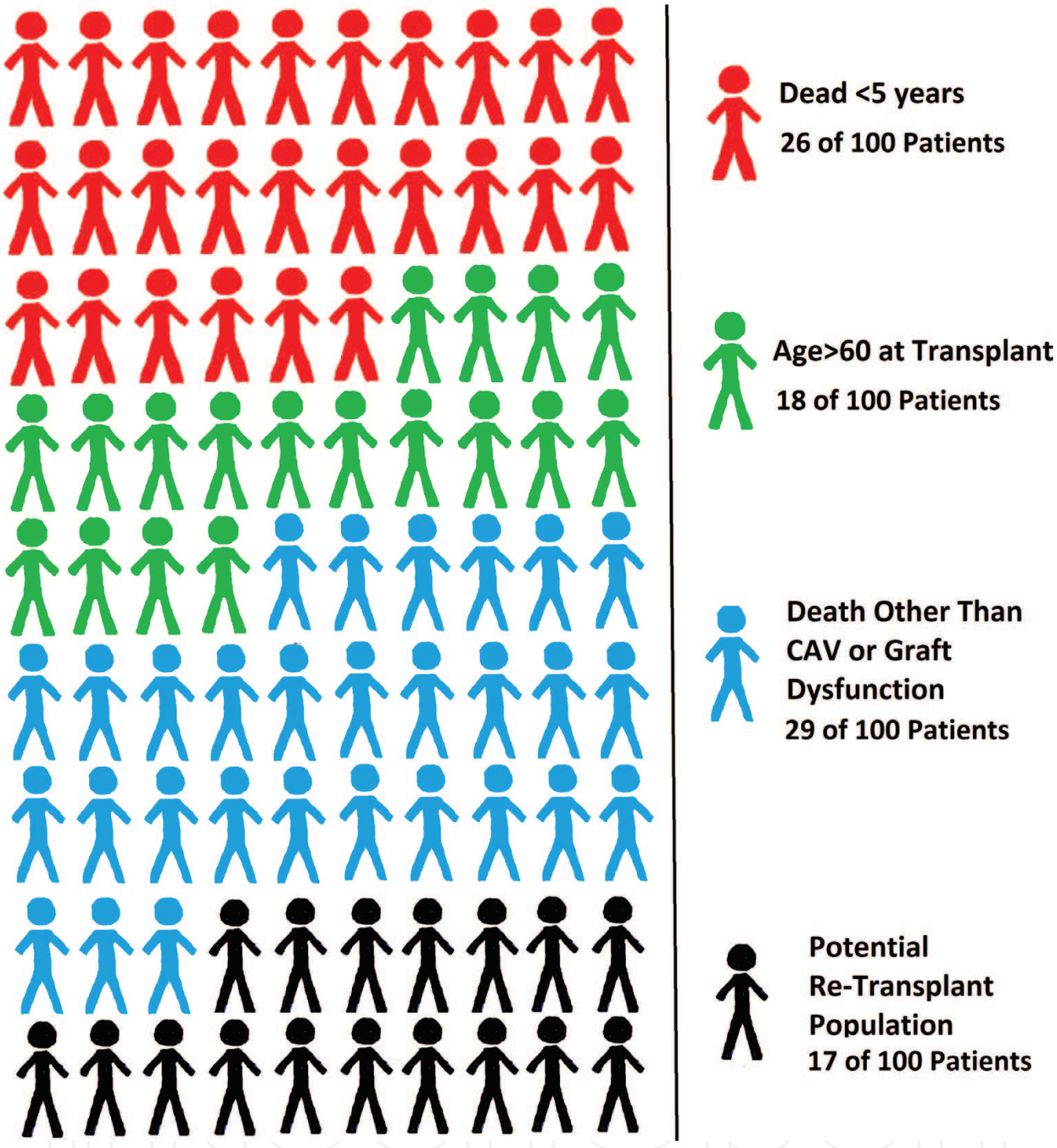

Figure 1. Estimate of the number of patients who may be candidates for cardiac ReTx. Estimates are based on ISHLT registry data [5, 9].

3. Characteristics of cardiac re-transplant recipients

Patients who undergo ReTx have characteristics distinct from those undergoing initial transplant. Some of these characteristics are related to procedures and immunosuppression required for the initial cardiac transplant. Meanwhile, other characteristics are related to surviving long enough to be considered for ReTx. However, as noted previously, this data only

reflects patients who have successfully undergone ReTx. The group of patients who may be considered candidates are likely older with more medical co-morbidities.

Many characteristics of patients undergoing ReTx are associated with better outcomes, and generally reflect being young and healthy enough to be considered for a second operation. ReTx patients are younger compared to patients undergoing initial cardiac transplant, with a mean age of 46 years compared to 54 years in the ISHLT database [9]. Amiodarone exposure at any time point is also less frequent in patients undergoing ReTx, occurring in 10% of patients compared to 32% of initial transplant recipients [9]. This is interesting in light of emerging evidence suggesting amiodarone use is associated with higher 1-year mortality after transplant [10]. This finding is likely due to the low incidence of atrial and ventricular arrhythmias in the transplant population [11]. Finally, patients undergoing ReTx have lower pulmonary vascular resistance compared to other indications for transplant [5]. Overall these characteristics reflect the selection bias inherent in selection of ReTx candidates.

In ReTx populations, the characteristics that predict improved survival after cardiac transplant are more than outweighed by characteristics associated with adverse outcomes. Most patients undergoing ReTx have been exposed to calcineurin inhibitors after the initial cardiac transplant. As a consequence, they are more likely to have hypertension and renal dysfunction. In the ISHLT database 15.6% of patients undergoing ReTx had received prior dialysis compared to 3.9% in patients undergoing initial transplant [9]. Baseline creatinine was also higher in the ReTx group, 1.6 mg/dl compared to 1.2 mg/dL in initial transplant patients [9]. Hypertension is present in 57% of ReTx compared to 46% of initial transplant patients [9]. Additionally, ReTx patients have been exposed to a previous allograft and blood products during the initial cardiac transplant. Due to previous exposures, patients undergoing ReTx are more likely to be sensitized or highly sensitized. Almost 10% of patients undergoing ReTx have a Panel of Reactive Antibodies (PRA) greater than 80% compared to 2% of the primary transplant group [9]. Conversely, less than 50% of ReTx patients have a PRA of 0 compared to 65% of initial transplant patients [9]. High degrees of sensitization may complicate ReTx, requiring desensitization treatments prior to transplant or more aggressive induction therapy after transplant. All patients undergoing ReTx have had a prior sternotomy, which increases operative mortality as well as increasing cardiopulmonary bypass time, which increases morbidity and 90 day mortality associated with the operation [12, 13]. Finally, patients undergoing ReTx are more likely to be hospitalized at time of transplant, with 52% of ReTx patients admitted at the time of transplant compared to 44% of initial transplant patients [9]. This may reflect a trigger point for considering ReTx. These factors highlight the high risk nature of the ReTx population.

The characteristics outlined above reflect the population of patients who successfully undergo ReTx. The broader population of patients who may have been considered candidates for ReTx includes patients who may be too old, have co-morbidities that result in prohibitive risk, or are too highly sensitized to be successfully matched for ReTx. This suggests that, overall, the population considered for ReTx will be at significantly higher risk for peri-operative, short-term, and long-term complications after transplantation.

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4. Patient outcomes following cardiac re-transplantation

There have been several attempts to characterize outcomes after ReTx. These studies span several eras of transplant management and reflect temoporal changes in patient selection criteria. What follows is not a comprehensive review of the available evidence, but a selected group of studies to highlight important concepts in the outcomes after ReTx.

4.1. Single-center studies

There have been several single-center studies outlining outcomes following ReTx, outlined in **Table 1**. Stanford reported a cohort of 66 patients who underwent ReTx before 1994 [14]. They found decreased one-year survival compared to primary heart transplant recipients (55 compared to 81%), with better survival in patients undergoing ReTx for CAV [14]. Schnetzler et al. investigated 24 patients who underwent ReTx before 1996 and found significantly reduced one-year survival for patient undergoing ReTx within a year (27.3%) compared to those undergoing ReTx after more than 1 year (61.5%) [15]. The patients transplanted within 1 year were exclusively patients with primary graft failure or intractable rejection [15]. A group from Columbia described a cohort of 43 patients undergoing ReTx before 1997 where 1-year and 5-year survival were decreased (66 vs. 76% and 51 vs. 60%) compared to initial transplant recipients [16]. They found that a shorter interval between ReTx and initial transplant as well as initial transplant for ischemic cardiomyopathy were associated with increased mortality compared to patients without those factors [16]. They

Author	Year	Center	Patients	Results
Smith	1995	Stanford	66 (26 acute, 40 chronic)	1-year survival 55% (vs 81%), 5-year survival 33% (vs 62%)
Schnetzler	1998	Paris	24 (11 acute, 13 chronic)	1-year survival 45.5% (vs. 71.6%), 5-year survival 31.2% (vs. 63.4%)
John	1999	Columbia	43 (13 within 2 years, 30 after 2 years)	1-year survival 66% (vs 76%), 5-year survival 51% (vs. 60%).
Schlechta	2001	Vienna	31 (16 acute, 15 chronic)	1-year survival 48.2% (vs. 80.2%), 5-year survival 36.8% (vs. 66.6%)
Topkara	2005	Columbia	41 patients	1-year survival 72.2% (vs. 85.5%), 5-year survival 47.5 (vs. 72.9%)
Alturi	2008	Pennsylvania	15 patients (11 chronic, 4 acute)	1-year survival 86.6% (vs 90.9%), 5-year survival 71.4% (vs. 79.1%)
Goerler	2008	Hannover	41 (18 acute, 23 chronic)	1-year survival 64% (vs. 83%), 5-year survival 47% (vs 72%)
Saito	2013	London, Ontario	22 (12 acute, 10 chronic)	Conditional 1-year survival 93.3% (vs. 93.0%) if surviving 30 days

Table 1. Single-center studies of re-transplant survival.

hypothesized that patients with ischemic cardiomyopathy may have atherosclerotic disease in other vascular beds leading to worse outcomes [16]. They also found improved survival in their population after excluding patients with acute graft failure and significant renal dysfunction [16]. A cohort of patients undergoing ReTx between 1984 and 1999 from Vienna had one-year survival as low as 48.2% in a cohort that was almost evenly split between acute and chronic indications for ReTx [17]. The authors suggested younger age, lack of peripheral vascular disease, and ability to actively rehabilitate after the primary transplant as criteria for ReTx candidacy [17]. These early studies were essential to identify the factors that influence survival, leading to better patient outcomes.

More contemporary cohorts have shown some improvement in ReTx outcomes through more rigorous patient selection. A single-center study from Germany reported a cohort of 41 patients who underwent ReTx prior to July 2006 [18]. Of those patients 18 underwent ReTx for acute graft failure and 23 for chronic graft failure [18]. They found decreased 1-year (64 compared to 83%) and 5-year survival (47 compared to 72%) in patients undergoing ReTx compared to initial transplant [18]. This finding was driven by high 30-day mortality (34.1 vs. 9.5%) in patients undergoing ReTx [18]. In their cohort, patients with chronic graft failure had better survival than those with acute graft failure as an indication for ReTx [18]. In a smaller Canadian study including patients transplanted between 1981 and 2011, patients who were retransplanted more than 1 year after initial implant had similar survival as patients undergoing initial transplantation [19]. Columbia reported improved survival in patients transplanted between 1992 and 2002 after selecting groups of patients with mostly CAV as the indication for ReTx [20]. The University of Pennsylvania heart transplant program had a similar experience in patients undergoing ReTx between 1987 and 2007 [20, 21]. While survival following ReTx is still lower compared to initial transplant patients, further improvements in patient selection may continue to decrease this disparity.

4.2. Registry studies

Survival after cardiac retransplantation has also been assessed using registry data, outlined in **Table 2**. An analysis from the International Society of Heart and Lung Transplant (ISHLT) database identified a total of 514 patients undergoing ReTx between 1987 and 1998, of whom more than 50% underwent ReTx for CAV. [22]. In this population, one-year survival was only 65%, but was higher after excluding patients who underwent ReTx within 2 years of the initial transplant [22]. However, post-transplant survival remained inferior in the subset of patients undergoing ReTx for chronic graft failure compared to patients undergoing initial transplant [22]. Patients undergoing ReTx at a low-volume center, older recipient age, and requiring ICU care prior to ReTx were associated with increased mortality [22]. An analysis of 107 patients undergoing ReTx between 1990 and 1999 in the Cardiac Transplant Research Database reported 56% 1-year survival [23]. In this cohort, patients undergoing ReTx for acute graft failure had 1-year survival of 50%, and in patients with acute rejection 1-year survival was even lower at 32% [23]. However, they found that retransplantation for CAV was associated with better survival with improvements in survival over time [23]. In the most recent analysis of the ISHLT database, patients undergoing ReTx between 2006 and June 2013 had one-year survival of 70%, but patients undergoing ReTx for primary graft failure had a one-year survival

Author	Year	Registry	Patients	Results
Srivasta	2000	ISHLT	514 patients (155 acute, 359 chronic)	1-year survival 65%, 3-year survival 55%
Radovancevic	2002	CTRD	107 patients (49 acute, 58 chronic)	1-year survival 56%, 5-year survival 38%
Lund	2014	ISHLT	820 patients (77% chronic, 23% acute)	1-year survival 70%, 5-year survival 54%

Table 2. Registry studies of re-transplant survival.

of 46% [9]. By comparison, patients undergoing ReTx for CAV had a one-year survival of 74% [23]. These studies highlight the importance of considering the indication for ReTx, which is a consistent predictor of mortality after correcting for other patient factors.

4.3. Outcomes in the pediatric population

Survival after ReTx is also strongly influenced by the age of the recipient. Therefore, authors have suspected that survival in the pediatric population may be better compared to adult populations. Select studies are outlined in **Table 3**. Razzouk et al. reported a cohort of 12 pediatric patients undergoing ReTx between 1985 and 1997 [24]. They found similar 1-year survival in patients undergoing ReTx compared to patients undergoing initial cardiac transplant [24]. Dearani et al. reported an updated cohort from the same center including 22 patients who underwent ReTx before 1999 [25]. One-year and 3-year survival was numerically, but not statistically, superior compared to initial transplant patients, with 3-year survival of 81.9 compared to 77.3% [25]. A cohort of 26 pediatric ReTx patients from Denver had similar one-year survival of 83% [26]. Conway et al. identified patients who underwent initial cardiac transplantation before age 18 in the ISHLT database [7]. They identified 602 patients who underwent ReTx between 1988 and 2010 and found that early mortality was similar to patients undergoing initial cardiac transplant, with a hazard ratio of only 1.07 [7]. However, patients undergoing ReTx were more likely to develop CAV, late rejection, and late renal dysfunction [7]. An important consideration in this group is that pediatric patients who are listed on adult transplant waitlists will wait for a longer period of time and are more likely to die on the waitlist [27]. Given

Author	Year	Center/registry	Patients	Results
Razzouk	1998	Loma Linda	12 patients	1-year survival 84.3 (vs. 83.3%), 4-year survival 74.4 (vs 83.3%)
Dearani	2001	Loma Linda	22 (16 chronic, 6 acute)	1-year survival 81.9% (vs 84.1%), 3-year survival 81.9% (vs 77.3%)
Karamichalis	2011	Denver	26 (10 chronic, 16 acute)	1-year survival 83%, 5-year survival 67%
Conway	2014	ISHLT	602 (acute and chronic)	1-year survival 83%, 5-year survival 69%

Table 3. Pediatric studies of re-transplant survival.

the improved proportional survival of pediatric ReTx patients compared to adult cohorts, it is likely that outcomes will also be acceptable in the younger adult population.

5. Patient selection for cardiac re-transplantation

The Consensus Conference on Retransplantation was sponsored by the American Society of Transplantation, the American Society of Transplant Surgeons, and the National Institute of Allergy and Infectious Diseases and was held in Atlanta in 2006 and outlined several important considerations for ReTx candidacy [6]. The working group concluded that patients undergoing ReTx should have either chronic graft failure in the absence of active rejection, or severe CAV not amenable to medical or surgical therapy. Additionally they suggested that patients with CAV should have either symptoms attributable to CAV or moderate to severe left ventricular dysfunction. Additionally, they proposed that patients with graft failure due to ongoing acute rejection, especially less than 6 months post-transplant, be ineligible for ReTx. In addition to considerations regarding the indication for ReTx, there are several other patient factors that warrant discussion given their strong associations with survival following ReTx.

Patient selection is a key component for improving short and long-term survival following ReTx. A summary of factors known to be associated with patient outcomes is presented in **Table 4**. Long-term survival is strongly driven by age at time of ReTx, as evidenced by relatively good outcomes seen in pediatric populations. Given the impact of age on survival, some groups have questioned the efficacy of ReTx in patients over the age of 60 years [6]. Patients undergoing ReTx have longer exposure to immunosuppression which may explain a possible increase in the risk of infections and malignancies; [28] therefore, careful attention should be given to excluding infection or occult malignancy when assessing ReTx candidacy. Poor renal function is also more common in ReTx patients and is associated with increased mortality. In a cohort of ReTx patients from Stanford, patients with creatinine >2.0 mg/dL had worse short-term outcomes, while patients undergoing simultaneous heart and kidney transplant had improved survival [14]. Similarly, patients on hemodialysis undergoing initial cardiac transplant in the UNOS database had better survival when undergoing simultaneous

Associated with worse patient outcomes	Associated with improved patient outcomes
Shorter interval between initial transplant and ReTx (<6 months)	Younger age
Primary/acute graft failure	Lack of peripheral vascular disease
Ischemic cardiomyopathy	CAV/Chronic graft failure
Renal dysfunction (Creatinine >2.0 mg/dL)	
Multiple previous sternotomies	
Requiring ICU care pre-operatively	

Table 4. Summary of predictors associated with patient outcomes.

heart-kidney transplant compared heart transplant alone [29]. Therefore, poor renal function should be considered a relative contraindication to ReTx unless the patient is a candidate for simultaneous heart-kidney transplant.

The number of previous sternotomies should also be considered when deciding if a patient is a candidate for ReTx. Multiple previous sternotomies from prior palliative congenital procedures or coronary artery bypass grafting adds to the burden of scar tissue, in addition to potentially complicated anastamotic sites from the initial transplant. Some authors have argued that this contributes to the high rates of multi-system organ failure in patients after ReTx, as well as high rates of early mortality [18, 28]. These findings are attributed to an increased incidence of mediastinitis, intrathoracic bleeding requiring reintervention, and primary graft failure [30]. These findings have also been seen in pediatric ReTx, many of which have had previous palliative procedures [26]. Lastly, patients admitted to ICU prior to ReTx, and particularly those requiring mechanical circulatory support, have worse outcomes [31]. In these patients it is important to not only ensure that organ dysfunction is reversible, but also that the patient will be capable of undergoing rehabilitation if the operation is successful. Consideration of these factors may help identify patients with the greatest potential benefit from ReTx.

Patients undergoing ReTx are more highly sensitized than patients undergoing initial cardiac transplant [5]. Higher sensitization increases the risk of CAV, acute rejection and post-transplant mortality [32, 33]. Therefore, it may be necessary to consider options to desensitize patients prior to ReTx in order to improve the chance of successful graft matching as well as improving outcomes following ReTx.

6. Management of patients following re-transplantation

Many studies have highlighted the high early mortality seen after ReTx and patient factors that might be driving this observation. This may reflect the increased complexity of the surgical operation as well as medical frailty in patients undergoing ReTx, but highlights the importance of careful early management. As mentioned previously, the most important aspect of patient management is careful selection of patients who are likely to benefit from ReTx. However, once an appropriate patient has been selected, it is important to optimize the peri-operative care in order to attain the best possible outcomes.

From a surgical perspective, it is important to identify the surgical technique used in the initial transplant. It may be especially pertinent to determine if the patient underwent bicaval or bi-atrial anastomosis as well as the level of anastomosis of the pulmonary artery and aorta. Dedicated thoracic imaging, either computed tomographic or magnetic resonance, may help identify anastomotic sites and areas with significant fibrotic tissue. It is not clear if it is necessary to completely excise all of the tissue from the initial cardiac transplant and no guidelines exist to advise clinical practice. Theoretically, it may help to reduce the potential for immunogenicity in those patients; however, this benefit needs to be weighed against increasing the complexity of the operation, which could potentially prolong bypass time and increase peri-operative complications. Finally, careful attention to hemostasis is important as always, but may be particularly important in ReTx patients in whom peri-operative bleeding is more frequent.

There are no clear guidelines on the post-operative care for patients undergoing ReTx. Theoretically, it may not be necessary to add induction therapy if patients have been maintained on high doses of immunosuppression, since their immune response is already significantly blunted. This is not the case for patients undergoing ReTx for refractory rejection or patients who are highly sensitized. However, most transplant centers have used similar induction and immunosuppressive regimens for their primary transplant and ReTx patients. Following induction, it may be reasonable to de-escalate immunosuppression more quickly than would be typical after initial transplantation in order to reduce the long-term risks associated with malignancy and infection.

7. Alternative therapies

Unfortunately, there are no established alternatives to ReTx for patients who have developed late complications of cardiac transplantation. There are no effective strategies for managing end-stage CAV and mortality rates are very high. Similarly, there are no established medical therapies for patients who have developed late graft dysfunction. Columbia has reported the use of mechanical circulatory support as a bridge to re-transplantation [34]. However, given the prevalence of restrictive filling dynamics and right ventricular dysfunction, long-term mechanical support is unlikely to be successful in many patients. Therefore, there are no clearly viable alternatives to ReTx and the default therapy has been, and will continue to be, palliative care. Therefore, it is important to review end-of-life planning and consider palliative care consultation in patients who develop long-term complications.

8. Ethical considerations in re-transplantation

A complete discussion of the ethical considerations of ReTx beyond the scope of this chapter and readers would be well-served to read dedicated manuscripts [18, 35–37]. Donor hearts are a limited resource and need to be valued appropriately. The number of patients listed for cardiac transplantation greatly outstrips this supply and will continue to do so until we use a much larger proportion of potential donor hearts, an alternate source of grafts is established, or fewer patients require cardiac transplantation. None of these events are likely to occur in the near future. Given the ongoing scarcity of donor hearts, it is important to offer organs to those patients who would derive the most benefit. This is a strong argument against ReTx for acute indications, where outcomes are consistently poor. ReTx for CAV or chronic graft dysfunction is also associated with worse survival compared to initial transplantation, but it is not clear if this is a sufficient reason to exclude all ReTx. Finally, there has been concern regarding the possible injustice inherent in ReTx. Many patients will not survive to receive a single heart transplant and it may not seem equitable for a single patient to receive two, or even three organs when there are patients who die before receiving their first. This debate will continue, but if clinical outcomes continue to improve in ReTx populations, there may be a shift towards broader acceptance of this procedure.

9. Conclusions

ReTx represents a small proportion of heart transplant procedures today; however, survival following cardiac transplantation has improved dramatically and more patients are surviving until they develop late complications such as CAV or graft failure. ReTx is the only therapy that offers meaningful improvement in survival to these patients. Survival after ReTx seems to be reduced, but may be acceptable in appropriately chosen patients. Tailored surgical and post-operative care is critical to improving patient outcomes in those accepted for ReTx.

Conflict of interest

The authors have no relevant conflicts of interest to declare.

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