Cardiac Retransplantation for Graft Vasculopathy in Children

Should We Continue to Do It?

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Background: Cardiac transplantation (CTx) has been established as an effective therapy for a variety of inoperable cardiac conditions in infants and children. However, graft vasculopathy (GV) has emerged as the main limiting factor to long-term survival of CTx recipients. The only treatment of severe GV is cardiac retransplantation (re-Tx). Controversy exists regarding the use of scarce donor organs for cardiac re-Tx.

Objective: To compare the outcome of cardiac re-Tx for GV with that of primary CTx in children.

Design: A 12-year retrospective cohort review.


Patients: All infants and children who underwent CTx (group 1, n = 322) had complete follow-up of 1389.7 patient-years. Graft vasculopathy was confirmed in 32 recipients (1.1-8.2 years after undergoing CTx). Thirteen patients died suddenly, 3 died waiting for cardiac re-Tx (1-17 days after relisting), 4 are pending cardiac re-Tx, and 12 (group 2) underwent cardiac re-Tx.

Intervention: Cardiac re-Tx at a mean (± SD) interval from the first CTx of 6.3 ± 1.8 years (range, 2.2-9.4 years). Two patients required additional aortic arch aneurysm repair with cardiac re-Tx.

Results: When group 1 was compared with group 2, there was no significant difference in operative mortality (9.0% vs 8.3%; P = .9), rejection rate (0.98 vs 0.86; P = .1), and hospital stay (23.0 ± 18.8 days vs 20.5 ± 11.6 days; P = .65). Actuarial survival for groups 1 and 2 at 1 and 4 years was 84.3% vs 83.3% (P = .59) and 74.4% vs 83.3% (P = .85), respectively.

Conclusions: The surgical outcome and intermediate survival of cardiac re-Tx for GV and primary CTx are similar. Children with severe cardiac GV are at risk of sudden death and can benefit from early cardiac re-Tx.

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During the past 15 years, cardiac transplantation (CTx) has been offered as therapy for a variety of inoperable cardiac conditions in infants and children. Worldwide, this therapy is now carried out in about 300 children a year with good (70%-80%) 3-year survival.1,2 As this population of children grows in size and enjoys a prolonged survival, diffuse, concentric graft atherosclerosis known as graft vasculopathy (GV) will develop in 10% to 35% of patients.3-5 This form of accelerated atherosclerosis has emerged as the leading cause of morbidity and mortality in long-term survivors of CTx. Cardiac retransplantation (re-Tx) is the only therapeutic option of proven benefit to children with primary GV. Recently, however, numerous ethical, moral, and fiscal concerns have been raised regarding the merits of cardiac re-Tx. Critics point to the cost of re-Tx and the shortage of suitable donor organs and, using data from the adult transplantation experience, argue that the outcomes of patients with cardiac re-Tx are inferior to those of patients with primary grafts.6,7

This single-institution, uncontrolled, nonrandomized, retrospective cohort study was undertaken to evaluate the outcome of a second pediatric CTx for GV and to compare the results with those of primary CTx.

RESULTS

The operative mortality for group 1 (primary CTx) was 9.0% and for group 2 (cardiac re-Tx for GV), 8.3% (P = .9). The 1 hospital death in group 2 was the 6-year-old boy who had hemodynamic and renal compromise before cardiac re-Tx. He died of sepsis and multiorgan system failure 4 weeks after reoperation. The 1 late death (5 weeks after cardiac re-Tx) in group 2 resulted from severe rejection of...
PATIENTS AND METHODS

PRIMARY CTx GROUP

From November 5, 1985, to October 30, 1997, 322 infants and children (group 1) underwent primary orthotopic CTx at Loma Linda University Medical Center and Children’s Hospital, Loma Linda, Calif (Table). The mean (± SD) age at primary transplantation was 1.8 ± 3.8 years (median, 63 days; range, 1.5 hours to 17.7 years), and 94 were neonates (≤ 30 days). The indications for CTx included hypoplastic left-sided heart syndrome (n = 131), cardiomyopathy (n = 75), other complex congenital heart disease (n = 113), and cardiac tumor (n = 3). Recipients were given methylprednisolone perioperatively for 2 days only and then received a regimen of cyclosporine and azathioprine sodium for long-term immunosuppression. Close monitoring during the first 6 months after CTx required biweekly visits to the outpatient transplantation clinic. Further follow-up was provided by the referring cardiologist and primary pediatrician. Cumulative follow-up has been complete as of December 30, 1997, and includes 1389.7 patient-years with a mean (± SD) follow-up of 4.3 ± 3.1 years.

The diagnosis of cardiac graft rejection was based more on a set of echocardiographic and clinical variables than on the use of endomyocardial biopsy, which was only performed selectively. Rejection episodes were defined as events requiring treatment with augmentation immunosuppression. The condition of the graft coronary arteries was evaluated by yearly coronary angiography, gross and histological examinations of explanted hearts (after cardiac re-Tx) or autopsy specimens, or a combination of angiography and pathological examination. Graft vasculopathy was considered severe when luminal obliteration was greater than 50%. Intravascular ultrasonography has been used for the past 2 years in some older children to corroborate the angiographic findings.

GROUP 2 MORBIDITY

Sternotomy infection developed in 1 patient, who was overimmunosuppressed 3 weeks after cardiac re-Tx. She recovered well after debridement and reclosure of the sternum. None of the recipients of a second graft required exploration for postoperative bleeding. Although perioperative peritoneal dialysis was instituted in 2 patients for 13 to 58 days, none of the survivors of cardiac re-Tx have required long-term dialysis. The mean serum creatinine level is 75 ± 20 μmol/L (0.85 ± 0.23 mg/dL) (range, 53-124 μmol/L [0.6-1.4 mg/dL]), and the mean glomerular filtration rate is 86.4 ± 27.1 mL·min⁻¹·1.73 m².

REJECTION

The linearized rejection rate (frequency per patient-month at risk) for group 2 patients was 0.77 after the initial transplantation and 0.98 after cardiac re-Tx (P = 1). The incidence of rejection among all group 1 (primary CTx) patients was 0.86.

HOSPITAL CHARGES

The mean hospital charge for the 12 patients undergoing cardiac re-Tx was $171 000 ± $25 000. This charge was not significantly different (P = .9) from that ($173 000 ± $20 000) of the patients undergoing primary CTx during the same period. These are hospital charges only and do not include pretransplantation charges incurred during the waiting period.

COMMENT

Continuous advances made in the past 2 decades in the detection of early rejection, prolonged organ preserva-

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tion, improved surgical and anesthetic techniques, and the introduction of new immunosuppressive therapy protocols have extended the benefits of heart transplantation to infants and children, with dramatic results. Graft vascular disease, however, remains the most serious threat to long-term survival of CTx recipients. This disease affects infants, children, and adults; may be evident as early as 2 months after CTx; and may cause the recipient's death 22 years later. The lower incidence of GV reported at 5 years in children compared with adults (10%-35% vs 40%-70%) is partly due to the fewer number of long-term pediatric survivors, the less frequent use of angiography in children, and the use of younger donors for pediatric recipients. The cause of GV is unclear, and its pathogenesis is complex and multifactorial. It may be due to immunologic and nonimmunologic damage to the endothelial cells resulting in myointimal proliferation.

This true form of GV differs from traditional atherosclerosis in that it is a concentric and diffuse hyperplastic process, the internal elastic lamina remains intact, and calcification is rare. The intramyocardial vessels also may be affected by this lesion. For this reason, the angiographic detection of small-vessel disease is often elusive. Coronary angioplasty is seldom, if ever, effective in patients with GV because discrete stenoses are rare. In hearts with GV, hypertrophy and disarray of myocytes often develop, with areas of scarring that can account for evidence of old ischemia, electrical irritability, and sudden death. These unique anatomical features of GV and the lack of effective alternative treatment modalities make cardiac re-Tx the only hopeful option for such children.

Successful re-Tx of the human heart was first performed at Stanford University Medical Center, Palo Alto, Calif, in 1977. Since that time, more than 800 cardiac re-Tx procedures, mostly in adults, have been performed worldwide, with mixed results. The actuarial survival among all recipients of cardiac re-Tx was clearly lower than in patients who received only 1 allograft in the 25-year Stanford series (1-year survival, 55% ± 8% vs 81% ± 2%), the 23-year Utah series (1-year survival, 73% vs 88%), and patients listed in the registry of the International Society for Heart and Lung Transplantation (1-year survival, 58% vs 79%). The results of cardiac re-Tx, however, have improved considerably since the introduction of cyclosporine in the early 1980s. The experience at Columbia Presbyterian Medical Center, New York, NY, with the use of cyclosporine in 408 recipients of primary transplants and 13 patients with cardiac re-Tx showed no significant difference in 1-year survival (75.1% ± 2.2% vs 71.4% ± 12.1%). Data collected from 13 transplantation centers in the United States identified 3 factors predictive of longer survival after cardiac re-Tx: longer (>6 months) interval between transplantations, accelerated coronary artery disease as the cause of allograft loss, and lack of preoperative mechanical assistance. In the Stanford series, patients since 1981 who underwent cardiac re-Tx for GV had a substantially better 1-year survival than those who underwent cardiac re-Tx for allograft rejection (69% ± 10% vs 33% ± 16%). At Loma Linda University Medical Center and Children's Hospital, 2 children not included in this series had "emergent" cardiac re-Tx for acute graft failure within 1 day of primary CTx, and both patients died. A similar experience is reported by independent groups who concluded that early cardiac re-Tx (<30 days) is associated with a high mortality.

Most children undergoing cardiac re-Tx for GV do not require cardiac re-Tx until 6 months or longer after the primary transplantation, and most do not require preoperative mechanical support. Thus, survivors of pediatric CTx who are thriving and functioning well except for the development of severe GV are "ideal" candidates for elective cardiac re-Tx. Michler et al were the first to report on the results of cardiac re-Tx in children. They retrospectively reviewed 17 pediatric heart transplant recipients at 4 different institutions who subsequently underwent cardiac re-Tx and evaluated the risks and outcome of cardiac re-Tx. Graft vasculopathy was the primary indication for cardiac re-Tx in 7 patients (41%), and in an additional 4 patients (24%), GV associated with ongoing rejection was the primary indication for cardiac re-Tx. The 1- and 3-year actuarial survival after cardiac re-Tx was 71% and 47%, respectively. Michler et al noted, however, that patients surviving longer than 6 months after cardiac re-Tx had a better actuarial survival of 92% and 65% at 1 and 3 years, respectively. Neither their multi-institution report nor the International Society for Heart and Lung Transplantation registry data on pediatric car-

### Pediatric Cardiac Transplantation Data

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<tr>
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<th>Primary CTx (n = 322)</th>
<th>Cardiac re-Tx for GV (n = 12)</th>
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</thead>
<tbody>
<tr>
<td>M/F ratio</td>
<td>191:131</td>
<td>8:4</td>
</tr>
<tr>
<td>Graft ischemia time, min Mean±SD</td>
<td>263.7 ± 119.4</td>
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<td>Range</td>
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<tr>
<td>Cardiopulmonary bypass time, min Mean±SD</td>
<td>103.9 ± 41.2</td>
<td>127.2 ± 35.8</td>
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<td></td>
<td>Range</td>
<td>43.0-411.0</td>
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*CTx indicates cardiac transplantation; re-Tx, retransplantation; and GV, graft vasculopathy.*
diac re-Tx (1-year survival, 56%) report survival according to indications for cardiac re-Tx, namely, for GV.

The present study is a single-institution experience with pediatric cardiac re-Tx for GV. The 4-year survival after elective cardiac re-Tx for GV of 83.3% justifies the use of donor hearts for this unique group of children. The rate of progression of GV is widely variable and most likely spans a continuous spectrum. A rapid progression of disease was seen in 13 recipients in our series, who suffered sudden death related to severe GV that developed within 1 year. Gao et al reported a similar experience with patients who sustained massive myocardial infarction several months after a normal coronary angiogram. The data in our study support their conclusion that the subset of patients in whom a fulminating progression of graft coronary artery disease develops within 1 year have a poor prognosis and are at risk for sudden death. This unpredictable course and the number of sudden deaths lead us to recommend early listing for elective re-Tx when substantial (>50%-diameter stenosis) graft coronary artery disease appears in more than 1 vessel.

Our data on rejection in this group of patients who underwent cardiac re-Tx confirms the observations of others that rejection episodes do not occur more frequently in recipients of second allografts. Moreover, the Stanford series noted that all patients who underwent cardiac re-Tx for acute rejection had at least 1 episode of acute rejection in their retransplanted heart during the first 6 months after the procedure, in contrast to the group who underwent cardiac re-Tx for GV in whom the actuarial freedom from rejection at 6 months was 33% ± 10%. The incidence of infection in CTx recipients does not increase after cardiac re-Tx. Aggressive, prolonged immunosuppression following cardiac re-Tx, however, may predispose a recipient to infection. High-level immunosuppressive therapy and overtreatment of acute rejection may cause neutropenia, thrombocytopenia, and superinfection to develop. Such was the case in the 9-year-old girl described here in whom mediastinitis developed 20 days after she underwent cardiac re-Tx. She responded to surgical débridement, antibiotic therapy, and lowering the immunosuppressive regimen.

Adults undergoing cardiac re-Tx have a higher morbidity compared with primary CTx recipients. In contrast, children who were described in this report and in the multicenter review did not have a higher incidence of surgical complications or an increased operative mortality. Long-term cyclosporine use is known to cause renal insufficiency. Although some cardiac re-Tx recipients in our study received postoperative dialysis, none have required long-term dialysis or renal transplantation.

One of the limitations of this study is the short follow-up period for this cohort of patients. Within the limited period studied after cardiac re-Tx, none of the patients had GV after cardiac re-Tx. Previous experience with adult patients revealed that the incidence of recurrent GV in patients undergoing cardiac re-Tx for GV is, in fact, no higher than in patients having cardiac re-Tx for other reasons. The incidence of recurrent GV in the second allograft is unknown, but it is likely to increase with longer follow-up, and the long-term survival of cardiac re-Tx recipients will again be dependent on better treatment of GV.

Pediatric patients undergoing cardiac re-Tx in our study had a higher incidence of HLA sensitization to the standard panel of antigens than recipients of primary CTx. This has been the case in other series, but the clinical implications of higher sensitization have not been important. In fact, in the Utah series, 13 patients with re-Tx had sensitization present in the first allograft, with no effect whatsoever on survival. Because of the small size of our series (n = 12), we lack the statistical power to define the predictors of outcome or to determine the correlation between panel-reactive antibody status and graft survival.

The scarcity of donor hearts and the long waiting list of recipients raise the concern that it is "unfair" to give a donor heart to a patient in need of cardiac re-Tx. When elective cardiac re-Tx is likely to be as successful as primary transplantation, as shown in this series, such arguments about fairness may no longer be valid. Physicians and institutions are, therefore, urged to selectively and carefully offer elective cardiac re-Tx to those patients who possess the best predictors for a good outcome and who have good potential for rehabilitation.

Graft vasculopathy is the major cause of late death in pediatric CTx recipients. Retransplantation is the only definitive therapy for GV. The use of donor organs for cardiac re-Tx remains controversial, but our experience has identified pediatric CTx recipients with severe GV as ideal candidates for elective cardiac re-Tx, and their intermediate-term outcome is as favorable as that of primary transplant recipients.

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REFERENCES

9. Berry GJ, Rizeq MN, Weiss LM, Billingham ME. Graft coronary disease in pedi-
Adnan Cohanoglu, MD, Portland, Ore: The Loma Linda group has brought a very important and difficult problem to our attention, namely, coronary artery vasculopathy in transplanted hearts. Over the past decade, short-term survival after CTx has increased markedly because of surveillance endomyocardial biopsies and improvements in immunosuppression.

Currently, it is not unrealistic to expect 85% to 90% 1-year survival and more than 70% 5-year survival rates. Despite this progress, chronic rejection with GV remains a substantial and intractable obstacle to long-term survival. This disease has been attributed to a whole host of recipient- and/or donor-related variables. It has unique morphology, as shown by Dr Razzouk, with obliterator intimal thickening and diffuse longitudinal luminal narrowing of the coronary arteries. The only potential treatment is re-Tx. This report is an analysis of the incidence of GV among 322 CTx recipients in a pediatric population. Of the 32 patients diagnosed with severe GV, 13 suffered sudden death, indicating the serious nature of this problem. Twelve patients so far have had cardiac re-Tx.

Our experience at the Oregon Health Sciences University now encompasses 320 CTx patients of all ages, and we have done cardiac re-Tx in a similar number of patients, including both adults and children, 12 patients. Unfortunately, we have not been able to duplicate the authors' excellent results. Our 1-year survival is about 50%, which goes along with that reported by many other centers in the country.

One shortcoming of this report by the Loma Linda group is that there are only 12 patients in this series, and the mean follow-up is only 1.8 years. With small numbers, it is difficult to reach meaningful late-follow-up conclusions, but most patients have survived a number of years—up to 4—and the functional results are excellent. So we can't argue with success.

The International Society for Heart and Lung Transplantation data show that cardiac re-Tx is the number one risk factor for 1- and 3-year mortality. So the authors' data are at odds with the data from the society's registry. Based on this, I think cardiac re-Tx remains as a very individual, center-specific decision based on the center's experience.

I have a few questions for the authors. What are their insights as to the lower incidence of GV in the pediatric patients than in adults recipients? The longest survivor in this series is 4 years out from re-Tx. What should be the 5-year survival rate to continue allocation of these rare organs to re-Tx candidates? Should there be a limit if these patients become candidates for a third transplantation, in another 6 or 8 years? Should they be transplanted a third time? Most of these patients will be only in their teens at that time.

The authors have compared the re-Tx group of patients with a mean age of 7 years with the overall group that includes many neonates and infants younger than 2 months. We all know that neonates and infants may have longer hospital stays and higher hospital costs. When these 12 patients are compared with an age-matched group of first-time recipients, the hospital stays may become lower and the costs higher. Has this been looked at?

John M. Rabkin, MD, Portland: The authors report a tremendous experience, and it addresses a very timely issue in transplantation. Unlike other high-expense modalities of care, the limitation here is of organ availability, and the first question the authors posed was, is re-Tx fair? I would like to pose 2 questions: The first is whether the authors can really explain why their re-Tx outcomes are as good as those for their primary transplants, which is really in conflict with all of the other organ transplant experiences where the re-Tx outcome is worse. I am wondering if there is a need to stratify for recipient age or time period, or is there a difference in management in these retransplants, such as viral prophylaxis or immunosuppressive regimens, that could be implicated in the improvement in survival. More important, my second question relates to whether it is fair to retransplant patients if others are waiting for their initial transplant. With the constraint in CTx of the size match between the donor and recipient being tight, I am wondering how these particular organs would have been utilized had they not been transplanted in these particular patients. As was just outlined, the median age for the primary transplants was 63 days vs 7 years in the re-Tx patients, an age of patients where there isn't as great a need for cardiac allografts. So I am wondering if the authors considered looking at what the list of potential recipients for those specific organs was (the UNOS waiting list) and what was the outcome in those patients who were listed who did not get these organs to address the question of whether or not these organs, if they hadn't been used for re-Tx, might not have been used at all.

Dr Razzouk: Graft vasculopathy is the main factor causing late death in pediatric CTx recipients. Why did we have better results in this study than in the published reports in the Journal of Heart and Lung Transplantation? We selected a particular group of patients who underwent elective re-Tx. Our experience with emergency or urgent re-Tx in children is not good. That is why we tried to define those patients who would best benefit from re-Tx, ie, those who would undergo elective and not emergency transplantation.

As far as the fairness in the use of scarce organs, this is no longer an issue when the results of re-Tx are as good as of primary CTx. Also, as pointed out by 1 of the discussants, the patients who need re-Tx are usually older. We tend to travel all across the continental United States, all the way up to Alaska, to retrieve organs that have been turned down by the regional community. So we are not taking organs from other patients who require it for the first time.

We looked at the risk factors for the development of GV; the frequency of rejection within the first year was not a risk factor. However, late rejection after 1 year is a predictor of the development of GV. Of the patients in whom this lesion developed, about 50% had some delayed rejection beyond 1 year of transplantation. Those are the patients who require close monitoring to prevent sudden death.

Yes, the hope is for gene therapy and more specific anti-rejection drugs. Until we find a method or way to control GV, or even prevent it, CTx and, for the same reason, cardiac re-Tx will remain a palliative therapy and certainly not a cure.