Cardiology in the Young

cambridge.org/cty

Effect of cardiac graft rejection on semilunar valve function: implications for heart valve transplantation

Deani H. McVadon[1], William A. Hardy[2], Katerina A. Boucek[1], William D. Rivers[2], Jennie H. Kwon[2], Minoo N. Kavarana[2], John M. Costello[1] and Taufiek Konrad Rajab[2]

[1]Division of Pediatric Cardiology, Medical University of South Carolina, Charleston, SC, USA and [2]Section of Pediatric Cardiothoracic Surgery, Medical University of South Carolina, Charleston, SC, USA

Original Article

Cite this article: McVadon DH, Hardy WA, Boucek KA, Rivers WD, Kwon JH, Kavarana MN, Costello JM, and Rajab TK (2023) Effect of cardiac graft rejection on semilunar valve function: implications for heart valve transplantation. *Cardiology in the Young* **33**: 1401–1408. doi: 10.1017/S104795112200258X

Received: 2 March 2022
Revised: 29 June 2022
Accepted: 23 July 2022
First published online: 15 August 2022

Keywords:
Semilunar valve; transplantation; rejection

Author for correspondence:
Dr. T. Konrad Rajab, Director of Congenital Cardiac Surgery Research, Section of Pediatric Cardiothoracic Surgery, Medical University of South Carolina, 10 McClennan Banks Drive, Charleston, SC 29425, USA.
Tel: +1 843 792 3361; Fax: +1 843 792 9783.
E-mail rajabt@musc.edu

Deani H. McVadon and William A. Hardy contributed equally.

John M. Costello and Taufiek Konrad Rajab are co-senior authors.

Abstract

Background: The treatment of neonates with unrepairable heart valve dysfunction remains an unsolved problem because there are no growing heart valve replacements. Heart valve transplantation is a potential approach to deliver growing heart valve replacements. Therefore, we retrospectively analysed the semilunar valve function of orthotopic heart transplants during rejection episodes. *Methods:* We included children who underwent orthotopic heart transplantation at our institution and experienced at least one episode of rejection between 1/1/2010 and 1/1/2020. Semilunar valve function was analysed using echocardiography at baseline, during rejection and approximately 3 months after rejection. *Results:* Included were a total of 31 episodes of rejection. All patients had either no (27) or trivial (4) aortic insufficiency prior to rejection. One patient developed mild aortic insufficiency during a rejection episode ($P = 0.73$), and all patients had either no (21) or trivial (7) aortic insufficiency at follow-up ($P = 0.40$). All patients had mild or less pulmonary insufficiency prior to rejection, which did not significantly change during ($P = 0.40$) or following rejection ($P = 0.35$). Similarly, compared to maximum pressure gradients across the valves at baseline, which were trivial, there was no appreciable change in the gradient across the aortic valve during ($P = 0.50$) or following rejection ($P = 0.42$), nor was there any meaningful change in the gradient across the pulmonary valve during ($P = 0.55$) or following rejection ($P = 0.91$). *Conclusions:* This study demonstrated that there was no echocardiographic evidence of change in semilunar valve function during episodes of rejection in patient with heart transplants. These findings indicate that heart valve transplants require lower levels of immune suppression than orthotopic heart transplants and provide partial foundational evidence to justify future research that will determine whether heart valve transplantation may deliver growing heart valve replacements for children.

Treatment of CHDs frequently involves heart valve replacement with an implant, and the first operation is often performed in early infancy.[1] However, conventional heart valve implants with preserved allograft valves degenerate over time and do not grow with recipient children, committing them to serial re-operations for successively larger heart valve implant exchanges.[2] These reoperations are associated with significant morbidity and mortality.[2] Therefore, there is an urgent clinical need for growing heart valve replacements. Current research initiatives to develop growing heart valve replacements are based on tissue engineering or mechanical engineering. However, despite decades of investigation, these approaches have failed to achieve clinical translation.[3] In this context, we have proposed that heart valve transplantation may be a new approach to deliver a growing heart valve replacement with the ability to self-repair and avoid thrombogenesis (Fig 1).[4] The viability of heart valve transplants is preserved by ABO blood type matching, controlling donor ischaemia time and recipient immune suppression as with orthotopic heart transplants. This approach distinguishes partial heart transplants from homografts. The donor heart valve would be obtained from donor hearts that are otherwise unusable for full orthotopic heart transplant. It is plausible that a transplanted heart valve with concurrent immunosuppression will grow proportionally with somatic growth of the recipient child, comparable to the growth observed with heart valves included in a conventional heart transplant.[5,6] Growth of auto transplanted pulmonary valves has been noted after the conventional neonatal Ross procedure.[4] While the neonatal Ross procedure is the preferred treatment strategy for neonatal aortic valve replacement, it is associated with an in-hospital mortality 29% with late mortality ranges from 66 to 100%.[7]

The susceptibility of these transplanted valves to rejection and the need for long-term immunosuppression is unclear. Long-term immunosuppression is not without risk and is associated with significant complications such as malignancy, infection, stunted growth, and

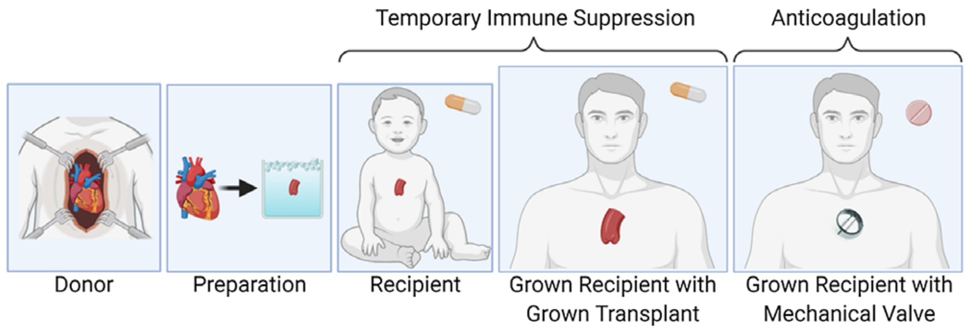

Figure 1 Partial heart transplantation could deliver a growing valve implant in children with unrepairable heart disease and allow patients to receive a single surgery during childhood and temporary immunosuppression (Reproduced with permission from Rajab TK. Evidence-based surgical hypothesis: Partial heart transplantation can deliver growing valve implants for congenital cardiac surgery. Surgery. 2021;169:983-985. Created with BioRender.com).

end-organ toxicity.[8] It is also uncertain how such a transplanted valve would behave during potential episodes of rejection. To provide partial justification for future heart valve transplantations in children, we thought it would be important to quantify the behaviour of valve function in children who had undergone orthotopic heart transplantation. The aim of this study was to assess the semilunar valve function of conventional heart transplants during rejection episodes. Based on prior clinical experience, we hypothesised that semilunar valve function would be preserved during episodes of myocardial rejection.

Materials and Methods

The institutional review board at the Medical University of South Carolina approved this retrospective study and granted a waiver of informed consent.

Study design

Inclusion criteria for this study were children less than 21 years old who underwent orthotopic heart transplantation at the Medical University of South Carolina between 1/1/2010 until 1/1/2020 and had at least one episode of rejection. Exclusion criteria included patients who underwent orthotopic heart transplant at our institution during the time period but did not experience any episodes of rejection. We also excluded co-transplantation of other organs and heart transplants that involved concurrent interventions on the semilunar valves of the donor heart.

Antibody-mediated and cellular rejection were both considered rejection episodes. Antibody-mediated rejection was defined by two of the four following criteria: graft dysfunction, presence of a circulating donor-specific antibody, positive immunofluorescence for C4d/C3d/pAMR1 on biopsy specimen, or enhanced immunosuppression therapy or any new treatment for suspected antibody-mediated rejection such as steroids or intravenous immunoglobulin. Cellular rejection was defined as a biopsy score for acute cellular rejection $\geq$ 2R on biopsy or a biopsy score $<$ 2R with clinical diagnosis of rejection treated with enhanced immunosuppression such as steroids or increased levels of chronic suppression. Each rejection episode was analysed separately with some patients in the study having multiple episodes. We also analysed the relationship between severity of rejection and semilunar valve function using stratification based on the International Society for Heart and Lung Transplantation 2004 rejection grades.[9] Rejection episodes were classified into episodes with low grade (0R or 1R) or high grade (2R and 3R) based on biopsy results.

Echocardiography

For each patient, data were extracted from reports of three echocardiograms per episode of rejection. The first set of data was obtained from the last echocardiogram obtained prior to the rejection episode. This echocardiogram was obtained under general anaesthesia during a surveillance catheterisation performed before any episodes of rejection during which a negative biopsy was obtained, and no evidence of current rejection was noted. The second set of data were obtained from the echocardiogram during an episode of rejection (as defined above) also while under general anaesthesia during catheterisation. The final set of data were obtained from an echocardiogram obtained approximately 3 months following each rejection episode. Aortic and pulmonary valve function was compared among these three echocardiograms using subjective classification of severe, moderate, mild, trivial, or no valve insufficiency. Pressure gradients through the aortic and pulmonary valve for each echocardiogram were also obtained. We focused on the semilunar valves because atrioventricular valve function could be influenced during rejection by ventricular dilation or papillary muscle dysfunction.

Statistical analysis

Binary and categorical variables were reported as count (percent). Continuous variables were reported as means (standard deviation) or medians (10^{th}–90^{th} percentile) as appropriate. Categorical variables were analysed using the Fisher's exact test and continuous variables were analysed using the Wilcoxon signed-rank test. Statistical analyses were conducted using R (Version 4.0.5).

Results

Patient population

A total of 30 orthotopic heart transplantations were performed at our institution during the study period of January 2010 through January 2020. Seventeen patients were included in the study each with at least one episode of rejection. A total of 31 rejection episodes were analysed with 9 patients having multiple episodes of rejection. The average number of rejection episodes in patients included in the study was 1.8 (range of 1–4). There were 8 patients with only 1 episode, 5 patients with 2 episodes, 3 patients with 3 episodes, and 1 patient with 4 episodes. Of the 17 patients, 13 were male and 4 were female. Patient age at the time of the first rejection episode ranged from 0 to 21 years old with a mean age of 12 years old.

https://doi.org/10.1017/S104795112200258X Published online by Cambridge University Press

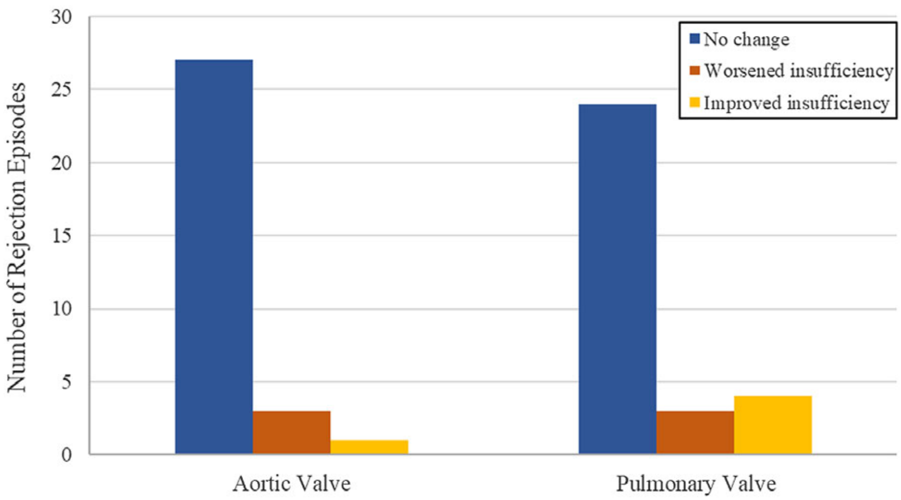

Figure 2 Rejection episodes stratified by no change, worsening, and improvement in insufficiency of the aortic and pulmonary valves from pre-rejection to during rejection.

Effect of graft rejection on aortic valve function

Prior to any episodes of rejection, aortic valve insufficiency was reported as severe in 0 patients, moderate in 0, mild in 0, trivial in 4, and none in 27. During the 31 rejection episodes, 27 patients had no change in aortic valve insufficiency, 1 patient had improvement, and 3 patients had worsening (Fig 2). Of the patients that had worsening insufficiency, two patients went from no aortic insufficiency to trivial insufficiency and one patient went from no aortic insufficiency to mild insufficiency. These results are summarised in Table 1. No statistically significant changes were seen in aortic valve insufficiency categories when comparing pre-rejection to during rejection ($P = 0.73$) and when comparing pre-rejection to post-rejection ($P = 0.40$). Similarly, no change was noted between aortic valve maximum pressure gradient prior to rejection and during rejection ($P = 0.50$) and pre-rejection to post-rejection ($P = 0.42$).

Effect of graft rejection on pulmonary valve function

Prior to any rejection episodes, pulmonary valve insufficiency was reported as severe in 0 patients, moderate in 0, mild in 3, trivial in 28, and none in 0. During rejection episodes, 24 patients had no change in pulmonary valve insufficiency, 4 patients had improvement, and 3 patients had worsening (Fig 2). Of the three patients who had worsening pulmonary valve function, all three transitioned from trivial insufficiency prior to rejection to mild insufficiency during rejection. No patient had worsening insufficiency to the moderate or severe category. These results are summarised in Table 1. No statistically significant changes were seen in pulmonary valve insufficiency categories when comparing pre-rejection to during rejection ($P = 0.40$) and when comparing pre-rejection to post-rejection ($P = 0.35$). No statistically significant change was noted between pulmonary valve maximum pressure gradients measured prior to rejection episodes and during rejection episodes ($P = 0.55$) or pre-rejection to post-rejection ($P = 0.91$).

Relationship between grade of rejection and semilunar valve function

We then analysed the relationship between the severity of rejection and semilunar valve function. Severity of rejection was stratified using the International Society for Heart and Lung Transplantation 2004 rejection grades. Rejection episodes were classified into episodes with low grade (0R or 1R) or high grade (2R and 3R) based on biopsy results. Patients were categorised by rejection grade (low, high) and insufficiency change during the rejection episode (worsened, improved, or improved). These results are summarised in Table 2. For low-grade rejection episodes, no statistically significant change in aortic valve maximum pressure gradient was detected when comparing pre-rejection to during rejection ($P = 0.53$) and pre-rejection to post-rejection ($P = 0.49$). Similarly, no significant change in pulmonary valve maximum pressure gradient for low-grade rejection episodes was detected when comparing pre-rejection to during rejection ($P = 0.79$) and pre-rejection to post-rejection ($P = 0.79$). For high-grade rejection episodes, no statistically significant change in aortic valve maximum pressure gradient was detected between pre-rejection to during rejection ($P = 0.53$) and pre-rejection to post-rejection ($P = 0.49$). Similarly, no significant change in pulmonary valve maximum pressure gradient for high-grade rejection episodes was detected when comparing pre-rejection to during rejection ($P = 0.26$) and pre-rejection to post-rejection ($P = 0.51$). The change in aortic valve and pulmonary valve insufficiency was further stratified into low-grade versus high-grade pathologic results using the same criteria based on biopsy results as above. These results are listed in Table 3. No statistically significant difference in changes of aortic valve insufficiency was seen when comparing low-grade to high-grade episodes from pre-rejection to during rejection ($P = 1.00$) and pre-rejection to post-rejection ($P = 0.22$). No statistically significant difference in changes of pulmonary valve insufficiency was seen when comparing low-grade to high-grade episodes from pre-rejection to during rejection ($P = 1.00$). However, a statistically significant difference in changes of pulmonary valve insufficiency was found when comparing low-grade to high-grade episodes from pre-rejection to post-rejection ($P = 0.02$). Despite this, the post-rejection insufficiency remained trivial or mild, which is clinically insignificant, and no patients developed moderate or severe pulmonary insufficiency post-rejection. Of the three cases that had worsening aortic valve insufficiency during a rejection episode, all occurred during a low-grade rejection episode. No patients had worsening aortic valve insufficiency during high-grade rejection. Of the three cases that had worsening pulmonary valve insufficiency during a rejection episode, all occurred during a low-grade rejection episode. Based on the data collected stratifying changes in semilunar valve insufficiency and maximum pressure gradient mean change into

https://doi.org/10.1017/S104795112200258X Published online by Cambridge University Press

Table 1. Echocardiographic measurements pre-, during, and post-rejection

Variable	Pre-rejection Median (10, 90%)	During rejection Median (10, 90%)	p-value[a]	Post-rejection Median (10, 90%)	p-value[b]
Aortic valve max PG (mmHg)	3.0 (1.9, 5.8)	3.2 (1.9, 5.1)	0.50	3.1 (1.7, 4.8)	0.42
Pulmonary valve max PG (mmHg)	2.7 (1.4, 4.9)	2.4 (1.0, 4.6)	0.55	3.2 (1.6, 4.9)	0.91

Variable	Pre-rejection n (%)	During rejection n (%)	p-value[a]	Post-rejection n (%)	p-value[b]
Aortic valve insufficiency			0.73		0.40
None	27 (87.1)	25 (80.6)		21 (75.0)	
Trivial	4 (12.9)	5 (16.1)		7 (25.0)	
Mild	0 (0.0)	1 (3.2)		0 (0.0)	
Moderate	0 (0.0)	0 (0.0)		0 (0.0)	
Severe	0 (0.0)	0 (0.0)		0 (0.0)	
Pulmonary valve insufficiency			0.40		0.35
None	0 (0.0)	2 (6.5)		1 (3.6)	
Trivial	28 (90.3)	25 (80.6)		22 (78.6)	
Mild	3 (9.7)	4 (12.9)		5 (17.9)	
Moderate	0 (0.0)	0 (0.0)		0 (0.0)	
Severe	0 (0.0)	0 (0.0)		0 (0.0)	

PG, pressure gradient.
[a]Comparison between pre-rejection to during rejection groups.
[b]Comparison between pre-rejection to post-rejection groups.

low-grade versus high-grade rejection episodes, there was no relationship between severity of rejection and changes in semilunar valve function.

Relationship between number of occurrences of rejection episodes and semilunar valve function

We assessed the relationship between number of occurrences of rejection episodes and semilunar valve function. Rejection episodes were stratified into two categories: initial episodes of rejection versus subsequent episodes of rejection. The subsequent episodes of rejection category included all episodes of rejection that occurred after the initial episode (i.e. second, third, or fourth rejection episodes). These results are summarised in Table 4. For first rejection episodes, no statistically significant change in aortic valve maximum pressure gradient was detected when comparing pre-rejection to during rejection ($P = 0.62$) and pre-rejection to post-rejection ($P = 0.83$). Similarly, no significant change in pulmonary valve maximum pressure gradient for first rejection episodes was seen when comparing pre-rejection to during rejection ($P = 0.21$) and pre-rejection to post-rejection ($P = 0.63$). For subsequent rejection episodes, no statistically significant change in aortic valve maximum pressure gradient was detected between pre-rejection to during rejection ($P = 0.12$) and pre-rejection to post-rejection ($P = 0.37$). Similarly, no significant change in pulmonary valve maximum pressure gradient for subsequent rejection episodes was detected when comparing pre-rejection to during rejection ($P = 0.48$) and pre-rejection to post-rejection ($P = 0.62$). The change in aortic valve and pulmonary valve insufficiency was also stratified into two categories: initial episodes of rejection versus those with two or more rejection episodes. These results are summarised in Table 5. No statistically significant difference in changes of aortic valve insufficiency was seen when comparing first to subsequent episodes from pre-rejection to during rejection ($P = 0.77$) and pre-rejection to post-rejection ($P = 1.00$). Similarly, no statistically significant difference in changes of pulmonary valve insufficiency was seen when comparing first to subsequent episodes from pre-rejection to during rejection ($P = 0.58$) and pre-rejection to post-rejection ($P = 0.46$). Of the three episodes of worsening aortic valve insufficiency, two episodes occurred during the first rejection episode and one during a non-first rejection episode. Of the three episodes of worsening pulmonary valve insufficiency, one episode occurred during the first rejection and two occurred during a subsequent rejection episode. These findings suggest the frequency of rejection episodes does not have an effect on the semilunar valve function.

Discussion

Heart valve transplantation is a potential novel treatment for young children with unrepairable severe heart valve disease[4]. The transplanted valve could potentially grow with the patient similar to growth of pulmonary autografts and paediatric heart transplants, and thus, potentially eliminate the need for serial mechanical or bioprosthetic valve replacements during childhood to accommodate growth and valve degeneration[10,11]. Heart valve transplants differ from homografts by measures taken to maintain viability of the donor cells in the valve replacement, namely ABO

https://doi.org/10.1017/S104795112200258X Published online by Cambridge University Press

Table 2. Comparison of aortic and pulmonary valve maximum pressure gradients pre-, during, and post-rejection between rejection episodes with low pathologic grades and episodes with high pathologic grades

	Low pathologic grade[a]				
	Pre-rejection	During rejection		Post-rejection	
Variable	Median (10, 90%)	Median (10, 90%)	p-value[b]	Median (10, 90%)	p-value[c]
Aortic valve max PG (mmHg)	2.8 (1.9, 6.7)	3.0 (1.7, 4.9)	0.53	2.7 (1.4, 4.9)	0.49
Pulmonary valve max PG (mmHg)	2.4 (1.5, 4.7)	2.2 (0.9, 4.5)	0.26	3.1 (1.7, 4.7)	0.51
	High pathologic grade[d]				
	Pre-rejection	During rejection		Post-rejection	
Variable	Median (10, 90%)	Median (10, 90%)	p-value[b]	Median (10, 90%)	p-value[c]
Aortic valve max PG (mmHg)	3.1 (1.9, 5.3)	3.4 (2.6, 4.7)	1.00	3.2 (2.6, 4.7)	0.79
Pulmonary valve max PG (mmHg)	3.7 (2.0, 6.0)	4.6 (2.3, 6.5)	0.79	4.3 (1.6, 4.8)	0.79

PG, pressure gradient.
[a]Rejection episodes were classified as low pathologic grade if myocardial biopsies taken during rejection were classified as either ISHLT 0R or 1R.
[b]Comparison between pre-rejection to during rejection groups.
[c]Comparison between pre-rejection to post-rejection groups.
[d]Rejection episodes were classified as high pathologic grade if myocardial biopsies taken during rejection were classified as either ISHLT 2R or 3R.

Table 3. Comparison of changes in aortic and pulmonary valve insufficiency categories during and after rejection between patients experiencing a first rejection episode and patients experiencing a subsequent rejection episode

	Pre-rejection to *during rejection*		
	Low pathologic grade[a]	High pathologic grade[b]	
Variable	n (%)	n (%)	p-value
Aortic valve insufficiency			1.00
No change	22 (84.6)	5 (100.0)	
Worsened	3 (11.5)	0 (0.0)	
Improved	1 (3.8)	0 (0.0)	
Pulmonary valve insufficiency			1.00
No change	19 (73.1)	5 (100.0)	
Worsened	3 (11.5)	0 (0.0)	
Improved	4 (15.4)	0 (0.0)	
	Pre-rejection to *post-rejection*		
	Low pathologic grade	High pathologic grade	
Variable	n (%)	n (%)	p-value
Aortic valve insufficiency			0.22
No change	17 (73.9)	4 (80.0)	
Worsened	5 (21.7)	0 (0.0)	
Improved	1 (4.3)	1 (20.0)	
Pulmonary valve insufficiency			0.02
No change	19 (82.6)	2 (40.0)	
Worsened	1 (4.3)	3 (60.0)	
Improved	3 (13.0)	0 (0.0)	

[a]Rejection episodes were classified as low pathologic grade if myocardial biopsies taken during rejection were classified as either ISHLT 0R or 1R.
[b]Rejection episodes were classified as high pathologic grade if myocardial biopsies taken during rejection were classified as either ISHLT 2R or 3R.

Table 4. Comparison of aortic and pulmonary valve gradients pre-, during, and post-rejection between patients experiencing a first rejection episode and patients experiencing a subsequent rejection episode

	1st rejection episode				
	Pre-rejection	During rejection		Post-rejection	
Variable	Median (10, 90%)	Median (10, 90%)	p-value[a]	Median (10, 90%)	p-value[b]
Aortic valve max PG (mmHg)	3.1 (2.2, 6.2)	2.5 (1.7, 4.6)	0.62	3.1 (2.1, 4.9)	0.83
Pulmonary valve max PG (mmHg)	3.5 (1.8, 5.2)	2.2 (1.7, 4.5)	0.21	3.3 (1.8, 5.0)	0.63
	≥ 2nd rejection episode				
	Pre-rejection	During rejection		Post-rejection	
Variable	Median (10, 90%)	Median (10, 90%)	p-value[a]	Median (10, 90%)	p-value[b]
Aortic valve max PG (mmHg)	2.5 (1.6, 5.3)	3.3 (2.4, 5.3)	0.12	2.8 (1.1, 4.6)	0.37
Pulmonary valve max PG (mmHg)	2.1 (1.3, 3.8)	2.5 (0.8, 4.7)	0.48	3.1 (1.0, 4.3)	0.62

PG, pressure gradient.
[a]Comparison between pre-rejection to during rejection groups.
[b]Comparison between pre-rejection to post-rejection groups.

Table 5. Comparison of changes in aortic and pulmonary valve insufficiency during and after rejection between patients experiencing a first rejection episode and patients experiencing a subsequent rejection episode

	Pre-rejection to *during rejection*		
	1st rejection episode	≥ 2nd rejection episode	
Variable	n (%)	n (%)	p-value
Aortic valve insufficiency			0.77
No change	15 (88.2)	12 (85.7)	
Worsened	2 (11.8)	1 (7.1)	
Improved	0 (0.0)	1 (7.1)	
Pulmonary valve insufficiency			0.58
No change	13 (76.5)	11 (78.6)	
Worsened	1 (5.9)	2 (14.3)	
Improved	3 (17.6)	1 (7.1)	
	Pre-rejection to *post-rejection*		
	1st rejection episode	≥ 2nd rejection episode	
Variable	n (%)	n (%)	p-value
Aortic valve insufficiency			1.00
No change	11 (73.3)	10 (76.9)	
Worsened	3 (20.0)	2 (15.4)	
Improved	1 (6.7)	1 (7.7)	
Pulmonary valve insufficiency			0.46
No change	12 (80.0)	9 (69.2)	
Worsened	1 (6.7)	3 (23.1)	
Improved	2 (13.3)	1 (7.7)	

matching the donor, controlling the ischaemic injury to the graft, and immune suppression of the recipient similar to orthotopic heart transplants. Similar to a pulmonary autograft, another potential benefit of heart valve transplantation is the freedom from anticoagulation therapy and potential bleeding risks that are associated with mechanical valves[12]. Transplanted valves could be harvested from donor hearts that are unable to be utilised for orthotopic heart transplant, which is currently the case for

https://doi.org/10.1017/S104795112200258X Published online by Cambridge University Press

approximately one-third of potential donor hearts from children less than 2 years of age. Another potential option could be harvesting donor valves from hearts that are being removed from a recipient patient for a conventional heart transplant, such as a dilated cardiomyopathy patient with normally functioning semilunar valves. However, it is unclear if these transplanted valves would be at risk for rejection and how a rejection of a heart valve transplant would affect its function. Rejection of conventional heart transplants primarily affects ventricular function[13]. Ventricular dilation and papillary muscle dysfunction muscle dysfunction may also result in incompetence of the atrioventricular valves.

In this study, we confirmed our hypothesis that rejection of heart transplants in children has no significant effect on semilunar heart valve function based on echocardiographic imaging. The amount of aortic valve and pulmonary valve insufficiency did not change significantly during or 3 months following a rejection episode when compared to data collected prior to the rejection episode. Similarly, the maximum pressure gradient across both the aortic and pulmonary valve did not have a significant change between the measurements obtained prior to the rejection episode and those obtained during or 3 months following a rejection episode. Additionally, neither severity of the rejection episode nor number of rejection episodes appear to have a significant effect on semilunar valve function. These data suggest that semilunar valves are not significantly affected by rejection.

Patients undergoing potential heart valve transplantation would likely need some form of chronic immunosuppression. However, the amount or duration of immunosuppression is unclear as the immunobiology of heart valve transplants may differ from conventional heart transplants. For instance, heart valves do not contain blood vessels and rejection of conventional heart transplants primarily occurs at the ventricular microvasculature via humoral or cell-mediated response[14]. The absence of vasculature may explain why semilunar heart valve function is not affected by rejection. Although the rejection did not significantly affect semilunar heart valve function in our conventional heart transplant recipients, we suspect that valve transplants may still be at risk for rejection. Heart valves contain valvular endothelial cells as well as valvular interstitial cells which are responsible for maintenance of the non-cellular components of the valve and leaflet repair in response to injury[15]. The supporting cuff of tissue that would be included in a heart valve transplant also contains myocytes and other life cells. We anticipate that the heart valve transplant, with appropriate immunosuppression, will contain viable cells that offer advantages over cryopreserved-allograft such as somatic growth and self-repair similar to what has been observed in pulmonary valve autografts following the Ross procedure. It is possible that we did not observe semilunar valve dysfunction in our heart transplant recipients because rejection was treated with augmented immunosuppression once recognised. Nonetheless, our data showing that semilunar valve function is not affected by treated episodes of rejection are encouraging.

Given the known and important side effects of immunosuppression, further work is needed to understand the risk-benefit ratio for using it in the context of heart valve transplantation. While this study provides partial foundational evidence for the preservation of heart valve function during rejection, further studies such as animal models are needed to demonstrate that the transplanted valves will grow and not undergo rejection in vivo. Algorithms and protocols would be needed to identify and manage potential recipients and the allocation of donor hearts. This study is one component of a larger programmatic research initiative at our centre to explore the feasibility of heart valve transplantation in infants and young children.

Limitations

This study was limited by retrospective design and single centre data collection. Data collected by echocardiogram are reliant on subjective classification of semilunar valve insufficiency and subject to bias of the echocardiogram reader. Low patient number and low number of total rejection episodes were another limiting factor and the confidence in our findings could be strengthened with a larger study.

Conclusion

While rejection episodes after paediatric heart transplantation often affect ventricular function and can potentially affect atrioventricular valve function, semilunar valve function remains intact. This study showed no difference in semilunar valve function during or following a rejection episode based on echocardiographic imaging. Therefore, it is possible that changes of heart valve transplant function during rejection, if any, would likely be slow and predictable. These findings provide partial foundational evidence to justify future research that will determine whether heart valve transplantation may deliver growing heart valve replacements for children.

Acknowledgements. Figures created with BioRender.com.

Financial support. This work was supported in part by a Darby Children's Research Institute Pilot Grant. T.K.R. is also funded by the American Association for Thoracic Surgery Foundation, the Brett Boyer Foundation, the Saving tiny Hearts Society, the Emerson Rose Heart Foundation, and the South Carolina Clinical & Translational Research (SCTR) Institute NIH/NCATS Grant Number UL1 TR001450.

Conflicts of interest. None.

References

1. Henaine R, Roubertie F, Vergnat M, Ninet J. Valve replacement in children: a challenge for a whole life. Arch Cardiovasc Dis 2012; 105: 517–528.
2. Jacobs JP, Mavroudis C, Quintessenza JA, et al. Reoperations for pediatric and congenital heart disease: an analysis of the Society of Thoracic Surgeons (STS) congenital heart surgery database. In Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. vol. 17, 2014: 2–8.
3. Fioretta ES, Motta SE, Lintas V, et al. Next-generation tissue-engineered heart valves with repair, remodeling, and regeneration capacity. Nat Rev Cardiol 2021; 18: 92–116.
4. Rajab TK. Evidence-based surgical hypothesis: partial heart transplantation can deliver growing valve implants for congenital cardiac surgery. Surgery 2021; 169: 983–985.
5. Bernstein D, Kolla S, Miner M, et al. Cardiac growth after pediatric heart transplantation. Circulation 1992; 85: 1433–1439.
6. Delmo Walter EM, Huebler M, Stamm C, et al. Adaptive growth and remodeling of transplanted hearts in children. Eur J Cardiothorac Surg 2011; 40: 1374–1382; discussion 1382-3.
7. Rajab TK, Zorrilla-Vaca A, Kavarana MN, et al. Ross operation in neonates: a meta-analysis. Ann Thorac Surg 2022; 113: 192–198.
8. Russo LM, Webber SA. Pediatric heart transplantation: immunosuppression and its complications. Curr Opin Cardiol 2004; 19: 104–109.
9. Stewart S, Winters GL, Fishbein MC, et al. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. J Heart Lung Transplant 2005; 24: 1710–1720.

https://doi.org/10.1017/S104795112200258X Published online by Cambridge University Press

10. Fernandez-Carbonell A, Rodriguez-Guerrero E, Merino-Cejas C, et al. Predictive factors for pulmonary homograft dysfunction after ross surgery: a 20-year follow-up. Ann Thorac Sug 2021; 111: 1338–1344.
11. Delmo Walter EM, Huebler M, Stamm C, et al. Adaptive growth and remodeling of tranplanted hearts in children. Eur J Cardiothoracic Surg 2011; 40: 1374–1381.
12. Said SM. The Ross-Konno procedure for congenital aortic stenosis. Ann Cardiothorac Surg 2021; 10: 527–537.
13. Moran AM, Lipshultz SE, Rifai N, et al. Non-invasive assessment of rejection in pediatric transplant patients: serologic and echocardiographic prediction of biopsy-proven myocardial rejection. J Heart Lung Transplant 2000; 19: 756–764.
14. Erdogan I, Varan B, Sezgin A, et al. Rituximab therapy for rejection in pediatric heart transplant. Exp Clin Transplant 2018; 16: 199–203.
15. Schoen FJ. Cardiac valves and valvular pathology: update on function, disease, repair, and replacement. Cardiovasc Pathol 2005; 14: 189–194.