Pediatric Transplantation

WILEY

ORIGINAL ARTICLE OPEN ACCESS

Semilunar Valve Function After Rejection in Heart Transplant Recipients: Implications for Partial Heart Transplantation

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Received: 15 April 2025 | **Revised:** 15 April 2025 | **Accepted:** 13 June 2025

Funding: The authors received no specific funding for this work.

Keywords: aortic valve | heart transplant | immunosuppression | partial heart transplantation | pediatric | pulmonary valve | semilunar valve

ABSTRACT

Background: Partial heart transplantation (PHT) is a promising procedure for pediatric patients with irreparable semilunar valve disease. Current immunosuppression regimens mirror orthotopic heart transplant (OHT) protocols. However, semilunar valves may have immune privilege, making true immunosuppressive requirements unclear. This study examines the effect of rejection on semilunar valves in OHT to inform immunosuppression strategies for PHT.

Methods: We conducted a single-center retrospective case–control study of pediatric OHT recipients from 2008 to 2023. Patients were grouped by the presence or absence of rejection episodes, with further stratification by rejection severity. Semilunar valve function was assessed via echocardiography at baseline, during, and after rejection episodes. Subgroup analysis was performed based on rejection severity and age at transplant (< 1 year of age).

Results: Of 113 eligible OHT recipients, 57 had ≥ 1 rejection episodes (32 high-grade). Baseline valve function was comparable between rejection and non-rejection groups. After a 3.8-year median follow-up, there were no significant differences in aortic or pulmonary valve gradients or in the prevalence of clinically significant regurgitation between groups. Paired analysis during rejection demonstrated no change in valve function compared to pre-rejection assessment. Similar findings were observed in infants transplanted < 1 year of age.

Conclusions: Over a median follow up of nearly 4 years, semilunar valve function in pediatric OHT recipients remained clinically unaffected by rejection, even in high-grade cases and among younger patients. These findings support the hypothesis of semilunar valve immune privilege and suggest that intensive immunosuppression may not be necessary to preserve valve function after PHT.

Abbreviations: ACR, acute cellular rejection; AMR, antibody mediated rejection; AR, aortic regurgitation; AS, aortic stenosis; cPRA, calculated panel reactive antibodies; DSA, donor specific antibodies; HLA, human leukocyte antigen; ISHLT, international society for heart and lung transplantation; OHT, orthotopic heart transplantation; PHT, partial heart transplantation; PR, pulmonary regurgitation; PS, pulmonary stenosis.

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1 | Introduction

Congenital heart disease involving semilunar valves presents significant clinical challenges in pediatric patients. Repair options are limited, and valve replacement procedures carry substantial morbidity and mortality risk, particularly among neonates and infants [1–3]. Additionally, appropriately sized bioprosthetic and mechanical valves for young children are often unavailable, frequently restricting choices to preserved cadaveric homografts [4]. Importantly, none of these available replacement valves possess viable cells required for valve growth and self-repair [4].

Semilunar valves must maintain unidirectional blood flow without significant obstruction or regurgitation. Native valves achieve this by continuously growing and undergoing self-repair throughout a patient's lifespan [5]. In contrast, current replacement options lack these essential biological properties, inevitably leading to stenosis or regurgitation over time [6, 7]. Consequently, pediatric patients receiving valve replacements often require repeated surgical interventions as they outgrow their valves or as valve dysfunction progresses [8].

Partial heart transplantation (PHT) is an emerging surgical technique that offers a promising solution to this problem. First described by Rajab in 2021, this surgical procedure replaces irreparable semilunar valves using fresh semilunar allograft tissue procured from an organ donor whose heart is non-utilized for a standard orthotopic heart transplant (OHT) [4]. The rationale for this procedure stems from observations that autograft valve replacements, such as those performed during the Ross procedure, and semilunar valves in transplanted hearts demonstrate sustained functionality and growth in pediatric patients [9, 10].

To date, there have been 20 reported partial heart transplants with clinical management largely mirroring standard OHT with respect to blood group and human leukocyte antigen matching, donor ischemic time, and the use of immunosuppression [11–13]. However, there is evidence suggesting semilunar valves possess some level of immunologic privilege which may allow reduced immunosuppression without compromising valve function and growth [14–16]. This is particularly important given the well-documented side effects associated with chronic immunosuppressive therapy, including opportunistic infections, renal injury, and post-transplant lymphoproliferative disorder [17, 18].

Previous studies have shown that long-term failure of pediatric OHT grafts is primarily due to myocardial dysfunction and coronary artery vasculopathy [19, 20], with limited evidence suggesting semilunar valve dysfunction contributes to graft failure. Valente et al. reported the post-mortem gross, histologic, and immunohistochemistry findings of 37 heart transplant recipients and found the aortic valves maintained tissue viability and preserved leaflet integrity with no valve tears or perforations, even in the presence of myocardial rejection [21]. Similarly, Mitchel et al. examined 16 aortic valves explanted from OHT recipients and found the aortic valves maintained normal histologic structure with no or mild inflammatory infiltrates even in patients who died of acute rejection [22]. These findings suggest immune activation has minimal impact on the structural integrity of transplanted semilunar valves; however, neither study specifically addressed long-term valve function and hemodynamic consequences after rejection episodes.

Other studies have demonstrated that implanted cryopreserved aortic and pulmonary allografts are recognized by the recipient's immune system and trigger immune activation, resulting in the production of anti-donor human leukocyte antigen (HLA) class I and II antibodies [23, 24]. Retrospective analyses have further linked histocompatibility mismatches between recipient and donor to being associated with accelerated allograft dysfunction [25]. However, studies evaluating the function of semilunar valves in OHT recipients are lacking. Unlike standard allograft valves, semilunar valves in OHT have not been exposed to cryopreservation and thus retain cellular integrity, which may confer growth and repair potential and reduce susceptibility to immune-mediated damage.

To better understand the clinical impact of immune system activation on semilunar valve function after transplantation, we conducted a single-center retrospective case–control study comparing OHT recipients who experienced rejection episodes with those who did not. We hypothesized that there would be no meaningful differences in valve function between these groups. Clarifying this relationship will inform future immunosuppression strategies following partial heart transplantation.

2 | Methods

This study was approved by the Institutional Review Board of the University of Virginia Medical Center. Due to its retrospective design, the requirement for informed consent was waived. Patients < 18 years of age who underwent an OHT at our institution between January 1, 2008, and December 31, 2023, were included. Patients who did not survive to 3 months post-transplant or whose graft exhibited significant structural disease at the time of transplantation were excluded. The determination of significant structural disease was performed on a case-by-case basis and excluded minor abnormalities, such as atrial level shunts or anastomotic gradients.

Control subjects were defined as patients without any episodes of rejection during the study period, while the rejection group included patients with ≥ 1 episode of rejection. Acute cellular rejection (ACR) was classified according to the 2004 International Society for Heart and Lung Transplantation (ISHLT) grading system [26], and antibody-mediated rejection (AMR) was classified according to the 2013 ISHLT grading system [27]. The rejection group was further stratified into high-grade and low-grade rejection categories. High-grade rejection was defined as ACR Grade 2R or 3R, pathologic AMR of any grade (pAMR 1–3), or clinical AMR (cAMR) characterized by graft dysfunction in the presence of donor-specific antibodies (DSAs). Low-grade rejection was defined as ACR Grade 1R that was treated due to graft dysfunction or institutional protocol.

We conducted a chart review of each transplant recipient to collect baseline demographic information at the time of transplantation. Recipients with documented rejection were identified based on pathology biopsy reports. Clinical AMR events were

similarly identified through chart review. Echocardiographic data were extracted from final echocardiogram reports. In cases where specific data elements were not explicitly reported, direct image review and data collection were performed by a single investigator (SD). Echocardiographic data were collected for all patients at post-transplant baseline and the most recent follow-up. Regurgitation severity was categorized as none, trivial, mild, moderate, or severe, while stenosis was quantified using peak instantaneous pressure gradients across the semilunar valves. Myocardial function was evaluated using fractional shortening and ejection fraction measurements obtained from echocardiographic studies. The baseline echocardiogram was defined as the earliest complete transthoracic echocardiogram performed within 1 week of transplantation. Echocardiograms performed while a patient was on mechanical circulatory support and/or those deemed incomplete studies were excluded.

For individuals who experienced rejection, echocardiographic data were collected at two additional timepoints: most recent echocardiogram preceding the first documented rejection episode and during the acute rejection episode. This was possible since all patients receive an echocardiogram after all biopsies. Each patient's highest-grade rejection classification and total number of rejection episodes were also documented for subgroup analysis. For paired analysis comparing valve function preceding and during acute rejection episodes, we utilized the earliest rejection episode for those with multiple rejection events.

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and GAUSS 24.0 (Aptech Systems, Maple Valley, WA). Categorical variables were compared using the Chi-squared test, while continuous variables were analyzed using the Wilcoxon rank-sum test for non-parametric data. Paired data were evaluated using the paired *t*-test for continuous variables and McNemar's test for categorical variables. A p-value of <0.05 was considered statistically significant for all analyses.

3 | Results

There were 118 patients who underwent OHT at our institution between 2008 to 2023. Four patients died before a 3-month follow-up period and were excluded from analysis. One additional patient was excluded because of structural heart disease identified in the graft immediately post-transplant, characterized by dynamic left ventricular outflow tract obstruction that limited analysis of baseline aortic valve function.

Baseline data were compared between the non-rejection and rejection groups (Table 1). The rejection group was older, with a higher proportion of males, and had a larger proportion of individuals with a detectable calculated panel reactive antibody (cPRA) level as compared to the non-rejection group. The groups had similar degrees of semilunar valve stenosis and a similar distribution of semilunar valve regurgitation classification at baseline.

Fifty-seven patients had at least one episode of rejection, of which 32 patients had at least one episode classified as high-grade. There were a total of 87 rejection events with a median time to rejection of 38 days. Among those with rejection, 37 patients had only one episode of rejection, 13 patients had two episodes, five patients had three episodes, one patient had four episodes, and another had five episodes of rejection. Within the high-grade rejection group, 18 (40%) had ISHLT Grade 2R, 3 (5%) had ISHLT Grade 3R, 8 had cAMR (14%), and 3 (5%) had pAMR. Within pAMR, 1 patient had pAMR1, 1 patient had pAMR2, and 1 patient had pAMR3.

The primary outcome comparison of semilunar valve function at the most recent follow-up between these groups is displayed in Table 2. There was not a significant difference in median aortic or pulmonary valve gradient between groups. There was not a significant difference in the severity of aortic regurgitation between groups at follow-up. There was a higher proportion of

TABLE 1 | Demographics and baseline valve function.

	Control $n=56$	Rejection $n=57$	p
Age at transplant (years)	0.8 (0.4–5.2)	6.2 (1.1–14.1)	<0.001
Gender (female)	32 (57%)	17 (30%)	0.010
Congenital heart disease	37 (66%)	29 (51%)	0.101
Number of cardiac surgeries	2 (1.5–3)	2 (1–3)	0.435
Patients with Detectable cPRA %	4 (7%)	12 (21%)	0.034
AS (mmHg)	4.0 (2.4–6.0)	4.0 (3.0–6.0)	0.589
AR			
None	3 (5%)	2 (4%)	0.529
Trivial	1 (2%)	0 (0%)	
Mild	0	0	
Moderate	0	0	
Severe	0	0	
PS (peak gradient) (mmHg)	4.1 (1.6–7.9)	4.1 (2.0–8.2)	0.610
PR			
None	46 (84%)	48 (84%)	0.997
Trivial	6 (11%)	6 (11%)	
Mild	3 (5%)	3 (5%)	
Moderate	0	0	
Severe	0	0	

Note: Data are presented as median (interquartile range) for numeric variables or *n* (%) for categorical variables.
Abbreviations: AR, aortic regurgitation; AS, aortic stenosis; cPRA, calculated panel reactive antibody; PR, pulmonary regurgitation; PS, pulmonary stenosis.

TABLE 2 | Follow up valve function.

	Control $n=56$	Rejection $n=57$	p	High-grade rejection $n=32$	p
Follow up (years)	3.56 (1.01–5.98)	3.84 (1.88–5.84)	0.928	2.91 (1.30–5.69)	0.667
AS (mmHg)	4.0 (3.0–5.0)	4.6 (4.0–5.0)	0.081	4.0 (4.0–5.2)	0.232
AR					
None	50 (89%)	51 (89%)	0.472	28 (88%)	0.700
Trivial	3 (5%)	5 (9%)		3 (9%)	
Mild	3 (5%)	1 (2%)		1 (3%)	
Moderate	0	0		0	
Severe	0	0		0	
PS (mmHg)	4.0 (3.0–5.5)	4.5 (3–5.3)	0.746	4.1 (3.0–5.3)	0.758
PR					
None	36 (64%)	19 (33%)	0.003	12 (38%)	0.029
Trivial	17 (30%)	35 (61%)		19 (59%)	
Mild	3 (5%)	3 (5%)		1 (3%)	
Moderate	0	0		0	
Severe	0	0		0	

Note: Data are presented as median (interquartile range) for numeric variables or *n* (%) for categorical variables.
Abbreviations: AR, aortic regurgitation; AS, aortic stenosis; PR, pulmonary regurgitation; PS, pulmonary stenosis.

patients with trivial pulmonary insufficiency in the rejection group. The groups had equivalent rates of mild pulmonary regurgitation, and there were no patients in either group who had moderate or severe pulmonary regurgitation.

Further subgroup analysis compared valve function at the most recent follow up between the non-rejection and high-grade rejection groups (Table 2). There were no significant differences in aortic valve stenosis, aortic regurgitation, or pulmonary valve stenosis. Similar to the larger rejection cohort, the high-grade rejection subgroup demonstrated a higher proportion of trivial pulmonary regurgitation. There was a lower proportion of mild pulmonary regurgitation in the high-grade rejection group, and neither group demonstrated moderate or severe semilunar valve regurgitation.

In the subgroup of seven patients who had three or more rejection episodes, five had trivial pulmonary regurgitation at follow-up, and one patient with five rejection episodes had mild aortic regurgitation. None of these patients experienced changes in their pulmonary or aortic valve gradients.

We further analyzed the rejection group through paired analysis comparing patients' valve function immediately preceding rejection to during rejection (Table 3). Patients experienced a minimal decrease in aortic valve gradient during rejection. There was no significant change in pulmonary valve gradient or aortic valve regurgitation before vs. during rejection. There was a significant increase in the proportion of patients with trivial pulmonary regurgitation during rejection compared to their pre-rejection baseline (33% versus 15%, $p=0.004$).

TABLE 3 | Paired analysis of valve function.

	Preceding rejection	During rejection	p
AS (mmHg)	4.0 (3.0–6.0)	3.0 (3.0–5.0)	0.001
AR			
None	50 (93%)	51 (94%)	0.564
Trivial	4 (7%)	3 (6%)	
Mild	0	0	
PS (mmHg)	4.7 (2.7–8.0)	4.0 (2.0–7.8)	0.148
PR			
None	46 (85%)	36 (67%)	0.004
Trivial	8 (15%)	18 (33%)	
Mild	0	0	

Note: Data are presented as median (interquartile range) for numeric variables or *n* (%) for categorical variables.
Abbreviations: AR, aortic regurgitation; AS, aortic stenosis; PR, pulmonary regurgitation; PS, pulmonary stenosis.

The primary outcome comparison was repeated on a subgroup of patients who were transplanted at less than 1 year of age (Table 4). The median time to rejection was 67 days (IQR 34–374). There was not a significant difference in aortic valve stenosis, aortic regurgitation, or pulmonary valve stenosis between groups. Similar to the larger cohort, pulmonary regurgitation classification distribution differed between groups at follow-up, with a larger proportion of infants with rejection

TABLE 4 | Subgroup analysis of patients transplanted in infancy.

	Control $n=32$	Rejection $n=14$	p
Follow up (years)	3.90 (1.02–5.90)	3.83 (2.05–7.84)	0.726
AS (mmHg)	4.0 (3.0–5.0)	4.5 (4.0–6.0)	0.178
AR			
None	28 (88%)	12 (86%)	0.450
Trivial	2 (6%)	2 (14%)	
Mild	2 (6%)	0 (0%)	
PS (mmHg)	4.4 (3.0–6.2)	4.6 (4.0–5.3)	0.998
PR			
None	25 (78%)	5 (36%)	0.006
Trivial	7 (22%)	9 (64%)	
Mild	0	0	

Note: Data are presented as median (interquartile range) for numeric variables or *n* (%) for categorical variables.
Abbreviations: AR, aortic regurgitation; AS, aortic stenosis; PR, pulmonary regurgitation; PS, pulmonary stenosis.

experiencing trivial pulmonary regurgitation. However, no patients in either group experienced mild or greater pulmonary regurgitation.

4 | Discussion

This study demonstrates that semilunar valve function remains largely unaffected by graft rejection following OHT. Over a median follow-up period of nearly 4 years, stable valve function was observed across all patient groups, including those experiencing high-grade rejection and multiple rejection episodes. Importantly, no patients exhibited clinically significant semilunar valve dysfunction during rejection episodes. Furthermore, patients transplanted during infancy, the population with the greatest valvar growth potential, did not demonstrate increased valve gradients after rejection, suggesting the valve annulus grew sufficiently to accommodate increasing cardiac output with somatic growth. This data provides a clinical correlate to previously described histologic findings demonstrating semilunar valves maintain cellular integrity and architecture with minimal immune cell infiltration in heart transplant recipients who experienced rejection episodes [22, 28].

Our results are consistent with findings from McVadon et al. who reported similar outcomes in a smaller cohort of 17 OHT recipients with 31 rejection events after a 3-month follow-up period. However, the study lacked a control group for comparison and included only five patients with ISHLT Grade 2R rejection or higher, limiting its ability to compare against the natural history of valve function after transplantation or stronger immune activation [29]. Our study expands on these findings by assessing a larger cohort size, a higher proportion of high-grade rejection, longer follow-up duration, as well as assessment of infant recipients who are most vulnerable to stunted annular growth.

There are several proposed mechanisms by which semilunar valve allografts maintain function despite immune system activation. These include intrinsic properties of valve tissue such as low antigenicity of valve leaflets, altered immune cell chemotaxis, as well as diminished immune cell response secondary to reduced costimulatory molecules within valvar interstitial cells [15]. Additionally, the physiologic consequences of their anatomical position are another proposed mechanism by which they achieve a relative degree of immune privilege. Semilunar valves are in constant motion with high-pressure blood flow which potentially reduces immune cell chemotaxis and extravasation.

While statistically significant, the increase in the proportion of patients with trivial pulmonary regurgitation does not represent a clinically meaningful change in valve function. Current ISHLT guidelines for the care of transplant recipients do not consider pulmonary valve regurgitation an indication for treatment escalation or rejection management in OHT recipients [30]. Additionally, extrapolation from management guidelines for Tetralogy of Fallot repairs or adult pulmonary valve disease [21, 31], indicates pulmonary regurgitation is not hemodynamically significant unless also accompanied by symptoms, reduced cardiac function, progressive right ventricular enlargement, or an increased risk of arrhythmia, which is not associated with trivial regurgitation [32].

To elucidate the effect of the acute inflammatory state on semilunar valve function, we conducted a paired analysis comparing valve function before and during the first acute rejection episode. This approach mitigates potential confounding effects from rejection treatments on sustained valve dysfunction. Consistent with our primary findings, higher rates of trivial pulmonary regurgitation were observed during acute rejection episodes. However, no cases of mild or greater regurgitation were identified for either semilunar valve.

Current immunosuppression strategies in partial heart transplants are modeled after those used in standard OHTs [12]. However, our study lends support to the growing understanding that semilunar valves may possess a degree of immune privilege. We observed that even years after rejection episodes, these valves continue to function without clinically significant stenosis or regurgitation, suggesting that the intensive immunosuppression regimens required for graft protection in OHT may not be necessary for semilunar valve protection in PHT. Since rejection episodes are typically managed with augmented immunosuppression after detection, we cannot reliably evaluate the impact of prolonged untreated rejection on semilunar valve function. Nevertheless, our analysis during acute rejection periods and long-term follow-up, including in those with multiple rejection episodes, demonstrates these valves remain functional. Given the known risks associated with immunosuppression, a more judicious approach to its use following PHT may be warranted [17]. Future studies assessing PHT outcomes with reduced immunosuppression are essential to determine the optimal medical regimen to protect valve function while minimizing adverse side effects of these medications. This strategy

has the potential to transform care for children with irreparable semilunar valve dysfunction.

5 | Limitations

Our study has limitations inherent to the retrospective design, which introduces the potential for missing or incomplete data. To address this, baseline echocardiographic studies with missing data were excluded, while follow-up studies with incomplete data were individually reviewed to maximize completeness. However, all baseline echocardiographic studies included for baseline assessment were completed within 1 week of transplantation. An additional limitation is the non-blinded nature of the reviewer, which could introduce bias. However, the measurements that were reviewed were quantifiable Doppler gradients and not the more subjective qualitative descriptions of regurgitation. Our institutional practice requires that valve regurgitation be quantified in echocardiogram reports, resulting in minimal missing data for this variable. Valve gradients were less frequently reported, particularly when within normal ranges.

6 | Conclusion

This study provides important insight into the function of semilunar valves following rejection in OHT recipients. Over a median follow-up of nearly 4 years, no patients exhibited clinically significant stenosis or regurgitation. Valve function remained stable even in those with high-grade rejection, multiple rejection episodes, and in infants. These findings support the hypothesis of immune privilege and suggest that less intensive immunosuppression regimens may be adequate after PHT.

Acknowledgments

The authors have nothing to report.

Disclosure

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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