

The Impact and Outcome of Transplant Coronary Artery Disease in a Pediatric Population: A 9-Year Multi-institutional Study

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Background: Transplant coronary artery disease (TCAD) limits survival in heart transplant recipients; however, its incidence in children is unknown. The purpose of this study was to determine the angiographic incidence of TCAD, potential risk factors, and outcomes in a large pediatric cohort.

Methods: From January 1993 to December 1, a total of 1,222 children, aged newborn to 17 years, underwent primary cardiac transplantation at 20 institutions. A total of 2,049 coronary angiograms were performed in 751 patients. All angiograms were graded for coronary disease and results were submitted to the Pediatric Heart Transplant Study database. We analyzed time-related freedom from graded severity and events from coronary disease, and we examined risk factors.

Results: The incidence of angiographic abnormalities at 1, 3, and 5 years was 2%, 9%, and 17%, respectively; however, moderate-to-severe disease occurred in only 6% at 5 years, compared with 15% in the adult transplant database ($p < 0.0001$). The major risk factors were older recipient and donor age. Two or more episodes of rejection in the 1st year correlated with coronary disease ($p = 0.05$). Overall freedom from graft loss caused by primary TCAD was 99%, 96%, and 91% at 1, 5, and 9 years after heart transplantation, respectively. Death or graft loss occurred within 2 years of diagnosis in patients with severe disease; 24% of patients with any coronary disease died within 2 years.

Conclusions: The incidence of TCAD in children is smaller than the incidence in adults, but increases with age. Graft loss is infrequent in children; however, severe coronary disease correlates with poor prognosis. *J Heart Lung Transplant* 2005;24:645–51. Copyright © 2005 by the International Society for Heart and Lung Transplantation.

Transplant coronary artery disease (TCAD) in the allograft limits survival in adult heart recipients as well as in children.^{1–3} In adults, risk factors have been identified and include immune and non-immune factors.⁴ Angiography remains the gold standard for detection, and in a large multicenter adult study of the Cardiac Transplant Research Database (CTRD), the risk factors for TCAD were older donor age, donor male sex, and donor hypertension; recipient risk factors included male sex and black race.⁵

Transplant coronary artery disease has been reported in pediatric recipients in survey and autopsy series; however, the angiographic incidence of TCAD in children has not been established, especially in a large population. Furthermore, risk factors for the development of TCAD in children have not been defined and may be different from adult risk factors, in which much older donors are used for transplantation. The purpose of this study was to determine the angiographic incidence of TCAD and, once detected, to determine the potential risk factors and outcomes in a pediatric heart transplant population.

METHODS

Patient Population

From January 1, 1993, to December 31, 2001, a total of 1,222 patients, aged newborn to 17 years, underwent primary cardiac transplantation at 20 institutions in the Pediatric Heart Transplant Study (PHTS, Appendix A). A total of 2,049 coronary angiograms were performed in 751 patients who had ≥ 1 angiogram; the majority of recipients survived >1 year and form the basis of this analysis. We reviewed all angiograms for the presence of TCAD and graded the presence as none, mild, moderate, or severe. We submitted the results to the

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Table 1. Classification of CAD

CTRD class	Angio lesion
None	Normal
Mild	<50% in any branch segment
Moderate	≥50% in 1 primary vessel or ≥50% in branch of 2 vessels
Severe	≥50% in 2 primary vessels OR ≥50% in branches of all 3 systems OR 50% left main

CAD, coronary artery disease; CTRD, cardiac transplant research database.

PHTS database. Severity of TCAD seen with angiograms was defined by published CTRD criteria, shown in Table 1.⁶ We analyzed time-related freedom from graded severity of TCAD and TCAD events and examined risk factors (Appendix B). Intracoronary ultrasound is not routine at most PHTS centers and was not assessed in this study.

Choice of immunosuppression was left to individual centers; some centers used lympholytic therapy for induction, and others did not. The use of statins for lipid-decreasing effect and the use of anti-hypertensive regimens were individualized for each patient and were not standardized.

Categorization of TCAD

Primary vessel refers to the proximal or mid-33% of the left anterior descending, left circumflex, and dominant or codominant right coronary artery.⁶ Table 1 shows in detail the classification of TCAD. Therefore, the classification as mild, moderate, or severe is based on involvement of the left main, primary vessel stenosis, or branch vessel stenosis, with the class determined by the most severe TCAD reported in each coronary angiogram. An "event" refers to death or retransplantation caused by TCAD.

Indications for Angiograms

The majority of angiograms were performed for routine surveillance (95.5%), and most patients underwent selective coronary angiography (Table 2). Some programs perform angiography yearly, others perform angiography every 2 years, and a few do not perform routine

Table 2. Indication for Angiogram N = 2,049

	n	%
Routine, per protocol	1,956	95.5%
Selective R & L	1,895	92.4%
Evidence of graft dysfunction/CAD	41	2.0%
Symptoms (CHF or angina)	32	1.6%
Prior non-invasive test: CAD	5	0.2%
Other	15	0.7%
Total	2,049	100.0%

CAD, coronary artery disease; CHF, congestive heart failure; L, left; R, right.

Table 3. Age Distribution for Routine Annual Angiograms

	Possible	Actual	
Age at Transplantation	n	n	%
<6 years	1,843	1,140	62%
6–12 years	434	279	64%
>12 years	706	457	65%
Total	2,983	1,876	63%

p value = 0.3.

angiography, thus the difference in number of studies available per patient. We observed no difference in the number of routine angiograms (62%–65%) performed among the age groups of <6 years, 6 to 12 years, or >12 years (Table 3).

Data Collection

Appendix B lists the potential donor and recipient risk factors analyzed. We analyzed the presence and degree of TCAD using the data collection forms that the investigator at each participating center provided and that reflected the results of the coronary angiograms, usually performed at regular intervals as determined by the individual centers. The data collection form also included findings at autopsy, if available, as well as a comment as to whether death or retransplantation were the result of TCAD as a primary or contributing cause.

Statistical Methods

We examined the data using standard descriptive statistics, including means, standard deviations, and standard errors. We compared sub-groups using contingency tables and *t*-tests. Time to disease was characterized by actuarial (Kaplan-Meier) methods and by parametric methods. We identified risk factors for coronary disease by multivariable risk factor, forward, stepwise analysis in the multiphase hazard domain.

All participating centers had approval from their institutional review boards to participate in this study.

RESULTS

Incidence and Development of TCAD

Table 4 lists the percentage of angiograms graded as normal, mild, moderate, or severe TCAD. The majority (92%) showed no TCAD. Table 5 lists grading for the

Table 4. Allograft CAD—All Angiograms

Allograft CAD	n	%
None	1,876	92
Mild	116	6
Moderate	39	2
Severe	18	0.9
Total angios	2,049	100

CAD, coronary artery disease.

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