Improved Detection of Cardiac Allograft Vasculopathy

A Multi-Institutional Analysis of Functional Parameters in Pediatric Heart Transplant Recipients

Steven J. Kindel, MD,* Yuk M. Law, MD, Clifford Chin, MD, Michael Burch, MD, MB CaB, James K. Kirklin, MD, David C. Naftel, PhD, Elizabeth Pruitt, MSPH, Michael P. Carboni, MD, Anna Arens, APN, NP,# Andrew M. Atz, MD,** William J. Dreyer, MD,† William T. Mahle, MD, Elfriede Pahl, MD#

ABSTRACT

BACKGROUND Recent guidelines recommend assessment of systolic function and filling pressures to augment angiographic grading of cardiac allograft vasculopathy (CAV); however, no data exist on the utility of these guidelines.

OBJECTIVES The aims of this study were to evaluate whether the assessment of systolic and diastolic graft function, in addition to angiography, improves recognition of patients at high risk of graft loss and to assess the ability of adult filling-pressure thresholds to discriminate graft dysfunction in pediatric patients.

METHODS This study reviewed Pediatric Heart Transplant Study data from 1993 to 2009. Graft dysfunction was defined as significant systolic dysfunction (ejection fraction [EF] <45%) or the presence of restrictive hemodynamic features. Additional pediatric hemodynamic cutpoints of right atrial pressure (RAP) >12 mm Hg or pulmonary capillary wedge pressure (PCWP) >15 mm Hg were analyzed.

RESULTS In the study, 8,122 angiograms were performed in 3,120 patients, and 70% of patients had at least 1 angiogram. Angiographic incidence of CAV was 5%, 15%, and 28% at 2, 5, and 10 years, respectively, and most disease was mild. The presence of graft dysfunction identified patients at greater risk for graft loss even in children with mild angiographic vasculopathy (p < 0.0001). An RAP >12 mm Hg or a PCWP >15 mm Hg was sufficient to detect patients at high risk of graft loss even with mild angiographic disease.

CONCLUSIONS Patients with only mild angiographic CAV have significantly better outcomes than do patients with moderate or severe disease. The presence of an EF <45%, an RAP >12 mm Hg, or a PCWP >15 mm Hg identifies children at increased risk of graft loss even in the presence of only mild angiographic vasculopathy. (J Am Coll Cardiol 2015;66:547–57) © 2015 by the American College of Cardiology Foundation.

Heart transplantation is a well-established therapy for children with end-stage heart failure. With nearly 30 years of experience and continued improvements in care, 1-year survival is >90% (1). As perioperative and early survival have improved, the need to understand and manage late complications more effectively has become a major focus for practitioners. In fact, much of the improvement seen in graft survival reflects decreased early mortality. When graft survival is evaluated...
CAV = cardiac allograft vasculopathy
EF = ejection fraction
ISHLT = International Society for Heart and Lung Transplantation
PCWP = pulmonary capillary wedge pressure
RAP = right atrial pressure

CAV is a chronic graft complication caused by immune and nonimmune processes (2-4). Earlier studies showed that factors such as donor age, recipient age, human leukocyte antigen (HLA) mismatch, allosensitization, frequent cellular rejection, and rejection with hemodynamic compromise are associated with increased risk of CAV in children (1,5-9). Single-center studies and a large collaborative retrospective analysis of the PHTS (Pediatric Heart Transplant Study) demonstrate that CAV is an important complication with a steady increase in prevalence over time. Rates of angiographically identified disease increase from 5% at 1 year to 15% by 5 years and to as much as 30% by 10 years post-transplant (6). Analysis of outcomes after initial diagnosis of disease have been limited, with registry data demonstrating a 20% to 40% graft loss by 6 to 10 years after discovery (1,6) and very little data reflecting the rate of graft loss stratified by disease severity.

In an attempt to define CAV for clinicians more clearly, the International Society for Heart and Lung Transplantation (ISHLT) released an updated set of nomenclature guidelines in 2010 (9). Important changes in this update included the addition of measures of systolic and diastolic graft function to the angiographic assessment of CAV. These additional metrics are designed to increase sensitivity to microvascular disease and consequent myocardial fibrosis, which cannot be well described by angiography. Although these recommendations were built around adult experience and data (10), the guidelines suggest application to pediatric patients, even though similar data and analyses in children are limited to small, single-center experiences (11,12).

This study sought to evaluate the validity of the ISHLT nomenclature guidelines in a large pediatric patient cohort and to examine the impact of functional assessment added to angiographic grading on the identification of patients at risk for death or retransplantation. We hypothesized that: 1) the addition of assessments of systolic performance by ejection fraction (EF) and diastolic filling by hemodynamic measurement would identify patients with less severe angiographic disease at increased risk for graft loss; and 2) the hemodynamic cutpoints proposed in the guidelines may not be sufficiently sensitive to discriminate graft dysfunction in younger patients. To test these hypotheses, we retrospectively graded the degree of vasculopathy in the patients followed through the PHTS dataset by using a combination of angiographic data, markers of systolic dysfunction, and restrictive filling and compared rates of graft loss with those found using an angiography-alone grading system.

METHODS

DATA COLLECTION. The multicenter PHTS collaborative collects data on heart transplantation from its member sites throughout the United States, Canada, and the United Kingdom. At the time of this analysis, data were contributed by 35 North American transplant centers and 1 U.K. center. Institutional review board approval is required from all member sites before submission of data to the PHTS, and certification of institutional review board approval is kept onsite at the PHTS data collection center. The PHTS collects data on all included patients from the time of their listing through the most recent annual follow-up, including information on patients’ status, transplant, rejection, infection, coronary artery evaluation and revascularization, malignant disease, and death. Data on patients listed for heart transplantation who are <18 years of age are collected by the PHTS, with patients censored when they are removed from listing or on transition to another hospital. For this analysis, all patients who were followed in this pediatric registry and who underwent heart transplantation between January 1993 and December 2009 with at least 1 coronary angiogram reported to the PHTS were included with follow-up through December 31, 2010.

Patient-related variables included initial listing demographic factors, cardiac disease, listing status, and complications, as well as donor characteristics including sex, age, weight, cause of death, and medical history. Data on management, outcomes, and annual follow-up were further examined, including angiographic grading, echocardiographic measures of systolic function through reported EF, invasive hemodynamic measurements, death, and retransplantation.

ANGIOGRAPHIC ANALYSIS. Angiographic data are reported to the PHTS for any patient who has had angiographic examination in the prior year during annual data submission. Information about coronary angiography has been a core data element collected.
since the inception of the PHTS. Although the data forms have evolved over time, they provide specific information about the presence and degree of stenosis in major and minor coronary vessels, the pattern of coronary artery dominance, and whether the lesion appears in the proximal, middle, or distal third of the artery. To determine the grade of CAV in each patient, all submitted angiogram forms were analyzed, and the angiographic criteria were applied according to the most recent ISHLT guidelines (9). In this manner, an angiographic score of CAV-1, CAV-2, or CAV-3 was created for each patient (Table 1).

SYSTOLIC FUNCTION AND HEMODYNAMIC ASSESSMENT. In addition to angiographic data, these forms also include the indication for the study, the EF and method obtained, the presence or absence of segmental wall motion abnormalities, and the type of angiographic injections performed. Although the EF may appear in other areas in the data submission, only those values reported on the angiography form were used in the analysis. Hemodynamic data are reported on the annual status follow-up form for any patient who had a cardiac catheterization procedure in the 12 months before each data submission period, along with an indication of the timing of collection. These data were reviewed and collated along with the angiographic data. All hemodynamic values available and collected within 3 months of the discovery of angiographic disease were included in the analysis, and those values reported more remotely were audited. Echocardiographic measures of diastolic function have not been collected by the PHTS database and therefore were not included in the current analysis.

Any abnormality in systolic function, as assessed by EF, or in diastolic performance, as assessed by right atrial pressure (RAP) or pulmonary capillary wedge pressure (PCWP), was considered a “functional abnormality” for the purpose of analyzing the impact of graft performance on graft survival after a diagnosis of vasculopathy. In accordance with the ISHLT guidelines, any EF <45% was considered a sign of significant systolic dysfunction, an EF of 44% to 35% was considered to represent moderate systolic dysfunction, and an EF <35% indicated severe dysfunction. Hemodynamic cutpoints of RAP >20 mm Hg or PCWP >25 mm Hg were initially assessed as adult markers of restrictive graft hemodynamics. These guidelines were selected on the basis of adult data and therefore may not provide ideal threshold derangements for pediatric patients. To examine this hypothesis, we defined an RAP ≤12 mm Hg and a PCWP ≤15 mm Hg as normal, an RAP of 13 to 20 mm Hg and a PCWP of 16 to 25 mm Hg as moderately elevated, and an RAP >20 mm Hg or a PCWP >25 mm Hg as severely restrictive, on the basis of the findings of 2 single-center pediatric analyses (11,13).

STATISTICAL ANALYSES. Descriptive statistics for continuous variables are presented as mean and range; categorical variables are presented as frequency and percent. The criterion for statistical significance was set at the traditional α = 0.05 level. Various Kaplan-Meier nonparametric curves demonstrating graft survival for patients with each classification of CAV were generated with respect to time to graft loss (death or retransplant) after the first discovery of CAV. Data on freedom from disease represent descriptive analysis over the pool of all follow-up observations with a varying number of time points per patient. Patients are censored from repeat tabulation once discovered with disease of any single grade, but they remain at risk for development of a more severe grade of CAV. Therefore, patients may appear on multiple curves over time. When EF values or hemodynamic values were not available, these patients were audited from those aspects of this study involving functional analysis.

RESULTS

PATIENT POPULATION. Our analysis included 3,120 pediatric heart transplant recipients from 1993 to 2009. Angiography was commonly performed; 2,078 (67%) patients had at least 1 angiogram, and a total of 8,122 angiograms were performed in the study cohort. For patients surviving 2, 5, and 10 years post-transplant, the rate of coronary angiography rose from 61% to 83% to 98%, respectively, with most programs reporting routine assessments annually or every other year. Most of these studies (96%) were done with a reported indication of “routine per protocol,” with

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Angiographic and Functional Nomenclature of CAVa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td>Description</td>
</tr>
<tr>
<td>CAV-0 (not significant)</td>
<td>No detectable angiographic lesion</td>
</tr>
<tr>
<td>CAV-1 (mild)</td>
<td>LM &lt;50%, any primary vessel &lt;70%, or any branch &lt;70%</td>
</tr>
<tr>
<td>CAV-2 (moderate)</td>
<td>LM 50%–70%, a primary vessel ≥70%, or branch ≥70% in branches of 2 systems</td>
</tr>
<tr>
<td>CAV-3 (severe)</td>
<td>LM ≥70%, 2 or more primary vessels ≥70%, or branch stenoses ≥70% in all 3 systems</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Functional Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional upgrading</td>
</tr>
<tr>
<td>Evidence of significant systolic dysfunction (EF &lt;45%)</td>
</tr>
<tr>
<td>Evidence of restrictive hemodynamics or CI &lt;2.1 L/min/m²</td>
</tr>
</tbody>
</table>

*Table representation of the angiographic descriptions of various degrees of CAV by angiography (upper part of table) and functional criteria for upgrading mild or moderate angiographic disease to severe (CAV-3) grading (lower part of table). Primary vessels: proximal and middle one-third of left anterior descending, left circumflex, ramus, and dominant or codominant right coronary artery with posterior descending and posterolateral branches. Branch vessels: distal one-third of any primary vessels or any segment within a large septal perforator, diagonal, and obtuse marginal branches or any portion of a nondominant right coronary artery. If any functional abnormality is present in combination with CAV-1 or CAV-2 angiographic changes, the patient is “upgraded” to CAV-3.

CAV = cardiac allograft vasculopathy; CI = cardiac index; EF = ejection fraction; LM = left main coronary artery.
another 3% done for “symptoms or graft dysfunction.” The remaining 1% of angiograms was performed for reasons including: “noninvasive testing positive for [CAV],” “other concern for [CAV],” “follow-up to prior intervention,” or “as part of a research protocol.”

**ANGIOGRAPHIC DISEASE.** Report of angiographic disease was relatively rare, and most disease was mild. Overall, 7,273 (89.6%) of angiograms showed no significant coronary disease (CAV-0). Angiographic disease was primarily mild (CAV-1; 7.8%) with a very small proportion of moderate (CAV-2; 1.4%) or severe (CAV-3; 1.2%) disease reported. The incidence of any angiographic disease was 2.3%, 13.9%, and 27.5% at 1, 5, and 10 years post-transplant, respectively. The incidence of moderate disease was 0.2%, 2.0%, and 5.4% at 1, 5, and 10 years, respectively, and it was 0.2%, 2.2%, 4.4% for severe disease at 1, 5, and 10 years, respectively (Figure 1A). Angiographic disease was seen significantly more frequently in older children (p < 0.0001), as shown in Figure 1B, in which the groups are stratified by age at time of transplant.

**SYSTOLIC FUNCTION ASSESSMENT.** Left ventricular EF was reported in conjunction with the angiographic data in 56.2% of the 8,122 angiograms performed. Analysis of these follow-up events in which both angiographic data and EF were reported revealed an EF >45% in 96.5% of cases, whereas an EF between 30% and 45% was reported in 3.2%, and only 0.4% showed severe systolic dysfunction with EF <30% (Table 2). A lower EF correlated with more severe angiographic disease (p < 0.0001), in which no adjustment was made for multiple observations. Patients with a normal coronary angiogram (CAV-0) rarely had an EF of <45% (2.8%), whereas patients with severe angiographic disease (CAV-3) had an EF <45% in 16.1% of angiograms (Table 2).

**HEMODYNAMIC ASSESSMENT.** Hemodynamic data were reported for 7,787 of 8,122 (95.9%) angiograms. For 58.0% of angiograms, hemodynamic variables were collected within 3 months of angiography and were therefore included in the following analyses. Using the previously described cutpoints for restrictive physiology, 1.2% of angiograms were associated with abnormal hemodynamic measurements. Of those, 0.7% had severely elevated RAP (>20 mm Hg), and 0.6% had marked elevation of PCWP (>25 mm Hg). Table 3 demonstrates the hemodynamic derangements found in patients in relation to the degree of angiographic disease at first discovery. Using the extended cutpoints of an RAP >12 and PCWP >15, another 3.7% of angiograms coincided with an RAP between 13 and 20 mm Hg, and 5.8% coincided with a PCWP between 16 and 25 mm Hg.

**ASSOCIATION OF DEGREE OF GRAFT DYSFUNCTION WITH RATES OF GRAFT LOSS.** Left ventricular EF showed a significant correlation with graft loss (death or retransplant). Patients with any degree of...
angiographic vasculopathy and an EF <45% had significantly worse graft survival than did patients with an EF >45% (p = 0.0009) (Figure 2A). There was no difference, however, between patients with moderate systolic dysfunction (EF 30% to 44%) and those with severe dysfunction (EF <30%).

Kaplan-Meier analysis of graft loss for patients after the initial diagnosis of any degree of

| TABLE 3 | Association of Hemodynamic Abnormalities With Angiographic Vasculopathy Grade* |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | RAP <12 mm Hg   | RAP 13-20 mm Hg | RAP >20 mm Hg   | PCWP <15 mm Hg  | PCWP 16-25 mm Hg | PCWP >25 mm Hg  |
| CAV-0 (n = 4,306) | 4,160 (96.61)   | 125 (2.90)      | 21 (0.49)       | 4,073 (94.59)   | 220 (5.11)       | 13 (0.30)       |
| CAV-1 (n = 335)  | 294 (87.76)     | 36 (10.75)      | 5 (1.49)        | 283 (84.48)     | 42 (12.54)       | 10 (2.99)       |
| CAV-2 (n = 58)   | 43 (74.14)      | 10 (17.24)      | 5 (8.62)        | 51 (87.93)      | 5 (8.62)         | 2 (3.45)        |
| CAV-3 (n = 15)   | 10 (66.67)      | 3 (20.00)       | 2 (13.33)       | 8 (53.33)       | 7 (40.67)        | 0 (0.00)        |
| Total (n = 4,714)| 4,507 (95.6)    | 174 (3.7)       | 33 (0.7)        | 4,415 (93.6)    | 274 (5.8)        | 25 (0.6)        |

Values are n (%). *N = 4,714 angiograms with hemodynamics reported with 3 months of angiogram (RAP p < 0.0001; PCWP p < 0.0001).

RAP = right atrial pressure; PCWP = pulmonary capillary wedge pressure; other abbreviations as in Table 1.

(A) Graft survival after diagnosis of any cardiac allograft vasculopathy (CAV) by ejection fraction (EF) in patients who received a transplant from 1993 to 2009 (n = 2,204). Association of EF with graft survival after the first discovery of angiographic CAV. (B) Graft survival after diagnosis of any CAV by right atrial pressure (RAP) in patients who received a transplant from 1993 to 2009 (n = 1,887). Association of RAP with graft survival after the first discovery of angiographic CAV. (C) Graft survival after diagnosis of any CAV by pulmonary capillary wedge pressure (PCWP) in patients who received a transplant from 1993 to 2009 (n = 1,887). Association of PCWP with graft survival after the first discovery of angiographic CAV. Time 0 is discovery of disease. Shaded areas are 70% confidence limits. Event: graft loss after diagnosis.
vascularopathy showed that an RAP >12 mm Hg was associated with higher rates of graft loss compared with patients with any degree of angiographic CAV and an RAP ≤12 mm Hg (Figure 2B). Severe RAP elevation (>20 mm Hg) was associated with a further increase in risk of graft loss, especially after year 2 after the first discovery of any CAV. Patients with a PCWP =15 mm Hg had significantly better graft survival over time than did patients with a PCWP of 16 to 25 mm Hg or >25 mm Hg (Figure 2C). Furthermore, those patients with the most severe PCWP elevations had very high early rates of graft loss and significantly worse graft survival compared with the other 2 groups.

**COMPARISON OF ANGIOGRAPHY ALONE WITH ANGIOGRAPHIC AND FUNCTIONAL ASSESSMENT.** Figure 3A is a Kaplan-Meier curve examining rates of graft loss over time after the first discovery of CAV for patients stratified by angiographic findings without considering EF or filling pressures. Patients with mild angiographic changes had the best graft survival, whereas those with moderate or severe angiographic disease had significantly increased graft loss, especially in the first year after discovery (p < 0.0001). One and 5-year graft survival rates, on the basis of degree of angiographic vasculopathy, were approximately 82% and 67% for mild (CAV-1), 65% and 45% for moderate (CAV-2), and 35% and 25% for severe (CAV-3) disease, respectively.

Figure 3B shows graft loss over time from first angiographic discovery of disease with measures of systolic and diastolic function now included in grading. Specifically, those patients with mild (CAV-1) or moderate (CAV-2) angiographic changes and a single functional abnormality are “upgraded” to CAV-3. The patients with an EF >45%, an RAP ≥20 mm Hg, a PCWP ≥25 mm Hg, and only mild angiographic disease had significantly lower rates of graft loss (p < 0.001) than did patients with moderate angiographic disease or severe angiographic disease or those with any degree of angiographic CAV and a single functional abnormality. Additionally, this curve demonstrated that patients with moderate angiographic disease combined with normal systolic function and hemodynamic values have rates of graft loss similar to patients with severe angiographic disease or those with mild or moderate angiographic disease coupled with functional abnormalities.

The Central Illustration shows a Kaplan-Meier curve with the less severe definition of restrictive filling as an RAP >12 mm Hg or a PCWP >15 mm Hg. A similar pattern is shown in which patients with mild angiographic changes, an EF >45%, and normal filling pressures have significantly better graft survival than do patients with more severe angiographic disease or those with mild or moderate coronary changes and a single functional derangement (p < 0.0001). By using these more inclusive hemodynamic cutpoints, graft survival after the first discovery of moderate angiographic disease and an EF >45%, an RAP ≥12 mm Hg, and a PCWP ≤15 mm Hg (CAV-2) again was not significantly different from graft survival in patients with either severe angiographic disease or mild or...
moderate angiographic disease and a single functional abnormality (Central Illustration).

**ANALYSIS OF PATIENTS WITH MILD ANGIOGRAPHIC DISEASE.** As noted earlier, most cases of CAV in children are mild, and as shown in Figures 3A to 3C, patients with mild angiographic disease have lower rates of graft loss than do patients with CAV-2 or CAV-3. To clarify the effects of hemodynamic changes in patients with mild angiographic disease, we performed an additional analysis including only patients with mild angiographic disease. In Figure 4, Kaplan-Meier survival curves demonstrate the effect of any abnormal functional parameter on patients with mild angiographic disease. In Figure 4A, the more severe cutpoints of an EF <45%, an RAP >20 mm Hg, or a PCWP >25 mm Hg are used and demonstrate a significant difference in graft survival (p <0.001) highlighted by very early attrition for those patients with any abnormal functional parameter. Figure 4B uses the lower pressure cutpoints of an RAP >12 mm Hg or a PCWP >15 mm Hg or an EF <45% and continues to show a statistically significant (p <0.002) but less dramatic rate of graft loss for patients with CAV-1.

**DISCUSSION**

This large study examined the diagnosis and outcomes in CAV in children, including 3,120 pediatric patients from 36 centers and >8,000 angiographic events. Further, this analysis examined functional and hemodynamic derangements associated with CAV as a risk factor for graft loss in a multicenter cohort and assessed the current ISHLT CAV nomenclature guidelines in a pediatric cohort. The findings...
A discovery of CAV-1.

Abnormal graft function (EF upgrades in patients who received a transplant from 1993 to 2009 (n

Graft survival after diagnosis of mild angiographic coronary allograft vasculopathy

**FIGURE 4** Graft Survival After Diagnosis of CAV-1 and After Diagnosis of CAV-1 Versus CAV-3 Redefined Upgrades

(A) Graft survival after diagnosis of mild angiographic coronary allograft vasculopathy (CAV-1) in patients who received a transplant from 1993 to 2009 (n = 315). Effect of abnormal graft function (EF <45%, RAP ≥20, PCWP ≥25) on graft survival after first discovery of CAV-1. **(B)** Graft survival after diagnosis of CAV-1 versus CAV-3 redefined upgrades in patients who received a transplant from 1993 to 2009 (n = 346). Effect of abnormal graft function (EF <45%, RAP >12, PCWP >15) on graft survival after first discovery of CAV-1. Time 0 is first discovery of mild angiographic disease. **Shaded areas** represent 70% confidence limits. Event: graft loss after diagnosis. Abbreviations as in Figure 2.

disease rising from 2% to nearly 30% over 10 years of graft life. The current data are similar to the rates seen in the PHTS analysis by Pahl et al. (6) from a decade earlier; however, with a greater length of data collection, the current report is able to show a constant hazard ratio out to 15 years of patient follow-up. Although the study is limited to the detection of angiographic disease and cannot fully account for patients with microvascular disease or those with sudden death resulting from coronary lesions, the earlier work by Pahl et al. (6) showed a similar reduced incidence of CAV in children versus adults by comparison with data from the Cardiac Transplant Research Database. As shown in this study and others (1,6,8), an age gradient exists, with the youngest patients having the lowest rate of coronary disease development over time (**Figure 1B**). This finding is likely related to several issues, including the relative naiveté of the infantile immune system leading to increased graft accommodation, younger age of donors, and less frequent rejection (and specifically, rejection with hemodynamic compromise) in these patients (7,8). Furthermore, children undergoing heart transplant tend to have less obesity, diabetes, hyperlipidemia, and hypertension than do typical adult transplant recipients, thus creating a healthier host environment for graft longevity (2,3).

In addition to seeing disease less frequently, most disease that was discovered was mild, as reported previously (6). The current data, however, now include 3 times as many patients with at least 1 angiogram and significantly more patients with outcomes of death or retransplantation, thus allowing for a more robust analysis of these events. The lack of severe disease is again likely multifactorial, representing the quality of donors (younger age, lack of donor hypertension, diabetes, hyperlipidemia, or coronary disease), the low rates of significant rejection in children after heart transplant, and the otherwise healthy milieu of the pediatric transplant recipient. In addition, the coronary artery changes in these children may be more subtle than in adults, and detection may be challenged by practitioners’ experience, vessel size, and other unknown factors (15-17). The PHTS only recently began collecting graded data for intravascular ultrasound, and the study does not contain data on cardiac computed tomography or cardiac magnetic resonance, which could have offered additional views into the degree of disease. However, these modalities are not routinely used in most pediatric centers at this time and are currently undergoing study as potential adjunctive means to identify CAV. Therefore, the analysis of angiographic findings is quite applicable to current pediatric practice.
Although moderate or severe vasculopathy is uncommon, when it is discovered the outcomes are quite severe. With greater patient numbers than in earlier series, we were able to examine moderate and severe angiographic disease separately, and a striking gradient effect was demonstrated (Figures 3 and 4). Mild CAV suggests a rather benign outcome with survival rates comparable to general outcomes for children after heart transplant. In contrast, moderate angiographic disease alone (without hemodynamic assessment) correlates with a higher rate of graft loss, with 50% of patients dead or undergoing repeat heart transplantation by 2 years and 67% by 5 years after discovery. Severe angiographic disease portends a very poor prognosis; 75% of children experience graft loss within 3 years of the initial diagnosis.

The available data from earlier registry reviews reported graft loss without delineation of disease severity (1) or stratified by angiographic grading (6). The current study aimed to go further and includes functional changes as recommended by the most recent ISHLT guidelines (9). When considering the low rate of moderate or severe angiographic disease seen in children, specifically the lack of high-grade proximal stenosis, investigators have questioned the value of angiographic studies for the assessment of CAV in children (15,18). Hemodynamic and functional changes are relatively easily obtained markers for small vessel and microvascular vasculopathy that can lead to fibrosis and graft dysfunction before graft loss (19). The revised nomenclature suggested by the ISHLT attempts to capture these interactions and help clinicians to define more clearly the severity of vasculopathy that may not be easily detected by angiography alone.

Although the EF has not been studied directly as a marker of more severe CAV in children, the presence of elevated filling pressures in pediatric heart transplant recipients has been reported before in a few small, single-center studies. More than 2 decades ago, it was demonstrated that in children after heart transplant, a larger rise in filling pressures after a saline bolus was associated with graft dysfunction (20). Law et al. (11) demonstrated an association between elevated filling pressures and the development of CAV. Neither study, however, was formulated to evaluate the effect of hemodynamic changes in patients with angiographic CAV on outcome. In an analysis by Aiyagari et al. (12), looking at single-center data over a 20-year period, the investigators found that elevation of filling pressures with an RAP >10.4 mm Hg or a PCWP >13.7 mm Hg were associated with a higher risk of retransplant or death. Due to the small sample size in their analysis, the investigators reviewed hemodynamic changes in all patients who had at least 1 angiogram (including those with no angiographic CAV), thereby demonstrating that elevation of filling pressures alone is a risk factor for graft loss. By including those without angiographic disease, however, the study was limited in its ability to determine any interaction between the presence and severity of angiographic changes and filling pressures as a marker of more severe vasculopathy.

In the current study, we are able to associate functional derangements with high rates of graft loss and demonstrate that the ISHLT nomenclature guidelines are relevant in children. Figure 4 demonstrates that reclassifying any patient with at least 1 significant functional abnormality to the “severe” or CAV-3 classification does identify an at-risk population. Notably, another effect of this change is to dampen the effect of a diagnosis of “severe” CAV inasmuch as the CAV-3 group outcomes, including patients with functional abnormalities, appear more similar to those observed in angiographic CAV-2. This finding is noteworthy because it may indicate that patients with severe proximal coronary disease (although quite rare in pediatric cohorts) are at particularly high risk of graft loss, whereas those with functional abnormalities and less severe angiographic disease have a slightly more benign outlook. However, these patients remain clearly differentiated from the patients with only mild angiographic changes and continue to have a very high rate of graft loss (nearly 50% by 2 years and 70% by 5 years after disease discovery).

Recognizing that the patients with only mild vasculopathy are by far the most prevalent and have significantly better outcomes, we repeated the analysis and focused on the group with mild angiographic disease, to remove the effects of patients with moderate or severe coronary artery changes. In these patients, the presence of any functional derangement is associated with a greater risk of graft loss. Using the high filling pressure definition of restrictive hemodynamics, the small group of patients with mild angiographic changes and severe filling pressure elevations had very poor outcomes. Nearly 80% of these patients either died or underwent retransplant procedures within 2 years of disease discovery.

When considering the current guidelines in a pediatric patient group, we were concerned that an overly severe definition of restrictive physiology would fail to identify some pediatric patients at risk for early graft loss. In the work by Law et al. (11), the mean RAP and PCWP in children with CAV were 11 mm Hg and 14 mm Hg, respectively, both significantly higher than in matched controls (RAP, 6 mm Hg; PCWP, 8 mm Hg). In the analysis by Aiyagari et al.
(12), using logistic regression, these investigators suggested that an RAP of 10 mm Hg and a PCWP of 12 mm Hg was indicative of CAV and that an RAP >10.4 mm Hg or a PCWP >13.7 mm Hg was associated with a higher rate of graft loss.

To examine pediatric thresholds of restrictive filling, we chose cutpoints in line with those earlier analyses. On the basis of the combined clinical experience of the writing group, we evaluated those patients with an RAP >12 mm Hg or a PCWP >15 mm Hg for increased risk of graft loss. When applying these “pediatric” standards to patients with less severe angiographic disease, a significant difference in outcomes was found compared with patients with mild CAV and normal functional studies. Specifically, subjects with CAV-1 and normal EF, RAP, and PCWP had a graft survival rate of 50% at 10 years after the diagnosis of CAV; the presence of just 1 functional abnormality indicated a 50% risk of graft loss by 3 years. In this manner, the presence of even a single functional change helps identify patients who could be offered more frequent follow-up and potentially changes in therapy to attempt to extend graft survival.

STUDY LIMITATIONS. This study is limited by several factors, as expected in a retrospective analysis of a large database subject to the selection and data collection biases typical of such analyses. There is potential for misreporting of data and mistiming of data entry. In particular, nearly 42% of the patients with angiograms had neither hemodynamic values nor an EF reported within 3 months of angiography, and these missing data are potential confounders of our analysis. Adjudication and blinded review of echocardiograms and angiograms was not possible given the large scope and breadth of patients reviewed. Although echocardiographic parameters are included in the ISHLT definition of restrictive physiology, they are not available through PHTS data collection and therefore could not be assessed in the current review. Additionally, screening protocols are not standardized among centers. This limitation led to some of the missing functional data and potential for bias because small numbers of patients were referred for angiography in response to symptoms or dysfunction. Because of the structure of the PHTS, patients are removed from analysis if they transition to a non-PHTS facility, and this protocol removed some outcomes from the analysis. Finally, the presence of other graft disease such as rejection, nonspecific graft dysfunction, effusion, or valve regurgitation—all of which could skew timing of disease discovery or functional measures—cannot be accounted for in this analysis. However, review of donor characteristics did not reveal an association between a donor death resulting from head trauma and later elevation of filling pressures.

Another key issue in the interpretation of these data is that the management decisions, including immunosuppression, treatments for CAV, and the performance of a repeat transplant procedure, were made solely on the basis of clinical decision making at the various institutions. The decision to offer retransplantation would be expected to be influenced by the severity of angiographic changes, as well as by practitioners’ concerns about hemodynamics. Finally, this study does not indicate that normal hemodynamics should be considered overly reassuring. In patients with moderate or severe angiographic changes even before application of functional assessments, there remains a high rate of graft loss, as recently described in a single-center experience by Hong et al. (21).

CONCLUSIONS

Despite the expected limitations, the current work represents a large analysis of CAV in children after heart transplantation and presents a multicenter assessment of the effect of functional changes in children with CAV on graft survival. CAV is a common long-term complication of heart transplant in children that is detected by angiography in nearly 30% of patients within 10 years of transplant. Most cases of this disease are mild by angiographic standards and, when coupled with normal hemodynamics and normal systolic function by echocardiogram, portend reasonable graft survival. Because of the detailed data collection at the PHTS, we are able to analyze a high level of complexity in the interactions between angiographic and functional disease. Furthermore, the large number of patients, angiograms, and functional assessments allowed for analysis of the cutpoints offered by the ISHLT guidelines. The current study would suggest that pediatric practitioners should consider an RAP >12 mm Hg or a PCWP >15 mm Hg to be a concerning finding in a child after heart transplant.

ACKNOWLEDGMENTS The authors thank the other investigators, the staff, and the statisticians at the University of Alabama at Birmingham and the Pediatric Heart Study Foundation. Special thanks to Margaret Tressler for her involvement in the development of this project.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Steven J. Kindel, Pediatric Cardiology, Cardiac Service Line, Children’s Hospital & Medical Center, 8200 Dodge Street, Omaha, Nebraska 68114. E-mail: skindel@childrensomaha.org.
PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:
Systolic ventricular dysfunction and diastolic ventricular dysfunction, as measured by reduced EF or elevated filling pressures, are important indicators of graft dysfunction and risk for graft failure even when angiographic changes are mild in children after heart transplantation.

TRANSLATIONAL OUTLOOK: Prospective studies of specific surveillance regimens and interventions to prevent the development of CAV should include assessments of ventricular systolic and diastolic function.

REFERENCES


KEY WORDS chronic rejection, coronary artery, graft loss, heart transplant, hemodynamics, vasculopathy