JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER INC.

VOL. 66, NO. 5, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.04.078

EDITORIAL COMMENT

Pediatric Heart Transplant Recipients and Cardiac Allograft Vasculopathy

The Importance of Hemodynamics*

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Cardiac transplantation remains the most durable therapy for patients with American College of Cardiology Foundation/American Heart Association stage D advanced heart failure who have exhausted other options, and it is the therapy associated with the best long-term outcomes. One of the major causes of morbidity and mortality beyond the first year after transplant is cardiac allograft vasculopathy (CAV), the diffuse transplant coronary artery disease unique to cardiac transplant recipients (1-3). Although survival after cardiac transplantation has improved over the past 30 years, this improvement primarily reflects improvements in patient management within the first year after transplant as a result of improved treatment and prevention of rejection and infections. Survival conditional to 1 year post-transplant has not changed in the past 30 years (1). CAV is observed in adult and pediatric patients, but the clinical characteristics, the predictors of clinical outcomes, and the role of the recent International Society of Heart and Lung Transplantation (ISHLT) grading system nomenclature for the severity of CAV for the prognostication of outcomes in pediatric patients have not been well defined (4).

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Earlier reports of the clinical predictors of poor outcomes in pediatric cardiac transplant recipients with CAV, as well as the incidence of CAV and the relative severity of the cases of CAV in pediatric patients, were, with a single exception, small, single-center studies and preceded the publication of the more recent ISHLT CAV guidelines and nomenclature. Therefore, the interpretation of these studies and their applicability to pediatric cardiac transplant recipients are generally unclear (5,6). Kindel et al. (7), participating in the Pediatric Heart Transplant Study, were able to use the data from this large registry of pediatric cardiac transplant recipients to better define the incidence of CAV, its development over time, and the incidence of the degrees of CAV severity, which could now be defined angiographically using the ISHLT CAV grading system. These investigators were also able to incorporate hemodynamic measures as a reflection of the restrictive hemodynamics associated with CAV and as part of the ISHLT definition of CAV and its severity. In this analysis of 8,122 angiograms from 3,120 pediatric cardiac transplant recipients from 35 U.S. and Canadian centers and 1 British center, the conditional incidence of CAV rose from 5% at 2 years post-transplant to 15% at 5 years and 28% at 10 years post-transplant. Of those patients with disease, 77% had CAV-1 (mild disease), 17% had CAV-2 (moderate disease), and only 6% had CAV-3 (severe disease). These results indicate that CAV is less frequent and less severe in pediatric heart transplant recipients than in adults, an observation made in other, smaller studies. What sets the study by Kindel et al. apart from the others and makes it a definitive analysis of CAV in pediatric heart transplant recipients is the very large number of patients studied from multiple centers and the up to 15 years of angiographic and clinical follow-up, providing a more complete picture of the time course of development, frequency of disease, and severity of disease in this patient population. Of particular interest is the application of left ventricular (LV) function defined

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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by LV ejection fraction (LVEF) and hemodynamic data, specifically right atrial pressure (RAP) and pulmonary capillary wedge pressure (PCWP) from this large patient cohort to the determination of clinical outcomes in patients with specific severities of CAV. This approach is logical and accomplishes the functional upgrades noted in the ISHLT CAV nomenclature (which is both angiographic and functional) and defined as LV systolic dysfunction with an LVEF <45% or evidence of restrictive hemodynamics, or both, or a cardiac index <2.1 l/min/m^2. As markers of restrictive hemodynamics, the investigators used an RAP >12 mm Hg or a PCWP >15 mm Hg. Although less elevated and less severe than hemodynamic cutoffs in other studies of pediatric patients, the definition of restrictive hemodynamics made using these values was robust in discriminating patients with worse outcomes, and these markers served as surrogates of the microvascular CAV that likely causes these restrictive hemodynamic features (8–10).

Although patients with CAV had much more favorable outcomes statistically than did those with CAV-2 or CAV-3, the addition of RAP, PCWP, and LVEF allowed the identification of patients with CAV-1 who had graft systolic dysfunction, restrictive hemodynamics, or both, and who had worse clinical outcomes, specifically graft loss, than did patients with CAV-1 and normal graft function and hemodynamics. Graft dysfunction, defined as an LVEF <45%, identified a population with a greater likelihood of graft loss regardless of angiographic evidence of CAV, thus adding credence and validity to this parameter as a predictor of post-transplant outcomes. Interestingly, more severe LV dysfunction with greater reductions in LVEF did not portend worse outcomes than did the presence of an LVEF <45%. This finding suggests that it is the reduction in LVEF as a result of CAV that causes worse outcomes and not the extent of LV dysfunction, thereby differentiating CAV from graft dysfunction in patients who are not transplant recipients in whom the extent of LV dysfunction has implications for survival. Patients with CAV-1 or CAV-2 and a single functional abnormality, such as elevated RAP or PCWP above the threshold defined in this study and described earlier, had significantly worse graft survival than did patients with CAV-1 and no functional abnormalities. Similarly, patients with CAV-1 and any functional abnormality, defined as reduced LVEF <45% or RAP >12 mm Hg or PCWP >15 mm Hg, had significantly worse graft survival than did patients with CAV-1 without any functional abnormalities (i.e., normal left ventricular function and normal right- and left-sided filling pressures).

The implications of these findings are several. One is that the extent of CAV angiographically, albeit important, cannot be used alone to identify patients with CAV and increased risk of graft loss; hemodynamic considerations reflecting the presence of restrictive hemodynamics and graft systolic dysfunction must also be taken into consideration. The extent of systolic dysfunction does not have to be severe but could be called “borderline” in patients who were not heart transplant recipients. In pediatric transplant recipients, an LVEF <45% should trigger concern. Moreover, the absence of functional abnormalities in patients with CAV-1 and CAV-2 may slightly mitigate these patients’ outcomes. These outcomes are still poor, however, confirming the importance of CAV severity in determining outcome. Finally, the study by Kindel et al. (7) provides validation of the ISHLT angiographic and functional nomenclature as a way of stratifying patients with CAV in terms of angiographic severity of CAV with or without functional derangement of the graft (also a manifestation of CAV) into those at greater risk of graft loss and reduced survival. From the work of Kindel et al., it appears that the ISHLT CAV nomenclature allows identification of pediatric patients with poor outcomes from CAV. Two single-center studies found that this is also true in adult cardiac transplant recipients, a finding that is not surprising (11,12).

There are limitations with this study, most of which the investigators addressed. These include the retrospective nature of the study, which analyzes a registry. This approach appears to be the only way that angiographic and functional data from such a large patient cohort could be obtained and analyzed. However, almost 42% of patients had no hemodynamic data at the time of their angiograms. Further, echocardiographic hemodynamic data, which are a part of the ISHLT CAV nomenclature, were not included in the Pediatric Heart Transplant Study database and could not be analyzed; this is an important deficit. Concomitant causes of graft dysfunction, such as acute cellular or antibody-mediated rejection, could not be included in the analysis, so the role of these factors in functional abnormalities and outcomes is unknown. The period of data collection was 1993 to 2009, during which time immunosuppression regimens changed those using cyclosporine and azathioprine as a basis to the more potent tacrolimus-based and mycophenolate mofetil-based regimens; however, these influences could not be assessed through this database, nor could the use of mTOR (mammalian target of rapamycin) inhibitors to try to ameliorate the progression of CAV. Additionally, the effect of changes in immunosuppressive

regimens or the use of medications for heart failure, such as beta blockers, renin-angiotensin-aldosterone antagonists, and diuretic agents, in response to functional abnormalities could not be evaluated. Despite these limitations, the investigators have provided a clearer view of the incidence, progression, and severity of CAV in children, as well as validation of the ISHLT CAV nomenclature stratification of severity of CAV by using the angiographic extent of CAV and functional abnormalities to identify pediatric cardiac transplant recipients at high risk of graft loss and poor survival. These investigators modified the functional abnormalities to be considered and relied on lower RAP and PCWP cutoffs to identify high-risk patients. The question whether these angiographic and functional abnormalities should trigger repeat transplantation or changes in immunosuppression could not be answered.

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KEY WORDS cardiac allograft vasculopathy, heart transplantation, hemodynamics, outcomes, pediatric, restriction