Multimodality Noninvasive Imaging in the Monitoring of Pediatric Heart Transplantation

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Orthotopic heart transplantation is a well-established and effective therapeutic option for children with end-stage heart failure. Multiple modalities, including noninvasive cardiac imaging, cardiac catheterization, angiography, and endomyocardial biopsy, are helpful to monitor these patients for graft dysfunction, rejection, and vasculopathy. Because of morbidities associated with invasive monitoring, noninvasive imaging plays a key role in the surveillance and evaluation of symptoms in pediatric transplant recipients. Echocardiography with or without stress augmentation may provide serial data on systolic and diastolic function, ventricular deformation, and tissue characteristics in children after transplantation. Although not perfectly sensitive or specific, advanced two- and three-dimensional echocardiographic detection of functional changes in cardiac grafts may allow early recognition of allograft rejection. Magnetic resonance imaging has shown promise for characterization of edema and scar and myocardial perfusion reserve, as well as potential application for the detection of microvasculopathic changes in the transplanted heart. Cardiac computed tomography is particularly well suited for the demonstration of coronary artery dimensions and anatomic residual lesions. In combination, these noninvasive imaging techniques help the transplantation cardiologist screen for graft dysfunction, detect critical graft events, and identify situations that require invasive testing of the transplanted heart. Advanced multimodality imaging techniques are likely to increasingly shape the monitoring practices for children following heart transplantation. (J Am Soc Echocardiogr 2017;30:859-70.)

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Heart transplantation is an accepted treatment for end-stage heart failure in children. One-year survival is >90%, with 50% of pediatric patients surviving nearly 17 years after transplantation.[1] Although perioperative survival has improved steadily over time, graft survival is still limited by rejection, infection, cardiac allograft vasculopathy (CAV), posttransplantation lymphoproliferative disease, and medication side effects. Late graft loss is caused primarily by CAV and primary graft dysfunction and less commonly by acute cellular or antibody-mediated rejection.[1,2]

Historically, monitoring for evidence of graft complications has been accomplished via cardiac catheterization with endomyocardial biopsy (EMB) and coronary angiography.[3-5] Because of risk for morbidity and mortality associated with these invasive tests, there is significant interest in noninvasive testing modalities to monitor graft function, vascular changes, graft fibrosis, and for evidence of acute rejection.[6] Most research has focused on standard echocardiographic approaches, including two-dimensional (2D) imaging, M-mode imaging, Doppler, and measures of systolic function, but more recently advanced echocardiographic techniques including Doppler tissue imaging (DTI), deformation imaging, and three-dimensional (3D) echocardiography have been investigated.[7-10] Cardiac magnetic resonance imaging (CMR) has been assessed as a means to better characterize cardiac tissue and provide more refined imaging of the coronary vascular bed.[11] In this review we describe the role of noninvasive imaging techniques in the monitoring and evaluation of the transplant graft in children after heart transplantation.

PERIOPERATIVE AND POSTOPERATIVE IMAGING

Transesophageal Echocardiography

Intraoperative transesophageal echocardiography (TEE) is commonly applied in pediatric heart surgery, including orthotopic heart transplantation. Intraoperative assessment allows the evaluation of graft function

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Abbreviations

2D = Two-dimensional

3D = Three-dimensional

CAV = Cardiac allograft vasculopathy

CMR = Cardiac magnetic resonance imaging

DSE = Dobutamine stress echocardiography

DTI = Doppler tissue imaging

ECV = Extracellular volume

EMB = Endomyocardial biopsy

GLS = Global longitudinal strain

IVUS = Intravascular ultrasound

LGE = Late gadolinium enhancement

LV = Left ventricular

LVEF = Left ventricular ejection fraction

TEE = Transesophageal echocardiography

immediately after implantation and reperfusion, assessment of valve regurgitation, and examination of anastomotic sites.

The most common surgical technique used in pediatric heart transplantation is direct connection of recipient left atrial cuff (including the pulmonary veins) to the donor left atrium and anastomoses at the superior and inferior vena cava, the "bicaval" technique[6] (Figure 1). Obvious suture lines may not be present with the bicaval technique, and the right atrial size appears smaller. The "biatrial" technique with direct anastomosis of donor to recipient right atrial tissue is still performed at some centers, particularly in small children or in the setting of atypical venous anatomy. The biatrial technique results in the appearance of prominent suture lines along the atrial wall, which should not be confused with thrombus. Stenoses at the supravalvar pulmonary and supravalvar aortic suture lines (Figure 2) are rare. Stenosis of the superior caval anastomosis is likewise uncommon on the whole,[12] although there is increased risk in pediatric patients, especially those with prior cavopulmonary anastomoses or other surgical manipulation of the cava.[12,13] Patients with congenital heart disease constitute nearly 40% of pediatric heart transplant recipients, and these patients are at increased risk for venous and arterial complications.[1,14,15] It is therefore critical that the echocardiographer performing TEE attempt to exclude obstruction at these anastomoses.

Assessment of Right Heart Failure

One of the early causes of graft loss is acute right heart failure. Right heart failure may result from prolonged ischemic time, poor cardiac protection, elevation of pulmonary vascular resistance, or acute graft rejection.[3] TEE offers an important opportunity to evaluate ventricular systolic function, chamber dimensions, valve regurgitation, and estimation of right ventricular and pulmonary artery pressures.[16,17] Right ventricular fractional area change, tricuspid annular plane systolic excursion by M-mode, tissue Doppler assessment of the maximal systolic tricuspid annular velocity, and myocardial performance index are potentially helpful right heart function parameters in children and have been applied in the operative and perioperative assessment of the right heart in adults.[17] Identification of significant right heart failure, tricuspid regurgitation or other evidence of cardiac dysfunction on TEE may prompt the clinician to consider intensified right heart inotropic support, pulmonary vasodilator therapy, or the need for mechanical circulatory support such as extracorporeal membrane oxygenation. Following return from the operating room, transthoracic echocardiography is a useful tool to help evaluate perioperative complications, including right heart failure, rejection or cardiac tamponade.[18-20]

NONINVASIVE ASSESSMENT FOR GRAFT REJECTION

EMB is considered the gold standard for monitoring of acute cellular and antibody-mediated rejection in children and is recommended with an evidence level C by the International Society for Heart and Lung Transplantation guidelines for posttransplantation care in most children.[3,21] Many authorities advocate its use for routine surveillance, especially early after transplantation, emphasizing its ability to detect clinically silent rejection episodes.[21-23] However, biopsy is not perfect for all patients. As one is sampling only a certain area of the myocardium, there is the potential for sampling error and for missing segmental inflammation. Additionally, there can be decreased yield with sequential biopsies because of scar forming in the location of prior biopsies.[24,25] Furthermore, EMB is an invasive test that is associated with risk for tricuspid valve injury (Video 1; available at www.onlinejase.com), myocardial perforation, vascular injury, and the risks associated with sedation and anesthesia.[26-29] Using transthoracic echocardiographic guidance for EMB can obviate exposure to radiation from fluoroscopy and help direct the bioptome away from tricuspid valve tissue. Nonetheless, tricuspid valve injury still occurs even in the most experienced hands.

Relatively low rates of significant cellular rejection >1 year after transplantation may limit the benefits of routine biopsy surveillance.[1,30,31] Given the small but real risks of sedation, anesthesia, vascular access, and biopsy, investigation into the utility of noninvasive testing to (1) identify patients with significant rejection or (2) increase the pretest probability of biopsies remains an important area of study.

Conventional Echocardiography

Although conventional 2D echocardiography is the most commonly performed imaging study in the follow-up management of children with heart transplantation, its utility for detecting presymptomatic rejection is debated.[7,32] Transthoracic echocardiography has advantages in that it is portable, is cost-effective, and does not require use of anesthesia or other personnel. Changes such as increased wall thickness, increased echogenicity of the ventricular myocardium, and presence of new valvular insufficiency or effusion have been associated with allograft rejection (Figure 3). However, these changes may not be reliably present even in moderate cellular rejection.[33,34]

Changes in ventricular systolic function detectable by 2D transthoracic echocardiography are often late findings seen only in progressive or severe rejection. However, because early changes in shortening fraction or ejection fraction can be correlated to cellular rejection, 2D transthoracic echocardiography remains routine in the early postoperative phase and at intervals during later follow-up.

Spectral Doppler and DTI

As 2D imaging has been shown to be limited in the assessment of rejection, there has been increasing interest in the use of spectral Doppler to detect more subtle changes associated with myocardial edema and rejection.[7,35,36] Myocardial inflammation affects ventricular relaxation and tissue characteristics, which become evident before overt systolic dysfunction.[11] Therefore, a number of investigators are actively evaluating various measures of diastolic function as indicators of graft rejection.[7,36,37] Not surprisingly,