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.)

Keywords: Pediatric heart transplantation, Noninvasive imaging, Echocardiography, Cardiovascular magnetic resonance imaging

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,

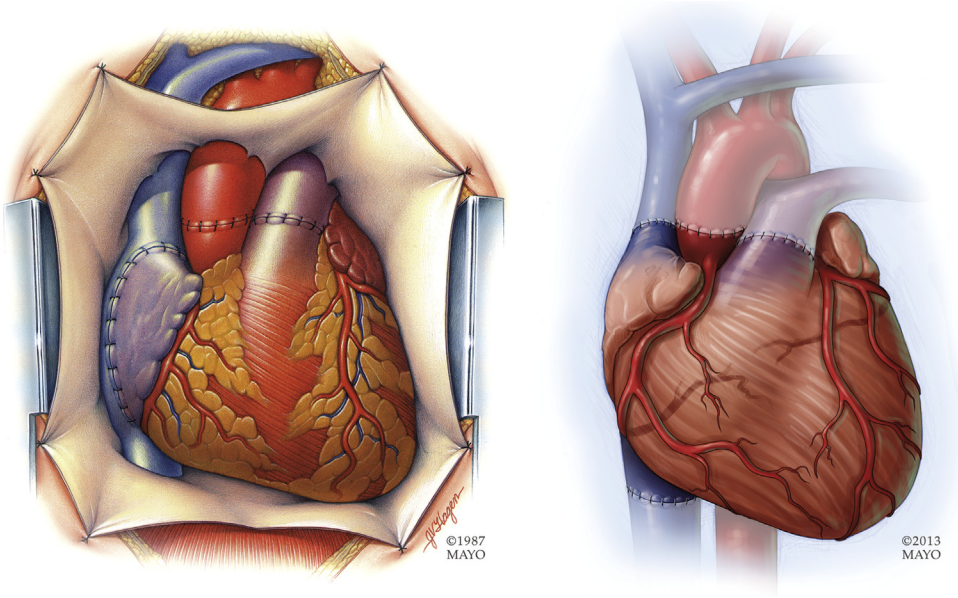

Figure 1 This image contrasts the biatrial and the bicaval techniques. In the biatrial connection (*left*), the recipient right atrium is excised roughly at the crista terminalis laterally, the donor superior cava is ligated, and an anastomosis is created to an oblique incision extending from the donor right atrial appendage to the donor inferior cava. It results in prominent suture lines along the atrial wall and atrial septum. In the bicaval technique (*right*), the superior and inferior cava are connected separately and obvious suture lines may not be present. Either technique results in a prominent left atrium. (Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.)[45]

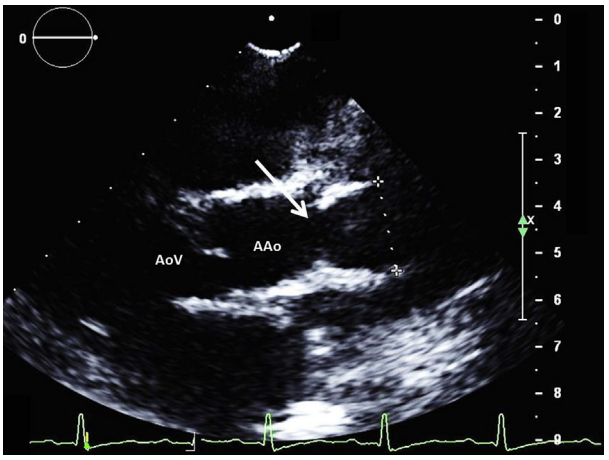

Figure 2 Parasternal long-axis 2D echocardiographic image in a 10-year-old male patient who underwent orthotopic heart transplantation demonstrating mild supravalvar aortic stenosis at the aortic anastomosis. Note the degree of narrowing in the mid ascending aorta (AAo) (*arrow*), where the surgical anastomosis was made. Color Doppler images from a parasternal long-axis view might not demonstrate the flow disturbance, because of unfavorable intercept angle, so continuous-wave Doppler interrogation of the LV outflow tract from an apical five-chamber view is recommended. *AoV*, Aortic valve.

studies assessing mitral inflow velocities by Doppler, including early diastolic (E) peak velocity, late diastolic (A), and their ratio (E/A) (Figure 3), as well as isovolumic relaxation time and E-wave pressure half-time, have all shown some promise.

The data on these various measures have produced conflicting results, especially in pediatric patients, leaving an unclear picture for clinicians.[38,39] Because of the inconsistency of single echocardiographic parameters to demonstrate rejection, echocardiographic scoring systems have been developed that combine various measures of systolic function, wall thickness, diastolic function, and Doppler velocities. One of these scoring systems has reported sensitivity of 88% and specificity of 83% for rejection, although these results have not been reproduced in other publications.[33] The same author group updated their scoring system using intrapatient changes in Doppler parameters and reduced the false-positive rate from 72% to 10% and enhanced the specificity from 90% to 99%.[34]

DTI allows better characterization of myocardial mechanics and has been a focus of investigation in attempts to use noninvasive imaging to monitor for acute cellular rejection in both adults and children.[7,38] Studies of DTI of septal and posterior basal segments of the left ventricle assessing early mitral excursion (Ea or E′) and systolic radial velocity (Sm) have shown changes associated with graft rejection.[39] The utility of the myocardial performance index, derived as a composite ratio of isovolumetric contraction time and isovolumetric relaxation time to ejection time, has also been studied in the evaluation of rejection.[40,41] There was a 98% mean increase in myocardial performance index during rejection compared with baseline, which returned to baseline after treatment, suggesting sensitivity as a marker of early diastolic and systolic performance.[40]

Others have shown that attempts to use DTI measures in children following heart transplantation met with mixed results.[37-39,42-44] The variability of such studies is not surprising, as there are many limitations to DTI in children, particularly in pediatric heart transplantation cohorts. Specifically, these groups represent a wide age range of patients with an even more diverse range of graft size and donor age. Abnormal interventricular septal motion complicates DTI interpretation and is common following heart transplantation because of factors such as elevation of right ventricular pressure or conduction abnormalities. The normal

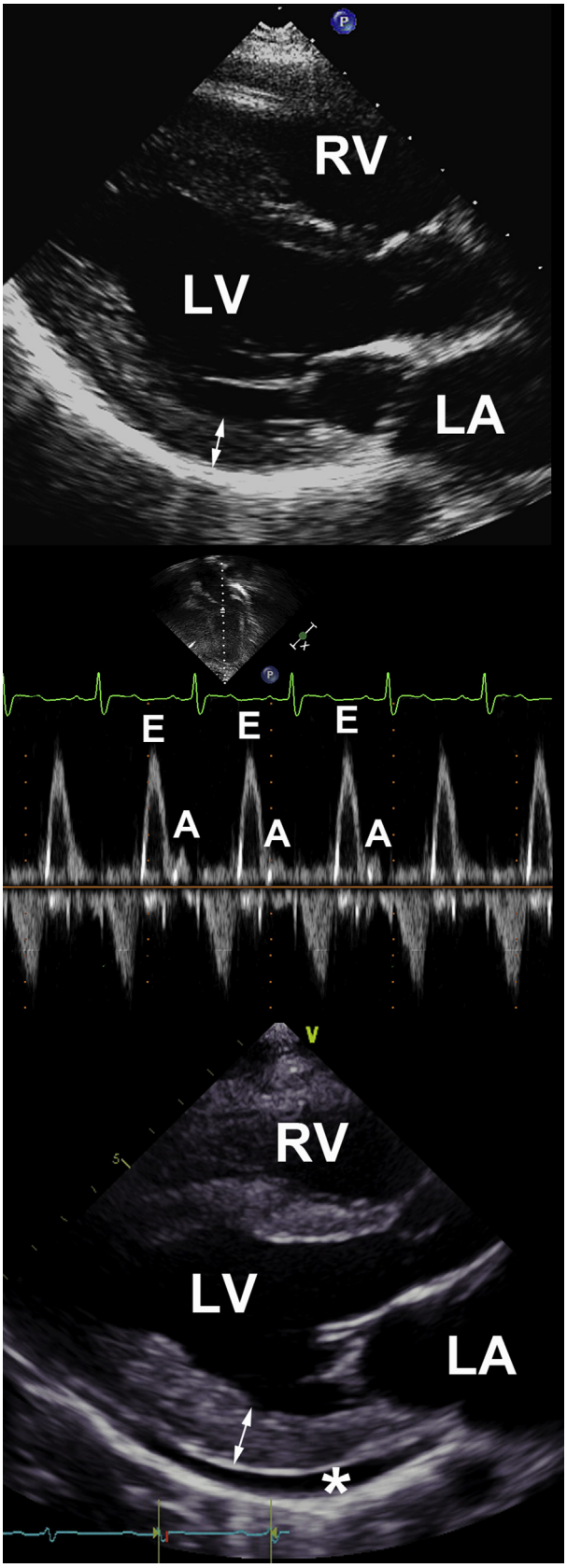

Figure 3 Baseline parasternal long-axis images in a patient after heart transplantation with normal left ventricular posterior wall thickness (*top*) and in the same patient at presentation 3 months later with allograft rejection (*middle and bottom*). Note the increased left ventricular posterior wall thickness (*white arrow*) and small rim of pericardial effusion (*asterisk*). *Middle image* shows pulsed-wave Doppler of the mitral inflow with increased E/A ratio. *LA*, Left atrium; *RV*, right ventricle.

ranges of values of diastolic function in children are poorly defined and inconveniently broad.[46] Moreover, DTI measures are generally decreased even in well-functioning cardiac grafts, so the application of normal ranges to these patients may be misleading.[42,43] Finally, collection of these measures is site and angle dependent, requiring a practiced team to obtain useful data, as even small changes in the acquisition angle will cause changes in DTI velocity.

To circumvent the issues associated with these wide ranges of normal values and the baseline abnormal velocities seen in many posttransplantation patients, authors have focused on changes in DTI measures as a more predictive metric to evaluate acute rejection.[7,8] Initial reports in adult heart transplant recipients demonstrated that a reduction in either E′ or Sm of >10% is associated with increased risk for rejection in adults following heart transplantation, with sensitivity of 90% and 86% and specificity of 94% and 96%, respectively.[8] Recently, Lunze *et al.*[7] reported a retrospective review of echocardiographic studies performed within 24 hours of EMB and compared with prior echocardiographic examinations in the same patients at a time of proven nonrejection, showing that a decline of <15% in S′ velocity and a decrease of <5% in A′ velocity predicted nonrejection with accuracy of >99%, without misclassifying any rejection episodes. This study is important in that it may better represent the role of noninvasive imaging in the pediatric population in which rejection is currently rare outside of the first year to be one of screening for normalcy and not for rejection. It is notable that this was a retrospective and single-center review, with a single reviewer providing the majority of interpretation of results. It has yet to be replicated in a prospective cohort, and small changes in velocity needed to have a "positive" result (indicating rejection) could occur with minor errors in data acquisition.

Although no broadly accepted single echocardiographic protocol currently exists to detect rejection, various similar echocardiographic scoring systems using multiple data points and intrapatient comparisons are in use at different centers.[43] Unfortunately at the present time, these data have not been reproducible at multiple centers to allow dissemination of a defined methodology for noninvasive detection of rejection.

Advanced Functional Imaging

In a prospective investigation using 3D echocardiography, we demonstrated abnormal left ventricular (LV) mechanics and high prevalence of mechanical dyssynchrony in children after heart transplantation (mean systolic dyssynchrony index, 6.2 ± 4.3% in the transplanted left ventricle vs 2.2 ± 1.1% in normal).[9] Both global and interventricular septal strain was lower in the transplantation group. The LV ejection fraction (LVEF) divergence was greater in transplantation patients and had a strong positive correlation with systolic dyssynchrony index and negative correlations with all measures of strain (Figure 4). These findings indicate that abnormal LV mechanics possibly contribute to differences in LVEF measurements by 2D and 3D echocardiographic methods, and LVEF should therefore be calculated using 3D echocardiography in the transplantation population.[9]

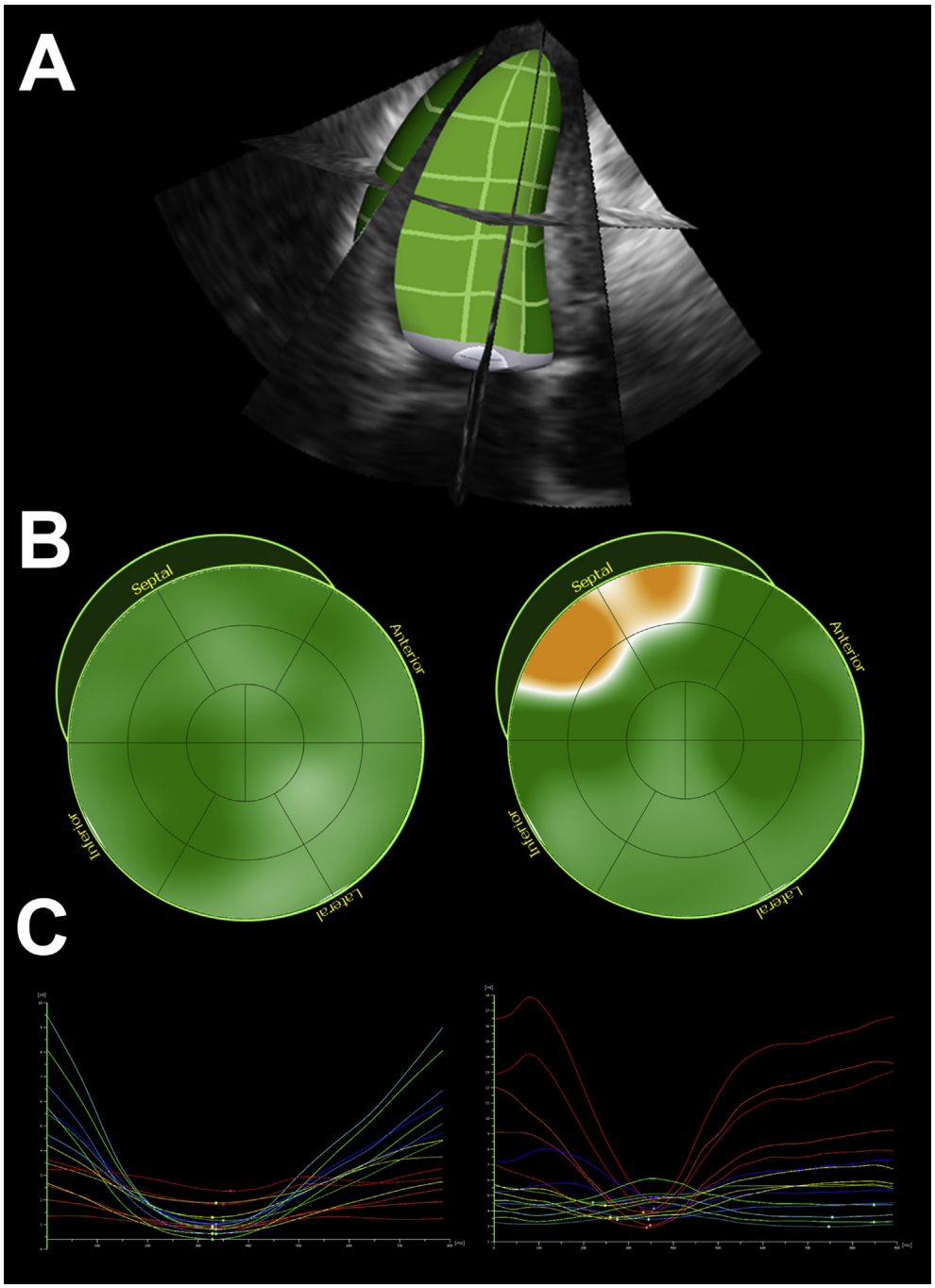

Figure 4 **(A)** Reconstructed LV model from a 3D echocardiographic data set in a pediatric patient after heart transplantation. **(B)** Sixteen-segment bull's-eye maps of 3D strain derived from semiautomated endocardial and epicardial tracking of the left ventricle in the same patient showing abnormal regional strain in the interventricular septum (*yellow*). **(C)** Volume-time curves of the 16 LV segments with *colored dots* on each *line* representing the minimal systolic volume for each segment. Note that there is wide scatter in the timing of minimum segmental volume, indicating a dyssynchronous left ventricle.

Buddhe *et al.*[10] studied 50 children with "normal" systolic function by traditional echocardiography 4 years after transplantation and demonstrated speckle-tracking-derived mitral early diastolic velocity–to–strain rate (E/SR[E]) to have a modest correlation with pulmonary capillary wedge pressure. Twenty-four percent of patients had global longitudinal strain (GLS) $> -18\%$, while patients with coronary vasculopathy had significantly higher E/SR (E) (71.9 ± 28.4) compared with those with normal coronary arteries (45.2 ± 10.8). Sehgal *et al.*[47] demonstrated the clinical utility of peak systolic strain for detecting acute allograft rejection in children. They reported significant decreases in peak systolic GLS (−11.7% vs −14.6%), circumferential strain (−14.4% vs −21.7%), and radial strain (18.3% vs 26.5%) during rejection. Mingo-Santos *et al.*[48] reported similar utility of deformation imaging in detecting acute rejection and suggested that systolic strain measurements may reduce the burden of repeated biopsy. Others have confirmed usefulness of peak diastolic strain in

predicting LV filling pressure and risk for rejection.[49] Nawaytou *et al.*[50] found baseline abnormalities in LV rotational mechanics in transplanted children without active rejection and proposed the slope of torsion-radial displacement loop as a marker of LV dysfunction. The European Association of Cardiovascular Imaging recommendations for the assessment and follow-up of patients after heart transplantation suggest GLS as a suitable parameter to diagnose subclinical allograft dysfunction and that GLS could be used in association with EMB to characterize an acute rejection or global dysfunction episode.[32] The very high negative predictive value of speckle-tracking echocardiography to exclude rejection, and its potential to minimize the burden of frequent EMBs within the first year after heart transplantation, was highlighted in a recent editorial comment.[51] However, others suggest that speckle-tracking echocardiography cannot be a replacement for biopsy, because of its inability to detect serial changes in patients with asymptomatic rejection.[52]

Cardiac Magnetic Resonance Imaging

More recent research has focused on the use of complementary imaging techniques such as CMR to assess graft function and rejection.[11,53] CMR has great appeal because of reliable whole-heart imaging throughout the cardiac cycle, excellent border definition allowing accurate measures of ventricular mass, volume, and LVEF, and tissue characterization superior to that obtained with echocardiography. Specifically, contrast-mediated imaging and analysis of T2 signal of heart tissue can reveal evidence of myocardial edema. Cellular rejection occurs because of the infiltration of lymphocytes and activation of cytokine pathways, leading to inflammation and edema in the muscle that can be quantified via T2 relaxation.[54-57] Marie *et al.*[56] suggested that a T2 relaxation time of >56 msec was sensitive (89%) and relatively specific (70%) for the detection of significant rejection (≥2R). However, Wisenberg *et al.*[54] had previously demonstrated that T2 prolongation is common early after transplantation, even in the absence of rejection, and suggested that this represents myocardial edema secondary to the transplant process.

Miller *et al.*[58] evaluated all patients receiving heart transplants at a single center with serial CMR on the same day as EMB. CMR included T1 mapping and T2 mapping, as well as evaluation for extracellular volume (ECV), late gadolinium enhancement (LGE), and absolute myocardial blood flow. Although improvements in function were noted with passage of time from transplantation, only circumferential strain was significantly different in patients with acute rejection (by EMB) compared with those patients without rejection. Unfortunately there was still significant overlap in circumferential strain between the two groups.

Others have shown high sensitivity and high negative predictive value for CMR in the diagnosis of acute cardiac allograft rejection.[59-61] The benefits of quantitative T2 mapping and its potential use in characterizing rejections have been highlighted by some,[62] whereas in other studies, multiparametric CMR was not able to accurately detect acute rejection during the early posttransplantation period.[63] Despite its promise, these studies leave the true predictive value of T2-weighted imaging open to debate.

Other CMR markers (native T1 times and ECV) have shown correlation with the degree of fibrosis on EMB in children after heart transplantation.[64,65] Coelho-Filho *et al.*[66] focused on CMR markers of tissue remodeling—myocardial ECV and intracellular lifetime of water (τ_{ic}), a measure of cardiomyocyte hypertrophy—in a study comparing 26 transplant recipients (mean age, 47 ± 7 years; median follow-up after transplantation, 6 months) with age-matched healthy volunteers. Transplant recipients had normal LVEFs (65.3 ± 11%) with higher LV mass relative to volunteers (114 ± 27 vs 85.8 ± 18 g). ECV and τ_{ic} were higher after transplantation (ECV, 0.39 ± 0.06 vs 0.28 ± 0.03; τ_{ic}, 0.12 ± 0.08 vs 0.08 ± 0.03), and ECV was associated with LV mass ($r = 0.74$). In follow-up, transplant recipients with normal biopsies (International Society for Heart and Lung Transplantation grade 0R) in the first posttransplantation year exhibited lower ECV relative to patients with any rejection ≥2R (0.35 ± 0.02 for 0R vs 0.45 ± 0). Higher ECV but not LVEF was associated with reduced rejection-free survival.[66] Further research on the impact of graft preservation and early immunosuppression on tissue-level remodeling of the allograft is necessary to delineate the clinical implications of these findings.

In summary, CMR has been studied as a potential means for noninvasive detection of rejection because it can identify areas of hyperemia, inflammation, and areas of scar and fibrosis using LGE. Single-center studies have reported using LGE patterns to identify areas of active inflammation, and others have examined signal intensity patterns in the early postcontrast phase to identify inflammation and necrosis.[11,57,67] Large prospective studies are needed to better understand the true sensitivity and specificity of these techniques. Currently, for cellular rejection, CMR is limited primarily to the detection of edema, reduced LVEF, or other alterations of tissue character, whether by prolonged T2, altered T1, or LGE.[68] Each of these signifies some degree of myocardial tissue damage. In the future, detection of rejection before these findings may be able to trigger intervention to minimize the irreversible damage to the allograft. Investigations are under way to detect immune activity in the allograft using CMR contrast agents specific to immune cells.[69-71] At the time of this review there are no studies directly addressing the use of CMR to detect acute rejection in children. Such a study is uniquely challenging because pediatric heart transplantation center volumes are generally low, rejection rates are much lower than adults, and many children require anesthesia for adequate CMR.

NONINVASIVE ASSESSMENT OF CAV

CAV is a unique form of coronary disease found in transplanted hearts that is related to both immunologic and nonimmunologic processes.[68,72] As opposed to typical coronary artery disease, CAV is a vasculitis that leads to intimal proliferation, obliteration of vascular lumens, and chronic ischemia of the allograft. CAV is a leading cause of graft loss and the primary indication for retransplantation in children and adults >5 years after transplantation.[1,73]

Currently coronary angiography is the most commonly used screening test, and intravascular ultrasound (IVUS) is considered to be the gold standard for detecting CAV (Figure 5). IVUS is used routinely at some adult centers for screening but is used to a much more variable degree in children, because of the relative size of the transducer and patient and the scarcity of operator experience.[68,74,75] Coronary angiography is performed routinely at many pediatric centers, although surveillance schedules vary widely.[5] The International Society for Heart and Lung Transplantation guidelines suggest that routine angiography is reasonable, but there are insufficient data to advocate it as a standard of care in all patients, especially considering its low yield among those transplanted in infancy, in whom the prevalence of disease is quite low.[5,21,76]

Although cardiac catheterization and coronary angiography are common diagnostic tests at most pediatric heart centers, the procedure carries risks associated with arterial injury, anesthesia, coronary vasospasm, and potential contrast allergy or nephropathy. Despite being

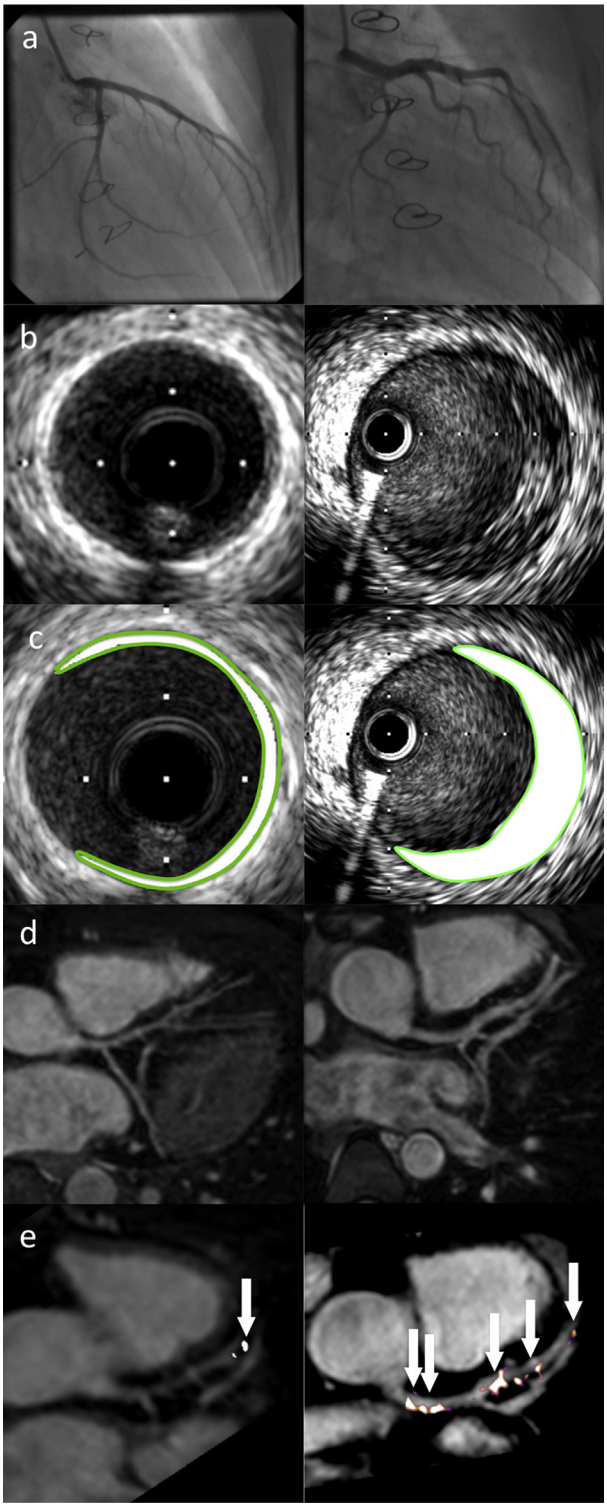

Figure 5 Two patients are shown side-by-side for comparison. Images on the *left* are from patient 1 with minimal disease on IVUS, and images on the *right* are from patient 2 with severe disease on IVUS. Left coronary artery angiography **(a)** shows normal lumen of the left system for both patients, demonstrating the poor sensitivity of conventional angiography. IVUS **(b)** shows minimal intimal thickening in patient 1 and severe disease in patient 2. The same IVUS images are shown in **(c)**, with the intimal layer segmented out in *white* (with *green border*) to demonstrate this more clearly. Magnetic resonance coronary angiography of the left coronary artery is shown in **(d)**, again showing normal lumen for both patients. The overlay of LGE is shown in **(e)**, highlighted with *white arrows*. Patient 1 shows minimal coronary enhancement, and patient 2 shows severe enhancement. The findings on late enhancement images are congruent with the IVUS findings, whereas luminal imaging is uninformative for the patients shown.

the most frequently used modality to assess for vasculopathy, there are several reasons why coronary angiography is not a perfectly sensitive test. CAV tends to be a diffuse disease, especially in children, and focal stenoses are rare.[72,76] Furthermore, relative coronary vasodilation following transplantation can preserve the luminal diameter even in the presence of significant intimal vascular change.[3,68,72]

Echocardiographic Monitoring with and without Stress

Standard resting echocardiography has historically had low sensitivity for the detection of CAV in adults in the absence of regional wall motion abnormalities.[58,77] Resting wall motion abnormalities are exceptionally uncommon in children after heart transplantation but, if newly detected following prior normal echocardiograms, should be considered an alarming sign prompting further investigation.[78,79] A recent study in adults demonstrated DTI-derived peak radial systolic velocity < 10 cm/sec (Sm) to have 97% sensitive for CAV, while others reported that serial examination revealing stable DTI measures can predict absence of CAV.[42,77] Unfortunately, no similar large study exists for pediatric patients.

Because cardiac denervation is part of the heart transplantation process, many patients have inadequate heart rate response to exercise to allow adequate sensitivity for the presence of CAV.[80-83] As such, dobutamine stress echocardiography (DSE) is often used (Video 2; available at www.onlinejase.com).[82,84,85] Although these studies used variable criteria to define and grade CAV, they all demonstrated reasonable specificity and negative predictive value, such that negative results could provide reassurance that more severe CAV is not present, allowing practitioners to avoid invasive testing. Few pediatric studies have specifically assessed the value of DSE in the evaluation of CAV following heart transplantation.[79] A prospective paired trial was performed in 102 patients who underwent both DSE and angiography on an annual basis. Results of this trial demonstrated a high correlation between abnormal results on DSE and an abnormality on coronary angiography.[86] These studies provide evidence that DSE can be used in select groups of pediatric patients as a noninvasive screening test to decrease the frequency of cardiac catheterization and angiography after transplantation. However, caution must be used in generalizing these results, as DSE is a highly operator-dependent test that requires significant experience to ensure adequate interpretation.

CMR and Computed Tomography

Whole-heart imaging, tissue characterization by LGE, feature tracking (Figure 6), and other advanced techniques have led to significant interest in using CMR as a noninvasive means to screen for CAV. At this point, the literature on the subject remains somewhat limited.

Using tagged CMR to evaluate deformation during pharmacologically mediated stress, it was demonstrated that reduction in mean diastolic strain rate was associated with mild CAV in a cohort of 69 adult patients.[87] Other groups have focused on evaluation of the

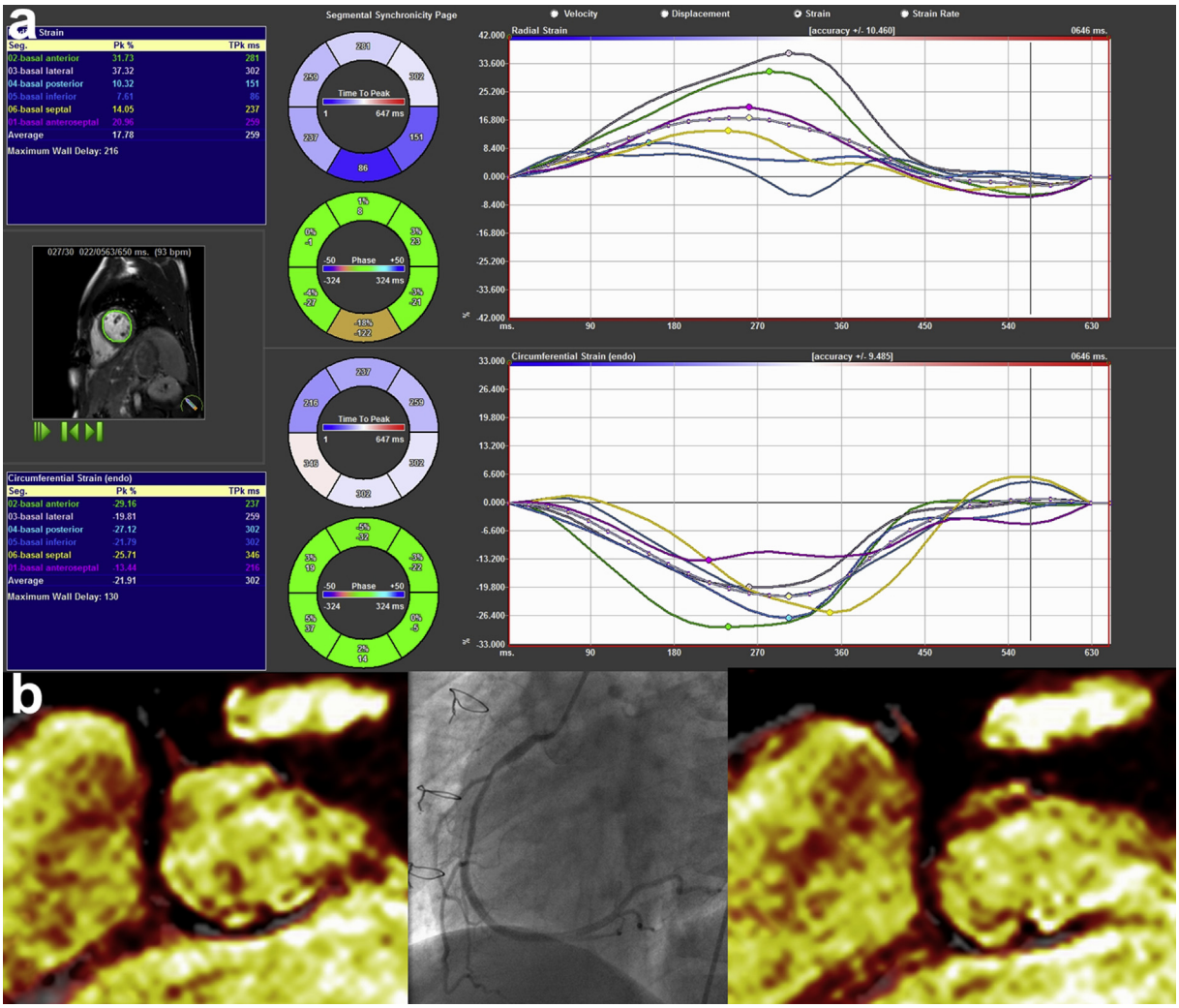

Figure 6 **(a)** Strain analysis for the midventricular short-axis slice. The endocardial border is detected and shown in the *middle left* of the images. Absolute values for peak radial peak strain and time to peak strain are shown at *top left* and corresponding circumferential strain at *bottom left*. To the *right* of **(a)**, the radial strain versus cycle time curve is shown (*top right*), and the circumferential strain curve is shown (*bottom right*). *Yellow and blue curves* represent septal and inferior segments. The radial strain (*top right*) is notably reduced, and the time to peak strain is increased in these segments with respect to the circumferential strain curve (*bottom right*). This correlated with the invasive right coronary artery angiographic findings (**b**, *center*) that showed a significant proximal narrowing just before the takeoff of the anterior conal branch. This was not easily seen on the coronary magnetic resonance angiogram (**b**, *left* and *right* nonreformatted images).

presence and pattern of LGE. Steen *et al.*,[88] in one such investigation, noted an increased rate of focal subendocardial hyperenhancement in patients with severe angiographic CAV (84%) compared with those with mild disease (27%). Coronary CMR angiography has demonstrated feasibility for the detection of stenoses in the setting of atherosclerosis,[89] and, with tailored pediatric protocols, it has diagnostic benefit even in small children with high heart rates.[90] However, most authors would agree that resolution and accuracy are not as high as with multidetector computed tomography, and indeed, one small trial looking at both modalities in the setting of CAV confirmed this statement.[91] CMR using adenosine stress perfusion and LGE is increasingly used in the assessment of adults with coronary artery disease,[92,93] but clinical utility has not been demonstrated in children. A promising adult study showing the utility of CMR was conducted by Miller *et al.*[63] In that study, 48 patients underwent both IVUS and coronary pressure-wire study to characterize both epicardial and microvascular CAV. Patients also underwent a multiparametric CMR approach including deformation analysis, T1 mapping, ECV calculation, myocardial LGE, and quantitative adenosine stress perfusion. The study showed that CMR-based myocardial perfusion reserve was independently predictive of both epicardial and microvascular components of CAV and that diagnostic performance was significantly higher than that of angiography. Others have associated CMR-derived myocardial perfusion reserve and early diastolic strain rate with histologically determined microvascular disease and proposed them for early detection of transplant microvasculopathy before manifest CAV.[53] Being able to quantitatively assess microvascular function early potentially paves the way for the development of specific coronary microvascular disease treatments.[94]

Preliminary studies in pediatric coronary artery disease suggests suitability of adenosine stress perfusion CMR as a screening test, in conjunction with anatomic imaging to confirm the extent of the culprit lesion.[95] Regadenoson is a newer adenosine receptor agonist, working more selectively on the A2A receptor. This means that it has

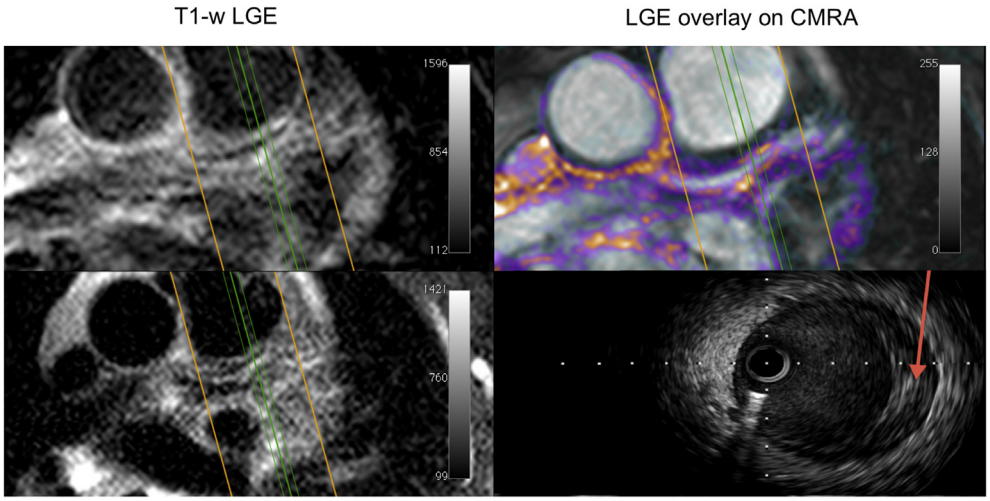

Figure 7 CMR with high-resolution LGE used to demonstrate vessel wall disease from coronary artery vasculopathy after heart transplantation. The raw images for coronary vessel wall late enhancement is shown at *top left* (T1-weighted [T1-w] LGE) demonstrating enhancement in the area (on the *green cross-line*). T2-weighted (T2-w) imaging shows that the enhancement represents an area of acute inflammation (*bottom left*; the *green-cross line* shows the exact same area again). Acute inflammatory plaque, as demonstrated, could represent active high-risk disease. In actuality, despite optimal medical therapy, this patient died of an acute coronary event within 6 months of this imaging. The *top right* image is a composite picture showing the overlay of the T1-w LGE enhancement (shown in *purple*) on a coronary magnetic resonance angiogram. It demonstrates how the enhancement is within the wall of the coronary artery and not the lumen (again, the *green cross-line* depicts the exact same area). The IVUS image (*bottom right*) illustrates intimal thickening in the exact same area predicted by the CMR images. The *red arrow* points to an eccentric area of severely thickened intima. Although IVUS shows the thickening very well, CMR may hold the ability to characterize acute inflammation.

a better side effect profile, and the pharmacokinetics are such that it can be given as a single bolus rather than an infusion, like adenosine. The practical advantage is that only a single intravenous access is required, a significant benefit for use in children. Theoretical issues regarding postdenervation hypersensitivity to adenosine would also be potentially reduced with a more selective agonist.[96] There are now limited pediatric data, which is encouraging.[97] Dobutamine stress CMR is another promising modality. In conjunction with dobutamine stress, CMR has been shown to perform better than echocardiography in the detection of coronary stenoses in ischemic heart disease.[98] This approach can also be used to determine coronary perfusion reserve in the setting of CAV.[99] However, the technique is more problematic for children, in terms of length of study, comfort, and the difficulty achieving the higher target heart rates.

No conclusive pediatric data have yet been reported on the use of CMR to identify significant CAV in children following heart transplantation. Using IVUS as the gold standard for detection of CAV, Hussain *et al.*[100] correlated LGE detected by CMR in the distribution of coronary vessel walls in children (Figure 7). LGE in this distribution, hypothesized to be coronary vessel wall thickening, was found to correlate well with IVUS measures of intimal thickening. These findings have some support from another small study by Madani *et al.*,[101] who described a novel measure, contrast-to-noise ratio, as a marker of inflammation of the coronary wall at multiple levels of the coronary tree and demonstrated significantly higher contrast-to-noise ratio in patients with CAV compared with those without. Additionally, two of the six patients with CAV had myocardial scar, whereas none was seen in the patients without CAV. Although these data come from small cohorts, they may represent another approach to noninvasive screening for CAV. The combination of serologic testing for cardiac injury with CMR is another fascinating strategy and may yield extremely accurate prediction. Early data in this regard using highly sensitive troponin T combined with CMR perfusion reserve suggest that this approach will be a promising avenue for future research.[102]

CONCLUSIONS

Management of pediatric heart transplantation patients requires expert understanding of the physiologic and immunologic aspects of graft function. Multimodality cardiac imaging plays a key role in the care of these patients. An understanding of the techniques, applications, and available evidence is essential for practitioners as they attempt to maximize graft and patient outcomes while minimizing the risks and discomforts of invasive testing. Standard echocardiography is widely available and promptly provides reproducible data relevant to graft health, though suboptimal at the present time with regard to early detection of rejection. Because of the high prevalence of mechanical dyssynchrony and regional strain abnormalities, LVEF is more accurately measured by 3D echocardiographic methods in this population. Baseline abnormalities in speckle-tracking-derived LV GLS and rotational mechanics are seen in transplanted children without active rejection. Alterations in diastolic functional indices become evident before overt systolic dysfunction, so changes in DTI-derived s′ and e′ waves, E/e′ ratio, left atrial volume, and GLS are associated with relatively high negative predictive values in the detection of rejection. Multiparametric mapping using CMR-based T1and T2 has also shown considerable promise in rejection surveillance, although pediatric data are limited. With regard to detection of CAV, coronary angiography is the gold standard. There is little published experience with computed tomographic coronary angiography in pediatric heart transplant recipients. DSE or CMR in conjunction with dobutamine stress or perfusion assessment and CMR coronary

wall imaging can be used for noninvasive screening in select patients. Large prospective studies are needed to better understand the true sensitivity and specificity of newer CMR markers of microvascular function in children, including myocardial perfusion reserve, ECV, and diastolic strain rate. Advanced multimodality imaging techniques are likely to increasingly shape the monitoring practices for children following heart transplantation.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.echo.2017.06.003.

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