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iREVIEWS

STATE-OF-THE-ART PAPER

The Role of Multimodality Cardiac Imaging in the Transplanted Heart

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Heart transplantation (HT) is an established life-saving treatment option for patients with end-stage heart failure. Despite many advances in the field, the development of acute cellular rejection (ACR) and cardiac allograft vasculopathy (CAV) represent significant causes of 1- and 5-year morbidity and mortality, respectively. The search for noninvasive techniques to assess cardiac allograft function and detect treatable ACR and CAV remains a priority objective for heart transplant professionals. In this review we will: 1) highlight the clinical significance of ACR and CAV in adult cardiac transplant recipients and 2) discuss how different noninvasive imaging modalities (echocardiography, cardiac computed tomography, myocardial perfusion imaging, and cardiac magnetic resonance) have been used in the evaluation of these clinical challenges after HT. (J Am Coll Cardiol Img 2009;2:1126–40) © 2009 by the American College of Cardiology Foundation

Heart transplantation (HT) is an established life-saving treatment option for patients with end-stage heart failure. Despite many advances in the field, the development of acute cellular rejection (ACR) and cardiac allograft vasculopathy (CAV) represent significant causes of morbidity and mortality (1). Historically, surveillance for ACR and CAV has been based on invasive procedures, which carry inherent risks and high costs. The search for noninvasive techniques to assess allograft function and detect treatable ACR and CAV remains a priority objective for heart transplant professionals. Noninvasive imaging techniques used in this regard include transthoracic echocardiography, multidetector computed tomography (MDCT), single-photon emission computed tomography-myocardial perfusion imaging (SPECT-MPI), and cardiac magnetic resonance (CMR). The ideal test for the detection of ACR and CAV should be highly sensitive and specific, able to evaluate changes before and after treatment, noninvasive with high reproducibility, and associated with low cost and favorable outcome. In this review, we will: 1) highlight the clinical significance of ACR and CAV in adult cardiac transplant recipients; and 2) discuss how different noninvasive imaging modalities have been used in the evaluation of these clinical challenges after HT.

ACR

Clinical significance. In ACR, effector T cells mediate an inflammatory response that leads to myocardial edema and myocyte damage. Routine surveillance of ACR is currently performed with endomyocardial biopsy (EMB) and is associated with good clinical results. The current management strategy depends on the his-

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tologic type and grade of rejection and the presence or absence of hemodynamic compromise (decreased allograft systolic function and/or hemodynamic instability). Using the International Society of Heart and Lung Transplantation revised grading system, EMB grade 2R (previously 3A) or higher rejection is considered clinically significant and prompts the use of high-dose corticosteroids and possibly the use of lymphocyte-depleting agents in patients with hemodynamic compromise.

Although EMB is considered the gold standard for the diagnosis of ACR, its value may be limited by sampling error, interobserver variability, and wide variability in the frequency and duration of its use as surveillance among transplant centers. Several noninvasive imaging techniques (clinically accepted and investigational) have been performed to detect ACR at different stages in the disease process (Fig. 1). With current advances in immunosuppression, the majority of patients who develop ACR have no significant changes in left ventricular (LV) ejection fraction regardless of the imaging modality used (2–4). However, monitoring cardiac allograft systolic function is important in suspected or proven ACR because more aggressive immunosuppression can lead to improvement in LV function in patients with depressed function.

Echocardiography and ACR. **CONVENTIONAL ECHOCARDIOGRAPHY.** Although wall thickness and LV mass measured by M-mode and 2-dimensional echocardiography have been shown to increase during ACR episodes (5), ACR-induced myocardial edema may manifest by subtle changes in relative wall thickness, accounting in part for the conflicting results on the usefulness of these echocardiography parameters to detect ACR (6–8). Investigators have also noted that the presence of a pericardial effusion in cardiac transplant recipients is associated with a higher incidence of ACR (9). Pericardial effusion, however, occurs frequently in the postoperative period, hence its low sensitivity (~49%) and specificity (~74%) to detect ACR (10).

SPECTRAL DOPPLER IMAGING. Early investigations demonstrated altered LV diastolic twist mechanics in the absence of systolic dysfunction to suggest that diastolic dysfunction precedes systolic abnormalities in patients with ACR (11). Multiple studies have also evaluated LV Doppler inflow indexes to detect ACR, including early diastolic (E) peak velocity, late diastolic (A) peak velocity, E/A ratio, E-wave pressure half time (PHT), and isovolumic relaxation time (IVRT) (12,13). Standard transmitral Doppler-derived indexes in cardiac transplant recipients have had limitations in predicting ACR; these limitations relate to the influence of several parameters on these indexes including donor age, heart rate (which may be variable in the setting of cardiac denervation), loading conditions, and the dissociation between the electrical activity of 2 atria (especially important with the biatrial anastomosis technique when evaluating older studies). Mena et al. (12) performed a systematic review of the published literature between 1967 and 2005 and reported that the majority of studies that examined the change in the mitral E and A peak velocities over time did not predict ACR and the correlation between ACR and PHT and IVRT was not consistent (sensitivity and specificity range for PHT 23% to 87% and 76% to 98%; IVRT 28% to 85% and 80% to 98%, respectively) (12). The discordance in the literature may be in part related to significant interpatient and intrapatient variability and the dependence of these indexes on multiple factors in addition to ACR (8). In addition to transmitral Doppler indexes, several studies have examined changes in pulmonary vein flow indexes (8,10,14), LV diastolic flow propagation (8,15), and the myocardial performance index (16,17) to detect ACR—with conflicting results.

TISSUE DOPPLER IMAGING (TDI). More recently, the use of TDI to detect ACR has been investigated, with improved results. Investigators from Berlin, Germany, using pulsed wave–TDI obtained from the basal posterior wall, have demonstrated that a reduction in peak systolic radial velocity (Sm) and peak early diastolic velocity (Em [also known as Ea]) is helpful in detecting cardiac rejection (sensitivity and specificity for Sm reduction >10%, ~87% and ~94%; sensitivity and specificity for Em reduction >10%, 90% and 96%, respectively) (3,18). These investigators have also reported on the value of serial TDI screening based on the high negative and positive predictive values of changes in diastolic parameters (i.e., >10% Em reduction) for ACR to guide the effective use of EMBs (19). In contrast, with the mitral valve annulus used as the site for analysis, some studies have found significant decreases in systolic velocities with ACR (8,20), whereas other investigators have not (15). Discordant results have also been seen by color Doppler or conventional TDI (12,20). These discrepancies with regard to the clinical usefulness of these parameters may be secondary to differences in methodology,

ABBREVIATIONS AND ACRONYMS

ACR = acute cellular rejection
CAV = cardiac allograft vasculopathy
CMR = cardiac magnetic resonance
DSE = dobutamine stress echocardiography
EMB = endomyocardial biopsy
HT = heart transplantation
IVUS = intravascular ultrasound
LV = left ventricular
MACE = major adverse cardiac events
MDCT = multidetector computed tomography
SPECT-MPI = single-photon emission computed tomography-myocardial perfusion imaging
TDI = tissue Doppler imaging

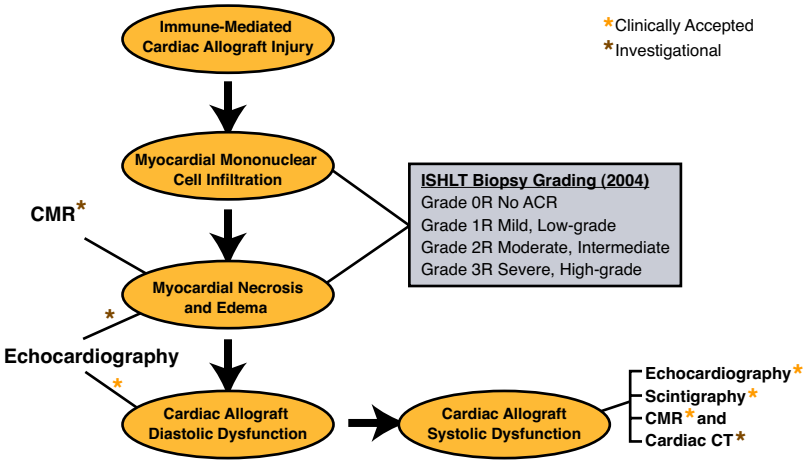

Figure 1. Different Noninvasive Imaging Techniques Performed at Various Stages of Cardiac Involvement to Detect Acute Cellular Rejection

ACR = acute cellular rejection; CMR = cardiac magnetic resonance; CT = computed tomography; ISHLT = International Society of Heart and Lung Transplantation.

some studies using pulsed wave versus color TDI and using tissue Doppler Ea from different myocardial walls or mitral valve annulus locations (3,14,15,20). Finally, the E/Ea ratio—a validated parameter for estimation of LV filling pressure in the transplanted heart (21) (Fig. 2)—has been evaluated by 2 different groups to detect ACR, with conflicting results (10,14). The clinical usefulness of this TDI-derived index to detect ACR remains unclear given that paradoxical septal motion is noted often in cardiac transplant recipients and in the current era of immunosuppression, patients with ACR are often asymptomatic with normal ventricular filling pressure.

PROMISING ECHOCARDIOGRAPHIC TECHNIQUES. Novel echocardiographic techniques have been recently developed and have been applied to the evaluation of ACR. These include strain and strain rate imaging (22) (Fig. 3), 2-dimensional derived integrated backscatter (6), automated border detection with acoustic quantification to measure LV peak filling rate (23), and color Doppler imaging to measure late isovolumic relaxation myocardial velocity gradients and early diastolic timing interval differences (14) (Table 1). These quantitative echocardiographic techniques of regional and global myocardial function show promise to identify subclinical LV dysfunction in a small number of cardiac transplant recipients and need further validation in larger studies.

CMR and ACR. Although many transplant centers use echocardiography to detect cardiac allograft systolic dysfunction in the setting of cardiac rejection, CMR enables imaging throughout the cardiac cycle and provides excellent spatial resolution to accurately measure diastolic and systolic volumes and hence left and right ventricular ejection fractions (24) (Fig. 4). CMR may also be useful in the detection of ACR by its ability to quantitate changes in myocardial mass (25) or more specifically to detect myocardial edema. The latter is accomplished by measurement of myocardial T2 values, which are elevated in the setting of increased myocardial water content. Marie et al. (26) demonstrated in 68 cardiac transplant recipients that a higher than normal T2 value (≥56 ms) was sufficiently accurate (sensitivity 89%; specificity 70%) to detect ACR defined by EMB (grade ≥2R). An abnormal T2 value was also a strong predictor of subsequent biopsy-defined ACR, suggesting early detection of ACR. Although promising, this investigation involved a select cohort of patients with suspected rejection on the basis of clinical or echocardiographic data; therefore, the true sensitivity and specificity of this method to detect ACR in unselected cohorts is currently unknown and needs further evaluation.

With the administration of a paramagnetic contrast medium, gadolinium, CMR studies have also been used to detect inflammatory changes in the myocardium. Almenar et al. (2), using gadolinium-diethylene triamine pentaacetic acid-enhanced CMR in 40 cardiac transplant recipients, showed an increase in relative myocardial contrast uptake in patients with necrosis on EMB compared with

those without necrosis. Although their series required extensive image analysis to compute changes in signal intensity in various tissues (heart and pectoralis muscle) before and after administration of contrast, our experience has shown that the use of traditional delayed enhancement CMR may also demonstrate areas of hyperenhancement in the setting of ACR. These areas appear to diminish after treatment of the ACR episode (Fig. 5). In general, CMR studies have been limited by small sample size with few confirmatory validations. In addition, gadolinium use in patients with acute or chronic severe renal insufficiency (estimated glomerular filtration rate <30 ml/min) carries a significant risk for development of nephrogenic systemic fibrosis. Because of these drawbacks and the lack of widespread availability, the role of CMR in evaluation of ACR is still evolving.

CAV

Clinical significance. Cardiac allograft vasculopathy, prevalent in approximately 54% of survivors 10 years after HT, is characterized by diffuse intimal hyperplasia that is likely the result of cumulative endothelial injuries (1,27). The early diagnosis of CAV is challenging because typical clinical symptoms of ischemia are lacking, given cardiac denervation and the fact that coronary angiography can underestimate the severity of disease. Early recognition is important because rapid CAV progression, as defined by intravascular ultrasound (IVUS), has been shown to be a powerful predictor of all-cause mortality and myocardial infarction (27). Although IVUS is considered the most sensitive tool to detect CAV, coronary angiography is still the standard in many transplant centers.

Treatment of CAV focuses on the use of proliferation signal inhibitors to decrease progression, statin therapy for long-term survival benefit, antiplatelet therapy, and percutaneous revascularization, although the benefit may be limited because of the diffuse nature of the disease (27). Given the drawbacks of the invasive nature and high cost of both IVUS and coronary angiography, a noninvasive imaging modality is needed to identify patients at risk for CAV. Several imaging modalities (clinically accepted and investigational) have been used for the detection of CAV at various stages in the disease process (Fig. 6).

Echocardiography and CAV. REST CONVENTIONAL ECHOCARDIOGRAPHY AND TDI. Resting wall motion abnormalities as detected by 2-dimensional

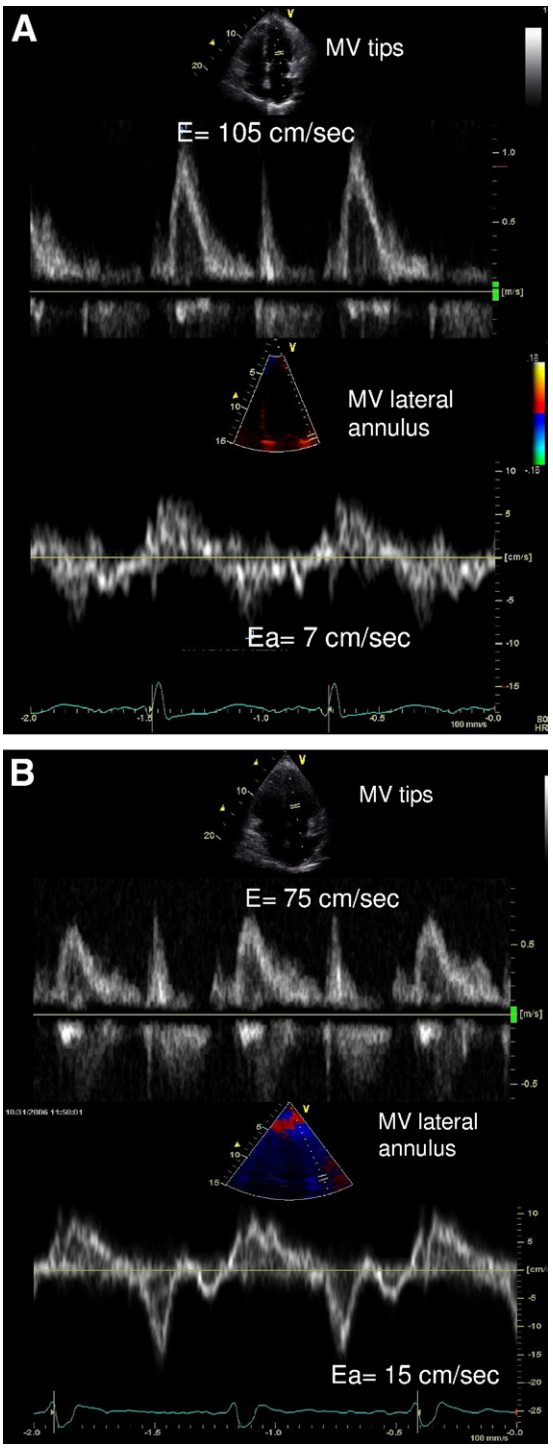

Figure 2. Noninvasive Detection of Elevated Left Ventricular Filling Pressure in Cardiac Transplant Recipients Using Doppler Echocardiography

(A) Pulsed Doppler recording of the mitral flow velocity and the corresponding annular velocities by tissue Doppler at the time of first right-sided cardiac catheterization. **(B)** Pulsed Doppler of mitral inflow and the corresponding tissue Doppler velocities at the time of the repeat right-sided cardiac catheterization (4 weeks later). Mean measured pulmonary capillary wedge pressure (PCWP) decreased from 24 to 11 mm Hg. The E/Ea ratio decreased from 15 to 5, predicting a decrease in estimated wedge pressure from 24 to 9 mm Hg (PCWP = 2.6 + 1.46 [E/Ea]). E = peak mitral inflow velocity; Ea = peak mitral annular velocity; MV = mitral valve.

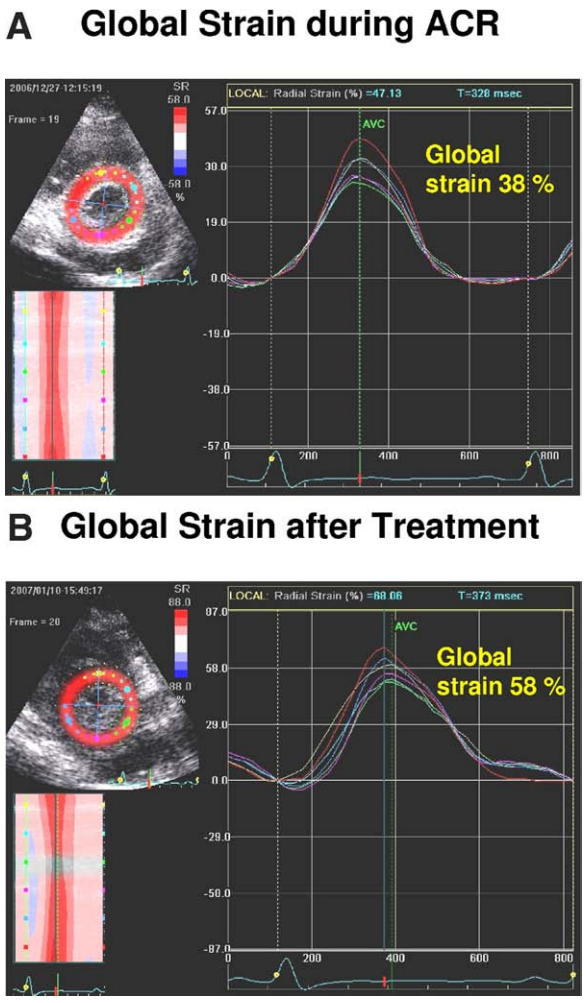

Figure 3. Global Radial Strain Derived From the Speckle-Tracking Technique

(A) Global radial strain (38%), peak 47%, obtained from the parasternal short axis view in a patient 1 week post-heart transplantation (biopsy grade 2R performed on the same day). **(B)** Improvement in the global radial strain (58%), peak 68%, 2 weeks later after enhancement in immunosuppression (biopsy grade 1R). ACR = acute cellular rejection; AVC = aortic valve closure.

echocardiography derived from 12 different studies are in general associated with low sensitivities (~47%; range 12% to 80%) but high specificity for the presence of CAV (~84%; range 69% to 100%), supporting the notion that this finding should prompt further testing to exclude CAV (13). A few studies have examined resting TDI to detect CAV (18,28). After excluding ACR, Hummel et al. (18) reported that pulse wave TDI-derived radial peak systolic velocity (Sm value <10 cm/s) was associated with a 97% likelihood for CAV, whereas Sm values >11 cm/s excluded accelerated CAV with 90% probability. This group of investigators also demonstrated that serial TDI can potentially spare patients unnecessary routine invasive examinations (28). These are promising results that need further validation but may point to advanced CAV, affecting myocardial properties at rest.

STRESS ECHOCARDIOGRAPHY. Stress echocardiography using exercise, dipyridamole, and dobutamine has been evaluated to detect CAV (Table 2). The blunted heart rate response to exercise because of cardiac denervation limits the sensitivity (range 15% to 33%) of exercise testing to detect CAV (29–31). In contrast, the use of pharmacologic stress testing (dipyridamole and dobutamine) to detect CAV has been shown to be more sensitive (~85%; range 50% to 100%) (32–43). The variable specificity (range 41% to 95%) of dobutamine stress echocardiography (DSE) is likely a reflection of the differences in defining the presence and severity of CAV by coronary angiography. When compared with IVUS—a more sensitive gold standard—the specificity of DSE for CAV is higher (83% to 88%) (42,43). In comparison, Eroglu et al. (40) demonstrated that quantitative DSE using strain rate imaging detects CAV accurately regardless of the angiographic significance and that a post-systolic strain index >34% at peak stress was the best parameter.

PROGNOSTIC VALUE OF ECHOCARDIOGRAPHY. The clinical usefulness of noninvasive imaging in CAV relates also to the test's prognostic value (Table 3). Several investigators have demonstrated the impact of resting wall motion abnormalities and DSE findings on major adverse cardiac events (MACE) after HT, including heart failure, unstable angina, myocardial infarction, revascularization, retransplantation, and cardiac death (32–37,42,44–48). The majority of studies were performed more than 3 years after HT, with a follow-up on average of <3 years. The negative predictive value of a normal DSE was very high (~3% risk of experiencing MACE over the ensuing year). As demonstrated by Spes et al. (42), serial DSE may best prognosticate based on the finding that worsening DSE results were as predictive of subsequent events as serial coronary angiography or IVUS. Based on these overall results, annual evaluation with DSE is an acceptable alternative to invasive means for detection of CAV in transplant centers experienced in stress echocardiography.

PROMISING ECHOCARDIOGRAPHIC TECHNIQUES. Contrast-enhanced echocardiography is a recent technique that allows quantification of coronary

Table 1. Studies Evaluating the Accuracy of Different Echocardiography Techniques to Detect Acute Cellular Rejection

Author, Year (Ref. #)	Total Patients (Prevalence of ACR)	Method (Parameter Cutoff Value)	Gold Standard (EMB Score)	Sensitivity	Specificity	NPV
Angermann et al., 1997 (6)	52 (18%*)	Integrated backscatter	Grade ≥1B			
		(PW 2D-IB increase >1.5 dB)		88%	89%	97%
		(Septal 2D-IB increase >1.5 dB)		83%	85%	96%
Puleo et al., 1998 (15)	121 (13%)	PW-TDI	Grade ≥3A			
		(Ea of inferior wall <16 cm/s)		76%	88%	96%
Mankad et al., 1999 (20)	78 (18%)	Color-coded TDI	Grade ≥1B			
		(combined peak MV systolic and peak diastolic velocity <135 mm/s)		93%	71%	98%
		(posterior wall tissue Doppler diastolic time-gradient integral <0.26)		91%	61%	97%
Moidl et al., 1999 (23)	94 (20%)	Automated border detection	Grade ≥2			
		(peak filling rate <4.0 EDV/s)		100%	70%	100%
		(peak filling rate <4.0 EDV/s and >18% reduction)		100%	95%	100%
Stengel et al., 2001 (8)	41 (39%)	PW-TDI	Grade ≥3A			
		(Aa of lateral MV annulus <8.7 cm/s)		82%	53%	82%
Dandel et al., 2002 (3)	190 (17%*)	PW-TDI	Clinically relevant†			
		(Sm of basal posterior wall reduction ≥10%)		88%	95%	97%
		(Ea of basal posterior wall reduction ≥10%)		89%	97%	98%
Palka et al., 2005 (14)	44 (27%)	PW and color M-mode TDI	Grade ≥3A			
		(Ea of septal MV annulus <12 cm/s)		69%	46%	80%
		(peak late IVR MVG‡ >0.1/s)		88%	58%	93%
		(onset E wave –onset Emed§ >−35 ms)		81%	84%	92%
		(onset ETric –onset EMitr‖ >15 ms)		81%	84%	92%
Sun et al., 2005 (10)	2-D and standard Doppler	Grade ≥1B				
		(≥2 among PE, IVRT <90 ms E/A >1.7)				
	223 (37%*)	Post-HT ≤6 months		57%	54%	68%
	183 (27%*)	Post-HT >6 months		60%	93%	86%
	264 (29%*)	PW-TDI				
		(Aa of septal/lateral MV annulus <9.0 cm/s)		67%	49%	78%
Marciniak et al., 2007 (22)	31 (32%)	Color TDI	Grade ≥1B			
		(mid-LVPW radial peak systolic strain ≤30%)		85%	90%	93%
		(mid-LVPW radial peak systolic SR <3.0 s-1)		80%	86%	90%

*Prevalence of ACR based on the percentage of biopsies with ACR defined by the EMB score. †Clinically relevant ACR defined as EMB grade >2 plus grades 1A and 1B when accompanied by clinical symptoms. ‡Peak late isovolumic relaxation myocardial velocity gradient of the left ventricular posterior wall. §Timing difference between onset of mitral early diastolic velocity (E wave) and early diastolic septal MV annulus velocity (EMed). ‖Timing difference between onset of early diastolic velocity at lateral tricuspid (ETric) annulus and LV early diastolic lateral MV annulus velocity (EMitr).

Aa = peak late diastolic velocity; ACR = acute cellular rejection; dB = decibels; Ea = peak early diastolic velocity; EDV = end diastolic volume; EMB = endomyocardial biopsy; HT = heart transplantation; IVRT = isovolumic relaxation time; LVPW = left ventricular posterior wall; MV = mitral valve; NPV = negative predictive value; PE = pericardial effusion; PW 2D-IB = pulsed wave 2-dimensional-integrated backscatter; Sm = peak radial systolic velocity; SR = strain rate; TDI = tissue Doppler imaging.

flow reserve and/or myocardial perfusion mismatch to detect significant coronary artery disease. Preliminary studies in cardiac transplant recipients using stress echocardiography with contrast (49,50) show relatively high accuracy (85% to 89%) to detect CAV (Table 2). Moreover, Tona et al. (51) have demonstrated the validity of a lower coronary flow velocity pattern and flow reserve with contrast echocardiography as noninvasive markers of CAV-related MACE. These results, however, are based on a small number of patients, and further validation studies are warranted before widespread adoption can be advocated.

MPI and CAV. MPI DIAGNOSTIC VALUE. Similar to DSE, several studies have examined MPI using exercise, dipyridamole, and dobutamine to detect CAV (Table 2). The overall sensitivity and specificity range of MPI to detect CAV is broad (21% to 92% and 55% to 100%, respectively) (45,46,52–56). This variability may be explained by differences in the timing of the examinations, the stressors and/or MPI agents used, and the variable criteria used to diagnosis CAV.

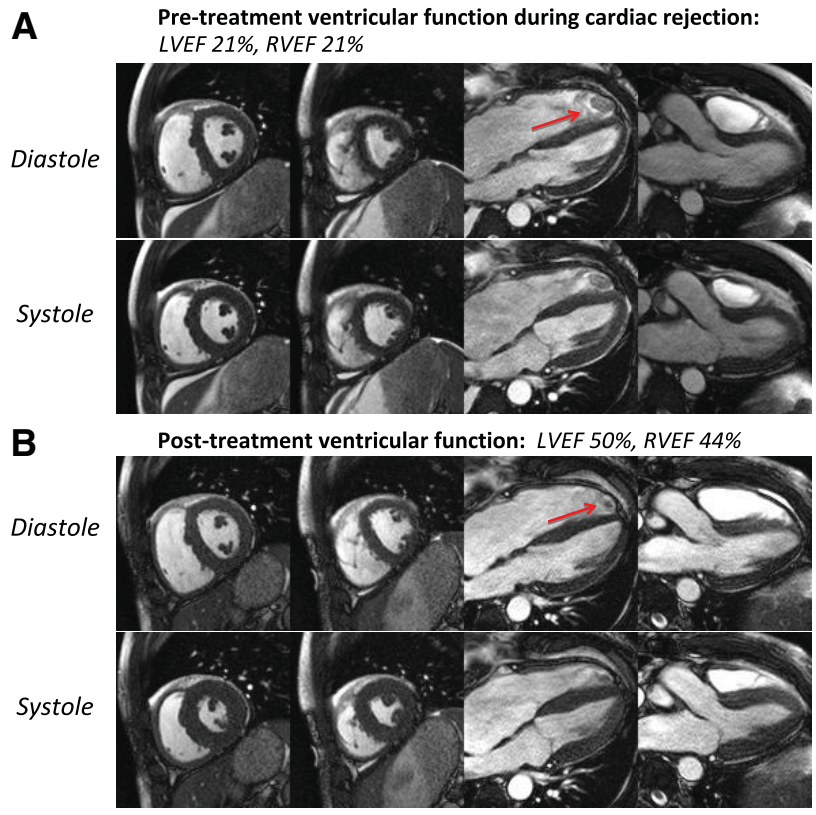

Figure 4. CMR Assessment of Left and Right Ventricular Systolic Function Pre- and Post-Treatment of an Episode of Cardiac Rejection

(**A**) Pre-treatment biventricular dysfunction with a large thrombus in the right ventricular apex **(arrow)**. (**B**) Two weeks post-treatment there was substantial improvement in biventricular function, and the thrombus appears to have decreased in size with anticoagulation therapy. Full-motion cine images can be viewed online. LVEF = left ventricular ejection fraction; RVEF = right ventricular ejection fraction.

Similar to the DSE literature, the sensitivity to detect CAV overall increases with the inclusion of studies that define CAV as coronary stenosis ≥50% (45,54,57). In addition, early studies were performed using thallium, which may encounter more attenuation artifacts than technetium-labeled radiopharmaceuticals and may account for the reported reduced accuracy compared with more recent studies (sensitivity ~86% and specificity ~80%) using technetium-labeled agents (46,52–54).

Compared with exercise and dipyridamole, dobutamine has been reported to be advantageous as a stressor because of its more reliable induction of ischemia in cardiac transplant recipients (inotropic effect, less blunted heart rate response). Moreover, the use of vasodilators with MPI may be limited in cardiac transplant recipients because the diffuse, microvascular CAV may impair the necessary increase in coronary flow reserve to trigger the flow heterogeneity to detect significant stenosis. Despite these observations, more recent studies using dipyridamole MPI have demonstrated comparable sensitivity (range 80% to 92%) and specificity (range 86% to 92%) to dobutamine stress MPI to detect CAV (46,52–54).

MPI PROGNOSTIC VALUE. Similar to DSE, the potential clinical usefulness of SPECT-MPI relates to its prognostic value. Although exercise testing linked with echocardiography and MPI is associated with low sensitivity to detect CAV, investigators have demonstrated that a normal exercise MPI at 1 year is a significant predictor of 1- and 5-year survival (45,48). Elhendy et al. (58) reported on 65 patients who underwent symptom-limited bicycle exercise with technetium-99m tetrofosmin MPI and demonstrated a similar ability to predict cardiac death in comparison with dobutamine. In contrast to these studies, Bacal et al. (34) reported that thallium scintigraphy with treadmill testing in a smaller number of patients was not an independent predictor of long-term 4-year survival.

Similar to the overall results of exercise MPI,

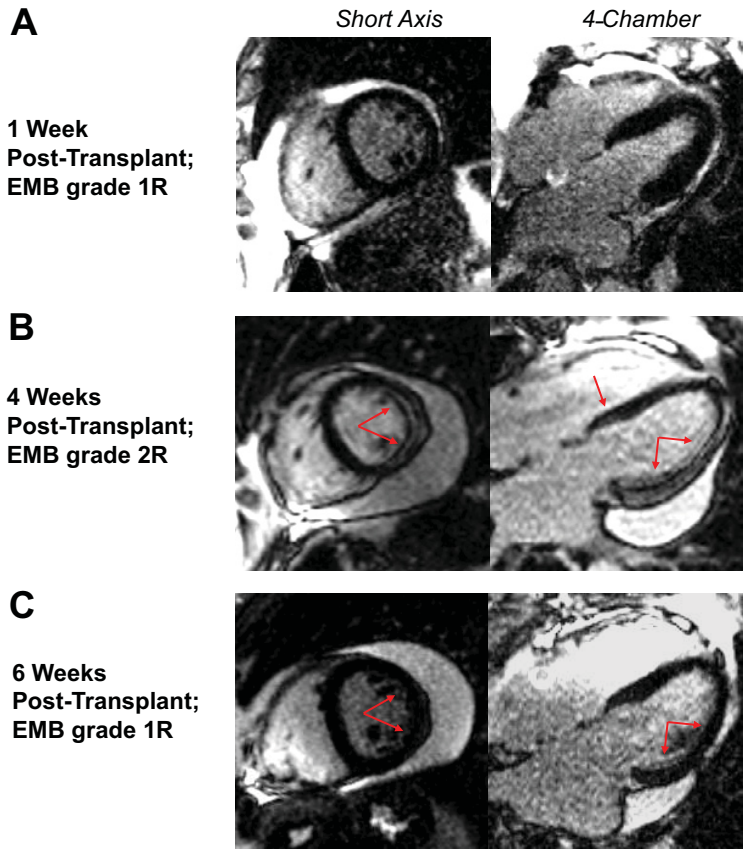

Figure 5. Hyperenhancement on Cardiac Magnetic Resonance Images in a Patient With ACR

(A) No hyperenhancement 1 week post-transplant. **(B)** Areas of hyperenhancement in the lateral wall and basal septum **(red arrows)** during an episode of (grade 2R) ACR. **(C)** Follow-up demonstrating near-complete resolution of the hyperenhancement in the lateral wall **(red arrows)** after treatment with intravenous steroids and enhancement of immunosuppression with corresponding EMB revealing resolving (grade 1R) ACR. ACR = acute cellular rejection; EMB = endomyocardial biopsy.

pharmacologic stress MPI also has significant prognostic value (Table 3). Two different investigators demonstrated that a normal dobutamine stress MPI study was associated with a 96% to 98% negative predictive value for MACE at ~2 years (54,58). In comparison, the use of dipyridamole MPI to predict MACE after HT is limited to 1 study (46) that demonstrated a lower sensitivity and negative predictive value, possibly because of the longer duration of follow-up (6.5 ± 2 years), supporting the notion that serial stress testing, whether with DSE or MPI, is required to maintain high sensitivity for subsequent events and for better prognostication.

MDCT coronary angiography and CAV. Initial studies with CT examined the diagnostic value of coronary calcium scoring with electron beam tomography to detect CAV, with conflicting results (59). MDCT coronary angiography, however, has been shown to detect significant coronary disease with relatively high sensitivities (70% to 100%) and specificities (81% to 100%) (60–66) (Table 2). MDCT offers the advantage of evaluating the coronary lumen as well as the wall. This may be potentially useful clinically to allow detection, grading, and follow-up of CAV, given that wall thickening and intimal hyperplasia are pathologic characteristics of CAV. Preliminary studies have demonstrated that changes in vessel wall can be accurately assessed using longitudinal and cross-sectional images of the coronary arteries to ensure adequate visualization of the concentric grey area surrounding the contrast-enhanced vessel lumen (63,66) (Fig. 7). Furthermore, up to ~ 50% of the segments considered thickened by MDCT may be considered normal by coronary angiography, highlighting the potential for early CAV detection (63). There is, however, a paucity of studies correlating changes in vessel wall by MDCT to IVUS to assess its true sensitivity.

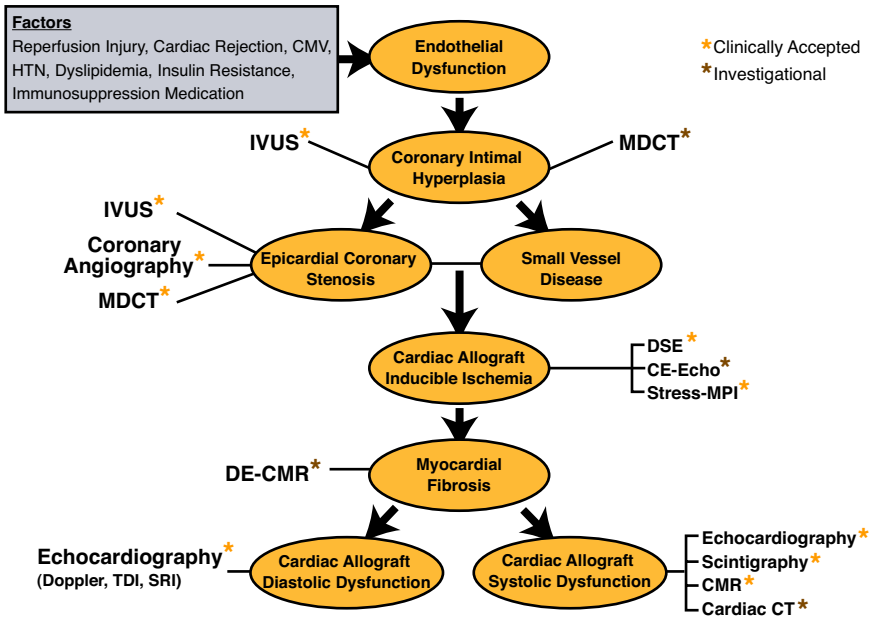

Figure 6. Different Noninvasive Imaging and Invasive Techniques Performed at Various Stages of Cardiac Involvement to Detect Cardiac Allograft Vasculopathy

CE = contrast-enhanced; CMR = cardiac magnetic resonance; CMV = cytomegalovirus; CT = computed tomography; DE-CMR=delayed enhancement cardiac magnetic resonance; DSE = dobutamine stress echocardiography; HTN = hypertension; IVUS = intravascular ultrasound; MDCT = multidetector computed tomography; MPI = myocardial perfusion imaging; SRI = strain rate imaging; TDI = tissue Doppler imaging.

The use of MDCT does pose the technical challenge of reducing the heart rate enough (ideally <65 beats/min) to minimize motion artifact. As a result of cardiac denervation, the resting heart rate in cardiac transplant recipients is typically elevated, between 80 and 110 beats/min. Pre-medication with beta-blockers has been associated with a decrease and delay in heart rate reduction. Pre-medication with relatively high doses and increased frequency of beta-blockers have reduced the heart rate in cardiac transplant recipients to an acceptable level in some studies (63,67), whereas heart rates remained high, despite similar efforts, in another study (66). A high mean heart rate during MDCT scanning can impair image quality, as reported by Pichler et al. (62) with incomplete visualization in 27% of patients (mean heart rate 87 ± 9.7 beats/min) mainly owing to cardiac motion. With newer 64-slice scanner technology and multisector reconstruction algorithms, however, a heart rate of ~80 beats/min may permit adequate visualization.

Despite this limitation, several studies report a relatively high diagnostic image quality with 81% to 96% of the coronary segments defined as either of diagnostic or satisfactory quality (60,62,63,66). A common reason, however, for nonevaluability of coronary segments relates to the small-vessel nature of CAV (60,66). The published reproducibility analysis of MDCT (64-slice) angiography to detect significant CAV seems good with an inter-rater kappa coefficient of 0.70 with a standard error of 0.104 (95% confidence interval: 0.496 to 0.905) (66). Potential limitations of MDCT scanning in cardiac transplant recipients relate to the radiation and contrast media exposure associated with this technique, which is especially important given that chronic renal failure is frequent in cardiac transplant recipients (1) and pre-existing renal disease is a well-accepted risk factor for contrast-induced nephropathy. Preliminary studies, however, have demonstrated that with pre- and post-test hydration and use of oral N-acetylcysteine in patients with normal baseline renal function, contrast-acquired renal dysfunction is an uncommon clinical problem (60,63,66).

CMR and CAV. Delayed enhancement CMR may be useful indirectly for the detection of CAV, based on the ability to identify areas of delayed hyperenhancement that likely correspond to silent myocardial infarctions (68). Steen et al. (68) examined 53 cardiac transplant recipients with delayed enhancement CMR performed within 4 weeks of coronary angiography. They classified patterns of hyperen-

Table 2. Studies Evaluating the Accuracy of Different Noninvasive Imaging Techniques to Detect CAV

Author, Year (Ref. #)	Total Patients (Prevalence of CAV)	Time Post-HT (yrs)*	Gold Standard	Sensitivity	Specificity
Exercise Stress Echocardiography					
Collings et al., 1994 (30)	51 (27%)	4.2 (1–17)	CCA†	29%	82%
Mairesse et al., 1995 (31)	37 (11%)	2.8 ± 1.4	CCA‡	0%	97%
Cohn et al., 1996 (29)	51 (51%)	2.5 (1–6)	CCA† (IVUS)§	33% (15%)	85% (85%)
Dipyridamole Stress Echocardiography					
Ciliberto et al., 1993 (35)	80 (31%)	2.3 ± .5	CCA†	100%	72%
Ciliberto et al., 2003 (36)	68 (37%)	2.9 ± 1.9	CCA†	100%	87%
Dobutamine Stress Echocardiography					
Akosah et al., 1994 (33)	41 (51%)	4.8 (0.25–10)	CCA†	100%	41%
Herregods et al., 1994 (41)	28 (50%)	3.2 ± 1.3	CCA‡	50%	71%
Akosah et al., 1995 (69)	45 (53%)	4.8 ± 0.3	CCA‡	96%	52%
Derumeaux et al., 1995 (37)	41 (38%)	3.3 ± 1.7	CCA†	100%	77%
Derumeaux et al., 1996 (38)	64 (47%)	3.3 ± 1.2	CCA†	100%	NR
Spes et al., 1996 (43)	46 (26%)	4.8 ± 2.6	CCA‡ (IVUS)‖	83% (79%)	56% (83%)
Akosah et al., 1998 (32)	22 (32%)	0.17 (0.04–0.33)	CCA†	100%	59%
Derumeaux et al.,¶ 1998 (39)	37 (46%)	3.1 ± 1.7	CCA‡	65%	95%
	37 (70%)	4.7 ± 1.8	CCA‡	92%	73%
Spes et al., 1999 (42)	109 (46%)	3.2 ± 3.1	CCA‡ and/or IVUS‖	72%	88%
Bacal et al., 2004 (34)	39 (38%)	7.2 ± 2.6	CCA†	64%	91%
Eroglu et al.,# 2008 (40)	42 (19%)	6.0 ± 4.0	CCA‡‡	75%–88%	79%–88%
Contrast-Enhanced Stress Echocardiography					
Rodrigues et al.,** 2005 (49)	35 (29%)	6.0 ± 2.6	CCA†	70%	96%
Tona et al.,†† 2006 (50)	73 (47%)	8.0 ± 4.5	CCA†	82%	87%
Exercise MPI					
Ciliberto et al., 1993 (45)	50 (30%)	1.7 (1–5)	CCA‡	67%	100%
Rodney et al., 1994 (55)	25 (52%)	3.1 ± 1.1	CCA‡‡	77%	100%
Dipyridamole MPI					
Smart et al., 1991 (56)	73 (26%)	2.5 ± 1.3	CCA† or autopsy§§	21%	88%
Ciliberto et al., 2001 (46)	78 (15%)	2.7 ± 1.9	CCA‡‡	92%	86%
Carlsen et al.,‖‖ 2000 (52)	67 (7%)	5.6 (2.1–12)	CCA†	80%	92%
Dobutamine MPI					
Elhendy et al., 2000 (53)	50 (60%)	6.4 ± 2.8	CCA†	90%	55%
Hacker et al., 2005 (54)	63 (17%)	7.4 ± 3.5	CCA†	82%	87%
MDCT Coronary Angiography					
Romeo et al., 2005 (63)	44 (14%)	7.6 ± 3.8	CCA†	83%¶¶	95%¶¶
Sigurdsson et al., 2006 (64)	54 (30%)	NR	CCA† (IVUS)##	94% (92%¶¶)	79% (95%¶¶)
Gregory et al., 2006 (60)	20 (80%)	5.8 ± 4.4	IVUS***	70%¶¶	92%¶¶
Pichler et al., 2008 (62)	60 (20%)	8.5 ± 5.2	CCA†††	88%	97%
von Ziegler et al., 2008 (66)	26 (19%)	7.7 ± 4.1	CCA†	100%	81%
Vermes et al., 2006 (65)	50 (19%)	7.7 ± 4.0	CCA†	87%¶¶	100%¶¶

*In years ± SD; if SD not reported, range of years is given. †Coronary stenosis >50% in at least 1 vessel. ‡Any coronary obstruction including luminal irregularities. §Standford IVUS class III to IV. ‖Modified mean Standford class III to IV. ¶Derumeaux et al. examined the accuracy of stress echocardiography in a single group of patients at 2 different time points. #Eroglu et al. used conventional and quantitative stress echocardiography (post-systolic strain index response). **Rodrigues et al. used contrast-enhanced dobutamine stress echocardiography to assess perfusion. ††Tona et al. used contrast-enhanced adenosine stress echocardiography to assess coronary flow reserve. ‡‡Coronary stenosis >50% in at least 1 vessel and/or significant diffuse luminal narrowing. §§Cross-sectional coronary obstruction >70% on autopsy. ‖‖Carlsen et al. study included 4 patients with bicycle exercise testing as the stressor. ¶¶Sensitivity and specificity analysis by coronary segment. ##Any abnormal wall thickening by IVUS. ***IVUS intimal thickness >0.5 mm. †††Coronary stenosis >70%. Modified from Thorn et al. (13).

CAV = cardiac allograft vasculopathy; CCA = conventional coronary angiography; HT = heart transplantation; IVUS = intravascular ultrasound; MDCT = multidetector computed tomography; MPI = myocardial perfusion imaging; NR = not recorded.

hancement with distinct subendocardial involvement as "infarct typical" and likely indicative of myocardial infarction. The prevalence of this pattern increased with worsening of CAV (present in only 25% of patients with mild CAV compared with 84% in patients with severe CAV). The presence of "infarct-typical" hyperenhancement was also associated with worse LV function and higher end-diastolic and -systolic volumes. Although these findings suggest that CMR might be useful in the

Table 3. Studies Evaluating the Accuracy of Different Noninvasive Imaging Techniques to Detect MACE

Author, Year (Ref. #)	Total Patients (Prevalence of MACE)	Time Post-HT (yrs)*	Length of Follow-Up (Months)	Detection of MACE		
				Sensitivity	Specificity	NPV
2-Dimensional Echocardiography WMA						
Ciliberto et al., 1993 (35)	80 (9%)	2.3 ± 1.5	9.8 ± 4.5	100%	73%	100%
Verhoeven et al., 1996 (48)	46 (11%)	NR	45 ± 20	40%	98%	93%
Spes et al., 1999 (42)	109 (15%)	3.2 ± 3.1	>60 in some cases	75%	65%	94%
Ciliberto et al., 2001 (46)	78 (22%)	2.7 ± 1.9	78 ± 24	41%	97%	85%
Ciliberto et al., 2003 (36)	68 (28%)	2.9 ± 1.9	72 ± 36	80%	68%	90%
Dipyridamole Stress Echocardiography						
Ciliberto et al., 1993 (35)	80 (9%)	2.3 ± 0.5	9.8 ± 4.5	100%	71%	100%
Ciliberto et al., 2003 (36)	68 (28%)	2.9 ± 1.9	72 ± 36	80%	68%	90%
Dobutamine Stress Echocardiography						
Akosah et al., 1994 (33)	76 (16%)	4.8 (0.25–10)	10 ± 2	100%	41%	100%
Derumeaux et al., 1995 (37)	41 (5%)	3.3 ± 1.7	6.0	100%	66%	100%
Akosah et al., 1996 (44)	64 (25%)	4.8 ± 2.4	24 (18–28)	100%	69%	100%
Lewis et al., 1997 (47)	63 (56%)	4.8 ± 2.6	8.0 (4–14)	83%	NR	NR
Akosah et al., 1998 (32)	22 (10%)	0.17 (0.04–0.33)	32 ± 11	100%	61%	100%
Spes et al., 1999 (42)	109 (15%)	3.2 ± 3.1	>60 in some cases	94%	57%	98%
Bacal et al., 2004 (34)	39 (25%)	>4.0	48	60%	86%	87%
CE-Stress Echocardiography						
Tona et al.,† 2006 (51)	66 (17%)	9.0 ± 4.0	19 ± 5	86%‡	75%‡	97%
				91%§	62%§	97%
Dipyridamole MPI						
Ciliberto et al., 2001 (46)	78 (22%)	2.7 ± 1.9	78 ± 24	53%	82%	86%
Dobutamine MPI						
Hacker et al.,‖ 2005 (54)	77 (13%)	7.4 ± 3.5	22 (12–48)	90%¶	72%¶	98%
				90%#	88%#	98%
Elhendy et al.,** 2002 (58)	166 (10%)	7.4 ± 2.5	30	69%	71%	95%

*Mean ± SD; if not available, range is provided. †Tona et al. used CE echocardiography to assess accuracy of deceleration time of diastolic flow velocity ‡(cutoff value <840 ms) and coronary flow reserve §(cutoff value <2.6). ‖Hacker et al. compared visual¶ and semiquantitative# (summed stress score >3) analysis. **Elhendy et al. study (65 of the 166 patients reportedly underwent exercise not dobutamine testing; however, both stress modalities shared similar ability to predict cardiac death). Modified from Thorn et al. (13).
CE = contrast enhanced; HT = heart transplantation; MACE = major adverse cardiac event; MPI = myocardial perfusion imaging; NPV = negative predictive value; NR = not recorded; WMA = wall motion abnormality.

detection of CAV, the clinical significance and pathologic basis of these findings are unknown. Validation and prospective outcome-based studies are currently underway.

Conclusions

Despite many advances in the field of HT, ACR, and CAV represent significant causes of early and late morbidity and mortality, respectively. Different imaging modalities, including echocardiography, SPECT-MPI, MDCT, and CMR have been used after HT to monitor multiple clinically important parameters of cardiac graft structure and function. In general, echocardiography represents the primary noninvasive modality for monitoring cardiac function in transplant recipients based on its ability to detect abnormalities of ventricular systolic function, provide estimation of right- and left-sided filling pressures with reasonable accuracy, and evaluate pericardial effusions or other complications from repeated biopsies.

With regard to the detection of ACR, when the echocardiography literature is taken as a whole, there are inconsistencies among various reports brought about by small sample size, variability in the reference gold standard used, and different cutoff points for the different echocardiography parameters evaluated. Today, echocardiographic techniques lack the sensitivity and specificity to replace EMBs to detect clinically significant ACR. Promising echocardiography techniques involving TDI and strain imaging are associated with relatively high negative predictive values in the detection of ACR. However, further validation and outcome-based studies are required before a specific echocardiography parameter can be recommended as a screening index to minimize the use of serial

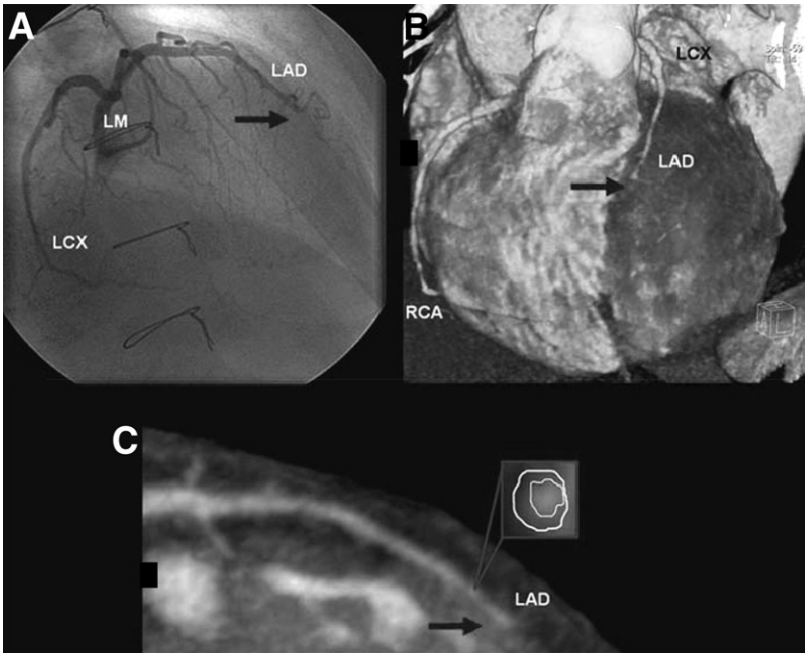

Figure 7. MDCT Coronary Angiography Demonstration of Cardiac Allograft Vasculopathy

(A) Total vessel occlusion of left anterior descending (LAD) is illustrated by conventional coronary angiography. **(B)** Corresponding LAD occlusion by MDCT volume-rendering angiography. **(C)** Maximum intensity projection; grey arrows indicate site of total vessel occlusion; proximal of occlusion, an excentric noncalcified plaque is depicted in a cross-sectional image (note diffuse hypodense vessel wall changes throughout the LAD course, causing no to minimal luminal irregularities in conventional coronary angiography). LCX = left circumflex; LM = left main coronary artery; MDCT = multidetector computed tomography; RCA = right coronary artery. Adapted from von Ziegler et al. (66) with permission.

biopsies. CMR, similar to echocardiography, can accurately detect ventricular systolic dysfunction, and newer CMR techniques may allow the detection of myocardial edema and necrosis—hallmarks of ACR.

In contrast, with respect to CAV, stress imaging with DSE and MPI and coronary angiography with MDCT are powerful techniques to identify this late complication with high accuracy. DSE is the most-studied technique with significant prognostic value comparable to that of IVUS and invasive coronary angiography. For transplant centers experienced in stress echocardiography, an invasive examination to detect significant CAV can be reserved for patients with an abnormal annual DSE. Although echocardiography has the advantage of lower cost, the use of MPI, especially with dobutamine, is a comparable alternative in cardiac transplant recipients given its prognostic value. MPI may be especially useful in patients with inadequate acoustic windows despite the use of a contrast echocardiography agent and in centers without adequate experience in DSE.

Newer CMR techniques may allow the detection of abnormal hyperenhancement to detect CAV noninvasively; further pathologic and outcome studies, however, are needed. With the ability of MDCT coronary angiography to evaluate the coronary wall in addition to the lumen, MDCT has the potential for earlier detection of CAV compared with echocardiography, MPI, and CMR. This earlier detection of CAV may enhance research in this field and prompt the early use of proliferation signal inhibitors or other investigations to minimize CAV disease progression and improve outcome. Further validation of MDCT, however, is needed in larger studies. Furthermore, because this technique is also associated with radiation and contrast exposure, the risk/benefit ratio needs to be concomitantly evaluated, given the need for serial examinations and the high incidence of renal insufficiency in this patient population.

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