Role of Noninvasive Imaging in the Diagnosis of Cardiac Allograft Vasculopathy

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Cardiac allograft vasculopathy (CAV) is common, with a prevalence of 52% at 10 years after transplantation, and represents a leading cause of death beyond the first year, responsible for approximately 15% of deaths annually. It is characterized by diffuse and concentric intimal proliferation, typically involving the intramural as well as epicardial coronary arteries. Its diagnosis is difficult to establish clinically because of denervation of the transplanted heart. Consequently, it presents late with silent myocardial infarction, progressive heart failure, or arrhythmic sudden death. Screening is therefore required for its early detection.

Although coronary intravascular ultrasound (IVUS) is considered the gold-standard technique for detecting the anatomic features of CAV (Table 1), its broad clinical use in this context is limited by cost and lack of widespread expertise, and its evaluation is limited to epicardial vessels. Coronary angiography, performed annually or biannually, remains the most common clinical screening method. However, because of the diffuse nature of CAV with a lack of normal reference segments and the relatively late occurring luminal narrowing, the sensitivity of angiography is as low as 30% when compared with IVUS (Figure 1). As a result, complications frequently occur before disease is evident angiographically. Furthermore, angiography is associated with significant albeit uncommon complications (overall complication rate, 7.4/1000 procedures, including rates of 0.65/1000, 1.6/1000, and 0.72/1000 for cerebrovascular accidents, vascular complications, and death, respectively), is disliked by transplant recipients, is costly, and repeated studies are associated with an important cumulative radiation dose.

Noninvasive screening would conceivably be safer, more tolerable and cheaper and as such is highly desirable. Echocardiography and single-photon emission computed tomography (SPECT) are the most extensively investigated, but neither has become widely accepted as an alternative to invasive screening. Preliminary data regarding positron emission tomography (PET), cardiovascular magnetic resonance (CMR), and coronary computed tomographic angiography (CTA) suggest that these modalities may prove to be more effective.

The evaluation of imaging modalities faces 2 particular challenges. First, invasive coronary physiological assessment demonstrates that the functional significance of CAV represents a complex interplay between epicardial and microvascular coronary compartments. Both must be taken into account for accurate diagnosis. Second, as described, the clinical standard for detecting CAV (ie, angiography) has limited sensitivity. Therefore, studies using this as the sole comparator are inherently limited in the information they provide. Furthermore, angiographic coronary stenoses of 50% or 70%, often used as the significance threshold in such studies, represent advanced disease. Adverse events frequently occur well before this degree of luminal narrowing is reached.

The pathophysiology, invasive diagnostic assessment, and treatment of CAV have been extensively reviewed in a recent article by Schmauss et al. This review will focus on the noninvasive imaging approaches for the diagnosis of CAV.

<table>
<thead>
<tr>
<th>Table 1. Stanford Classification of CAV Severity on IVUS</th>
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<tr>
<td>Severity</td>
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<tr>
<td>Intimal thickness</td>
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<td>or</td>
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<td>Extent of plaque</td>
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CAV indicates cardiac allograft vasculopathy; IVUS, intravascular ultrasound.


Echocardiography

The sensitivity of resting left ventricular ejection fraction and regional wall motion for detecting CAV is low, at <50% across multiple studies, although the specificity of regional...
dysfunction is much higher (>80%) and should prompt further investigation. Tissue Doppler imaging may improve sensitivity; indeed, a study using pulsed-wave tissue Doppler obtained at the basal left ventricular inferolateral wall in nearly 300 transplant recipients found a peak systolic wall motion velocity ≥10 cm/s had a 97% positive predictive value for CAV, whereas a value of ≥11 cm/s had a 90% negative predictive value. The comparator was angiography and IVUS (those without angiographic evidence of CAV also underwent IVUS) (Figure 2).

Stress echocardiography is the most widely investigated functional imaging technique for detecting CAV, although published studies are relatively small with heterogeneous design and varying results (Table 2). Dobutamine-stress appears to be more sensitive than exercise, most likely because allograft denervation results in a blunted heart-rate response to exercise. The largest study, which included 109 patients, found dobutamine stress echocardiography (DSE) to have a sensitivity and specificity of 72% and 88%, respectively, for the diagnosis of CAV, defined as approximately Stanford class III or IV on IVUS (Table 1) or any luminal irregularities on angiography.

Quantitative DSE analysis using regional deformation parameters may improve sensitivity. In a study of 42 patients undergoing DSE with color myocardial Doppler imaging, a peak systolic longitudinal strain rate of <0.5/s had a sensitivity of 88% for detecting any angiographic abnormalities including minor diffuse irregularities, compared with 63% for...
conventional DSE analysis. Mitral annular systolic, early diastolic, and late diastolic velocities at peak dobutamine-stress are also reduced in transplant recipients despite no demonstrable abnormality in regional systolic function.

The value of myocardial contrast echocardiography (MCE) to assess myocardial perfusion remains to be established in CAV. In a study of 33 patients undergoing dobutamine stress, semiquantitative MCE (ratio of stress and rest myocardial signal intensity upslopes) had a sensitivity and specificity of only 58% and 67%, respectively, for detecting significant CAV, defined as a combination of ≥50% stenosis on angiography or significant wall irregularities on IVUS and an associated reversible perfusion defect on SPECT. However, when MCE analysis was combined with conventional DSE analysis, sensitivity and specificity improved to 86% and 91%, respectively, compared with 71% and 83%, respectively, for conventional DSE analysis alone. In another study, qualitative dobutamine-stress MCE performed in 35 patients had a sensitivity and specificity of 70% and 96%, respectively, for detecting angiographic stenoses >50%. Correlation with coronary territory was poor except for the left anterior descending artery (LAD), and it failed to identify disease extent.

Direct measurement of coronary blood flow velocity at rest and during adenosine stress in the distal LAD, using contrast-enhanced transthoracic Doppler echocardiography to calculate coronary flow reserve (CFR) has also been used to assess for CAV. In a study of 22 patients, a CFR of <2.9 had sensitivity, specificity, and negative predictive value of 80%, 100%, and 89%, respectively, for detecting a maximal intimal thickness of ≥0.5 mm on IVUS.

Both resting and stress echocardiography provide useful prognostic information, with DSE in particular having a high negative predictive value for adverse cardiac events. In the largest prognostic study, 1 of 159 normal DSEs (0.6%) were followed by an adverse cardiac event during a mean 2.5-year follow-up.

**Nuclear Imaging**

As with the DSE literature, there is considerable variation in methodology and results of studies assessing the accuracy of
SPECT for detecting CAV. Of note, SPECT has only been assessed in relation to angiography, most commonly using luminal narrowing of ≥50% (Table 3). In the largest study, dipyridamole-stress sestamibi SPECT had a sensitivity and specificity of 92% and 86%, respectively, when compared with luminal narrowing of ≥50% but a sensitivity of only 56% when compared with any angiographic abnormalities including minor luminal irregularities.31

Like DSE, dobutamine-stress SPECT provides important prognostic information. In 2 studies of 77 and 166 patients followed up for 22 and 30 months, respectively, 12-month negative predictive values for major cardiac events were 98% and 95%.33,35 The prognostic value of dipyridamole-stress SPECT may be lower (negative predictive value of 86% in a study of 78 patients), although this has only been assessed in a single study with a substantially longer follow-up (mean, 78 months).31

The ability of PET to readily quantify myocardial blood flow (MBF) has provided insight into coronary artery function in CAV; indeed there are data, albeit limited at present, to suggest that this ability may allow PET to be more sensitive for detecting CAV than other noninvasive techniques.

Studies using PET have shown that resting MBF is higher in transplant recipients than in healthy control subjects, thought to be due to the increased resting heart rate secondary...
PET has also been used to demonstrate impaired endothelial function in CAV, with an abnormal MBF response to cold-pressor testing due to impairment of vasodilatory capacity. Furthermore, PET data have shown that MBF is homogeneous across coronary territories, in keeping with the diffuse nature of the CAV. This finding may explain in part the limited sensitivity of conventional functional imaging techniques that rely on the development heterogeneity in MBF or contractility (Figure 3).

In 2 studies using $^{13}$N-ammonia PET, myocardial perfusion ratio (MPR, ratio of absolute MBF during stress and rest) correlated significantly with IVUS measures of CAV severity, albeit with modest correlation coefficients. In the first study, using adenosine stress in 27 patients with normal angiographic appearances, MPR showed a significant inverse correlation with plaque volume index, defined as total plaque volume divided by total vessel volume×100 ($r = -0.40$; $P < 0.05$). In the second study using dipyridamole stress in 32 patients, MPR showed a significant inverse correlation with mean maximal intimal thickness and intimal index, defined as intimal area divided by intimal plus luminal area ($r = -0.61$; $P < 0.005$ and $r = -0.52$; $P < 0.05$, respectively).

Further highlighting the advantage of absolute MBF, 20% of subjects regarded as normal by semiquantitative PET analysis (summed stress and rest scores) had a significantly abnormal MPR. In another study in which dipyridamole-stress $^{13}$N-ammonia PET and IVUS were performed in 17 patients at 18 months after transplant, MPR predicted the changes in total vessel area and luminal diameter seen on repeat IVUS 15 months later.

A limitation of nuclear imaging as a screening tool is the associated radiation dose, particularly with serial studies. PET also remains expensive with limited availability.

**Cardiac Magnetic Resonance**

The versatility and safety profile of CMR make it attractive as a screening modality for CAV, but evidence is limited at present.

In a study of 69 transplant recipients with no evidence of acute rejection, mean diastolic strain rate (mean strain rate
Figure 4. Midventricular short-axis circumferential strain and strain rate derived from tagged cardiac magnetic resonance (CMR) images in patients in minimal (A through D) and severe (E through H) cardiac allograft vasculopathy. Strain maps (B and F), derived from tagged CMR images (A and E, respectively), use color to display degree of strain. Strain and strain rate (peak systolic and diastolic) were reduced in the patient with severe disease (G and H) compared with the patient with minimal disease (C and D). Left ventricular ejection fraction was normal in both patients.
from peak systole to 50% of diastole) measured using CMR tagging at 1.5 T was significantly reduced in patients with severe CAV (angiographic luminal narrowing ≥50%) and with minor CAV (lumen irregularities or focal stenoses <50%), compared with age-matched healthy control subjects. Mean diastolic strain rate also allowed differentiation between transplant recipients with severe CAV, minor CAV, and normal angiographic appearances. Systolic parameters were less sensitive (Figure 4).

The prevalence of infarct-typical late-gadolinium enhancement (LGE) and mean infarct mass per patient on CMR imaging in a study of 53 transplant recipients correlated significantly with the degree of CAV visible at angiography. The majority of infarcts were found in the mid and apical segments, with no correlation to coronary territory. Interestingly, nearly a quarter of patients with mild angiographic CAV (minor irregularities causing <30% stenosis) had infarct-typical LGE. The authors suggested this was due to “silent” myocardial infarction occurring in the presence of nonsignificant angiographic disease and may provide further evidence of prognostically significant CAV occurring in the absence of significant angiographic changes. However, patients were not scanned at baseline (ie, shortly after transplant) and therefore unrecognized infarct in the donor heart or perioperative infarction could not be excluded as the cause. The study also described the presence of infarct-atypical LGE patterns unrelated to angiographic severity, the cause and significance of which are not clear.

In a study of 69 transplant recipients undergoing adenosine-stress perfusion CMR, semiquantitative MPR (ratio of stress and rest signal intensity upslopes) was significantly reduced in transplant recipients with severe CAV (angiographic luminal narrowing ≥50%), minor CAV (irregularities causing <50% stenosis), and even those with angiographically normal arteries compared with aged-matched healthy volunteers. MPR also allowed differentiation between grades of CAV. In another study that included 27 patients, those with severe CAV (angiographic stenoses ≥50% in all major epicardial vessels) had a significantly lower MPR (ratio of stress and rest maximum signal intensity) and resting endocardial:epicardial maximal signal intensity ratio than patients without angiographically evident disease.

Interestingly, in a subgroup of patients with normal angiographic appearances but with significantly reduced coronary flow reserve on invasive Doppler assessment, MPR and resting endocardial:epicardial ratio were significantly reduced. In a further study of 17 patients, resting absolute endocardial blood flow and resting endocardial:epicardial blood flow ratio were significantly lower in patients with severe CAV (≥50% stenosis in all major epicardial vessels and an invasive coronary flow reserve of <2.5) than in patients with a normal invasive parameters (Figure 5).

Noncontrast, respiratory-navigated, 3D, steady-state free precession CMR coronary angiography performed at 1.5 T in 16 patients had a sensitivity and specificity of 60% and 100%, respectively, for detecting CAV, defined as any irregularities on conventional angiography (per-segment analysis). Vessels with a diameter of <1.5 mm were excluded from analysis. Presently there are no published data on the prognostic value of CMR in CAV, although work is underway.
Nephrogenic systemic fibrosis (NSF) is an extremely rare but serious complication of gadolinium contrast administration that causes fibrosis of the skin and other organs and can result in significant functional impairment and reduced life expectancy. It is particularly associated with advanced chronic kidney disease or severe acute renal failure. Because renal dysfunction is common after transplant, with approximately 4% and 10% of patients having an estimated glomerular filtration rate (eGFR) of <30 mL/min per 1.73 m² at 5 and 10 years after transplant, respectively, NSF may limit the role of CMR in CAV screening.44 In one of the largest registries, overall incidence of NSF after a gadolinium contrast-enhanced magnetic resonance examination was 0.02%.45 All cases occurred in patients with an eGFR of <30 mL/min per 1.73 m²; particularly in those with an acute deterioration in renal function. Hemodialysis, especially when performed on the same day as imaging, was associated with a significant reduction in NSF incidence. Other risk factors for NSF include gadolinium dose administration of >0.1 mmol/kg, severe liver failure or liver transplant, and proinflammatory events such as tissue injury secondary to surgical procedures.

Cardiac devices for example, pacemakers, implantable cardioverter-defibrillators, and retained wires, also represent a potential limitation to CMR, although increasingly CMR-compatible devices are being manufactured.

**Computed Tomographic Angiography**

The potential combination of noninvasive luminal and vessel wall assessment makes CTA attractive for CAV screening.

Sixty-four detector CTA has been assessed in a small number of studies (Table 4). Two studies have compared CTA with IVUS, both defining CAV as intimal thickening >0.5 mm. In the first, which included 20 patients, sensitivity and specificity of CTA was 70% and 92%, respectively (analysis performed per-segment).46 β-Blockers were administered when resting heart-rate was above 65 bpm. Although this sensitivity may initially appear disappointing, the sensitivity of conventional angiography was only 11%. The considerably higher sensitivity of CTA was because it was able to visualize vessel wall changes and coronary plaque. Indeed, other studies have found 30% to 50% of coronary segments classified as normal by conventional angiography have wall thickening visible on CTA (Figures 6 and 7).47,51 In the second study, which included 30 patients, dual-source 64-detector CTA had a sensitivity and specificity of 85% and 84%, respectively, including correct identification of all 17 patients with CAV.50 Heart rate–limiting medication was not used. The authors suggested the greater sensitivity of CTA in this study was due to the higher temporal resolution afforded by dual-source technology.

Temporal resolution remains a weakness of CTA; indeed, motion artifact accounted for the majority of the 20% to 30% nonanalyzable coronary segments in the available studies. As such, the high resting heart-rate of transplant recipients (typically 80 to 110 bpm) together with a delayed and variable β-blocker response (mean heart rate in the available studies was 77 to 86 bpm after prescan β-blocker and 79 to 87 bpm without) represent particular challenges. Newer technology may lead to significant improvements; indeed, only 4% of segments were nonanalyzable in the described study utilizing dual-source CTA, despite a mean heart rate of 80 bpm.50 No studies have reported the use of I1 channel blockers.

CTA also has limited ability to assess smaller vessels, particularly important given the nature of CAV. Many of the available studies excluded vessels <1.5 mm from analysis, including the study using dual-source CTA.48

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**Table 4. Studies Evaluating the Accuracy of 64-Detector CTA for the Diagnosis of CAV**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n</th>
<th>CAV Diagnosis</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gregory et al,46 2006</td>
<td>20</td>
<td>IVUS*</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Iyengar et al,47 2006</td>
<td>19</td>
<td>Angiography†</td>
<td>100</td>
<td>67</td>
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<tr>
<td>Pichler et al,48 2008</td>
<td>60</td>
<td>Angiography‡</td>
<td>88</td>
<td>97</td>
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<tr>
<td>Von Ziegler et al,49 2008</td>
<td>26</td>
<td>Angiography¶</td>
<td>100</td>
<td>81</td>
</tr>
<tr>
<td>Schepis et al,50 2009</td>
<td>30</td>
<td>IVUS*</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>Nunoda et al,43 2010</td>
<td>10</td>
<td>Angiography¶</td>
<td>90</td>
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</tr>
</tbody>
</table>

*CTA indicates cardiac allograft vasculopathy; CAV, cardiac allograft vasculopathy; and IVUS, intravascular ultrasound.

**Intimal thickness >0.5 mm; †coronary stenosis <50% or minor luminal irregularities; ‡coronary stenosis >70%; §coronary stenosis ≥50%; ¶any angiographic abnormalities including luminal irregularities; |analysis by coronary segment.**

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**Figure 6.** Computed tomographic angiography of a patient 5 years after transplant showing diffuse concentric thickening of the wall of the mid left anterior descending artery (A, arrows), best seen in curved multiplanar reformatted (B, arrows) and short-axis images (C, arrowheads), but difficult to appreciate on invasive angiography (D, arrows).
Another drawback of CTA as a potential screening technique is the associated radiation dose. Average dose per CTA in the available studies was 9.5 to 21.4 millisieverts, compared with 2.0 to 6.0 millisieverts for conventional angiography. The latest CTA technology used in experienced centers for assessing native coronary artery disease is reported to be associated with much lower doses, although such technology often requires controlled heart-rates.

Furthermore, patients at risk of CAV are also at increased risk of contrast-induced nephropathy. High iodine concentration contrast is usually required for CTA in similar or greater volumes than for conventional angiography. Mean eGFR in patients 5 years after transplant is approximately 55 mL/min per 1.73 m², and the incidence of contrast-induced nephropathy is known to increase when eGFR is <60 mL/min per 1.73 m².44 Up to a quarter of potential patients were excluded from the available studies due to renal impairment.

Coronary calcium scoring is of limited value in CAV because calcification is often absent even in severe disease.52 There is no prognostic data for CTA in the context of CAV yet.

**Adenosine Supersensitivity**

Enhanced sensitivity of the denervated sinus and atrioventricular nodes to adenosine is well recognized in transplant recipients and therefore high vigilance is required for any functional imaging technique using this stressor agent.53 In a study of 102 transplant recipients undergoing SPECT, adenosine infusion at a dose of 140 μg/kg per minute over 6 minutes was associated with significantly higher rates of sinus pauses (4.9% versus 0%) and second-degree (11.8% versus 4.9%) and third-degree (2.9% versus 0%) atrioventricular block, compared with age and sex-matched nontransplant patients, resulting in early termination of 1.9% of studies, although there were no significant immediate or long-term sequelae.54

**Guidelines**

The 2010 International Society of Heart and Lung Transplantation Guidelines for the Care of Heart Transplant Recipients assign DSE and SPECT a class IIa recommendation, Level of Evidence B; stating that they “may be useful for the detection of CAV in transplant recipients unable to undergo invasive evaluation.”55 CTA is assigned a class IIb recommendation, Level of Evidence C; with the description “CTA shows promise in the evaluation of CAV although higher resting heart rates in these patients limit the technical quality.” PET and CMR are not included in the guidelines. Annual or biannual invasive coronary angiography is given a class I recommendation, Level of Evidence C. CAV screening is not included in the respective Appropriate Use Criteria for the imaging techniques described.

**Conclusions**

The development of accurate noninvasive imaging techniques for CAV screening is important, given the impact of the disease and the significant limitations of the current clinical surveillance technique. Echocardiography and SPECT are the most extensively investigated however most published studies are small with markedly differing methodologies and often discrepant results and as such, neither technique as found widespread acceptance for CAV screening. Newer techniques allowing quantification of myocardial deformation, visualization of myocardial injury, absolute MBF quantification, and arterial wall imaging hold potentially greater promise however supporting data are limited at present. Further investigation is needed in appropriately powered studies with evaluation against gold standard methods for characterizing the anatomic and physiological manifestations of CAV.

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**Disclosures**

None.

**References**


**KEY WORDS:** transplant vasculopathy ■ myocardial perfusion imaging ■ echocardiography ■ cardiac magnetic resonance imaging ■ cardiac computed tomography
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