Single photon emission computed tomography myocardial perfusion imaging to detect cardiac allograft vasculopathy

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Aims
Cardiac allograft vasculopathy (CAV) is a major cause of morbidity and mortality in cardiac transplant recipients. This study evaluates the usefulness of single photon emission computed tomography (SPECT) and various SPECT-derived diastolic variables to detect CAV in heart transplant patients.

Methods and results
A retrospective review of 141 SPECT studies with corresponding coronary angiograms within 12 months was performed on 99 transplant recipients. Diastolic function was assessed using computer-derived measures of peak filling rate (PFR), time to peak filling rate (TPFR), and mean first one-third filling rate (MFR/3). Angiography identified CAV in 53 of the 141 studies (38%). Of the 53, SPECT identified 7 with reversible myocardial defects (sensitivity 13%) and stress-induced electrocardiographic evidence of ischaemia was seen in one patient (sensitivity 2%). SPECT imaging was negative in 86 of the 88 negative coronary angiograms (specificity 98%). The positive predictive value and negative predictive value were 78 and 65%, respectively. If a more stringent definition of CAV was used (≥70% stenosis), the sensitivity and specificity were unchanged (14 and 98%, respectively). There was no statistical difference in diastolic variables between patients with or without angiographic evidence of CAV in regard to PFR (3.57 ± 1.14 vs. 3.18 ± 1.21 EDV/s, P = 0.90), TPFR (149 ± 32 vs. 153 ± 43 ms, P = 0.33), or MFR/3 (1.37 ± 0.43 vs. 1.27 ± 0.42 EDV/s, P = 0.94).

Conclusion
Adenosine stress/rest technetium-99m tetrofosmin-gated SPECT is not a sensitive test for detection of CAV in heart transplant recipients. Diastolic dysfunction, as assessed by SPECT, was not shown to be associated with development of CAV.

Keywords
Single photon computed tomography • Cardiac allograft vasculopathy • Cardiac transplantation • Myocardial perfusion imaging

Introduction
Cardiac allograft vasculopathy (CAV) is a major cause of morbidity and mortality in cardiac transplant recipients.1 It occurs in about 50% of heart transplant recipients in the first several years after surgery,2 and may manifest itself as progressive heart failure, ventricular arrhythmias, or sudden cardiac death.3 The pathogenesis of CAV is complex and poorly understood. Immunological factors as well as ischaemia and infections have been proposed as being responsible for causing the concentric intimal thickening that arises diffusely throughout the coronary circulation.2

Accurate detection of CAV has been proven to be challenging. Although coronary angiography is considered to be the ‘gold standard’ in diagnosing CAV, screening for CAV is often done with myocardial perfusion stress imaging using single photon emission computed tomography (SPECT). The sensitivity and specificity for detection of CAV using SPECT have been reported to be highly variable.4–7
The main objective of our current study was to determine the usefulness of gated SPECT for the detection of CAV. It is well recognized that coronary artery disease is a major cause of diastolic dysfunction among those who have not undergone heart transplantation. Our second objective was to assess various diastolic parameters using SPECT and determine their usefulness as an early marker of CAV in heart transplant recipients.

Methods

Patients

Between 2003 and 2009, we identified all cardiac transplant recipients at our institution (Loyola University Medical Center) who underwent both adenosine stress/rest technetium-99m tetrofosmin-gated SPECT imaging and coronary angiography within 12 months. All patients underwent adenosine vasodilator stress. A retrospective review was done of 141 SPECT imaging studies corresponding to 141 coronary angiograms performed on 99 patients post-orthotopic heart transplantation.

The local institutional review board approved the evaluation and presentation of the data. Informed consent was not required because all diagnostic testing performed was considered routine follow-up care for heart transplantation recipients in our institution.

Single photon emission computed tomographic imaging

Myocardial scintigraphy was performed using technetium-99m tetrofosmin. Patients were injected with 12 mCi dose of technetium-99m tetrofosmin and then underwent rest imaging using a Phillips Forte gamma camera. Approximately 30–45 min following the resting images, adenosine stress testing was performed using a 6 min infusion of adenosine at a standard dose of 140 mcg/kg/min. Electrocardiographic data were monitored continuously and were recorded at each 1 min interval until at least 2 min after the completion of adenosine infusion. Ischaemia was defined as ≥1 mv of horizontal or downsloping ST segment depression occurring 80 ms after the J point.

At 3 min into the adenosine induction, ~25 mCi of technetium-99m tetrofosmin was administered intravenously. SPECT stress images began ~10–15 min after the completion of the adenosine infusion.

Diastolic function was assessed using computer analysis-derived measures of peak filling rates (PFRs), time to peak filling rates (TPFRs), and mean first one-third filling rate (MFR/3). There were 117 studies available that contained these diastolic parameters. For 23 SPECT imaging studies, these data were unavailable.

Stress and resting images were reviewed by an experienced attending physician. A positive study was defined as any reversible perfusion defect. A negative study was defined as either normal perfusion or fixed perfusion defect. These data were then compared with coronary angiography results to determine the accuracy of detecting CAV.

Where indicated, Student’s t-test was used to detect statistically significant differences between group means, where \( P < 0.05 \) was considered significant.

Cardiac catheterization

All patients underwent coronary angiography within 12 months of their respective myocardial perfusion imaging tests. CAV was defined as ≥50% stenosis in one or more vessels and was interpreted by an experienced interventional cardiologist.

Results

All diagnostic testing was performed between the years 2003 and 2009. The study consisted of 99 patients (79% men, 31% with diabetes, 87% with a history of hypertension, and 88% with a history of hyperlipidaemia). The mean time from transplantation was 8.6 years (range 1–22.5 years). The mean age at the time of heart transplantation was 48. The various aetiologies of heart failure among our patient cohort are listed in Table 1.

Data obtained from 141 test results among 99 patients are shown in Table 2. The sensitivity, specificity, and positive and negative predictive values of SPECT to detect CAV are shown in Table 3. Among all coronary angiograms performed, 53 of 141 studies (38%) were found to have angiographic evidence of CAV. Of these 53 cases, only 7 had reversible myocardial perfusion defects (sensitivity 13%). SPECT imaging was negative in 86 of the remaining 88 negative coronary angiograms (specificity 98%). The positive predictive value and negative predictive value were 78 and 65%, respectively. If a more stringent definition of CAV were used (≥70% stenosis), the sensitivity and specificity remained unchanged (14 and 98%, respectively) and the positive predictive value and negative predictive value changed minimally (71 and 78%, respectively).

### Table 1  Aetiology of chronic heart failure among all patients

| Percentage | Ischaemic | 46 |
| Non-ischaemic | 54 |
| Idiopathic | Restrictive |
| Valvular | Peri-partum |
| Connective tissue disease | Congenital |
| Drug induced |  

### Table 2  Total number of SPECT perfusion imaging results, in comparison with the total number of coronary angiography tests performed

<table>
<thead>
<tr>
<th>Angiographic disease (≥50% stenosis)</th>
<th>No angiographic disease (&lt;50% stenosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPECT+ (≥70% stenosis)</td>
<td>SPECT− (≥70% stenosis)</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>44</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>30</td>
<td>104</td>
</tr>
</tbody>
</table>
All of the seven patients with both angiographic CAV and SPECT perfusion defects had significant stenoses in either the left main coronary artery or in at least two major epicardial coronary arteries (not minor branches). Characteristic of CAV, the lesions were all diffuse and there was no clear preponderance of proximal vs. distal locations.

In addition to the lack of an association of a positive SPECT with angiographic evidence of CAV, there was no association with stress-induced ischaemic electrocardiographic changes and angiographic evidence of CAV. Of the 53 studies found to have angiographic evidence of CAV, only one had ischaemic ECG changes (sensitivity 2%). There were only four patients who displayed ischaemic ECG changes during adenosine infusion. Of these four patients, only one patient had angiographic evidence of CAV (positive predictive value 25%).

As shown in Table 4, there was no statistical difference between the diastolic variables (PFR, TPFR, or MFR/3) among those who did or did not demonstrate evidence of CAV.

### Discussion

The diagnosis of CAV remains challenging when managing heart transplant patients. While coronary angiography remains the gold standard, this test is invasive; therefore, using a non-invasive screening method such as SPECT to detect early transplant vasculopathy is theoretically quite attractive. Furthermore, SPECT provides functional data and quantitative information about the amount of ischaemic myocardium at risk.

In our cohort of patients, adenosine stress/rest technetium-99m tetrofosmin SPECT was positive in only 7 of 53 cases of angiographically detected allograft vasculopathy. The low sensitivity makes it a poor screening test for CAV in heart transplant recipients. These results are similar to those obtained by Smart et al. who found a sensitivity of 21% using oral dipyridamole thallium-201 SPECT. However, these data conflict with other studies, which observed considerably higher degrees of sensitivity for detection of CAV using SPECT. Some of these differences may be explained by various criteria used to define a positive SPECT study; in the studies by Ciliberto et al. and Manrique et al., the authors define an abnormal SPECT as demonstrating reversible or fixed defects. Fixed defects are thought to represent old areas of myocardial injury which typically do not gain benefit from revascularization.

In our study, we defined a positive SPECT study as the one which showed a reversible perfusion defect; therefore, our study is felt to be more clinically relevant, in that it represents a patient population with reversible ischaemia, who would derive more benefit from cardiac catheterization and revascularization.

The explanation for the extremely low sensitivity of adenosine stress/rest technetium-99m tetrofosmin-gated SPECT is unclear. It may be due to a relative reduction in maximal coronary flow reserve using adenosine, combined with the diffuse nature of CAV in heart transplant patients. Ostó et al. have shown that the severity of CAV in heart transplant patients independently contributed to a reduction in coronary flow reserve. Heart transplant patients with angiographic evidence of CAV have a reduced vasodilator response to papaverine, and even minor CAV has been shown to reduce coronary flow reserve. Further evidence suggesting endothelial dysfunction in patients with angiographic evidence of CAV has been reported. Muggé et al. showed impaired flow velocity in response to injection of substance P, as well as decreased vasodilatory response of epicardial arteries to papaverine. In a study by Wolford et al., significant intra-patient variability in coronary flow reserve was observed in heart transplant patients with even minimal angiographic abnormalities, compared with those with no angiographic abnormalities. Mazur et al. showed a deterioration of coronary flow reserve over time in heart transplant patients that seemed to be independent of various haemodynamic parameters. They proposed that the decrease in coronary flow reserve over time may be due to primary abnormalities of the microcirculation; although others have shown that left ventricular hypertrophy, hypertension, and tachycardia, all of which often develop after heart transplantation, could negatively influence coronary flow reserve. In addition, Klaus et al. showed that higher donor age seems to contribute to a decrease in coronary flow reserve. Although not directly analyzed in our study, many of these aforementioned factors may have played a role in reducing maximal coronary flow reserve. Furthermore, given the diffuse nature of CAV and the global reduction in coronary flow during stress, it is possible that these baseline haemodynamic factors could influence the relative flow reserve to a greater degree than would be expected in patients without a history of heart transplantation.

### Table 3

<table>
<thead>
<tr>
<th>Percentage</th>
<th>CAV ≥ 50% stenosis</th>
<th>CAV ≥ 70% stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Specificity</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>PPV</td>
<td>78</td>
<td>71</td>
</tr>
<tr>
<td>NPV</td>
<td>65</td>
<td>78</td>
</tr>
</tbody>
</table>

NPV, negative predictive value; PPV, positive predictive value.

### Table 4

<table>
<thead>
<tr>
<th></th>
<th>Angiographic CAV</th>
<th>No angiographic CAV</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFR (EDV/s)</td>
<td>3.57 ± 1.14</td>
<td>3.18 ± 1.21</td>
<td>0.898</td>
</tr>
<tr>
<td>TPFR (ms)</td>
<td>149 ± 32</td>
<td>153 ± 43</td>
<td>0.322</td>
</tr>
<tr>
<td>MFR/3 (EDV/s)</td>
<td>1.37 ± 0.43</td>
<td>1.27 ± 0.42</td>
<td>0.941</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation.

EDV/s, end-diastolic volumes per second; MFR/3, mean first one-third filling rate; PFR, peak filling rate; TPFR, time to peak filling rate.
There may be other factors that impede coronary flow reserve, and thus potentially affect the response of the coronary circulation to adenosine. For example, it has been shown that plasma endothelin levels are elevated after heart transplantation.23 A net endothelin release in the coronary vasculature has also been associated with development of CAV.

Lastly, the effects of adenosine on the denervated heart may be altered. Substantial sympathetic reinnervation of the heart after transplantation may take years to occur.24 The magnitude of reinnervation that occurs 1 year or later after transplantation has been shown to be less compared with non-transplanted hearts. Furthermore, the process of reinnervation may be regionally heterogeneous. This may explain the inpatient variability in coronary flow reserve that has been demonstrated.15

It is important to consider the possibility that SPECT failed to detect adenosine-inducible hyperaemic perfusion defects in transplant recipients with angiographically significant coronary artery stenoses because there were no discrete perfusion abnormalities in these patients. It is well known that the extent of anatomical stenoses as determined by coronary angiography may not predict functional limitation of coronary blood flow.25 It is also possible that because of the diffuse nature and extent of the coronary stenoses characteristic of allograft vasculopathy, there could be extensive collateral formation leading to “balanced” adenosine-induced hyperaemia or “balanced” ischaemia. As such, in the presence of significant multivessel coronary artery disease, a heterogeneous distribution of blood flow upon adenosine vasodilator stimulus would be negated, resulting in homogeneous uptake of isotope throughout the myocardium resulting in no discrete perfusion defects.

Our results also demonstrate a lack of ischaemic ECG changes during adenosine infusion in patients who exhibited angiographic evidence of CAV. Furthermore, when ischaemic ECG changes were observed during stress, these were not predictive of angiographic evidence of CAV. These results are similar to previous studies demonstrating poor sensitivity of stress ECG to detect CAV.26,27 Furthermore, the 2% incidence of ischaemic-type ST segment depression is in the range of the 7.6% incidence reported as measured by these three variables, could be an early marker of CAV.6,26,27

We concluded that the diastolic variables of PFR, TPFR, or MFR/3 did not differ between patients with or without angiographic evidence of CAV. Our hypothesis was that diastolic dysfunction, as assessed by SPECT, was not shown to be associated with development of CAV.

Limitations
There are some limitations with our study. First, it is a retrospective analysis of a large cohort of heart transplant patients; therefore, it is subject to bias inherent in retrospective studies. In addition, although potential aetiologies influencing a reduction in coronary flow reserve were hypothesized, we did not specifically analyse these variables in our patient population. Lastly, because of the interval between angiography and SPECT imaging (in some instances up to 12 months), there could have been progression of the allograft vasculopathy which might have altered the results. Nevertheless, this possibility is not likely to substantially change the major conclusion of the study.

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References
Pulsatile thoracic mass after transcatheter aortic valve implantation

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A 85-year-old woman was referred to our hospital with a pulsatile mass in the surgical wound of a previous left thoracotomy (A: Supplementary data online, Video S1). Three months earlier, the patient underwent transcatheter aortic valve implantation via subclavian access with a 26-mm CoreValve prosthesis (Medtronic, Inc., Minneapolis, USA) due to severe aortic stenosis and predicted mortality of 25.3% (according logistic EuroSCORE). The procedure was complicated by cardiac tamponade related to a perforation in the left ventricle apex due to the guidewire, which required urgent thoracotomy and direct myocardial suture using 3/0 monofilament between two layers of Teflon (arrows). At admission, the patient was in good general appearance, afebrile, and haemodynamically stable. Suspecting content post-surgical ventricular pseudoaneurysm, it was performed a portable echocardiography study at emergency room that showed an apical left ventricular akinesia without images of rupture or aneurysms, or significant pericardial effusion (B and C: Supplementary data online, Videos S2 and S3). Subsequently, a contrast-enhanced multislice computed tomography (CMCT) was performed to define the aetiology of the mass. CMCT demonstrated a pericardial fluid collection (asterisks) that fistulized through the intercostal muscles into the subcutaneous tissue, showing no blood density and with no evidence of contrast leakage from cardiac chambers (D, E, and F). With image diagnosis of post-surgical seroma, it was decided to drain. Despite the gross appearance of purulent drainage, microbiological culture was negative and the patient had no fever or leucocytosis in the clinical. Finally, she was discharged with oral antibiotic treatment and outpatient local cure, and had good clinical course.

Supplementary data are available at European Journal of Echocardiography online.

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