Predicting Outcomes in Heart Transplantation
PET Project or Actionable Data

Michael M. Givertz, MD

I was not predicting the future; I was trying to prevent it.
Ray Bradbury (1920–2012)

For highly selected patients with end-stage heart failure, cardiac transplantation has offered a viable treatment option for more than 40 years. In the most recent report from the International Society for Heart and Lung Transplantation Registry, an estimated 6300 transplants were performed worldwide in 2012, a number that seems to be slowly increasing, particularly in North America. For patients transplanted in the past decade, expected median survival is ≈11 years. Despite this optimism, long-term survival has changed little during the past 2 decades with 1-, 5-, and 10-year survival rates of 84%, 72%, and 52%, respectively. Survival rates are slightly higher in the United States at 88% and 75% at 1 and 5 years, respectively. The major limitation to long-term survival is the development of cardiac allograft vasculopathy (CAV). CAV is a chronic, immune-mediated, inflammatory process that leads to marked intimal proliferation, epicardial and branch coronary artery stenoses, and diffuse distal vessel tapering. Vasomotor function of both large and small coronary arteries, as well as the microvasculature, is also adversely affected. CAV is common, with incidence rates by screening coronary angiography of 10% to 20% at 1 year and 30% to 50% at 5 years post transplant.

Because of cardiac denervation, angina is uncommon in heart transplant patients, and the clinical presentation of CAV is highly variable, ranging from asymptomatic electrocardiographic changes to severe heart failure or sudden cardiac death. Therefore, early diagnosis is considered key to management. Initial clinical studies sought to define risk factors for the development of CAV, with both recipient and donor characteristics being identified (Table 1). In addition, the frequency and the severity of acute cellular rejection are strong independent predictors of early onset and rapid progression of CAV. Rapidly progressive CAV as assessed by intravascular ultrasound (IVUS), especially within the first 3 to 5 years post transplant, is a potent predictor of cardiovascular morbidity and mortality. Although IVUS is the most sensitive test for diagnosing CAV, coronary angiography remains the test of choice at most centers. Both modalities, however, are invasive and carry small, but significant risk. Noninvasive tests, including dobutamine stress echocardiography and stress myocardial perfusion imaging, are safer and widely available but have their own advantages and disadvantages (Table 2).

In this issue of Circulation: Cardiovascular Imaging, Mc Ardle et al sought to determine the prognostic value of Rubidium-82 positron emission tomography (PET) in heart transplant patients. Between 2009 and 2013, 140 patients greater than 1 year post-transplant were enrolled in a prospective PET registry. Using a semiquantitative, 17-segment, perfusion analysis, these investigators assessed myocardial blood flow (MBF) at rest and following dipyridamole stress, and calculated myocardial flow reserve (MFR). During follow-up, 14 patients experienced an adverse clinical event, including death (9), heart failure admission (4), or acute coronary syndrome (1). Not surprisingly, patients with an adverse event had a higher prevalence of CAV on invasive angiography and worse renal function. PET scanning revealed higher summed stress and rest scores and reduced MFR (1.6 versus 2.3; P=0.006) in this high-risk group. The event rate in the majority of patients (76%) with a normal PET scan (eg, summed stress score <4, rest ejection fraction >45%, and MFR >1.75) was <5%, compared with 27% in patients with abnormal PET results. Although derived from a single center with a limited cohort of early post-transplant patients, these data are noteworthy and deserve further comment.

Cardiac PET imaging is limited by availability, expertise, and cost, but it is not a new technology for assessing CAV. More than 20 years ago, Rechavia et al reported normal MBF at rest (when accounting for higher baseline rate-pressure product), but lower stress-induced MBF in heart transplant patients versus controls. Subsequently, Allen-Auerbach et al demonstrated an association between early CAV as assessed by IVUS and impaired PET vasodilatory capacity. Others have also observed reduced MFR in patients early (<3 months) post-transplant, but in the absence of CAV attributed this to ischemic injury. Wu et al studied 27 patients an average of 2.5 years out from transplant with normal coronary angiograms, normal left ventricular function, and no rejection and found an inverse correlation between MFR and plaque volume as assessed by IVUS. The study by Mc Ardle et al extends these mechanistic findings by suggesting that MFR is an important surrogate of the pathobiology of CAV.

Beyond heart transplant, the prognostic value of MFR as assessed by PET imaging has been demonstrated in patients with ischemic, dilated, and hypertrophic cardiomyopathies. Advantages over other noninvasive techniques include...
superior spatial resolution leading to greater sensitivity and specificity, and high negative and positive predictive values. When performed with dipyridamole stress, PET imaging integrates global and regional vasodilatory capacity, as well as endothelium-dependent vasomotor and epicardial conduit vessel function.13 The data by Mc Ardle et al4 suggest that PET imaging may provide a more reliable tool for detecting early CAV and targeting high-risk patients, while avoiding unnecessary coronary angiography and IVUS in those at low risk of future events. However, several unique features of the transplanted heart may alter the response to dipyridamole stress. Denervation results in higher resting heart rate and decreased diastolic flow, which can change coronary driving pressure. Left ventricular hypertrophy caused by hypertension, acute cellular rejection, and immunosuppressants can also alter the response to vasodilatory stress. Importantly, the presence of donor-derived epicardial atherosclerosis or more commonly the codevelopment of recipient atherosclerosis and CAV (Figure)14 can confound the results of PET imaging. Additional studies are needed to clarify these issues.

It can be argued that imaging to diagnose and risk-stratify heart transplant patients with CAV is only as good as available therapy to prevent or treat the disease. Unfortunately, herein lies the unmet patient need. Administration of statins, CMV prophylaxis, and antihypertensive agents are routine post transplant. An emerging, but limited body of data also suggests a role for proliferation signal inhibitors (eg, sirolimus, everolimus) to attenuate CAV and decrease CAV-related morbidity and mortality.6 For patients with focal epicardial coronary stenoses, percutaneous or surgical revascularization may provide medium-term benefit, but in-stent restenosis and bypass graft failure are common. For

### Table 1. Risk Factors for the Development of Cardiac Allograft Vasculopathy

<table>
<thead>
<tr>
<th>Recipient Factors</th>
<th>Donor Factors</th>
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<tbody>
<tr>
<td>Younger age</td>
<td>Older age</td>
</tr>
<tr>
<td>Obesity</td>
<td>Male gender</td>
</tr>
<tr>
<td>History of coronary artery disease</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Traditional cardiac risk factors*</td>
<td>CMV infection</td>
</tr>
<tr>
<td>Increased allosensitization</td>
<td></td>
</tr>
</tbody>
</table>

*Hypertension, dyslipidemia, and smoking.

### Table 2. Tests for Diagnosis and Prognosis of Cardiac Allograft Vasculopathy

<table>
<thead>
<tr>
<th>Test</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
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<tbody>
<tr>
<td>Exercise treadmill testing</td>
<td>Widely available</td>
<td>Poor specificity because of baseline ECG abnormalities</td>
</tr>
<tr>
<td>Dobutamine stress echocardiography</td>
<td>Good screening test with high negative predictive value</td>
<td>Variable sensitivity (65%–85%) and specificity (55%–88%)</td>
</tr>
<tr>
<td>Stress myocardial perfusion imaging</td>
<td>Widely available</td>
<td>Reduced sensitivity (60%–77%) because of submaximal exercise tolerance</td>
</tr>
<tr>
<td>Multidetector CT angiography</td>
<td>High negative predictive value compared with invasive angiography May characterize lesion</td>
<td>Low negative predictive value compared with IVUS Contrast and radiation exposure</td>
</tr>
<tr>
<td>Invasive angiography</td>
<td>Predicts adverse events and death</td>
<td>Decreased sensitivity compared to IVUS for early stage disease Invasive Contrast exposure</td>
</tr>
<tr>
<td>IVUS</td>
<td>High sensitivity for detecting early stage disease Presence and progression of CAV predicts adverse cardiac events and death</td>
<td>Unable to image distal vessel Lack of expertise and availability Cost</td>
</tr>
</tbody>
</table>

CAV indicates cardiac allograft vasculopathy; CT, computed tomography; and IVUS, intravascular ultrasound.

### Table 3. Potential Uses of Cardiac Positron Emission Tomography Imaging in Heart Transplant Patients

<table>
<thead>
<tr>
<th>Use</th>
<th>Selected Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment of MFR during and following treatment of acute cellular rejection</td>
<td>Chan et al15</td>
</tr>
<tr>
<td>Demonstration of sympathetic reinnervation and its effects on exercise performance</td>
<td>Bengel et al16</td>
</tr>
<tr>
<td>Assessment of atherosclerotic lesion morphology and degree of inflammation</td>
<td>Nahrendorf et al19</td>
</tr>
<tr>
<td>Diagnosis of post-transplant infection or malignancy (eg, adenocarcinoma, PTLD)</td>
<td>Graute et al17</td>
</tr>
<tr>
<td>Tracking of stem cells and assessment of viability post infarction</td>
<td>Gyongyosi et al20</td>
</tr>
<tr>
<td>Documentation of improved myocardial perfusion following HELP-apheresis</td>
<td>Jaeger et al18</td>
</tr>
</tbody>
</table>

HELP indicates heparin-mediated extracorporeal low-density lipoprotein/fibrinogen precipitation; MFR, myocardial flow reserve; and PTLD, post-transplant lymphoproliferative disorder.
highly selected patients with allograft failure caused by severe CAV, cardiac retransplantation may be considered. Although overall survival after retransplantation is lower than de novo transplant, 70% at 1 year and 38% at 10 years, of the different retransplant indications (eg, myopathy, primary failure, CAV, and rejection), CAV has the best prognosis.

While waiting for larger multicenter data sets with more events (only 6% of the patients in the study by Mc Ardle et al had documented CAV, with only 4 cardiac deaths in follow-up), PET imaging has other potential clinical and research uses in heart transplantation (Table 3). Although specificity is limited, Chan et al showed an improvement in MFR after treatment of acute cellular rejection. Whether similar findings are true in antibody-mediated rejection remains to be determined. Several investigators have studied the timing and regionality of sympathetic reinnervation post-transplant using C-11 adrenaline. This type of physiological data may help guide initiation and dosing of β-blockers and calcium channel blockers. Whole-body 18-fluorodeoxyglucose PET imaging has been used successfully to diagnose infection and malignancy in patients with nonspecific unexplained symptoms. Other complications after heart transplant, including dyslipidemia and myocardial infarction, may also be alleviated by therapies guided by PET.

Beyond PET imaging, newer techniques for diagnosis and prognosis of CAV are emerging. Coronary flow reserve with contrast dobutamine stress echocardiography and higher resolution computed tomographic angiography may provide more sensitive tools for assessing distal vessel structure and function. High-resolution computed tomographic angiography can also assess the arterial wall in vivo. Similarly, radiofrequency IVUS and optical coherence tomography can characterize plaque composition and may allow identification of high-risk inflammatory lesions. Finally, recent studies have shown diagnostic and prognostic value of biomarkers, such as vascular endothelial growth factors and intracellular adhesion molecules, which in turn may provide targets for much needed therapy. The bridge between prediction and prevention of CAV remains to be crossed, but the journey has begun.

Disclosures

None.

References

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