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 taping. 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.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Cardiovascular Division, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA.
Correspondence to Michael M. Givertz, MD, Cardiovascular Division, Brigham and Women’s Hospital, 75 Francis St, Boston, MA 02115.
E-mail mgivertz@partners.org
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Exercise treadmill testing

Widely available

Poor specificity because of baseline ECG abnormalities.

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

<table>
<thead>
<tr>
<th>Test</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<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 Invasive Cost.</td>
</tr>
</tbody>
</table>

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

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) 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.

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.

**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 al</td>
</tr>
<tr>
<td>Demonstration of sympathetic reinnervation and its effects on exercise performance</td>
<td>Bengel et al</td>
</tr>
<tr>
<td>Assessment of atherosclerotic lesion morphology and degree of inflammation</td>
<td>Nahrendorf et al</td>
</tr>
<tr>
<td>Diagnosis of post-transplant infection or malignancy (eg, adenocarcinoma, PTLD)</td>
<td>Graute et al</td>
</tr>
<tr>
<td>Tracking of stem cells and assessment of viability post infarction</td>
<td>Gyongyosi et al</td>
</tr>
<tr>
<td>Documentation of improved myocardial perfusion following HELP-apheresis</td>
<td>Jaeger et al</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,2 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 al10 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).15–20 Although specificity is limited, Chan et al15 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.16 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.17 Other complications after heart transplant, including dyslipidemia and myocardial infarction, may also be alleviated by therapies guided by PET.18,20

Beyond PET imaging, newer techniques for diagnosis and prognosis of CAV are emerging.13 Coronary flow reserve with PET imaging has other potential clinical and research findings are true in antibody-mediated rejection remains to be crossed, but the journey has begun.

Disclosures

None.

References


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