Interventional Cardiology

Invasive Assessment of Coronary Physiology Predicts Late Mortality After Heart Transplantation

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Background—The aim of this study is to determine the prognostic value of invasively assessing coronary physiology early after heart transplantation.

Methods and Results—Seventy-four cardiac transplant recipients had fractional flow reserve, coronary flow reserve, index of microcirculatory resistance (IMR), and intravascular ultrasound performed down the left anterior descending coronary artery soon after (baseline) and 1 year after heart transplantation. The primary end point was the cumulative survival free of death or retransplantation at a mean follow-up of 4.5±3.5 years. The cumulative event-free survival was significantly lower in patients with a fractional flow reserve <0.90 at baseline (42% versus 79%; P=0.01) or an IMR ≥20 measured 1 year after heart transplantation (39% versus 69%; P=0.03). Patients in whom IMR decreased or did not change from baseline to 1 year had higher event-free survival compared with patients with an increase in IMR (66% versus 36%; P=0.03). Fractional flow reserve <0.90 at baseline (hazard ratio, 0.13; 95% confidence interval, 0.02–0.81; P=0.03), IMR ≥20 at 1 year (hazard ratio, 3.93; 95% confidence interval, 1.08–14.27; P=0.04), and rejection during the first year (hazard ratio, 6.00; 95% confidence interval, 1.56–23.09; P=0.009) were independent predictors of death/retransplantation, whereas intravascular ultrasound parameters were not.

Conclusions—Invasive measures of coronary physiology (fractional flow reserve and IMR) determined early after heart transplantation are significant predictors of late death or retransplantation. (Circulation. 2016;133:1945-1950. DOI: 10.1161/CIRCULATIONAHA.115.018741.)

Key Words: heart transplantation  ■ physiology  ■ treatment outcome

Cardiac allograft vasculopathy (CAV) is the main cause of late mortality after heart transplantation.1-3 The characteristic of CAV is diffuse intimal proliferation involving both the epicardial artery and the microvasculature.3,4 Coronary angiography lacks the resolution to diagnose early stages of CAV.5 Intravascular ultrasound (IVUS) has greater resolution and has been shown to detect changes in epicardial CAV predictive of late adverse outcome after cardiac transplantation.

Clinical Perspective on p 1950

The functional assessment of the epicardial vessel with fractional flow reserve (FFR) and of the microvasculature with the index of microcirculatory resistance (IMR) predicts adverse outcomes in subsets of patients who have not undergone heart transplantation.6-8 In cardiac transplant recipients, changes in FFR have been shown to correlate with IVUS parameters,9 whereas IMR is a predictor of development of CAV and poor cardiac function in this population.10 However, the ability of FFR or IMR measured early after heart transplantation to predict late death or retransplantation has not been studied previously.

Study Design

This study included patients from 2 consecutive prospective trials at Stanford University Medical Center between 2002 and 2014. The aim of the first study was to evaluate the role of cytomegalovirus in the development of CAV (1 PO1-AI50153). The second study evaluated the role of the angiotensin-converting enzyme inhibitor ramipril in the development of CAV (5 R01 HL093475-02; ClinicalTrials.gov number NCT01078363). Patients were included if they were >18 years old, received their first cardiac transplantation, survived >1 year, and were willing and able to provide informed written consent. All patients underwent a baseline coronary angiogram with measurement of FFR, coronary flow reserve (CFR), and IMR and performance of IVUS of the left anterior descending artery (LAD) within 8 weeks and 1 year after transplantation. The study protocols were approved by the Stanford University Institutional Review Board on Human Subjects Research, and informed consent was obtained from all patients before enrollment.

Immunosuppressive Regimen

All patients received standard immunosuppressive therapy, including induction therapy with daclizumab, an anti–interleukin-2 monoclonal antibody, OKT3, or antithymocyte globulin. Corticosteroid therapy

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DOI: 10.1161/CIRCULATIONAHA.115.018741
was initiated postoperatively and tapered progressively over the first 8 months after transplantation in the absence of rejection. A calcineurin inhibitor (tacrolimus or cyclosporine) and cell-cycle inhibitor (mycophenolate mofetil, sirolimus, or azathioprine) were used for maintenance therapy, and a proliferation signal inhibitor (everolimus or sirolimus) was used according to the clinical status. Cytomegalovirus prophylaxis was used in those with evidence of a seropositive donor or seropositive recipient status with ganciclovir or valganciclovir. Sixty-seven patients (91%) received statin therapy.

**Coronary Physiology Measurements**

After performance of coronary angiography, heparin was administered intravenously (50–70 U/kg), and a 6F guiding catheter was used to access the left main coronary artery. Intracoronary nitroglycerin (100–200 μg) was administered. FFR was measured in the usual fashion with a coronary pressure wire (St. Jude Medical) placed in the distal two thirds of the LAD (=10 cm down the vessel) and defined as the mean distal coronary pressure divided by the mean aortic pressure at maximal hyperemia induced with intravenous adenosine at 140 μg·kg⁻¹·min⁻¹ through a central vein. CFR and IMR were measured simultaneously with the same coronary pressure wire (St. Jude Medical) using a previously described thermodilution technique. IMR was calculated as the distal coronary pressure at maximal hyperemia divided by the inverse of hyperemic mean transit time. CFR was calculated as resting mean transit time divided by hyperemic mean transit time.

**Intravascular Ultrasound**

IVUS was performed in the LAD with a 40-MHz mechanical catheter connected to a Galaxy or iLab IVUS system (Boston Scientific) and an automatic pullback at 0.5 mm/s. Offline 3-dimensional IVUS analyses (EchoPlaque, Indec Systems, Santa Clara, CA) were performed in the Stanford University IVUS core laboratory according to the American College of Cardiology clinical expert consensus document. Quantitative analyses included vessel, lumen, and plaque volumes and calculated percent plaque volume, defined as total plaque volume divided by vessel volume times 100%. All IVUS analyses were performed on the first 50 mm of the LAD.

**Definitions**

The primary end point was the cumulative survival free of all-cause death or the need for retransplantation occurring 1 year or later after transplantation. All patients were followed up until October 2014. Significant rejection was defined as an event that led to an acute augmentation of immunosuppression in conjunction with an International Society for Heart and Lung Transplantation grade ≥2R right ventricular endomyocardial biopsy result or noncellular rejection with hemodynamic compromise (increase in relative left ventricular ejection fraction >25%).

**Statistical Analysis**

Continuous variables are presented as mean±SD, and categorical variables are presented as frequency (percentage). Continuous variables were compared by use of the Student t test; categorical variables were compared by use of the χ² test or Fisher exact test. Cutoff values of 20 for baseline and 1-year IMR, 2.5 for baseline and 1-year CFR, 0.90 for baseline FFR, and 0.85 for 1-year FFR were obtained from the literature. Time-to-event data were analyzed with the Kaplan–Meier method and compared by use of the log-rank test. Cox regression analysis was performed to determine predictors of death/retransplantation. Statistical analyses were performed with the PASW software (PASW 18.0 Inc, Chicago, IL). A value of P<0.05 was considered statistically significant.

**Results**

**Baseline Clinical Characteristics**

A total 112 heart transplant recipients were enrolled in this study. Of these, 74 patients completed the coronary physiology studies and IVUS at both baseline and 1 year. Thirty-eight patients were excluded for the following reasons: 26 patients did not undergo the baseline coronary physiology studies; 11 patients did not undergo the annual coronary physiology studies; and in 1 patient, the target vessel was the left circumflex artery, not the LAD. There were no significant differences in baseline characteristics between those included and those excluded. The mean age was 53±10 years, and 78% of recipients were men. Thirty-six patients (49%) received transplantation as a result of dilated cardiomyopathy, and 20 patients (27%) received transplantation as a result of ischemic cardiomyopathy. Rejection during the first year after heart transplantation occurred in 18 patients (24.3%). Ten patients (7.4%) received rapamycin-based immunosuppressive therapy during the first year after transplantation. The mean follow-up duration was 1640±1266 days (4.5 years; Table 1).

**Coronary Physiology and IVUS Results**

The mean FFR decreased significantly (0.89±0.05 versus 0.87±0.05; P=0.03) and IMR decreased (22.4±13.3 versus 18.5±13.8; P=0.07) from baseline to 1 year after heart transplantation. IVUS-derived maximal intimal thickness (MIT; 0.7±0.47 versus 0.91±0.52 mm; P<0.001), plaque volume (130.4±70.3 versus 164.0±87.0 mm³; P<0.001), and percent plaque volume (16.1±7.5% versus 21.9±9.7%; P<0.001) increased significantly and vessel volume decreased (783.6±211.1 versus 730.5±211.1 mm³; P=0.02) from baseline to 1 year (Table 2).

Thirty-nine patients (52.7%) had an FFR <0.90 at baseline, and 18 patients (24.3%) had an FFR <0.85 at 1 year. Twenty-two patients (29.7%) had an IMR ≥20 measured at 1 year after heart transplantation. Patients with an IMR ≥20 at 1 year had a significantly higher incidence of rejection during the first year after transplantation compared with those with an IMR <20 at 1 year (40.9% versus 17.3%; P=0.03). The percentage of patients with a left ventricular ejection fraction <50% tended to be greater in those with an IMR ≥20 compared with those with an IMR <20 (22.7% versus 7.7%; P=0.12).

**Table 1. Baseline Characteristics (n=74)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53±10</td>
</tr>
<tr>
<td>Sex, M/F (%)</td>
<td>58/16 (78/22)</td>
</tr>
<tr>
<td>Donor age, y</td>
<td>32±12</td>
</tr>
<tr>
<td>Donor sex, M/F (%)</td>
<td>54/20 (73/27)</td>
</tr>
<tr>
<td>History of diabetes mellitus, n (%)</td>
<td>9 (12)</td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>29 (39)</td>
</tr>
<tr>
<td>History of hyperlipidemia, n (%)</td>
<td>20 (27)</td>
</tr>
<tr>
<td>Recipient CMV IgG positive, n (%)</td>
<td>49 (66)</td>
</tr>
<tr>
<td>ABO mismatch, n (%)</td>
<td>11 (14.9)</td>
</tr>
<tr>
<td>Donor ischemic time, min</td>
<td>224±41</td>
</tr>
<tr>
<td>Statin at year 1, n (%)</td>
<td>67 (91)</td>
</tr>
<tr>
<td>Rapamycin therapy at year 1, n (%)</td>
<td>10 (7.4)</td>
</tr>
<tr>
<td>Rejection during first year, n (%)</td>
<td>18 (24)</td>
</tr>
</tbody>
</table>

Values are mean±SD when appropriate. CMV indicates cytomegalovirus.
Clinical Outcome
During a mean follow-up of 4.5±3.5 years, 14 patients (20.3%) died and 1 patient (1.4%) underwent retransplantation. Of the coronary physiological parameters, patients with an FFR <0.90 at baseline had a lower cumulative event-free survival (42% versus 79%; *P*=0.01; Figure 1). At 1 year, patients with an IMR ≥20 had significantly lower event-free survival (39% versus 69%; *P*=0.03; Figure 2).

On Cox regression analysis, FFR <0.90 at baseline (hazard ratio [HR], 0.13; 95% confidence interval [CI], 0.02–0.81; *P*=0.03), an IMR ≥20 at 1 year (HR, 3.93; 95% CI, 1.08–14.27; *P*=0.04), and rejection during the first year after transplantation (HR, 6.00; 95% CI, 1.56–23.09; *P*=0.009) were independent predictors of death/retransplantation after heart transplantation. Included variables were those with a value of *P*<0.1 in univariate analysis: an FFR <0.90 at baseline, an IMR ≥20 at 1 year, rejection during the first year after transplantation, an MIT ≥0.6 mm at 1 year, donor age, hypertension, an FFR <0.85 at 1 year, percent plaque volume ≥11% at baseline, and ABO mismatch.

Patients with a decrease or no change in IMR from baseline to 1 year had a higher event-free survival compared with those patients with an increase in IMR during this time period (66% versus 36%; *P*=0.03; Figure 3). A change in FFR or CFR was not related to clinical outcomes.

Among the IVUS parameters measured, patients with an MIT >0.6 mm at 1 year had a significantly lower event-free survival during follow-up (44% versus 90%; *P*=0.04; Figure 4). However, the event-free survival of patients with a change in MIT >0.5 mm from baseline to 1 year was not statistically different compared with that in patients with a change in MIT ≤0.5 mm (35% versus 65%; *P*=0.52).

Discussion
The principal finding of this study is that invasively assessing coronary physiology, in particular identifying microvascular dysfunction (IMR ≥20) at 1 year after heart transplantation and donor-related epicardial disease (FFR <0.90) at baseline, significantly predicts death/retransplantation during longer-term follow-up of cardiac transplant recipients. Moreover, patients with an improvement in microvascular function as assessed by a decrease in IMR from baseline to 1 year had better survival compared with those with worsening microvascular function.

Epicardial Artery
CAV is a progressive and diffuse process involving both the epicardial artery and the microcirculation and is the major cause of late mortality in heart transplant recipients. FFR is an index specific for identifying epicardial disease responsible for myocardial ischemia. It has been shown to be a predictor of clinical outcomes in nontransplantation patients\(^6\),\(^7\) and correlates with IVUS findings in cardiac transplant recipients.\(^9\) However, the role of FFR for predicting clinical outcomes in cardiac transplant recipients has not been evaluated previously.

Table 2. Coronary Physiology and IVUS Results

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>At 1 y</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFR</td>
<td>0.89±0.05</td>
<td>0.87±0.05</td>
<td>0.03</td>
</tr>
<tr>
<td>CFR</td>
<td>3.3±1.5</td>
<td>4.3±2.9</td>
<td>0.01</td>
</tr>
<tr>
<td>IMR</td>
<td>22.4±13.3</td>
<td>18.5±13.8</td>
<td>0.07</td>
</tr>
<tr>
<td>MIT</td>
<td>0.7±0.47</td>
<td>0.91±0.52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vessel volume, mm(^3)</td>
<td>783.6±211.0</td>
<td>730.5±211.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Lumen volume, mm(^3)</td>
<td>654.9±183.3</td>
<td>566.4±175.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plaque volume, mm(^3)</td>
<td>130.4±70.3</td>
<td>164.0±87.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plaque volume, %</td>
<td>16.1±7.5</td>
<td>21.9±9.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean±SD. CFR indicates coronary flow reserve; FFR, fractional flow reserve; IMR, index of microvascular resistance; IVUS, intravascular ultrasound; and MIT, maximal intimal thickness.
This study demonstrated that identifying abnormal epicardial artery physiology on the basis of an FFR < 0.90 soon after transplantation predicts clinical outcomes. Interestingly, an abnormal FFR 1 year after transplantation was not a significant predictor. Although the baseline coronary angiograms appeared normal in this study, the baseline abnormal FFR presumably is detecting donor-related atherosclerosis, the presence of which has been demonstrated by IVUS in previous studies to be a predictor of adverse events during follow-up.14

The explanation for why the FFR measured at 1 year was not a predictor of longer term outcomes may be related to the fact that FFR is influenced by microvascular dysfunction. We have shown previously that over time microvascular function deteriorates, the maximum achievable flow down a vessel decreases, and FFR increases despite no change in IVUS assessment of epicardial disease.15 Thus, during longer-term follow-up, FFR may increase or stay the same as patients develop more significant microvascular dysfunction, despite the presence or even worsening of epicardial CAV.

Importance of Microvascular Dysfunction
Microvasculopathy as detected by endomyocardial biopsy predicts a poor prognosis after heart transplantation independently of epicardial CAV.18 To date, there is no standard tool for identifying microvascular dysfunction after heart transplantation. The International Society for Heart and Lung Transplantation guidelines suggest measuring CFR invasively during coronary angiography as an option for detecting microvascular disease in cardiac transplant recipients in whom CAV is suspected.3,19 However, CFR is not a specific parameter for microvascular dysfunction because it interrogates the entire coronary circulation, both the epicardial vessel and the microvasculature, and therefore is affected by epicardial artery stenosis. Moreover, because CFR is defined in part by resting flow, it is influenced by changes in resting hemodynamic conditions such as blood pressure, heart rate, and ventricular contractility.20,21 These factors may explain why some studies have found a relationship between clinical outcome and CFR and others have not.4,22,23 In our study, CFR measured at baseline and 1 year did not predict longer-term clinical outcome after heart transplantation. For these reasons, one could argue that measuring CFR invasively in this setting should be abandoned.

Thermodilution-derived IMR is a quantitative method for specifically assessing microvascular function, which is reproducible and independent of changes in resting hemodynamic conditions.21 Microvascular dysfunction assessed by IMR after ST-segment–elevation myocardial infarction predicts long-term clinical outcomes.6 In this study, patients with an IMR ≥ 20 measured at 1 year after heart transplantation had a significantly lower survival free of death or retransplantation compared with those with an IMR < 20. It is important to realize that microvascular function and IMR are not affected by epicardial CAV and FFR, whereas the reverse is not true, as previously mentioned. Moreover, in patients with an increase in IMR from baseline to 1 year, there was a lower freedom...
from death/retransplantation compared with those patients with no change or a decrease in IMR. This finding may be explained by the facts that microvascular dysfunction at 1 year is associated with impaired ventricular function and that an increase in IMR correlates with a decrease in cardiac index and stroke volume index and more hemodynamically compromising rejection. The lack of correlation between an elevated IMR at baseline and outcomes implies that whatever factors contribute to an abnormal IMR at baseline (eg, inflammation and edema resulting from the transplantation process) are likely not important mediators of long-term outcome. Others have reported that in the absence of significant epicardial CAV, episodes of rejection are associated with microvascular dysfunction, which also was found in this study.

The clinical implications of these findings are that more emphasis should be placed on the invasive assessment of coronary physiology in cardiac transplant recipients, in particular the microvasculature. Potentially, the transplant recipient’s medical regimen could be adjusted by switching to sirolimus or agents known to improve microvascular function such as angiotensin-converting enzyme inhibitors, although the benefit of this class of medicines in this setting is unknown.

Limitations of this study include its single-center nature and relatively small sample size. Physiology and IVUS measurements were performed only in the LAD. Interrogation of coronary physiology in cardiac transplant recipients, in particular microvascular dysfunction, in particular microvascular dysfunction (IMR ≥ 20) identified at 1 year and abnormal epicardial artery function (FFR < 0.90) at baseline, are independent predictors of late death or the need for retransplantation.

Conclusions

In cardiac transplant recipients, measures of coronary physiology, in particular microvascular dysfunction (IMR ≥ 20) identified at 1 year and abnormal epicardial artery function (FFR < 0.90) at baseline, are independent predictors of late death or the need for retransplantation.

Acknowledgments

We acknowledge Hyun Young Lee, PhD, Ajou University Hospital, Suwon, South Korea, and Manisha Desai, PhD, Stanford University, Stanford, CA.

Sources of Funding

This work was funded by 1 PO1-AI50153 (Dr Valantine) and 5 R01 HL095475-02 (Dr Fearon).

Disclosures

Dr Fearon receives research support from St. Jude Medical and Medtronic and has a consulting relationship with Medtronic and HeartFlow. The other authors report no conflicts.

References


Cardiac allograft vasculopathy is the major cause of late mortality in patients surviving >1 year after heart transplantation. Intravascular ultrasound examination of the epicardial coronary artery for intimal thickening is the accepted method for evaluating for early evidence of cardiac allograft vasculopathy, which is not apparent on invasive coronary angiography or noninvasive testing and is predictive of adverse events. Recently, abnormal epicardial and microvascular coronary physiology, invasively assessed with a pressure/thermistor-tipped coronary guide wire by measuring fractional flow reserve (FFR) and the index of microcirculatory resistance (IMR), has been shown to predict adverse events in nontransplantation patients. The prognostic value of FFR and IMR in cardiac transplant recipients is unknown. In this study, intravascular ultrasound, FFR, and IMR were performed in the left anterior descending artery of 74 cardiac transplant recipients soon after transplantation (baseline) and 1 year later. At a mean follow-up of 4.5 years, freedom from death or retransplantation was significantly lower in patients with an abnormal baseline FFR (presumably reflecting donor-related coronary artery disease) and in patients with an abnormal IMR (reflecting microvascular dysfunction) 1 year after transplantation. Moreover, freedom from death or retransplantation was significantly lower in patients with a lack of improvement in IMR from baseline to 1 year. Freedom from death or retransplantation was significantly lower in patients with an abnormal baseline FFR and an abnormal IMR at 1 year were independent predictors of death/retransplantation, whereas intravascular ultrasound parameters were not. Invasive measurements of coronary physiology (FFR and IMR) determined early after heart transplantation are significant predictors of late death or retransplantation.

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*Circulation*. 2016;133:1945-1950; originally published online April 20, 2016; doi: 10.1161/CIRCULATIONAHA.115.018741

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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