Simultaneous Assessment of Fractional and Coronary Flow Reserves in Cardiac Transplant Recipients
Physiologic Investigation for Transplant Arteriopathy (PITA Study)

William F. Fearon, MD; Mamoo Nakamura, MD; David P. Lee, MD; Mehrdad Rezaee, MD; Randall H. Vagelos, MD; Sharon A. Hunt, MD; Peter J. Fitzgerald, MD; Paul G. Yock, MD; Alan C. Yeung, MD

Background—The utility of measuring fractional flow reserve (FFR) to assess cardiac transplant arteriopathy has not been evaluated. Measuring coronary flow reserve (CFR) as well as FFR could add information about the microcirculation, but until recently, this has required two coronary wires. We evaluated a new method for simultaneously measuring FFR and CFR with a single wire to investigate transplant arteriopathy.

Methods and Results—In 53 cases of asymptomatic cardiac transplant recipients without angiographically significant coronary disease, FFR and thermodilution-derived CFR (CFRthermo) were measured simultaneously with the same coronary pressure wire in the left anterior descending artery and compared with volumetric intravascular ultrasound (IVUS) imaging. The average FFR was 0.88 +/− 0.07; in 75% of cases, the FFR was less than the normal threshold of 0.94; and in 15% of cases, the FFR was ≤0.80, the upper boundary of the gray zone of the ischemic threshold. There was a significant inverse correlation between FFR and IVUS-derived measures of plaque burden, including percent plaque volume (r = 0.55, P < 0.0001). The average CFRthermo was 2.5 +/− 1.2; in 47% of cases, CFRthermo was ≤2.0. In 14%, the FFR was normal (≥0.94) and the CFR was abnormal (<2.0), suggesting predominant microcirculatory dysfunction.

Conclusions—FFR correlates with IVUS findings and is abnormal in a significant proportion of asymptomatic cardiac transplant patients with normal angiograms. Simultaneous measurement of CFR with the same pressure wire, with the use of a novel coronary thermodilution technique, is feasible and adds information to the physiological evaluation of these patients. (Circulation. 2003;108:1605-1610.)

Key Words: transplantation ▪ coronary disease ▪ pressure ▪ imaging

Cardiac transplant–related arteriopathy remains a leading cause of morbidity and mortality in patients after cardiac transplantation.1 Coronary angiography is the most common method of screening for transplant arteriopathy, but lacks sensitivity.2 Intravascular ultrasound (IVUS) is more sensitive, but it requires some degree of expertise to perform and interpret the images and it only interrogates the epicardial coronary system. Noninvasive techniques for evaluating the coronary system, such as MRI, may eventually replace these invasive methods, but they are not yet widely available and require further refinement and testing.3

A number of investigators have evaluated the physiological status of both the epicardial coronary artery and microcirculation in transplant recipients by measuring coronary flow reserve (CFR) with a Doppler wire.4–8 This method can be technically challenging and is limited because an abnormal value cannot distinguish between epicardial and microcirculatory pathology, unless coupled with IVUS.9 Moreover, intimal thickening detected in the epicardial artery with IVUS did not appear to affect the conduit or resistive vessel vasodilatory response, based on Doppler wire–derived CFR measurements.7,8 It remains unclear whether mild, diffuse intimal thickening in the epicardial arteries of transplant recipients affects the functional status of the coronary tree.

Assessing the functional status of the epicardial coronary artery by measuring the pressure-derived fractional flow reserve (FFR) is well validated, not only in the settings of intermediate coronary lesions, unstable angina, and after myocardial infarction but also in angiographic “normal” coronary arteries with suspected diffuse disease.10–14 FFR appears to correlate with IVUS measurements in assessing de novo lesions, as well as after percutaneous coronary interventions.15–17 To date, FFR has not been evaluated in cardiac transplant recipients. FFR may provide a more accurate method than CFR for determining the functional significance of epicardial artery intimal thickening.
Recently, De Bruyne et al\textsuperscript{18} described a novel coronary thermodilution technique for measuring CFR at the same time as FFR by using a single coronary pressure wire. Pijs et al\textsuperscript{19} showed that coronary thermodilution–derived CFR (CFR\textsubscript{thermo}) correlates with Doppler wire–derived CFR. The ability to measure easily, rapidly, and simultaneously both FFR and CFR may be useful in screening for transplant arteriopathy and in distinguishing between epicardial and microcirculatory pathology.

The goal of this study was to compare a physiological investigation for transplant arteriopathy by measuring FFR and CFR\textsubscript{thermo}, with IVUS, in patients with asymptomatic cardiac transplantation without angiographic evidence of transplant arteriopathy.

**Methods**

The study protocol was approved by Stanford University’s Administrative Panel on Human Subjects. Every patient provided informed written consent. Patients with asymptomatic cardiac transplantation who were undergoing either baseline angiography (within 6 weeks of transplantation) or annual coronary angiography to screen for transplant arteriopathy were eligible for this study. Patients with angiographic evidence of transplant arteriopathy or previous revascularization of the transplanted heart were excluded. Unstable or hospitalized patients were also ineligible for enrollment.

Every patient underwent routine right heart catheterization followed by right ventricular endomyocardial biopsy. After diagnostic coronary angiography was performed, 3000 to 5000 U of intravenous heparin was administered and a 6F left coronary guiding catheter was used to engage the left coronary artery. Intracoronary nitroglycerin (200 μg) was given. A 0.014-inch coronary pressure wire (Radi Medical Systems) was calibrated, equalized to the guiding catheter, and then advanced to the distal portion (at least two thirds of the way down the vessel) of the left anterior descending coronary artery. FFR and CFR\textsubscript{thermo} were then measured as described below. A 2.6F, 40-MHz mechanical ultrasound catheter, connected to a Galaxy IVUS system (Boston Scientific Corp), was advanced so that the IVUS transducer was positioned as close as possible to the pressure sensor, 3 cm from the tip of the standard coronary guiding catheter, and modified software (Radi Medical Systems). The software allows offline quantitative coronary angiography (QCA).

**Physiological Measurements**

FFR, defined as the mean distal coronary pressure, measured with the pressure wire, divided by the mean proximal coronary pressure, measured with the guiding catheter, at maximum hyperemia, was measured after administering either 48 μg of intracoronary adenosine or 15 mg of intracoronary papaverine.

CFR\textsubscript{thermo} was measured with the use of the same pressure wire and modified software (Radi Medical Systems). The software allows the pressure sensor, 3 cm from the tip of the standard coronary pressure wire, to act also as a distal temperature sensor while the shaft of the wire acts as a proximal temperature sensor; the transit time of an injectate can then be calculated. Approximately 3 mL of room-temperature saline was rapidly injected into the left coronary artery 3 times. The resting mean transit time was recorded each time and then averaged. Intracoronary papaverine (15 mg) was given, and 3 more injections of 3 mL of room-temperature saline were quickly performed. The hyperemic mean transit time was recorded each time and then averaged. CFR\textsubscript{thermo} was defined as the average resting mean transit time divided by the average hyperemic mean transit time.\textsuperscript{18}

**Intravascular Ultrasound**

After the IVUS catheter was positioned as described above, an automated pullback at 0.5 mm/s was performed and the IVUS images were recorded on a 0.5-inch s-VHS videotape. The images were digitized, and 3-dimensional volumetric analysis was performed by means of Simpson’s method (echoPlaque, Indec Systems, Inc.).\textsuperscript{20} Measurements included the vessel volume, the lumen volume, and the plaque volume. To standardize for vessel size and for length of the IVUS pullback, the percent plaque volume, defined as the plaque volume divided by the vessel volume, was calculated. Standard 2-dimensional measurements were performed as well. These included maximum and minimum vessel and lumen diameters and areas. Maximum intimal thickness was measured, and the minimum and maximum plaque area of any cross-sectional image in the left anterior descending artery (LAD) was recorded. The maximum percent plaque area or intimal index was defined as the maximum plaque area divided by the corresponding vessel area. All measurements were performed by one individual from the Stanford IVUS Core Laboratory, blinded to clinical and angiographic information. Intraobserver variability has been previously reported.\textsuperscript{20} Figure 1 shows an example of the angiographic pressure, flow, and IVUS images in one case.

**Quantitative Coronary Angiography**

The Stanford QCA Core Laboratory, blinded to the physiological and IVUS results, performed QCA on the proximal, mid, and distal left anterior descending coronary artery. Using the guiding catheter for calibration and an edge detection system (Sanders Data Systems), the reference diameters and minimum lumen diameter for the 3 sites were calculated and the greatest percent diameter stenosis recorded.

**Analyses**

Values are presented as mean±SD. Correlations between continuous variables were calculated by using linear regression analysis. Mean values were compared by means of the Student’s t test. A value of \(P<0.05\) was considered significant. Statistical calculations were performed with Statview software (SAS Institute Inc).

**Results**

Fifty-three examinations were performed in 46 patients (7 patients underwent annual angiography twice during the study period). The mean time from transplantation to enrollment was 3.1±3.7 years (range, 1 month to 17 years). The most severe LAD stenosis, based on QCA, was 42%. The mean LAD stenosis was 17±10%. IVUS was performed successfully in 52 of the 53 cases (98%). The mean maximum percent plaque area or intimal index was 42±19%. The mean percent plaque volume was 24±12%. The mean maximum intimal thickness was 1.1±0.6 mm.

FFR was measured successfully in all cases. The mean FFR was 0.88±0.07. In 75% of cases, the FFR was less than the normal threshold of 0.94. In 15% of cases, the FFR was ≤0.80, the upper boundary of the gray zone of the ischemic threshold, and in 6% the FFR was ≤0.75 (Figure 2).\textsuperscript{21} FFR correlated significantly with a number of IVUS parameters (Table). FFR correlated most strongly with indexes of plaque burden: \(r=0.52, P<0.0001\) for FFR and minimum percent plaque area and \(r=0.48, P=0.0002\) for FFR and maximum percent plaque area (2-D analysis); and \(r=0.55, P<0.0001\) for FFR and percent plaque volume (3-D analysis). The mean percent plaque volume in cases in which the FFR was ≤0.80 was 37±11%, compared with 23±11% in cases in which the FFR was >0.80 but <0.94 (\(P=0.002\)) and compared with 18±9% in cases in which the FFR was ≥0.94 (\(P<0.001\)) (Figure 3).

CFR\textsubscript{thermo} was measured successfully in 49 of the 53 cases (93%). The CFR\textsubscript{thermo} software was not available for
1 case, and in the other 3 cases, positioning of the guide catheter limited the ability to inject saline rapidly down the LAD. The average resting mean transit time was 1.0±0.41 seconds. The average hyperemic mean transit time was 0.47±0.25 seconds. The mean CFRthermo was 2.5±1.2. In 47% of cases, CFRthermo was ≥2.0. In 14% of cases, FFR was ≥0.94 (normal) and CFRthermo was ≤2.0 (likely abnormal), suggesting predominant microcirculatory dysfunction (Figure 2). The mean percent plaque volume and mean maximum percent plaque area in these 14% of cases were 20±12% and 35±16%, respectively. These values were not significantly different from those in the cases in which the FFR was ≥0.94 and the CFR was >2.0 (15.5±3% and 39±27%, respectively). FFR and CFRthermo did not correlate (r<0.1, P=NS). CFRthermo correlated weakly with the IVUS-derived average maximum lumen diameter (r=0.31, P=0.03) and did not correlate with any other IVUS parameter (r<0.30, P=NS). In the cases with an FFR ≤0.80, the percent plaque volume did not differ significantly in those with a lower CFRthermo, compared with those with a higher CFRthermo.

**Discussion**

The main findings in this study are that a majority of asymptomatic cardiac transplant recipients without angiographic evidence of hemodynamically significant coronary artery disease have abnormal physiology in their epicardial artery, based on FFR. Moreover, in a proportion of these cases, the FFR value suggested ischemia in the LAD territory. FFR correlated significantly with parameters of plaque bur-
den, based on IVUS, implying that the anatomic changes resulting from transplant arteriopathy are responsible for the physiological changes detected by FFR measurement. Finally, in a unique proportion of cases, predominant microcirculatory dysfunction was present, based on a normal FFR and abnormal CFR; these cases would not have been detected by IVUS alone.

**FFR in Relation to IVUS**

In 75% of the cases, despite insignificant angiographic disease based on QCA, FFR in the LAD was below 0.94, the lower limit of the normal range for FFR. The FFR in the LAD was below the upper limit of the ischemic threshold in 15% of the cases, suggesting that a proportion of asymptomatic transplant recipients with angiographic coronary disease have silent ischemia. Studies assessing stress echocardiography in this setting found similar incidences of silent ischemia.22,23 This is the first study to show that the epicardial artery alone can be the cause of the physiological impairment.

FFR correlated best with IVUS-derived parameters of overall plaque burden and less well with parameters suggestive of focal stenoses, such as minimum lumen diameter or area. In the 15% of cases in which the FFR was <0.80, almost 40% of the vessel volume consisted of atherosclerotic plaque. This was significantly greater than the approximately 20% plaque volume found in the cases in which the FFR was >0.80 (Figure 3). The lack of correlation between lumen dimensions and FFR may be explained by the fact that vessels without angiographic stenoses were studied. In this setting, the lumen of a diffusely atherosclerotic artery in one case will be equal to the lumen of a nonatherosclerotic artery, but because the diseased vessel supplies a larger myocardial territory, the decrease in lumen size will prohibit sufficient perfusion during peak hyperemia. For these reasons, the absolute lumen dimensions did not predict the physiological findings, but the plaque burden did.

These data suggest that a diffuse atherosclerotic process, which does not result in a focal encroachment of the lumen, can lead to a significant decline in pressure along the vessel. This theory was first suggested by De Bruyne et al,14 who found a similar percentage of low FFR values in angiographically normal vessels adjacent to stenotic ones in nontransplant patients. These investigators did not use IVUS to validate their hypothesis, and it was suggested that measuring FFR and performing IVUS in patients with typically diffuse atherosclerosis, such as transplant recipients, would be necessary to confirm this theory, as we have performed here.24

**Simultaneous FFR and CFRthermo**

To date, the physiological interrogation of transplant arteriopathy has consisted of assessing Doppler-derived CFR. Past studies have found that intimal thickening detected with IVUS did not result in abnormal Doppler-derived CFR and that the absolute Doppler-derived CFR was similar in transplant recipients with minimal angiographic disease compared with those with no angiographic disease.7,8,22,23 These results are best explained by the fact that CFR interrogates the entire coronary system, including both the conduit and the resistive vessels, and by the fact that CFR does not have the same normal value in every patient. To overcome these limitations, CFR has been coupled with IVUS to include a specific interrogation of the epicardial artery. Unfortunately, this can

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**Correlations Between FFR and a Variety of IVUS Parameters**

<table>
<thead>
<tr>
<th>IVUS Variable</th>
<th>r Value</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td><strong>2D analysis</strong></td>
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<td></td>
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<tr>
<td>Average lumen diameter</td>
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<tr>
<td>Average lumen area</td>
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<tr>
<td>Maximum lumen area</td>
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</tr>
<tr>
<td>Minimum lumen area</td>
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</tr>
<tr>
<td>Average plaque area</td>
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<td>0.001</td>
</tr>
<tr>
<td>Maximum % plaque area</td>
<td>0.48</td>
<td>0.0002</td>
</tr>
<tr>
<td>Minimum % plaque area</td>
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<tr>
<td><strong>3D analysis</strong></td>
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<tr>
<td>Plaque volume</td>
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<tr>
<td>% plaque volume</td>
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be unwieldy and provides an anatomic assessment only and not a physiological evaluation of the conduit vessel.9

In this study, we applied a novel method of simultaneously measuring CFR and FFR. Pijls, De Bruyne, and others have shown that with modified software the pressure sensor on a standard coronary pressure wire can act also as a thermistor and allow calculation of the transit time of an injectate.18,19 By comparing the transit time, a surrogate to coronary flow, at rest with the transit time at peak hyperemia, CFRthermo can be derived.

We found that measuring CFRthermo and pressure-derived FFR is relatively simple and that the combination of the two provides information regarding the functional status of the coronary system that would not be available with either technique alone or coupled with IVUS. In particular, in almost 15% of cases, FFR was normal and CFRthermo was markedly abnormal, implying predominant microvascular disease. This finding may be particularly relevant to transplant recipients, in whom the presence of microvascular dysfunction has been correlated with the future development of epicardial transplant arteriopathy and clinical events.25 Because the CFR values in these cases were similar to the CFR values in cases in which the FFR was <0.94, it is unlikely that the FFR was normal because the microvasculature was so impaired that a pressure gradient could not be generated. Further support for the assertion that the epicardial function was normal in these cases comes from the IVUS data demonstrating a similar plaque burden as found in those cases in which both CFR and FFR were normal.

Finally, as in previous studies evaluating Doppler wire-derived CFR, in this study, CFRthermo did not correlate well with IVUS findings, further highlighting the need for a method of interrogating the status of the epicardial artery that is independent of the microcirculation. CFRthermo was >2.0 in a proportion of cases with epicardial disease, based on IVUS and FFR. This is not contradictory but reflects the fact that the normal CFR in these cases should be much higher.

Limitations

This study is limited in that it lacks clinical correlation to the physiological findings. It is also limited because of a lack of serial data in the same patients. Currently, we are attempting to address these limitations by following this cohort for clinical events and by repeating the physiological interrogation during follow-up angiograms.

We did not routinely perform slow pullbacks of the pressure sensor during maximal hyperemia to document progressive declines in pressure rather than localized pressure gradients from a focal narrowing. However, the IVUS findings suggest that diffuse intimal thickening and not angiographically undetected focal stenoses was responsible for the observed pressure gradients.

Conclusions

The simultaneous measurement of FFR and CFRthermo is a feasible and relatively easy invasive technique for screening asymptomatic cardiac transplant recipients for angiographically inapparent transplant arteriopathy. FFR was markedly abnormal in a majority of cases and frankly ischemic in 15%; moreover, FFR correlated with IVUS findings, suggesting that diffuse anatomic changes resulting from transplant arteriopathy impair the functional status of the epicardial artery. Assessment of FFR and CFRthermo simultaneously helped to distinguish between abnormal epicardial and microvascular physiology and revealed that a different proportion of patients have predominant microvascular dysfunction. The ability to detect and distinguish changes in epicardial and microvascular function in this patient population may aid in identifying modifiable factors that lead to transplant arteriopathy.

References


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