Heterogeneity of Coronary Flow Reserve in the Examination of Multiple Individual Allograft Coronary Arteries

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Background—Epicardial and resistance vessel function in the transplanted heart has been evaluated primarily in regions supplied by a single vessel. Heterogeneity of flow among multiple perfusion fields as a marker of early endothelial dysfunction in the microcirculation has not been evaluated previously. This study tested the hypothesis that increased variability of coronary flow reserve (CFR) among multiple vascular regions would be associated with allograft coronary vasculopathy.

Methods and Results—One hundred six posttransplant patients undergoing cardiac catheterization had measurement of CFR in at least 3 major epicardial vessels. Patients were divided into those with minimal angiographic abnormalities (n=37) and those with no angiographic abnormalities (n=69). The ranges, coefficients of variation, and univariate and multivariate regression analyses of CFR were computed to determine the major clinical factors influencing the degree of variability. The abnormal angiographic group was older (54±11 versus 47±13 years; P<0.003), had older hearts (35±11 versus 27±10 years; P<0.005), and were further posttransplant (162±1022 versus 931±984 days; P<0.0009). There was no difference in global CFR between groups (normal, 3.4±0.8 versus abnormal, 3.4±0.7; P=NS). The coefficient of variation of CFR was higher for the abnormal group (16.3±8.6% versus 11.0±5.5%; P<0.0006). Univariate and multivariate predictors of increased variability in CFR included angiographic abnormalities, patient age, and body mass index. Both angiographic abnormalities and an elevated CV of CFR were predictive of a combined end point of death, congestive heart failure, or subsequent development of ≥50% coronary stenosis.

Conclusions—These data demonstrate that increased variability of CFR is associated with discernible allograft coronary arteriopathy and is predictive of outcome in patients after heart transplantation. (Circulation. 1999;99:626-632.)

Key Words: blood flow ▪ transplantation ▪ arteries

Orthotopic heart transplantation is established as an effective therapy for end-stage congestive heart failure. Since the advent of cyclosporine, graft failure due to acute cellular rejection has diminished and allograft vasculopathy has emerged as the major obstacle to long-term survival. Allograft vasculopathy is difficult to detect clinically because patients are often asymptomatic secondary to denervation, and the results of noninvasive testing have been disappointing. The peculiar features of allograft vasculopathy include its circumferential involvement of the epicardial vessels and extension into the intramyocardial vessels. Standard coronary angiography is limited because a normal angiogram does not exclude extensive myointimal proliferation, and angiography can provide little information on intramyocardial resistance vessels.

To assess allograft resistance vessel function, various techniques, including intracoronary Doppler and PET, have been used to measure both resting and hyperemic blood flow. Coronary flow reserve (CFR), defined as the ratio of hyperemic to resting blood flow, has been used as an index of resistance vessel integrity. Previous studies have yielded conflicting results regarding the question of whether epicardial and microvascular disease occur concordantly. These studies have been limited by either presentation of mean flow data or evaluation of a single vascular distribution. Given that epicardial angiographic abnormalities can appear at different rates in different vascular beds, we hypothesized that abnormalities in resistance vessel function would also have a nonuniform time course across various perfusion fields. We further hypothesized that asymmetry of resistance vessel function would manifest as differences in CFR measured in different vascular beds. If the development of epicardial and resistance vessel arteriopathy occurs simultaneously, then variability of CFR should be most evident in patients with angiographic abnor-
malities. This heterogeneity of microvascular dysfunction may indicate early endothelial dysfunction before the appearance of flow-limiting epicardial stenoses. The purpose of this study was to measure intrapatient flow reserve variability in a posttransplant population and assess its relationship to early manifestations of epicardial disease and other clinical variables.

Methods
Orthotopic heart transplant patients undergoing surveillance cardiac catheterization were candidates for the study. Between April 15, 1993, and June 15, 1994, 133 posttransplant patients had coronary flow measurements performed in at least 3 major epicardial vessels. Twenty-seven patients were excluded: 9 had diameter stenoses >50%, 10 had poor-quality flow signals, and 8 had regional wall motion abnormalities. Oral and written consent were obtained before the studies, which were approved by the Institutional Review Board. All vasoactive medications were withheld for 12 to 24 hours before the study. No patients had been receiving a long-acting β-blocker. Patients routinely received 2 mg of diazepam and 25 mg of diphenhydramine before catheterization.

Cardiac Catheterization Protocol
Right ventricular endomyocardial biopsy and right and left heart catheterization with hemodynamic measurements were performed from the femoral approach. Right coronary angiography was performed in standard fashion after 150 to 200 μg of intracoronary nitroglycerin.

Coronary Flow Velocity Measurements
After completion of the right coronary arteriograms, heparin 5000 U IV was administered, and an 0.018-in Doppler-tipped guidewire (FloWire, Cardiometrics, Inc) was advanced past the most distal acute marginal branch of the right coronary artery and positioned proximal to the origin of the posterior descending artery. Flow velocity measurements were obtained at baseline and at peak hyperemia after bolus injection of adenosine 12 to 18 mg IC.21 Bolus injection of adenosine was used because it produces peak increases in coronary flow velocity without changes in epicardial vessel diameter, so that flow velocity changes are accurate surrogates of flow velocity with changes in epicardial vessel diameter, so that flow velocity changes are accurate surrogates of total flow changes.22 The CFR was calculated as the quotient of hyperemic to baseline average peak velocity (APV). Left coronary angiography was then performed after administration of nitroglycerin 150 to 200 μg IC. After completion of angiography, the Doppler guidewire was placed in the proximal left anterior descending coronary artery. Baseline and peak hyperemic flow velocities were measured. The protocol was then repeated with the guidewire in the proximal circumflex artery. In patients with left dominant circulation, either the first obtuse marginal, median ramus, or first diagonal artery was also studied, depending on which artery was largest.

Endomyocardial Biopsy Analysis
Five specimens of right ventricular endomyocardium were obtained at each study. The specimens were examined by light microscopy and graded according to standard criteria.23 The biopsy results were assigned a numerical score (0=0, 1A=1, 1B=1.5, 2=2, 3A=3, 3B=3.5, 4=4).

Left Ventricular Function Analysis
Each patient underwent either gated equilibrium radionuclide scanning or 2-dimensional echocardiographic assessment of left ventricular function within 24 hours of catheterization. For those patients undergoing echocardiography, 2-dimensional and M-mode evaluations of wall motion and wall thickness were performed according to the standards of the American Society of Echocardiography.24 Radionuclide studies using technetium-labeled red blood cells were obtained in a standard fashion visualizing the heart in 3 projections. After a cine endless-loop display was created, wall motion was assessed with anterior, septal, inferior, apical, and lateral segments classified as normal, hyperkinetic, akinetic, or dyskinetic. All evaluations were performed by observers unaware of catheterization flow results.

Angiographic Data Analysis
Each coronary angiogram was evaluated by 2 independent observers blinded to the results of the flow data and clinical history. Angiographic evidence of disease was defined as type A (luminal irregularities or narrowings in a primary or secondary coronary vessel) or type B (distal tapering, loss of distal branches, or blunt occlusion identified on serial studies) as described by Gao et al.25

Quantitative angiographic evaluation was performed on-line with the Philips DCI-ACA system, with the contrast-filled catheter serving as a reference standard. The dimensions of the nonobstructed proximal artery segments and absolute luminal diameter of the coronary artery 5 mm distal to the tip of the Doppler-tipped guidewire were measured. An off-line evaluation of any stenosed vessel with a type A lesion was performed with a quantitative caliper system (ImageCon Systems, Inc). The normal adjacent segment was used as the reference for measurement of the extent of stenosis. If the vessel had multiple lesions, all lesions were measured by electronic calipers.

Patients were divided into 2 groups: normal, with no angiographic abnormalities, and abnormal, with type A and/or B lesions. No patient had a stenosis >50% diameter narrowing.

Coronary Flow Velocity Data Analysis
Flow velocity data were printed on an integrated video page printer that provided computer-calculated variables of intracoronary flow velocity. The APV was used in the calculation of CFR. Flow data were reviewed by 2 physicians (T.L.W., T.J.D.) blinded to the angiographic findings to verify satisfactory computerized tracking of the velocity signal. If the automatic tracking of the velocity profile was inadequate, both baseline and hyperemic flow velocity signals were planimetered off-line with a commercially available digitizing tablet interfaced with a microcomputer as previously validated.21

Hemodynamic Data
Blood pressure and heart rate were continually monitored and recorded for each baseline and hyperemic flow velocity signal measurement. For every patient, the double product was calculated as heart rate×systolic pressure.

Analysis of Flow Heterogeneity
Heterogeneity of CFR in an individual patient was evaluated as follows: A global CFR was calculated as the average value from the studied vessels. The following measures of intrapatient variability of CFR were then derived: (1) range: maximum CFR−minimum CFR; normalized range: range/global CFR×100; and (2) coefficient of variation (CV): SD of CFR/mean CFR×100 for each patient (Table 1 demonstrates a sample calculation).

An analysis of hemodynamic variability was performed to determine whether the variability in CFR could be due to changes in hemodynamic parameters. Calculations identical to those described above for CFR were made for heart rate×systolic pressure product, mean blood pressure, and heart rate.

Statistical Analysis
Statistical analysis between groups was made with Student’s unpaired t test as indicated. For groups with nonnormal distributions, a Mann-Whitney U test was performed. For comparisons of >2 groups, 1-way ANOVA was used. For groups with nonnormal distributions, the nonparametric version of a 1-way ANOVA, the Kruskal-Wallis test, was used. For standard 1-way ANOVA, post hoc testing was done with Tukey’s highly significant difference test. Survival data were analyzed with a Cox proportional hazards regression model.
TABLE 1. Sample Calculations for Measures of Variability of Coronary Flow Velocity and Reserve

<table>
<thead>
<tr>
<th>Artery</th>
<th>Coronary Flow Velocity Reserve (CFR)</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>4.7</td>
<td>0.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Circumflex</td>
<td>4.8</td>
<td>0.5</td>
<td>0.3</td>
</tr>
<tr>
<td>RCA</td>
<td>3.8</td>
<td>0.5</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Global CFR±SD=4.43±0.55
Range=4.8−3.8=1.0
Normalized range=\(\frac{1.0}{0.55}×100=18.2\%\)

CV CFR=\(\frac{SD}{\text{Global CFR}×100}×100=12.4\%\)

LAD indicates left anterior descending coronary artery; RCA, right coronary artery.

Multivariable analysis was performed with a logistic regression model. For correlations between groups, the nonparametric correlation coefficient Spearman’s \(\rho\) was used for nonnormal distributions and a Pearson’s correlation coefficient was used for normal distributions. Unless otherwise stated, all values are presented as mean±SD. Statistical difference was accepted at a value of \(P<0.05\). The statistical calculations were made with a commercially available statistical package (JMP 3.15, SAS Institute).

Results

The clinical characteristics of the population are shown in Table 2. The 106 patients were on standard immunosuppression regimens, the majority managed either with standard 3-drug therapy with cyclosporine, azathioprine, and prednisone (36%), and/or azathioprine (6%). The majority of patients were on standard immunosuppression regimens, the majority managed either with standard 3-drug therapy with cyclosporine, azathioprine, and prednisone (11%), methotrexate (1%), and/or azathioprine (6%). The majority of patients were male and had a nonischemic cause for their heart failure. The average age of the transplanted heart (donor age time posttransplant) was 30±11 years. The average time posttransplant was 1173±1047 days (3.2 years). Sixty-nine patients had angiographically normal studies, and the remaining 37 patients had angiographic abnormalities in at least 1 of the 3 coronary arteries. No patient had angina or heart failure. In 88 patients (83%), 3 vessels were studied, and in 18 patients (27%), 4 vessels were studied, for a total of 336 vessels. The results of endomyocardial biopsy were as follows: grade 0, 39 (36.8%); grade 1A, 30 (28.3%); grade 1B, 15 (14.1%); grade 2, 8 (7.5%); grade 3A, 12 (11.3%); and grade 3B, 2 (1.9%). Patients with abnormal angiographic findings were significantly older, were further posttransplant, and had older donors.

<table>
<thead>
<tr>
<th>Angiographic Group</th>
<th>Normal (n=69)</th>
<th>Abnormal (n=37)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic origin, n (%)</td>
<td>24 (35)</td>
<td>17 (45)</td>
<td>0.26</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>54/15</td>
<td>31/6</td>
<td>0.49</td>
</tr>
<tr>
<td>Age, y</td>
<td>47±12.6</td>
<td>54±10.5</td>
<td>0.0027</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>11 (16)</td>
<td>5 (13.5)</td>
<td>0.73</td>
</tr>
<tr>
<td>Lipid-lowering agents, n (%)</td>
<td>26 (38)</td>
<td>17 (46)</td>
<td>0.28</td>
</tr>
<tr>
<td>Time posttransplant, d</td>
<td>931±984</td>
<td>1625±1022</td>
<td>0.0003</td>
</tr>
<tr>
<td>Age of hearts, y</td>
<td>27±9.7</td>
<td>34.6±11.3</td>
<td>0.0007</td>
</tr>
<tr>
<td>Biopsy grade</td>
<td>1.2±1.1</td>
<td>0.7±0.7</td>
<td>0.13</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.4±1.9</td>
<td>13.5±2.0</td>
<td>0.006</td>
</tr>
<tr>
<td>Arterial oxygen saturation</td>
<td>93.9±1.8</td>
<td>93.7</td>
<td>0.69</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.5±4.5</td>
<td>27.2±3.7</td>
<td>0.047</td>
</tr>
<tr>
<td>Hypertensive treatment, n (%)</td>
<td>22 (32)</td>
<td>13 (35)</td>
<td>0.61</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>49.8±19.2</td>
<td>40.8±11.1</td>
<td>0.011</td>
</tr>
</tbody>
</table>

TABLE 3. Hemodynamic Data

<table>
<thead>
<tr>
<th>Angiographic Group</th>
<th>Normal</th>
<th>Abnormal</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>99±11</td>
<td>101±11</td>
<td>0.53</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>85±14</td>
<td>85±10</td>
<td>0.69</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>63.4±7.2</td>
<td>60.2±7.3</td>
<td>0.03</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>10.8±3.2</td>
<td>11.1±3.6</td>
<td>0.54</td>
</tr>
<tr>
<td>RPP, (mm Hg×bpm/1000)</td>
<td>11.26±2.3</td>
<td>11.41±2.2</td>
<td>0.74</td>
</tr>
</tbody>
</table>

LVEF indicates left ventricular ejection fraction; PCWP, mean pulmonary capillary wedge pressure; and RPP, rate-pressure product.

Coronary Flow Velocity Data

For the entire patient group, the APV at baseline was lower for the right coronary artery (15.1±5.3 cm/s) than the circumflex or left anterior descending coronary arteries (Table 4). The left anterior descending had the highest and the right coronary artery had the lowest absolute peak hyperemic APV. Despite differences in absolute flow velocities, there was no difference in CFR among vessels. There were also no differences for hemodynamic values at the time of individual coronary artery flow reserve measurements (Table 5).

TABLE 4. Average Peak Velocity, cm/s

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Baseline</th>
<th>Hyperemia</th>
<th>CFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD (n=105)</td>
<td>19.8±7.2</td>
<td>65.2±17.8†</td>
<td>3.46±0.90</td>
</tr>
<tr>
<td>RCA (n=94)</td>
<td>15.1±5.3*</td>
<td>49.5±13.3‡</td>
<td>3.43±0.79</td>
</tr>
<tr>
<td>Circumflex (n=96)</td>
<td>17.9±7.1</td>
<td>56.6±16.5</td>
<td>3.39±0.86</td>
</tr>
<tr>
<td>Secondary (n=38)</td>
<td>16.8±5.8</td>
<td>49.5±15.1</td>
<td>3.07±0.72</td>
</tr>
</tbody>
</table>

LAD indicates left anterior descending coronary artery; RCA, right coronary artery; and secondary, obtuse marginal or diagonal.

*\(P<0.003\) vs LAD and circumflex.
†\(P<0.003\) vs RCA, secondary, and circumflex.
‡\(P<0.003\) vs circumflex.

Hemodynamic and Angiographic Data

Baseline hemodynamics are shown in Table 3. Both groups had normal ejection fractions, with the angiographically normal group having a slightly higher value than the abnormal group (63±7% versus 60±7%; \(P=0.03\)). There were no significant differences in baseline hemodynamics between groups. In the abnormal group, the mean diameter stenosis was 23.7±11% (range, 14% to 49%).

The 106 patients were on standard immunosuppression regimens, the majority managed either with standard 3-drug therapy with cyclosporine, azathioprine, and prednisone (44%) or with cyclosporine and azathioprine alone (38%). The remainder of the patients were receiving cyclosporine in combination with prednisone (11%), methotrexate (1%), and/or azathioprine (6%). The majority of patients were male and had a nonischemic cause for their heart failure. The average age of the transplanted heart (donor age time posttransplant) was 30±11 years. The average time posttransplant was 1173±1047 days (3.2 years). Sixty-nine patients had angiographically normal studies, and the remaining 37 patients had angiographic abnormalities in at least 1 of the 3 coronary arteries. No patient had angina or heart failure. In 88 patients (83%), 3 vessels were studied, and in 18 patients (27%), 4 vessels were studied, for a total of 336 vessels. The results of endomyocardial biopsy were as follows: grade 0, 39 (36.8%); grade 1A, 30 (28.3%); grade 1B, 15 (14.1%); grade 2, 8 (7.5%); grade 3A, 12 (11.3%); and grade 3B, 2 (1.9%). Patients with abnormal angiographic findings were significantly older, were further posttransplant, and had older donors.

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TABLE 5. Hemodynamic Variables During Individual Artery CFR Measurements

<table>
<thead>
<tr>
<th>Vessel</th>
<th>RPP, (mm Hg×bpm)/1000</th>
<th>MBP, mm Hg</th>
<th>HR, bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD (n=105)</td>
<td>11.46±2.40</td>
<td>101±12</td>
<td>84±13</td>
</tr>
<tr>
<td>RCA (n=94)</td>
<td>11.06±2.26</td>
<td>98±11</td>
<td>84±13</td>
</tr>
<tr>
<td>Circumflex (n=96)</td>
<td>11.33±2.40</td>
<td>101±12</td>
<td>84±13</td>
</tr>
<tr>
<td>Secondary (n=58)</td>
<td>11.14±2.50</td>
<td>98±13</td>
<td>86±14</td>
</tr>
</tbody>
</table>

RPP indicates rate-pressure product; MBP, mean blood pressure; HR, heart rate; LAD, left anterior descending coronary artery; and RCA, right coronary artery.

Coronary Flow Variability

There were no differences in baseline or hyperemic APVs or global CFR between the normal and abnormal angiographic groups (Table 6). The range (normal, 0.75±0.46 versus abnormal, 1.1±0.55; P=0.0008) and the normalized range of CFR (normal, 21.8±10.9% versus abnormal, 32.2±16.3%; P=0.0006) were lower in the normal group. The coefficient of variation of CFR (CV CFR) was also lower in the normal group (11.0±5.5% versus 16.3±8.6%; P=0.0006). The population mean for CV CFR was 12.8±7.2%. There was no difference in CV CFR for patients with type B versus type A angiographic disease (18.5±14% versus 16±7%, P=NS).

The CV CFR was not different whether 3 vessels were due to hemodynamic factors, the same statistical analysis was performed on hemodynamics measured at the time of the coronary flow velocity measurements. There were no differences in any measures of hemodynamic variability between the normal and abnormal groups (Table 7).

Left ventricular mass and mass index had inverse relationships with CFR (r=-0.23, P=0.04 and r=-0.29, P=0.017, respectively). Despite this finding, there was no relationship between either left ventricular mass or left ventricular mass index and CV CFR (r=0.008, P=NS and r=0.09, P=NS, respectively).

To assess the effects of time posttransplant, the correlation between CV CFR and both the age of the heart and the time after transplantation was examined. There was no correlation between age of the heart (r=0.14, P=0.1412) or time posttransplantation (r=0.18, P=0.065) and CV CFR.

A logistic regression model to find predictors of increased flow variability was performed at 2 levels (Table 8). First, patients above the 75th percentile were defined as abnormal for CV CFR. By this standard (CV CFR >16.2%), 4 factors (angiographic abnormality, age, blood pressure, body mass index, and ischemic cause of heart failure) had a direct relationship. In a multiple logistic regression model, the factors that remained significant were angiographic abnormality, arterial oxygen saturation, CV of mean blood pressure, and body mass index.

A second logistic regression was performed using the population mean of CV CFR±SD as the measure of abnormal variability (ie, CV CFR >20%, approximating the 90th percentile in this nonnormally distributed population). By

TABLE 6. Coronary Flow Velocity Variability

<table>
<thead>
<tr>
<th>Angiographic Group</th>
<th>Normal</th>
<th>Abnormal</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>APV, cm/s</td>
<td>17.6±5.3</td>
<td>17.6±6.0</td>
<td>0.99</td>
</tr>
<tr>
<td>Hyperemic APV, cm/s</td>
<td>56.4±11.1</td>
<td>56.7±14.8</td>
<td>0.91</td>
</tr>
<tr>
<td>Global CFR</td>
<td>3.37±0.77</td>
<td>3.40±0.66</td>
<td>0.81</td>
</tr>
<tr>
<td>CV CFR, %</td>
<td>11.0±5.5</td>
<td>16.3±8.6</td>
<td>0.0006</td>
</tr>
<tr>
<td>Range CFR</td>
<td>0.75±0.46</td>
<td>1.1±0.55</td>
<td>0.0008</td>
</tr>
<tr>
<td>Normalized range CFR, %</td>
<td>21.8±10.9</td>
<td>32.2±16.3</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

TABLE 7. Hemodynamic Variability

<table>
<thead>
<tr>
<th>Angiographic Group</th>
<th>Normal</th>
<th>Abnormal</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, range, bpm</td>
<td>3.8±3.4</td>
<td>4.1±4.0</td>
<td>0.66</td>
</tr>
<tr>
<td>RPP range, mm Hg×bpm</td>
<td>1.0±0.68</td>
<td>1.14±0.62</td>
<td>0.32</td>
</tr>
<tr>
<td>MBP range, mm Hg</td>
<td>8.8±4.7</td>
<td>9.1±6.0</td>
<td>0.77</td>
</tr>
<tr>
<td>CV heart rate, %</td>
<td>2.4±2.3</td>
<td>3.0±3.2</td>
<td>0.31</td>
</tr>
<tr>
<td>CV RPP, %</td>
<td>4.7±3.0</td>
<td>5.3±3.1</td>
<td>0.34</td>
</tr>
<tr>
<td>CV MBP, %</td>
<td>4.5±2.3</td>
<td>4.69±2.9</td>
<td>0.77</td>
</tr>
<tr>
<td>HR range/mean HR×100, %</td>
<td>4.6±4.2</td>
<td>5.1±5.0</td>
<td>0.55</td>
</tr>
<tr>
<td>RPP range/mean RPP×100, %</td>
<td>9.2±5.7</td>
<td>10.4±6.0</td>
<td>0.30</td>
</tr>
<tr>
<td>MBP range/mean MBP×100, %</td>
<td>9.0±4.8</td>
<td>9.4±6.1</td>
<td>0.72</td>
</tr>
</tbody>
</table>

RPP indicates rate-pressure product; MBP, mean blood pressure; and HR, heart rate.

*Defined as >75th percentile of CV CFR (16.2).
univariate logistic regression, angiographic abnormality, body mass index, total cholesterol/HDL ratio, and hemoglobin had a direct relationship and arterial oxygen saturation had an inverse relationship. In a multiple logistic regression analysis, only angiographic abnormality ($P = 0.043$) and arterial oxygen saturation ($P = 0.041$) were significant (Table 9).

**Rejection and CFR**

Previous studies have suggested that cellular rejection results in a diminished CFR. In this study, the CFRs of the 39 patients with grade 0 biopsies were not significantly different from CFRs of rejecting patients ($3.5 \pm 0.6$ versus $3.3 \pm 0.8$; $P = 0.06$). Similarly, intrapatient flow reserve variability by biopsy grade showed no significant relationship. The CV CFR in patients with grade 0 biopsies was $14 \pm 8.4\%$, versus $12.1 \pm 6.3\%$ ($P = 0.36$) in patients with $\geq 1A$ grade biopsy. There was no relationship between average biopsy score at 1 month, 6 months, 12 months, or the life of the graft and CV CFR. There was also no relationship between number of treated rejections at any time point and CV CFR.

**Clinical Events**

The patients were followed up for an average of $26 \pm 7.3$ months. To evaluate the effects of variability of flow on clinical events, a composite endpoint was devised of cardiac death (sudden death, myocardial infarction, or left ventricular failure), development of congestive heart failure unrelated to death, or development of a $>50\%$ diameter stenosis in a primary epicardial vessel. A univariate Cox proportional hazards model found that angiographic abnormalities (risk ratio, 2.0; 95% CI, 1.24 to 3.4; $P = 0.0040$), CV CFR (risk ratio per decile percent, 2.4; 95% CI, 1.4 to 4.0; $P = 0.0036$), CV of resting flow (risk ratio per decile percent, 2.2; 95% CI, 1.4 to 3.4; $P = 0.0011$), and variability of hyperemic flow velocity (risk ratio per decile percent, 1.6; CI, 1.04 to 2.3; $P = 0.0314$) were all significant in determining event rates. A multivariate Cox proportional hazards model found that only CV CFR (risk ratio, 2.1; CI, 1.01 to 4.1; $P = 0.0489$) was significant. Angiographic abnormality ($P = 0.55$) and variability of hyperemic flow were not significant. There was a trend toward significance for variability of resting flow ($P = 0.06$).

**Discussion**

This study demonstrated that in a posttransplant population, there is a finite degree of intrapatient variability in CFR. Although the absolute flow velocities and CFRs were not different between the angiographically normal and abnormal groups, the intrapatient variability of resting APV, hyperemic APV, and CFR was significantly greater in the abnormal group.

The initial hypothesis that epicardial angiographic disease would be associated with different microvascular perfusion field responses was supported by these findings. CFR is not uniform across the left ventricular myocardium, and this variation increases in patients with angiographic evidence of disease. Variability in CFR is not due to hemodynamic parameters, because the magnitude and direction of hemodynamic variability cannot explain the variability seen in the CFRs within an individual patient.

Regional variability for resting and hyperemic APV is to be expected, given the relative differences in perfusion field size supplied by the different interrogated epicardial vessels. The increase over baseline variability found in the angiographically abnormal group suggests that endothelial dysfunction may play a role in this group. Basal blood flow autoregulation is strongly influenced by local release of endothelium-derived mediators such as endothelium-derived relaxing factor, which interacts with myogenic and passive properties of vascular walls to coordinate blood flow distribution. Prior work has demonstrated significant spatial heterogeneity of basal and hyperemic blood flow in a canine model. CVs of 24.3% in basal flow and 30.4% in peak hyperemic flow were found between milligram-sized sections of the left ventricular free wall. The present study demonstrated variability when regional perfusion fields were examined, rather than small sections of a single perfusion field. The enhanced degree of blood flow variability found in patients with mild-to-moderate angiographic abnormalities may explain, at least in part, the enhanced variability found in the CFR of these 2 groups.

The finding of this increased variability suggests that early endothelial dysfunction may predominate the appearance of hemodynamically significant angiographic abnormalities and disrupt the usual endothelium-derived local control of vascular tone and flow.

**Sources of Variability of CFR**

A variety of causes may lead to enhanced variability of CFR. One possible explanation is the influence of reinnervation on the transplant coronary circulation. In animal models, the distribution of adrenergic receptors, in particular $\alpha_2$-receptors, across the microcirculation is heterogeneous and may explain enhanced vasoreactivity in response to adenosine. Because reinnervation is heterogeneous, the minimal achievable coronary vascular resistance in innervated versus denervated beds may be different. Reinnervation differences could potentially modify regional left ventricular metabolism and subsequently regional blood flow. Denervated myocardium is not metabolically equivalent to innervated myocardium. Data on patients studied early posttransplant, who are therefore completely denervated, may offer indirect evidence in support of this hypothesis. The CV CFR in patients studied at $\geq 1$ year posttransplant was $13.7 \pm 7.5\%$, versus $9.4 \pm 4.2\%$ ($P = 0.01$) in patients studied within 42 days.
was no relationship, however, between days posttransplant and CV CFR ($r=0.18$, $P=0.065$).

Cellular rejection has also been shown to affect CFR.12 Higher grades of rejection may represent a more widespread process, presumably leading to a more uniform effect on CFR.58 We found no evidence, however, that differences in flow reserve were related to the grade of rejection.

Previous studies using PET suggest an elevated variability in flow reserve in patients with abnormal cholesterol.39 Correlation analysis of CV CFR showed a significant relationship between total cholesterol/HDL ratio and flow variability ($r=0.28$, $P=0.0051$). In the multiple logistic regression analysis, however, no lipid variable was a significant independent predictor of CFR variability.

PET studies have also shown that resistance vessel function in vascular beds remote from the affected epicardial artery in patients with single-vessel disease is abnormal relative to control patients with no arterial disease.40,41 A similar finding in transplant patients is not unexpected. A functional abnormality in the resistance bed and an absolute decline in microvascular cross-sectional area are 2 possible explanations. Given that absolute CFRs were not different between the normal and abnormal groups, it is difficult to implicate any significant loss of recruitable microvascular cross-sectional area. The findings suggest that the development of epicardial and small-vessel disease may be asymmetrical processes resulting in enhanced intervessel CFR variability. It is likely that the involvement of the intramyocardial vessels may be as heterogeneous as that found in the epicardial vessels.

Lower arterial saturation was associated with increased CV CFR. This finding is probably closely linked to the question of innervation. Denervated arteriolar smooth muscle has primarily anaerobic metabolism,42 whereas innervated arteriolar smooth muscle is primarily aerobic.43 The complex interplay between innervation and resistance vessel smooth muscle metabolism could be affected by changes in arterial oxygen saturation.

Increased body mass index was also predictive of increased CFR variability. Studies have demonstrated a correlation between elevated body mass index and development of a diffuse variant of transplant coronary arteriopathy.44 On the basis of the present data, a more pronounced arteriopathy should be associated with increased variability. Obesity has also been associated with insulin resistance, which has been correlated with both macrovascular and microvascular abnormalities. The microvascular abnormalities are thought to be related to increased sympathetic outflow; thus, heterogeneous reinervation may again be implicated in increased variability.45,46

The proportional hazards analysis suggests that increased variability is associated with an increased frequency of an adverse outcome. Variability of CFR appears to have important clinical implications in a posttransplant patient population. The detection of increased variability, however, requires a more thorough evaluation of coronary blood flow than has been attempted in previous studies. The long-term resolution of the importance and source of enhanced variability will require characterization by postmortem examinations.

**Limitations**

CFR determinations in all 3 vessels could not be performed simultaneously. Although changes in heart rate and blood pressure may affect CFR measurements in patients, the mean blood pressure and heart rate recorded during these studies did not change significantly.47 There was no relationship between heart rate or mean arterial pressure and CV CFR.

Absolute CFR values with the Doppler guidewire are lower than those reported in other studies using an intracoronary Doppler catheter.11 Previous studies have measured the Doppler shift with a zero-cross methodology that appears to overestimate flow compared with the fast Fourier transform spectral analysis used by the Doppler guidewire.20,21,48 The Doppler guidewire has been validated in both in vitro and in vivo models.20 CFRs measured in PET studies in transplant patients correlate more closely with measurements made with the Doppler guidewire than those made with the intracoronary Doppler catheter.

**Conclusions**

The findings in this study suggest that in a posttransplant population, evaluation of resistance vessel function in a single coronary artery by Doppler technology will fail to identify variability among vascular regions. A complete evaluation of resistance vessel function should include the calculation of the variability of both baseline coronary flow and coronary vasodilatory reserve. Those patients with modest angiographic abnormalities who do not have diminished CFR may have subtle microvascular abnormalities not readily appreciated by other methods. Although the precise clinical association of increased variability of baseline flow and CFR with outcome has not yet been established, increased coronary vasodilatory reserve variability correlates with a significantly increased risk of cardiovascular events and most likely heralds the presence of allograft arteriopathy at the microvascular level.

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Heterogeneity of Coronary Flow Reserve in the Examination of Multiple Individual Allograft Coronary Arteries
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_Circulation_. 1999;99:626-632
doi: 10.1161/01.CIR.99.5.626

_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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