Correlation of Pharmacological $^{99m}$Tc-Sestamibi Myocardial Perfusion Imaging With Poststenotic Coronary Flow Reserve in Patients With Angiographically Intermediate Coronary Artery Stenoses

D. Douglas Miller, MD; Thomas J. Donohue, MD; Liwa T. Younis, MD, PhD; Richard G. Bach, MD; Frank V. Aguirre, MD; Mark D. Wittry, MD; Henry M. Goodgold, MD; Bernard R. Chaitman, MD; Morton J. Kern, MD

Background The physiological assessment of angiographically intermediate-severity stenoses remains problematic. Functional measurements of poststenotic intracoronary Doppler coronary flow reserve can be performed in humans but have not been correlated with hyperemic myocardial perfusion imaging or angiographic data in this patient population.

Methods and Results Thirty-three patients undergoing diagnostic quantitative coronary angiography (QCA) for assessment of intermediate-severity coronary artery disease (mean QCA percent diameter stenosis, 56±14%) were studied. Proximal and distal poststenotic Doppler coronary flow velocities were measured (left anterior descending coronary artery, 16; right coronary artery, 10; left circumflex artery, 7 patients) before and during peak maximal hyperemia with intracoronary adenosine (8 to 12 μg). Intravenous pharmacological stress (adenosine, 20 patients; dipyridamole, 13 patients) $^{99m}$Tc-sestamibi tomographic perfusion imaging was performed within 1 week of coronary flow-velocity studies. $k$ statistics were calculated to measure the strength of correlation among coronary flow velocities, perfusion imaging data, and QCA results. QCA stenosis severity (abnormal, ≤50% diameter stenosis) and poststenotic Doppler coronary flow reserve (ratio of abnormal distal hyperemic to basal flow, ≤2.0) were correctly correlated in 20 of 27 patients (74%; $k=.48$). QCA stenosis severity and $^{99m}$Tc-sestamibi imaging (abnormal if one or more reversible myocardial segments were present in the poststenotic zone) were correlated in 28 of 33 patients (85%; $k=.63$). $^{99m}$Tc-sestamibi imaging results agreed with the basal (nonhyperemic) proximal-to-distal velocity ratio (normal, < 1.7) in 15 of 31 patients (48%; $k=.17$). The strongest correlation occurred between hyperemic distal flow-velocity ratio measurements and $^{99m}$Tc-sestamibi perfusion imaging results in 24 of 27 patients (89%; $k=.78$). All 14 patients with abnormal distal hyperemic flow-velocity values had corresponding reversible $^{99m}$Tc-sestamibi tomographic defects. More reversibly hypofused segments were present in patients with abnormal poststenotic hyperemic flow-velocity ratios (abnormal, 2.4±0.7 segments; normal, 0.6±1.0 segments; $P<.05$). The number of poststenotic myocardial $^{99m}$Tc-sestamibi perfusion defects was correlated with the QCA percent cross-sectional area reduction ($P<.02$) and with minimal luminal diameter ($P<.05$) of intermediate-severity coronary artery stenoses.

Conclusions Two technologically diverse functional measures of stenosis severity—Doppler-derived poststenotic hyperemic intracoronary flow reserve and vasodilator stress $^{99m}$Tc-sestamibi myocardial perfusion imaging—are highly (89%) correlated. The physiological assessment of coronary stenoses of angiographically intermediate severity may be improved by the use of these techniques. (Circulation. 1994;90:2150-2160.)

Key Words • $^{99m}$Tc-sestamibi • perfusion • tomography • angiography • coronary artery disease

Several diagnostic techniques have been developed and validated for the assessment of poststenotic myocardial perfusion and for the direct measurement of intracoronary blood flow velocity and quantitation of coronary stenosis severity. These methods are clinically useful in that they can reproducibly discriminate normal vessels and mild coronary stenoses from severe coronary obstructive lesions. Quantitative coronary angiography cannot, however, evaluate the physiological impact of coronary artery stenoses on coronary blood flow. In addition, the diagnostic accuracy of tomographic perfusion imaging for the detection of coronary stenoses is diminished when a lesion severity of ≥50% versus ≥70% is considered significant. The clinical implications for the management of patients with "intermediate" coronary artery stenoses associated with this diagnostic problem are considerable.

The physiological relation between blood flow and radiotracer tissue uptake has been previously described and tested in perfused heart and intact animal models. For the two most widely used myocardial perfusion radiotracers—$^{201}$Tl and $^{99m}$Tc-sestamibi—myocard-
dial radiotracer extraction and tissue retention decrease at hyperemic flow rates.3-7 This transition from the linearly increasing flow-limited phase of tracer exchange to a barrier or diffusion-limited plateau phase at hyperemic flow rates theoretically may increase the frequency of false-negative vasodilator myocardial perfusion imaging studies.7,8 Normal hyperemic coronary flow reserve (CFR) values derived indirectly using contrast coronary angiography9,10 and positron emission myocardial tomography11-17 vary from 2.5- to 5.5-fold basal flow levels. As such, measurements of CFR based on myocardial perfusion tracer activity may be inaccurate in arterial beds with mild or moderate non-flow-limiting stenoses, which retain a greater hyperemic response.

Directly measured human proximal coronary artery hyperemic flows yield calculated CFR values ranging from 3.5 to 4.5.9,11 These data were obtained using relatively large (3F) Doppler catheters (20 MHz, zero-cross method) after vasodilator drug administration. Previous limitations of catheter size and steerable ability prevented the evaluation of more distal flow-velocity responses in normal vessels and beyond coronary stenoses. Recent technical advances have made the direct assessment of distal intracoronary Doppler flow velocity possible in humans through the use of a 0.018-in. Doppler-tipped (12 MHz) flexible angioplasty guide wire.8,19 CFR values are lower (2.5 to 3.0) when intracoronary flow velocities are recorded distally in normal arteries during maximal hyperemia.20,21

Quantitative coronary angiographic analysis was developed and validated to minimize the recognized problems of high interobserver and intraobserver variabilities of visual angiographic interpretation.22-25 Quantitatively derived minimal cross-sectional area, derived using this technique, effectively predicts the degree of hyperemic response to transient total coronary artery occlusion.26 Advanced quantitative angiographic technologies cannot accurately evaluate the physiological impact of moderate-severity coronary artery stenoses.27

The primary goal of the current investigation was to compare directly measured distal intracoronary flow-velocity measurements of CFR with vasodilator drug stress 99mTc-sestamibi myocardial perfusion tomography in patients with coronary stenoses of intermediate angiographic severity. It was hypothesized that the correlation between these two functional assessments of coronary vasodilatory reserve would exceed their correlations with coronary anatomic data.

Methods

Patient Recruitment
A total of 33 patients undergoing diagnostic coronary angiography were studied between May 20, 1991, and October 13, 1992. Doppler flow-velocity data were acquired for the functional assessment of coronary stenosis severity during diagnostic angiography in 27 patients (82%) and before coronary angioplasty in 6 patients (18%). A majority of the patients studied (27 of 33, or 82%) met a predetermined quantitative angiographic definition of “intermediate” stenosis severity of 30% to 70% luminal diameter reduction. Five patients with stenoses of more than 70% luminal diameter reduction who were under consideration for coronary angioplasty had equivocal objective findings of myocardial ischemia on stress testing (n=3) or had atypical angina (n=2). One patient with a 20% diameter stenosis of the left anterior descending coronary artery underwent flow-velocity and myocardial perfusion studies because of a clinical history of typical exertional angina that could not be explained by the mild angiographic findings. Patient selection was made independent of available myocardial perfusion imaging data. This population represented 10% (33 of 320) of all patients undergoing coronary flow-velocity assessment and quantitative coronary angiography during the same time interval. Patients with clinical or ECG evidence of prior myocardial infarction in the area subtended by the Doppler-interrogated artery were excluded from this study. Twenty-seven of 33 patients had hyperemic studies of CFR performed for correlation with myocardial perfusion imaging. 99mTc-sestamibi tomography and Doppler coronary flow-velocity studies were performed within 1 week, without interim coronary intervention with antianginal therapy. This investigation was approved by the Human Research Committee of St Louis University Medical Center. All subjects provided informed written consent before participation.

Study Protocol

Coronary Velocity Measurement
All coronary flow-velocity measurements were performed with a Doppler angioplasty guide wire (Flowire, Cardiometrics, Inc) as previously described.19,21 The Flowire Flowwire is a 175-cm-long, flexible, steerable, 0.018-in. angioplasty guide wire equipped with a 12-MHz piezoelectric ultrasound transducer at its tip that permits velocity acquisition with a high pulse repetition frequency (up to 90 kHz) from a sampling depth of 5 mm. Coronary flow velocities can be recorded up to 4 m/s without aliasing. This forward-directed ultrasound beam with a 25° divergent angle samples a large portion of the coronary flow profile. Blood flow velocities are determined from the Doppler frequency shift based on the difference between the transmitted and returning signals, calculated from the Doppler equation. The velocity data are processed by on-line fast Fourier transformation with a real-time scrolling spectral gray-scale display. Velocity data are recorded on 1/2-in. videotape. Single-frame images can be printed for off-line analysis.

After diagnostic angiography (ie, before angioplasty) and after administration of 5000 U heparin IV, the Doppler guide wire was advanced through a 6F angiographic catheter into the coronary artery. Proximal flow velocities were obtained at least 1 cm proximal to the stenosis at baseline and again during coronary hyperemia induced by administration of intracoronary adenosine (8 µg in the right coronary artery and 12 µg in the left coronary artery).11 The Doppler guide wire was then advanced beyond the stenosis (5 to 10 artery diameters distally), and baseline and hyperemic velocities were again recorded. Coronary vasodilators were not routinely administered before contrast injection during coronary angiography. The contrast agent used in all patients was ioxaglate meglumine (39%) and ioxaglate sodium (20%) (Hexabrix). The technique for Doppler flow-wire positioning was the same as that used without complications in more than 300 studies at our institution.21,29 The artery diameter is easily determined with branch points used to ensure that wire positioning is reproducible and not subject to poststenotic flow artifacts. All stenoses were in the proximal portion or midportion of a major epicardial vessel. Very distal lesions were not studied to ensure adequate perfusion beds for comparisons. No vessels subtended by collateral flow or a bypass graft were studied. Hyperemic flow reserves were not measured in adjacent normal or less-diseased vessels.

Doppler Signal Analysis

The coronary Doppler flow-velocity spectral envelope was digitized off-line using a PC/AT computer with custom-developed software interface with a digitizing tablet. The outermost margin of the velocity spectrum was digitized to minimize significant intraobserver and interobserver variabilities. Digitized spectral peak velocity waveforms from five cardiac cycles
were averaged to compute the mean velocity (MV) under basal and hyperemic conditions. The total velocity integral (TVi) was computed as the area under the curve defined by the combined systolic and diastolic coronary velocity spectra. The proximal-to-distal ratio of TVi was computed under basal conditions. Previous validation studies in our and other laboratories have demonstrated that proximal-to-distal TVi ratios of <1.7 corresponded to translesional pressure gradients of <0.3 mm Hg in 98% of branching arteries (>95% confidence interval). The distal CFR (dCFR) was computed as the poststenotic hyperemic-to-basal MV ratio. Based on previous studies, the normal dCFR was defined as >2.0, the mean population 

Quantitative Coronary Angiography

Multiple orthogonal coronary angiographic views were obtained in all patients. When feasible, two orthogonal angiographic views separated by approximately 90° were acquired for each coronary lesion of interest. End-diastolic cineangiographic frames were selected for quantitative analysis to minimize cardiac motion artifact and maximize contrast filling of the coronary vessel. Whenever possible, overlapping vessels and backfield boney structures adjacent to the coronary lesion were avoided. A commercially available quantitative cardiovascular angiographic software program (AUTOMATED CORONARY ANALYSIS, Philips, DCI; References 23 through 25) was used by experienced operators blinded to the Doppler and scintigraphic data to derive the following coronary stenosis parameters: proximal, distal, and lesional coronary artery dimensions, diameter stenosis, diameter stenosis over the respective cross-sectional area stenosis, and stenosis length. Data from the orthogonal view demonstrating the most severe stenosis were used for comparison with the coronary flow and myocardial imaging data in the subsequent analysis.

99mTc-Sestamibi Myocardial Tomography

99mTc-sestamibi single-photon emission computed tomography (SPECT) was performed according to a same-day rest-stress imaging protocol. In brief, a large-field-of-view, single-crystal tomographic imaging system equipped with a high-resolution collimator (Elscint 409 ECT) was used to acquire imaging data into a 64×64 APEX computer matrix with a 2.0 zoom. A noncontinuous rotational acquisition was performed with 30 stops of 40 seconds each in the prone position over a 180° angle of rotation beginning at +150°. Resting images were performed at 45 to 60 minutes after the injection of 7 to 10 mCi 99mTc-sestamibi. Stress images were acquired within 60 minutes after the injection of 20 to 25 mCi 99mTc-sestamibi.

Standard filtered back-projection techniques were used to generate transaxial tomograms using a Butterworth filter with a cutoff frequency of 0.66 cycles per centimeter and power of 2.5 (stress) or frequency of 0.50 cycles per centimeter and power of 5.0 (rest). Oblique angle tomograms had a thickness of 1 pixel (0.625 cm). Image intensity was maximized for rest and stress studies to the highest pixel in each image set. A y-directional filter was used for interslice averaging.

Raw data sets were carefully reviewed by rotation projection for evidence of soft tissue attenuation and motion artifact. Oblique image reconstruction was performed in the vertical long-axis, horizontal short-axis, and horizontal long-axis views. A 20-segment-per-study division of myocardial activity was used, based on previous published reports for same-day 99mTc-sestamibi SPECT imaging. Myocardial territories subtended by each of the three main coronary arteries (left anterior descending, left circumflex, and right coronary arteries) were assigned based on previous reports of 201Tl SPECT imaging perfusion territories. Images were reviewed by two blinded independent expert observers using both radiographic film and computerized (DELTA MANAGER SYSTEM, Medimage Co) displays of corresponding rest and stress oblique tomograms. By definition, a perfusion abnormality was present when at least one segment in the perfusion territory of the vessel being interrogated by the Doppler technique demonstrated decreased activity in poststress images, with partial or complete reversibility of the defect on corresponding rest images. Apical segments were counted as defects only when contiguous with adjacent abnormal myocardial segments. Discordance between the two observers occurred in 1 of 33 studies (3%) and was resolved by consensus review of the study in question. A high correlation (96%) has been previously reported between expert visual analysis of defect extent and quantitative analysis programs for same-day rest-stress 99mTc-sestamibi myocardial perfusion SPECT. The total number of reversible myocardial segments within the perfusion territory of the Doppler-interrogated vessel was computed for subsequent comparison with angiographic and flow-velocity data.

Hyperemic Pharmacological Stress Testing

Adenosine and dipyridamole infusion protocols for imaging studies used standard intravenous drug doses that are routinely used in our and other laboratories. All drug infusions were performed in the morning with the patient in a fasting state by experienced personnel who randomly selected the pharmacological stress agent to be used. Preinfusion heart rate, 12-lead ECG, and blood pressure measurements were obtained with the patient in the supine position and at 1-minute intervals thereafter. Adenosine was infused in 20 patients (61%) with a controlled-infusion pump system at a rate of 0.14 mg·kg⁻¹·min⁻¹ over 6 minutes. This intravenous dose of adenosine produces sustained coronary hyperemia that is equal to that produced by the intracoronary doses used during distal coronary flow-velocity studies. Isometric hand-grip exercise was performed with the patient in the supine position for 3 minutes after the completion of adenosine infusion.

Dipyridamole was infused in 13 patients (39%) at a rate of 0.14 mg·kg⁻¹·min⁻¹ for 4 minutes. After dipyridamole infusion, the patient assumed a sitting position and began active leg swinging for 4 minutes. 99mTc-sestamibi was infused 5 minutes after the initiation of adenosine infusion and 5 minutes after the completion of dipyridamole infusion. Cardiac medications were not interrupted before vasodilator drug infusion, although methylxanthine-containing medications were withheld for 48 hours before these studies. Sublingual nitroglycerin and parenteral aminophylline were available to reverse persistent side effects, as needed.

Statistical Analysis

Correlations among quantitative coronary angiography, Doppler flow velocity, and 99mTc-sestamibi SPECT imaging data were evaluated using a x statistic (BMDP, University of California Berkeley). k<.40 indicates poor agreement between two categorical parameters, whereas k=.40 to .75 and >.75 indicate fair-to-good and strong correlations, respectively. Correlations among continuous angiographic, Doppler flow, and myocardial imaging data were accomplished by linear regression (Pearson product-moment) or nonlinear curve fitting (least-squares method). Two-way ANOVA was used to compare multiple subgroups of continuous variables. Continuous angiographic and clinical variables are reported as mean±1 SD. Intergroup differences were considered significant at P<.05.

Results

Clinical Characteristics

The study population consisted of 33 patients (22 men and 11 women) with a mean age of 58±13 years (Table). Six patients (18%) had a previous myocardial infarction. Seventeen patients (52%) had one-vessel coronary artery disease, 7 patients (21%) had two-vessel coro-
Clinical, Angiographic, Flow, and Myocardial Imaging Parameters

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, y</th>
<th>Diameter Stenosis, %</th>
<th>Minimal Lumen Diameter</th>
<th>Stenosis Area, %</th>
<th>No. of Vessels with CAD</th>
<th>Flow-Mapped Vessel</th>
<th>Proximal-to-Distal TVI</th>
<th>Distal CFR</th>
<th>Reversible Doppler Zone</th>
<th>MIBI Segment Location</th>
<th>No. of Poststenotic Reversible Segments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>41</td>
<td>49</td>
<td>1.23</td>
<td>74</td>
<td>1</td>
<td>LAD</td>
<td>1.9</td>
<td>3.1</td>
<td>0</td>
<td>Anteroseptal</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>52</td>
<td>59</td>
<td>0.8</td>
<td>83</td>
<td>2</td>
<td>LAD</td>
<td>1.7</td>
<td>1.9</td>
<td>Anteropical</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>75</td>
<td>71</td>
<td>0.65</td>
<td>91</td>
<td>1</td>
<td>LAD</td>
<td>6.0</td>
<td>1.2</td>
<td>Anterior</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>46</td>
<td>20</td>
<td>2.16</td>
<td>33</td>
<td>1</td>
<td>LAD</td>
<td>1.0</td>
<td>2.1</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>74</td>
<td>59</td>
<td>1.31</td>
<td>83</td>
<td>1</td>
<td>LAD</td>
<td>0.9</td>
<td>1.3</td>
<td>Anteropical, anteroseptal</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>41</td>
<td>80</td>
<td>0.43</td>
<td>96</td>
<td>2</td>
<td>LAD</td>
<td>2.8</td>
<td>0.9</td>
<td>Anteropical</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>70</td>
<td>68</td>
<td>1.05</td>
<td>90</td>
<td>3</td>
<td>RCA</td>
<td>1.2</td>
<td>1.5</td>
<td>Inferopical</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>52</td>
<td>51</td>
<td>1.01</td>
<td>76</td>
<td>2</td>
<td>LAD</td>
<td>1.0</td>
<td>2.0</td>
<td>Anteropical</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>53</td>
<td>56</td>
<td>1.35</td>
<td>80</td>
<td>1</td>
<td>RCA</td>
<td>1.3</td>
<td>NA</td>
<td>Basaloseptal</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>67</td>
<td>49</td>
<td>1.35</td>
<td>74</td>
<td>2</td>
<td>LAD</td>
<td>1.2</td>
<td>2.1</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>40</td>
<td>55</td>
<td>1.63</td>
<td>80</td>
<td>1</td>
<td>RCA</td>
<td>1.2</td>
<td>2.6</td>
<td>Inferopical</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>69</td>
<td>55</td>
<td>1.24</td>
<td>80</td>
<td>1</td>
<td>LAD</td>
<td>1.1</td>
<td>1.9</td>
<td>Anteroseptal, apical</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>70</td>
<td>51</td>
<td>1.25</td>
<td>76</td>
<td>1</td>
<td>LCx</td>
<td>1.0</td>
<td>NA</td>
<td>Inferopical</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>53</td>
<td>58</td>
<td>1.25</td>
<td>82</td>
<td>3</td>
<td>LAD</td>
<td>1.7</td>
<td>2.9</td>
<td>Anteropical</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>70</td>
<td>84</td>
<td>0.38</td>
<td>97</td>
<td>1</td>
<td>RCA</td>
<td>2.0</td>
<td>NA</td>
<td>Lateroseptal</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>31</td>
<td>60</td>
<td>0.91</td>
<td>85</td>
<td>3</td>
<td>LAD</td>
<td>1.3</td>
<td>NA</td>
<td>0</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>80</td>
<td>52</td>
<td>1.15</td>
<td>77</td>
<td>1</td>
<td>LAD</td>
<td>0.9</td>
<td>NA</td>
<td>Anteroseptal</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>68</td>
<td>45</td>
<td>1.03</td>
<td>70</td>
<td>3</td>
<td>LAD</td>
<td>1.4</td>
<td>2.1</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>19</td>
<td>M</td>
<td>64</td>
<td>62</td>
<td>NA</td>
<td>NA</td>
<td>1</td>
<td>DIAG</td>
<td>1.3</td>
<td>NA</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>F</td>
<td>44</td>
<td>79</td>
<td>0.83</td>
<td>96</td>
<td>3</td>
<td>LAD</td>
<td>NA</td>
<td>2.4</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>21</td>
<td>M</td>
<td>74</td>
<td>66</td>
<td>1.38</td>
<td>89</td>
<td>3</td>
<td>LCx</td>
<td>NA</td>
<td>1.3</td>
<td>Interfocal</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>22</td>
<td>M</td>
<td>47</td>
<td>52</td>
<td>1.23</td>
<td>77</td>
<td>1</td>
<td>RCA</td>
<td>1.3</td>
<td>2.5</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>23</td>
<td>M</td>
<td>56</td>
<td>31</td>
<td>1.85</td>
<td>52</td>
<td>1</td>
<td>RCA</td>
<td>1.6</td>
<td>2.6</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>24</td>
<td>M</td>
<td>49</td>
<td>40</td>
<td>1.49</td>
<td>64</td>
<td>2</td>
<td>LCx</td>
<td>1.7</td>
<td>2.3</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>25</td>
<td>M</td>
<td>61</td>
<td>60</td>
<td>1.61</td>
<td>84</td>
<td>1</td>
<td>RCA</td>
<td>0.6</td>
<td>2.2</td>
<td>Inferofacial</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>26</td>
<td>M</td>
<td>74</td>
<td>53</td>
<td>1.15</td>
<td>78</td>
<td>2</td>
<td>RCA</td>
<td>1.6</td>
<td>1.5</td>
<td>Inferofacial</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>27</td>
<td>M</td>
<td>48</td>
<td>60</td>
<td>1.5</td>
<td>84</td>
<td>1</td>
<td>RCA</td>
<td>1.8</td>
<td>2.0</td>
<td>Inferopical</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>28</td>
<td>M</td>
<td>59</td>
<td>47</td>
<td>1.38</td>
<td>71</td>
<td>1</td>
<td>LCx</td>
<td>1.1</td>
<td>2.1</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>29</td>
<td>M</td>
<td>67</td>
<td>51</td>
<td>1.17</td>
<td>75</td>
<td>3</td>
<td>LCx</td>
<td>1.4</td>
<td>1.3</td>
<td>Interpapotal</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>30</td>
<td>M</td>
<td>48</td>
<td>54</td>
<td>1.63</td>
<td>79</td>
<td>1</td>
<td>LCx</td>
<td>1.3</td>
<td>1.3</td>
<td>Posteroapical</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>31</td>
<td>F</td>
<td>63</td>
<td>74</td>
<td>0.6</td>
<td>93</td>
<td>3</td>
<td>RCA</td>
<td>1.1</td>
<td>2.1</td>
<td>0</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>32</td>
<td>F</td>
<td>42</td>
<td>35</td>
<td>1.3</td>
<td>58</td>
<td>2</td>
<td>LAD</td>
<td>1.4</td>
<td>1.5</td>
<td>Anteropical</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>33</td>
<td>M</td>
<td>51</td>
<td>1.55</td>
<td>76</td>
<td>3</td>
<td>LCx</td>
<td>1.0</td>
<td>1.6</td>
<td>Inferofacial</td>
<td></td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Mean±SD 58±13 56±14 1.21±0.39 78±13 1.5±0.9 1.9±0.6 1.7±1.4

CAD indicates coronary artery disease; TVI, total velocity integral; CFR, coronary flow reserve; MIBI, 99mTc-sestamibi; RCA, right coronary artery; LAD, left anterior descending coronary artery; and LCx, left circumflex coronary artery. n=33.

Cardiac artery disease, and 9 patients (27%) had three-vessel coronary artery disease. Previous remote (>3 months) coronary revascularization had been performed by angioplasty in 11 patients (33%) or bypass surgery in 3 patients (9%). The distribution of coronary arteries evaluated by Doppler flow analysis was left anterior descending coronary artery, 16; right coronary artery, 10; and left circumflex coronary artery, 7 patients. The range of quantitative stenosis severity in these vessels was 20% to 84%, with a mean stenosis severity of 56±14%.

Nonreversible Perfusion Defects

Because this study was restricted to patients without clinical history or ECG evidence of myocardial infarction in the Doppler-interrogated poststenotic bed, fixed perfusion defects were infrequently encountered (9 of 33, or 27%). Only 5 patients (15%) had nonreversible
components in addition to reversible defects in the index poststenotic perfusion bed. Patients (4 of 33, or 12%) with fixed defects in other vascular beds were not excluded in the study. Noncontiguous apical fixed defects were present in 5 of 33 patients (15%) but were not counted in the subsequent analyses.

**Basal and Hyperemic Coronary Flow-Velocity Data**

Of 31 patients who had basal assessments of proximal-to-distal TVi, 23 were normal (<1.7) and 8 were abnormal (mean proximal-to-distal TVi, 1.2±0.2 versus 2.5±1.5; P<.05). Of 27 patients who had measurements of dCFR, 13 were normal and 14 were normal (dCFR, 2.4±0.3 versus 1.5±0.3; P<.05).

**Coronary Flow Velocity and \(^{99}\text{Tc}\)-Sestamibi Imaging Correlation**

Examples of corresponding concordant normal and abnormal dCFR and \(^{99}\text{Tc}\)-sestamibi studies are provided in Figs 1 and 2. An example of discordant responses between an abnormal \(^{99}\text{Tc}\)-sestamibi study with normal dCFR is shown in Fig 3. The overall agreement between basal proximal-to-distal TVi measurements and \(^{99}\text{Tc}\)-sestamibi SPECT in 31 patients was 15 of 31 (48%; \(\kappa = .17\)). Fourteen patients with an abnormal \(^{99}\text{Tc}\)-sestamibi SPECT study in the poststenotic myocardial perfusion zone had normal basal proximal-to-distal TVi ratios (Fig 4A).

Of 27 patients with hyperemic distal coronary Doppler flow-velocity measurements and \(^{99}\text{Tc}\)-sestamibi SPECT imaging data (Fig 4B), 24 studies (10 normal and 14 abnormal) were in agreement (89%; \(\kappa = .78\)). In 3 patients, abnormal \(^{99}\text{Tc}\)-sestamibi SPECT myocardial perfusion in the poststenotic zone was noted despite normal dCFR. Further evaluation revealed that these results occurred after adenosine stress in patients with a mean percent diameter stenosis of 53±7% (left anterior descending coronary artery, 1; right coronary artery, 2). The dCFR values in these patients were 2.2, 2.6, and 2.9.

**Quantitative Coronary Angiography: Flow Velocity and Perfusion Imaging Correlations**

There was no difference between the mean quantitative angiographic percent diameter stenosis in 13 patients with normal hyperemic dCFR compared with 14 patients with abnormal poststenotic CFR (51±16% versus 58±11%; \(P=\text{NS}\)). Similarly, there was no significant difference in
the mean quantitative percent diameter stenosis between 11 patients with normal poststenotic $^{99m}$Tc-sestamibi SPECT imaging and 22 patients with abnormal reversible hypoperfusion in the relevant poststenotic myocardial bed ($50\pm17\%$ versus $59\pm11\%; P=NS$).

The categorical relation between quantitative angiographic percent diameter stenosis (ie, abnormal, $\geq50\%$; normal, $<50\%$) and dCFR is given in Fig 5A. Agreement was noted in 20 of 27 patients (74%; $\kappa=.48$). Six of 13 patients with stenoses $\geq50\%$ had normal (>2.0) dCFR responses. When correlated with poststenotic hyperemic $^{99m}$Tc-sestamibi SPECT data, quantitative angiographic percent diameter stenosis agreed with the poststenotic imaging findings studies in 28 of 33 patients (85%; $\kappa=.63$). Only 4 of 25 patients with stenoses $\geq50\%$ demonstrated normal $^{99m}$Tc-sestamibi SPECT perfusion in poststenotic myocardial segments (Fig 5B).

**Hyperemic dCFR and Angiographic Correlations**

Nonlinear correlations between dCFR and percent cross-sectional area stenosis ($R=.33$) and stenosis length ($R=.01$) were not significant. A trend toward statistical significance was found between dCFR and percent diameter stenosis in diseased arteries ($R=.36$, $P=.07$). When data from 13 patients with normal coronary artery flow data were included (Fig 6), the relation between dCFR and percent diameter stenosis achieved significance ($R=.57; P<.001$). A similar significant correlation existed between dCFR and percent cross-sectional area stenosis ($R=.57; P<.001$).

**Proximal-to-Distal TVi and Angiographic Correlations**

Despite the lack of correlation between basal TVi ratio and angiographic percent diameter stenosis by categorical ($\kappa$) analysis, significant ($P<.05$) linear correlations existed between proximal-to-distal TVi data and percent diameter stenosis ($R=.38$), stenosis luminal diameter ($R=.51$), stenosis length ($R=.39$), and cross-sectional stenosis area ($R=.42$) values. However, in each case, the slope of these correlations approximated zero (0.01 to 0.11), indicating little change in proximal-to-distal TVi ratio despite increasing quantitative coronary angiographic stenosis severity.
Baseline Rest-MIBI

Hyperemia (Adenosine 12 μg)

Stress-MIBI (Adenosine)

Fig 3. \(^{99m}\)Tc-sestamibi single-photon emission computed tomography (SPECT) study in a 53-year-old patient with a 58% proximal-to-distal left anterior descending coronary artery stenosis by quantitative coronary angiography. Although proximal-to-distal total velocity integral was abnormal (1.7) under basal conditions, a normal distal coronary flow reserve response was observed in this patient after administration of intracoronary adenosine (2.9). Three segments of reversible anteroapical hypoperfusion were noted in the poststenotic perfusion bed on \(^{99m}\)Tc-sestamibi SPECT studies. This patient also had a 20 mm Hg increase in the transstenotic pressure gradient during adenosine stress.

Extent of Poststenotic Myocardial Hypoperfusion and Hyperemic dCFR Correlations

The dCFR and the number of reversible \(^{99m}\)Tc-sestamibi myocardial segments in the zone perfused by the Doppler-interrogated artery were correlated (\(R=0.54; P<0.01\)). Between one and four (2.4±0.7) reversible segments were present in patients with abnormal dCFR ≤2.0 compared with zero to three (0.6±1.0) abnormal segments in poststenotic perfusion beds with normal dCFR values (\(P<0.05\)).

Extent of Poststenotic Myocardial Hypoperfusion and Angiographic Correlations

The relation between the number of reversible poststenotic segmental perfusion defects and the mean minimal luminal stenosis diameter (\(R=0.36; P<0.05\)) showed a trend toward smaller luminal diameter in patients with three or more defects compared with those with no defects (0.99±0.37 versus 1.32±0.46 mm). The relation between the number of reversible myocardial \(^{99m}\)Tc-sestamibi defects and quantitative coronary angiographic percent cross-sectional area reduction was also significant (\(R=0.42; P<0.02\)). Other quantitative coronary angiographic parameters (eg, percent diameter stenosis, stenosis length) did not correlate with the segmental extent of myocardial \(^{99m}\)Tc-sestamibi hypoperfusion.

Discussion

The present study has examined for the first time in humans the correlations among directly measured hyperemic dCFR, quantitative angiographic stenosis severity, and poststenotic myocardial perfusion imaging data. In this population of patients with angiographically intermediate-severity coronary stenoses, a significant (89%) correlation occurred between two technologically diverse functional assessments of coronary hyperemia: dCFR and pharmacological stress \(^{99m}\)Tc-sestamibi myocardial SPECT perfusion imaging data. The correlation between the resting proximal-to-distal coronary Doppler TVi ratio and hyperemic myocardial perfusion imaging data was suboptimal (48%), a finding that might not have been expected based on previous studies\(^{18,19,21}\) that have demonstrated that TVi ratios <1.7 correspond to translesional pressure gradients of less than 30 mm Hg in branching coronary arteries.

Categorical quantitative coronary angiographic findings (≥50% versus <50% diameter stenosis) were correlated with both calculated hyperemic dCFR (74%)
group, angiographic percent luminal diameter stenosis and cross-sectional area stenosis were also correlated with the number of poststenotic $^{99m}$Tc-sestamibi perfusion defects.

Doppler-derived dCFR abnormalities (CFR $\leq 2.0$) were found in association with at least one poststenotic reversible $^{99m}$Tc-sestamibi SPECT myocardial hypoperfusion defect in 100% (14 of 14) of patients. In this study, the capability to accurately measure the hyperemic flow reserve of a particular perfusion bed distal to an epicardial stenosis significantly increased the correlation between flow reserve and perfusion imaging. More proximal CFR measurements are diagnostically limited because they concurrently assess regions of varying vasodilatory reserve and therefore must reflect a weighted average of these disparate zones.

These data indicate that distal hyperemic poststenotic coronary flow is accurately reflected by myocardial perfusion heterogeneity as detected by $^{99m}$Tc-sestamibi perfusion defect imaging. Despite the potential for nonlinear myocardial radiotracer uptake during hyperemia, perfusion defect detection was not compromised with commonly used intravenous doses of either adenosine or dipyridamole in humans.

A limitation to the reliance on distally measured, poststenotic hyperemic flow reserve is the potential complicating feature of an abnormal microcirculation. The vasodilatory capacity of a perfusion bed is governed not only by epicardial characteristics but also and, perhaps more important, by the functional integrity of the microcirculation. Arteriolar disease, which is beyond the resolving abilities of coronary angiography, would have significant effects on perfusion bed vasodilatory reserve that should be detectable by both distal flow-velocity measurements and pharmacological perfusion imaging. Microcirculatory abnormalities, however, would alter the relation between quantitative angiography and both hyperemic flow reserve and perfusion imaging. Although patients with clinical evidence microcirculatory disease were not included in this study, this may (in part) have accounted for the relatively poorer anatomic-to-functional correlations.

**Functional Correlates of Quantitative Angiographic Stenosis Severity**

The clinical significance of intermediate-severity coronary artery stenoses is best defined by their capacity to

---

**Fig 4.** A, Correlation between basal (nonhyperemic) proximal-to-distal total velocity integral (p/d DVI) ratio and $^{99m}$Tc-sestamibi (MIBI) single-photon emission computed tomography (SPECT) imaging in 31 patients was poor (15 of 31, or 48%). Fourteen of 23 patients with abnormal hyperemic $^{99m}$Tc-sestamibi imaging (one or more reversible poststenotic segments) had normal basal p/d DVI values of less than 1.7. B, Correlation between hyperemic poststenotic measurements of distal coronary flow reserve (d CFR) and $^{99m}$Tc-sestamibi SPECT imaging in 27 patients was good. An agreement existed between these two functional hyperemic measurements of stenosis severity in 24 of 27 patients (89%). N indicates normal; Abn, abnormal.

**Fig 5.** A, Correlation between quantitative coronary angiography and distal coronary flow reserve (d CFR) in 27 patients. A significant stenosis was prospectively defined as $\geq 50\%$ diameter narrowing (D.S.). The agreement between this quantitative angiographic value and d CFR was 74% (20 of 27). Eleven patients with quantitative diameter stenoses $\geq 50\%$ had a normal d CFR $\geq 2.0$. B, Correlation between quantitative angiographic percent diameter stenosis and $^{99m}$Tc-sestamibi (MIBI) single-photon emission computed tomography (SPECT) imaging in 33 patients. Overall agreement between these two parameters was 85% (28 of 33). Only 4 of 25 patients (16%) with quantitative diameter stenoses $\geq 50\%$ had a normal $^{99m}$Tc-sestamibi SPECT study in the poststenotic perfusion bed. N indicates normal; Abn, abnormal.

**Fig 6.** Plot of nonlinear relation between Doppler-derived distal coronary flow reserve (CFR) and percent angiographic diameter stenosis when normal (c) and intermediate severity stenosis (a) were correlated ($R = 0.57$, $p < 0.001$). A similar relation ($P < 0.001$) existed between distal CFR and percent cross-sectional area stenosis (not shown).
limit coronary blood flow under conditions of increased demand or hyperemic stress. Previous studies have derived CFR from angiographic picture element time-density relations or have used coronary angiographic dimensions to derive CFR based on a fluid dynamic analysis of stenosis effects on flow. Most recently, poststenotic intracoronary Doppler spectral flow-velocity analysis has been used to functionally assess intermediate-severity stenoses.

Prior studies have addressed the relation among quantitative stenosis geometry, digital angiographic CFR, and tissue perfusion in humans. Correlations among these parameters vary with collateral flow and vasomotor tone changes during high-flow states, creating wide 95% confidence limits for the prediction of individual stenosis severity. Although experimental and theoretical data have demonstrated that the relation between angiographic hyperemic flow reserve and stenosis severity may be linear or nonlinear, the distal intracoronary flow reserve data demonstrated a significant (P < .001) nonlinear correlation with angiographic stenosis severity (both percent diameter stenosis and percent cross-sectional area stenosis). No one quantitative angiographic stenosis dimension is predictive of the hyperemic myocardial perfusion measured by positron emission tomography imaging in individual patients. Angiographic CFR has been shown to correlate linearly with hyperemic positron emission tomography-derived relative myocardial perfusion reserve.

Angiographic CFR has been studied as a physiological measure of stenosis severity that integrates stenosis geometry with assumptions of coronary blood flow and fluid dynamic principles. Although not addressed in this study, significant correlations have been demonstrated between angiographic CFR and the transtenotic pressure gradient, minimal cross-sectional area, and percent stenosis. The hyperemic transtenotic pressure gradient has been shown to be highly (>90%) predictive of exercise SPECT imaging results in patients with quantitative diameter stenoses of 6% to 75%, corresponding to angiographic CFR values of 5.5 to 0.4. In the present study of patients with stenoses of intermediate severity, the percent cross-sectional area stenosis also correlated with the number of 99mTc-sestamibi myocardial poststenotic defects, a value that is also dependent on the location of the stenosis along the artery and the possible overlap of defects from adjacent diseased arterial beds.

### Study Limitations: Flow-Velocity Assessment

Although intracoronary boluses and intravenous infusions of adenosine produce comparable peak coronary hyperemia, the hyperemia produced after the intracoronary injection of adenosine may not have been equal to that observed after intravenous infusion of dipyridamole. Additional methodological limitations of Doppler assessments of distal coronary flow-velocity assessments include potential aliasing effects, heart rate variability, and competitive flow in branching or collateral vessels.

Although categorical (κ statistic) comparisons of dCFR with 99mTc-sestamibi results were highly significant, analyses of continuous data were well correlated, due in part to the relatively narrow range of stenosis severities evaluated. The exclusion of both normal coronary vessels and of significant numbers of severe stenoses contributed to this statistical failure, as evidenced by the improved correlation coefficients derived when normal coronary flow data were included.

Transcapillary radiotracer exchange depends on the rate of delivery to the perfused region, the time available for tracer exchange, and the permeability of the barrier surrounding the flow stream (ie, capillary permeability multiplied by surface area product). This fundamental kinetic requirement of perfusion tracers, myocardial accumulation in direct proportion to coronary blood flow, is lacking in experimental studies of the two most widely used myocardial perfusion tracers (201Tl, 99mTc-sestamibi). However, as in previous distal Doppler coronary flow studies, mean poststenotic hyperemic flow rates did not generally surpass the threefold increase beyond basal flow levels that is reported to reduce radiotracer uptake in animal studies.

A hyperemic coronary flow-pressure gradient discrepancy, which has also been observed by other investigators, was noted in two of three patients with abnormal sestamibi perfusion studies despite a normal dCFR response. Further investigation of this phenomenon is warranted in larger numbers of patients.

The site for distal intracoronary Doppler flow-velocity sampling used in this and previous studies is subject to the influence of vessel branching and microcirculatory abnormalities that cannot be controlled. Instrumentation differences and coexisting cardiovascular conditions (ie, hypertensive heart disease) that may limit coronary vasodilation may have also contributed to the significant variability in "normal" CFR values of this and prior Doppler, angiographic, and perfusion imaging studies. Given the wide range of "normal" hyperemic responses (2.5- to 5.5-fold control levels) that have been reported in these multiple investigations, it is probable that no one parameter is perfectly representative and reproducible and that more than one functional measurement of stenosis severity will be needed to define the physiological impact of moderate-severity coronary stenoses in humans.

### Study Limitations: Myocardial Perfusion Imaging

Although the extent of poststenotic myocardial hypoperfusion was semiquantitatively measured as the number of reversible perfusion defects, no quantification of defect severity or size was performed in this study. Despite this apparent lack of precision in perfusion defect assessment compared with intracoronary Doppler and quantitative angiography measurements, the categorical and continuous imaging data acquired in this pharmacological stress sestamibi SPECT and previous planar exercise 201Tl studies are significantly correlated with both dCFR and percent stenosis severity, suggesting that semiquantitative image analysis, which is frequently performed in clinical practice, may be of value in this setting. Also, a low intraobserver variability (3% in this study) and high qualitative-quantitative concordance have been reported for 99mTc-sestamibi tomography. The application of newly developed quantitative positron emission tomography and 99mTc-sestamibi image analysis techniques theoretically should improve the precision of perfusion defect measurements. Although half of the patients in this and a similar study had one-vessel coronary artery disease, the presence of...
“balanced” proximal stenoses in all three coronary arteries can reduce the flow heterogeneity response on which hyperemic stress myocardial defect detection is predicated. Routinely performed 60-minute poststress $^{99m}$Tc-sestamibi SPECT, as used in this study, does not usually detect increased lung tracer uptake or transient cardiac dilation (noted in only 2 of 33, of 6% of patients), each of which is reflective of multivessel coronary artery disease. Technical limitations prevented the simultaneous measurement of CFR in all epicardial arteries.

**Clinical Implications**

These data confirm the results of previous studies\textsuperscript{2,13,37} that indicate that angiographic assessments of stenosis severity are correlated with measurements of poststenotic myocardial perfusion. In a population of patients with angiographically “intermediate” coronary artery stenoses, distal intracoronary flow reserve and myocardial perfusion reserve were strongly correlated functional indicators of stenosis severity. However, the importance of functional assessments of CFR and poststenotic myocardial perfusion do not vitiate the significant clinical utility of quantitative angiography for defining the number and location of coronary lesions, which may then be targeted for angiographically directed intravascular diagnostic measurements and the performance of coronary revascularization, where appropriate.

Optimization of a diagnostic approach for determining the physiological significance of intermediate-severity coronary stenoses requires a maximal vasodilatory stimulus for increasing coronary flow and the capacity to either measure poststenotic flow directly or use a myocardial perfusion radiotracer that distributes in proportion to hyperemic perfusion.\textsuperscript{43} In this study, two technically distinct but physiologically related functional measures of poststenotic coronary flow enhancement—Doppler-derived dCFR and $^{99m}$Tc-sestamibi myocardial perfusion heterogeneity—have fulfilled these criteria and appear to have improved coronary physiological assessment beyond quantitative angiography for the complex problem of intermediate-severity stenosis.

These data provide preliminary evidence that in patients with angiographic stenoses of intermediate severity, the measurement of poststenotic hyperemic CFR at the time of coronary angiography and the separate, noninvasive assessment of comparable pharmacological stress-induced myocardial hyperperfusion by $^{99m}$Tc-sestamibi tomography are largely equivalent. The independent power of either technique is augmented when both techniques confirm (or refute) the physiological significance of such an angiographic coronary stenosis. This dual physiological assessment would be most valuable in planning for coronary revascularization and might also be used to enhance the recognized prognostic value of myocardial perfusion imaging alone. However, practical issues of technique availability, laboratory time, personnel experience, and study cost must be considered before the implementation of this clinical approach at individual medical centers.

At our hospital, a midwestern university-affiliated tertiary referral medical center, the total institutional technical and professional charges for coronary angiography with Doppler flow-velocity analysis and stress myocardial perfusion tomography are equivalent ($2190 versus $2189). In the current milieu of health care cost containment, the availability of two cost-equivalent and highly correlated physiological markers of coronary stenosis severity could obviate the reduplication of diagnostic studies in this population.

**Acknowledgments**

The authors would like to thank Lori Gallini for her secretarial assistance; Sheila Byers, RN, Marilyn Cauley, RN, and Carol Mechem, RN, for their technical support; Leslee Shaw, PhD, for statistical consultation; and the staff of the J.G. Mudd Catheterization Laboratory.

**References**


Correlation of pharmacological 99mTc-sestamibi myocardial perfusion imaging with poststenotic coronary flow reserve in patients with angiographically intermediate coronary artery stenoses.

D D Miller, T J Donohue, L T Younis, R G Bach, F V Aguirre, M D Wittry, H M Goodgold, B R Chaitman and M J Kern

Circulation. 1994;89:2150-2160
doi: 10.1161/01.CIR.89.5.2150

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/89/5/2150

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/