Assessment of Anatomic and Physiological Severity of Single-Vessel Coronary Artery Lesions by Dipyridamole Echocardiography

Comparison With Positron Emission Tomography and Quantitative Arteriography

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Background The aim of this study was to compare the results of dipyridamole-echocardiography test (DET: two-dimensional echo monitoring during dipyridamole infusion up to 0.84 mg/kg over a period of 10 minutes) with both anatomic and physiological parameters of coronary artery disease severity, assessed by computer-assisted quantitative coronary arteriography, and regional coronary flow reserve, measured by \[^{[13N]}\]ammonia (\[^{[14N]}\]NH\(_3\)) and dynamic positron emission tomography (PET), respectively.

Methods and Results We studied 31 patients with a history of chest pain and neither previous myocardial infarction nor resting wall motion abnormalities. Eighteen patients had single-vessel disease (>50% stenosis of one major coronary vessel), and 13 had normal coronary arteries. The criterion for DET positivity was the appearance of a new transient regional wall motion abnormality. In patients with a positive DET, two parameters were evaluated: the dipyridamole time (i.e., the time from the beginning of drug infusion to the development of obvious dyssnergy) and the wall motion score index (WMSI, a semiquantitative integrated estimation of extent and severity of the stress-induced dyssnergy). WMSI was derived by summation of individual segment scores divided by the number of segments interpreted. Quantification of regional myocardial blood flow was obtained by PET measurements of \[^{[15N]}\]NH\(_3\) arterial input function and left ventricular myocardial tissue concentration both at control and after dipyridamole (0.56 mg/kg over 4 minutes). Maximal regional blood flow after dipyridamole in the region supplied by the stenotic vessel was significantly lower in the 11 patients with coronary artery disease and positive DET than in the 7 patients with coronary artery disease and negative DET (1.08±0.33 versus 1.98±0.37 mL·min\(^{-1}·g\(^{-1}\), P<.01). In patients with a positive DET, regional coronary flow reserve correlated well with dipyridamole time (r=0.87, P<.01) but not with peak WMSI (r=0.25, P=NS). Patients with dipyridamole-induced akinesia or dyskinesia (n=6) had a greater reduction in regional coronary flow reserve than did those showing hypokinesia (n=5): 1.38±0.51 versus 2.17±0.42, P<.05. Percent area reduction was more severe in patients with DET positivity than in those with DET negativity (93.7±8.7% versus 77±10.3%, P<.01), and it was related with regional coronary flow reserve (r=0.64, P<.01) and dipyridamole time (r=−0.59, P<.01).

Conclusions In patients with single-vessel disease, DET shows an excellent specificity but a limited sensitivity; in these patients, DET positivity is associated with a physiologically important coronary stenosis. Severity of the anatomic stenosis and impairment in regional flow reserve are greater when the dipyridamole-induced dyssnergy appears earlier during the test. Therefore, a stratification of the anatomic-physiological severity of coronary artery disease can be obtained with DET, based mainly on the temporal allocation of the transient dyssnergy. (Circulation. 1994;89:753-761.)

Key Words • dipyridamole • echocardiography • ischemia • tomography

The dipyridamole echocardiography test (DET) has been proposed as a highly feasible and safe tool for the noninvasive diagnosis of coronary artery disease.1-3 Conventional sensitivity/specificity analysis has been based on description of the relation between dipyridamole-induced transient dyssnergy and coronary disease. With such an approach, DET showed good overall sensitivity and excellent specificity.4-7 However, in an ideal study design, anatomic as well as physiological correlates of coronary disease should be assessed simultaneously, with evaluation of coronary stenosis and regional coronary flow reserve in a population without myocardial infarction and not on antianginal therapy.8 This kind of validation has already been performed for different forms of physiological testing, including exercise electrocardiography,9 exercise thallium imaging,10 and radionuclide ventriculography.11 To the best of our knowledge, no such data are available for stress echocardiography, a technique that has recently gained widespread clinical acceptance.12 We therefore assessed anatomic lesion geometry by quantitative coronary arteriography and measured regional myocardial blood flow by means of positron emission tomography (PET) and \[^{[13N]}\]ammonia (\[^{[14N]}\]NH\(_3\))13,14 both at baseline and after dipyridamole-induced vasodilation in 31 patients with either angio-
graphically normal vessels or single- vessel coronary artery disease (CAD).

Methods

Patient Population

A total of 31 in-hospital patients with a history of chest pain were enrolled in the study. Exclusion criteria for the study were (1) acute or old myocardial infarction by history and/or 12-lead ECG and/or wall motion; (2) left ventricular hypertrophy (defined as left ventricular mass index, calculated by echocardiography with the Penn convention, >110 g/m² in women and >134 g/m² in men); (3) left ventricular dysfunction (left ventricular ejection fraction <50% or focal wall motion abnormalities at either left ventriculography or two- dimensional echocardiography); (4) valvular or congenital heart disease; and (5) presence of multivessel coronary disease (which makes the correlation between an ischemia-producing lesion and its functional correlates uncertain) or single-vessel disease of the right coronary artery (whose perfusion territory is not readily identifiable with the tomograph used). There were 19 men and 12 women: mean age was 52±9 years (range, 37 to 70 years). Thirteen patients had entirely normal coronary arteries; they represented the control group. They had a history of atypical chest pain, negative maximal exercise stress test, negative ergonovine test, and normal regional and global ventricular function. Eighteen patients had stable angina pectoris and a single discrete proximal stenosis in one major coronary artery. Twelve of these 18 patients underwent a bicycle exercise ECG stress test, which was positive in 5 and negative in 7.

All patients—off antianginal therapy, on different days, in random order, and within 2 weeks—had a DET, a coronary flow reserve study by PET, and a coronary angiography. Caffeine, theophylline, and theophylline derivatives were withheld 12 hours before dipyridamole tests to prevent interference with the hyperemic effect of dipyridamole.

Dipyridamole-Echocardiography Test

Two-dimensional echocardiographic and 12-lead ECG monitoring were performed in combination with dipyridamole infusion at an initial rate of 0.56 mg/kg over a period of 4 minutes. This was followed by 4 minutes of observation and then, in case of negative response by echocardiographic criteria, by an additional 0.28 mg/kg dipyridamole over a period of 2 minutes. The maximal cumulative dose reached was therefore 0.84 mg/kg over a period of 10 minutes.2 Aminophylline, which promptly reverses the effect of dipyridamole, was at hand. Two-dimensional echocardiograms were continuously recorded during and up to 5 minutes after the dipyridamole administration. Commercially available wide-angle phased-array imaging systems (Hewlett-Packard Sonos 1000, Andover, Mass; Toshiba Sonolayer FFA270A, Japan; or ESAOTE Biomedica SIM 7000, Genoa, Italy) were used. In the baseline studies as well as during stress, all standard echocardiographic views were obtained when possible. During the test, new areas of abnormal wall motion were identified on multiple views by rapidly moving the ultrasound transducer through various positions. A digital acquisition of images of interest was obtained either on-line (by ESAOTE Biomedica SIM 7000 or Hewlett Packard Sonos 1000) or off-line by an array-processor-based computer for medical image processing (Mipron, Kontron, Germany), and a side-by-side display of images at rest and peak stress in a cine-loop mode was obtained. The videotapes were analyzed by the cardiologist/echocardiographer performing the test, who was blind to the clinical, angiographic, and flow data. The low level of intraobserver and interobserver variability obtained in our laboratory between experienced observers has been previously documented.16 A wall motion score index was derived for rest and peak dipyridamole echocardiograms in each patient. The left ventricle was divided into 11 segments: apex, proximal and distal anterior septum, proximal and distal inferior septum, proximal and distal anterior wall, proximal and distal lateral wall, and proximal and distal inferior wall.17 Segmental wall motion was graded as normal: normal motion at rest, with normal/increased wall motion (hyperkinesis) after dipyridamole (score of 1); hypokinetic: marked reduction in endocardial motion (score of 2); akinetic: virtual absence of inward motion (score of 3); or dyskinetic: paradoxical wall motion away from the center of the left ventricle in systole (score of 4). The wall motion score index was derived by summation of individual segment scores divided by the number of segments interpreted. Inadequately visualized segments were not scored. In positive tests, the dipyridamole time, ie, the minutes from the beginning of drug infusion to the development of the stress-induced dyskinesis, was also evaluated. In negative tests, the dipyridamole time was arbitrarily assumed to be 15 minutes (when aminophylline was given).

Coronary Angiography and Left Ventriculography

Standard coronary angiography in multiple views was performed according to the standard Judkins or Sones technique. At least five and two views were acquired for the left and right coronary arteries, respectively. All angiograms were visually evaluated by two independent observers who identified the stenotic segments and scored control arteries as smooth or irregular. All stenotic segments were evaluated by an automated edge detection system (Mipron; Kontron, Germany) providing the percent area reduction. The intraobserver and interobserver variabilities of the method were 7% and 6%, respectively.

Patients with CAD were selected because of the angiographic documentation of single-vessel disease (≥50% lumen reduction in only one coronary artery); the stenosis was located either in the left anterior descending (12 patients) or in the left circumflex coronary artery (6 patients). Patients with lumen irregularities on the remaining coronary arteries were admitted to the study only in case of <25% diameter reduction. All patients had a dominant right coronary artery. Biplane left ventriculography was performed in all patients. Left ventriculograms were blindly evaluated by two independent observers and were referred to a third evaluation in case of disagreement. Left ventricular ejection fraction was evaluated by the modified Dodge and Baxley method.16

Regional Coronary Flow Reserve Study

Quantification of regional myocardial blood flow at rest and after dipyridamole infusion was obtained by means of 13NH3 and PET in a single-day protocol. All patients were studied after an overnight fasting period. A three-lead ECG was continuously monitored, and a nine-lead ECG and arterial blood pressure by cuff manometer were obtained during 13NH3 injection in resting conditions and every minute during the dipyridamole test. The patients were positioned on the bed of a two-ring ECAT III positron tomograph (CTI Inc, Tenn), providing three simultaneous cross-sectional planes (two from direct planes and one from the interplane). Before the emission study was performed, a tomographic transmission scan of the chest was obtained with 92.5 MBq (2.5 mCi) of 68Ga source. Transmission images were acquired for 15 to 20 minutes (up to the collection of 60 million counts) and subsequently used to generate attenuation correction factors. Correct positioning was maintained throughout the study by use of a light beam and indelible marks on the subject's torso. Thereafter, 7.4 MBq/kg body weight (0.2 mCi/kg) of 13NH3, synthesized according to previously described methods,19 was infused as a slow bolus over a period of 10 to 20 seconds via a venous cannula positioned in the left antecubital vein. Dynamic PET data acquisition was started simultaneously with the beginning of tracer injection; a total of 28 frames were
acquired over 8 minutes (16 frames \(\times 3\) seconds, 11 \(\times 12\) seconds, and 1 \(\times 300\) seconds).

After acquisition of the baseline study, a period of 50 minutes was allowed for the physical decay of \(^{13}\text{N}\) (physical half-life, 9.9 minutes); thereafter, dipyridamole (0.56 mg/kg body weight) was infused intravenously over a period of 4 minutes. The second injection of \(^{13}\text{NH}_3\) was started 2 to 3 minutes after the end of dipyridamole infusion. The dynamic PET data acquisition followed the same protocol as used in the baseline study. Aminophylline (120 to 240 mg) was always injected intravenously \(\geq 3\) minutes after tracer injection to antagonize the effects of dipyridamole.

**Regional Myocardial Blood Flow Analysis**

Computation of regional myocardial blood flow was performed according to a method previously validated in our laboratory.\(^{20}\) Briefly, sinograms were normalized according to the tomograph nonuniformity map, corrected for attenuation, and then reconstructed with a Hanning filter with a cutoff of 0.5, thus having a transaxial spatial resolution of about 9 mm at full width half maximum. The sum of the rates of randoms and multiples related to each sinogram was used for dead-time loss correction. Quantitative analysis was performed on the slice that best encompassed the septum and the posterolateral wall of the left ventricle. A small region of interest was drawn within the left ventricular cavity; to minimize the spillover from the myocardial wall and avoid underestimation of the count density, the size and shape of this region were assessed on the last 300-second equilibrium image. The time-activity curve (expressed in counts per voxel) inside this region was plotted and corrected for decay and dead-time loss; then, the tracer input function was estimated by fitting the initial portion of the curve with a gamma-variate function and calculating its integral. On the last “equilibrium” frame, six circular myocardial regions of interest (size, 13 to 22 pixels) were drawn (two in the posterolateral wall, four in the anteroseptal wall). For each defined myocardial region, the count density (counts per voxel) was obtained after correction for decay and dead-time loss, and the values were then mediated to obtain the average myocardial blood flow in the two conditions; the anterior and the posterolateral walls were considered to be the territories of the left anterior descending and left circumflex coronary arteries, respectively.

Regional myocardial blood flow times \(^{13}\text{NH}_3\) myocardial extraction (rMBFe) was calculated according to the equation

\[
r_{\text{MBFe}} = C_m \times 60 / C_C(t) \times dt
\]

where \(C_m\) and \(C_C\) are \(^{13}\text{N}\) activity concentrations (counts per voxel) in the myocardium (as measured in the last frame) and in the arterial blood (at each time \(t\), respectively. The curve \(C_C(t)\) was fitted by a gamma-variate function for the integration. The final regional myocardial blood flow times \(^{13}\text{NH}_3\) myocardial extraction, expressed as milliliters per minute per milliliter, was then converted to milliliters per minute per gram by dividing by tissue gravity (1.08 g/mL).

To adjust for the loss in linearity between \(^{13}\text{NH}_3\) uptake and blood flow resulting from the decrease in the \(^{13}\text{N}\) extraction with increasing flow rates, regional myocardial blood flow times \(^{13}\text{NH}_3\) myocardial extraction values were corrected with an equation obtained in the experimental preparation from the relation between this index and regional myocardial blood flow by radioactive microspheres.\(^{20}\)

**Statistical Analysis**

Mean values and SD of the data were calculated. Intergroup comparisons were performed by the unpaired \(t\) test. Linear and polynomial regression analyses were performed. Multiple group comparisons were performed with ANOVA and the Duncan test for individual comparisons within groups. A value of \(P<.05\) was considered significant.

**Results**

Individual echocardiographic, angiographic, and coronary flow data of the study patients are summarized in Table 1.

**Dipyridamole-Echocardiography Test**

There were 11 positive and 20 negative studies. In the 11 positive studies, timing of the asynergy was 6.5±3.3 minutes (range, 3 to 11 minutes) from the beginning of dipyridamole infusion, and the wall motion score index at peak dipyridamole was 1.28±0.11. Diagnostic (>0.1 mV from baseline) STE segment changes occurred in 1 patient with negative DET and in 6 with positive DET. All the 7 patients with electrocardiographically positive DET had angiographically assessed CAD. Hemodynamic data are reported in Table 2. There was no difference between patients with positive and negative DET, either in resting conditions or at peak stress, with the exception of slightly higher values of systolic blood pressure in positive patients after dipyridamole.

**Angiographic Findings**

Thirteen patients had angiographically normal coronary arteries and 18 had CAD by gross visual inspection of the coronary angiograms. The diseased vessel was the left anterior descending artery in 12 patients and the left circumflex in 6. In the 18 obstructed vessels, average cross-sectional area reduction was 82±12%. A collateral circulation was present in all 5 patients with occluded vessels.

**Positron Emission Tomography Findings and Correlation With Coronary Angiography**

A representative example of a coronary flow study in a patient with regionally depressed flow reserve is shown in Fig 1. Myocardial blood flow in the stenotic region was significantly lower with respect to mean values in normal subjects both at baseline (0.73±0.20 versus 1.02±0.19 mL·min\(^{-1}\)·g\(^{-1}\), respectively, \(P<.01\)) and after vasodilatation (1.43±0.61 versus 3.46±0.82 mL·min\(^{-1}\)·g\(^{-1}\), respectively, \(P<.01\)). The coronary reserve (dipyridamole/resting blood flow) was significantly lower in the stenotic regions with respect to mean values of normal subjects (1.98±0.71 versus 3.49±0.91, respectively, \(P<.01\)). The severity of coronary arterial stenosis was significantly correlated with both maximal blood flow (\(r=.81, P<.01\)) and coronary reserve (\(r=.64, P<.05\)). No correlation was found between resting myocardial perfusion and severity of coronary arterial obstruction (\(r=.41, P=NS\)).

**DET Results: Correlation With Coronary Angiography and Positron Emission Tomography Results**

Of the 18 patients with single-vessel coronary disease, 11 patients had a positive DET and 7 patients had a negative DET (sensitivity, 61%). Dipyridamole-induced
### Table 1. Angiographic, Coronary Flow, and Stress Echocardiographic Data of the Study Patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Coronary Arteries</th>
<th>Average Regional Blood Flow, mL · min⁻¹ · g⁻¹</th>
<th>Coronary Reserve</th>
<th>% Area Reduction</th>
<th>DET</th>
<th>DET Time</th>
<th>WMSI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>Basal Dipyridamole</td>
<td></td>
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</tr>
<tr>
<td>1</td>
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<td>1.23 3.30</td>
<td>2.68</td>
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<td></td>
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</tr>
<tr>
<td>2</td>
<td>Normal</td>
<td>1.29 3.58</td>
<td>2.77</td>
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<td>Neg</td>
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</tr>
<tr>
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<td>Normal</td>
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<td>2.32</td>
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<td>Normal</td>
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<td>12</td>
<td>Normal</td>
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<td>3.12</td>
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<tr>
<td>13</td>
<td>Normal</td>
<td>0.90 2.94</td>
<td>3.26</td>
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<td>1</td>
</tr>
<tr>
<td>Mean±SD</td>
<td></td>
<td>1.01±0.19</td>
<td>3.46±0.82</td>
<td>3.49±0.91</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients With CAD</th>
<th>Stenotic Region Blood Flow</th>
<th>Basal</th>
<th>Dipyridamole</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>LAD</td>
<td>0.67</td>
<td>1.51</td>
</tr>
<tr>
<td>15</td>
<td>LAD</td>
<td>0.57</td>
<td>1.92</td>
</tr>
<tr>
<td>16</td>
<td>LAD</td>
<td>0.89</td>
<td>1.41</td>
</tr>
<tr>
<td>17</td>
<td>LAD</td>
<td>1.21</td>
<td>2.25</td>
</tr>
<tr>
<td>18</td>
<td>LAD</td>
<td>0.81</td>
<td>1.61</td>
</tr>
<tr>
<td>19</td>
<td>LAD</td>
<td>1.13</td>
<td>2.24</td>
</tr>
<tr>
<td>20</td>
<td>LCx</td>
<td>0.85</td>
<td>2.93</td>
</tr>
<tr>
<td>Mean±SD</td>
<td></td>
<td>0.88±0.25</td>
<td>1.98±0.37</td>
</tr>
<tr>
<td>21</td>
<td>LAD</td>
<td>0.65</td>
<td>0.61</td>
</tr>
<tr>
<td>22</td>
<td>LAD</td>
<td>0.49</td>
<td>0.54</td>
</tr>
<tr>
<td>23</td>
<td>LAD</td>
<td>0.70</td>
<td>1.38</td>
</tr>
<tr>
<td>24</td>
<td>LAD</td>
<td>0.64</td>
<td>1.26</td>
</tr>
<tr>
<td>25</td>
<td>LAD</td>
<td>0.61</td>
<td>1.26</td>
</tr>
<tr>
<td>26</td>
<td>LAD</td>
<td>0.73</td>
<td>1.21</td>
</tr>
<tr>
<td>27</td>
<td>LCx</td>
<td>0.66</td>
<td>1.13</td>
</tr>
<tr>
<td>28</td>
<td>LCx</td>
<td>0.59</td>
<td>1.01</td>
</tr>
<tr>
<td>29</td>
<td>LCx</td>
<td>0.61</td>
<td>1.47</td>
</tr>
<tr>
<td>30</td>
<td>LCx</td>
<td>0.48</td>
<td>1.33</td>
</tr>
<tr>
<td>31</td>
<td>LCx</td>
<td>0.85</td>
<td>0.67</td>
</tr>
<tr>
<td>Mean±SD</td>
<td></td>
<td>0.64±0.10</td>
<td>1.08±0.33</td>
</tr>
</tbody>
</table>

DET indicates dipyridamole echocardiography test; WMSI, wall motion score index; CAD, coronary artery disease; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; Neg, negative; and Pos, positive.

Wall motion abnormalities were always located in the stenosis-related regions. All 13 patients with normal coronary arteries had a negative DET (specificity, 100%). Among the 18 CAD patients, the severity of coronary arterial stenosis (percent area reduction) was significantly correlated with dipyridamole time ($r = .59$, $P < .01$) but not with peak wall motion score index ($r = .44$, $P = \text{NS}$). The 11 CAD patients with positive DET showed a tighter stenosis with respect to the 7 patients with negative DET (percent area reduction, $94 \pm 9\%$ versus $77 \pm 10\%$, $P < .01$). All 5 patients with coronary occlusion had a positive low-dose DET.

Maximal myocardial blood flow in the stenotic regions was significantly lower in patients with a positive DET than in those with a negative DET ($1.08 \pm 0.33$ versus $1.98 \pm 0.37$ mL · min⁻¹ · g⁻¹, respectively, $P < .01$), Fig 2.
Regional coronary flow reserve in the stenotic areas tended to be lower in the CAD patients with positive DET than in the CAD patients with negative DET (1.74 ± 0.61 versus 2.35 ± 0.62, P = .07). Maximal coronary blood flow in the stenotic areas correlated with dipyridamole time (r = .81, P < .01) and, to a lesser extent, with peak wall motion score index (r = .66, P < .01). Regional coronary flow reserve correlated significantly with dipyridamole time (r = .67, P < .01) but not with peak wall motion score index (r = .46, P = NS).

When only patients with a positive DET were considered, the correlation between dipyridamole time and coronary reserve improved further (r = .87, P < .01), whereas the correlation between peak wall motion score index and coronary reserve remained not significant (r = .25, P = NS).

No significant correlation was found between regional coronary flow reserve and wall motion score, even when this was calculated only for the myocardial segments supplied by the epicardial coronary arteries that were

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**TABLE 2. Hemodynamic Findings in the Study Patients in Resting Conditions and After Dipyridamole Infusion**

<table>
<thead>
<tr>
<th>Patients With Negative DET (n=20)</th>
<th>Patients With Positive DET (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>68.8±8.7</td>
</tr>
<tr>
<td>DAP, mm Hg</td>
<td>81.5±6.8</td>
</tr>
<tr>
<td>SAP, mm Hg</td>
<td>128.7±12.8</td>
</tr>
<tr>
<td>RPP, bpm×mm Hg</td>
<td>8821±1250</td>
</tr>
</tbody>
</table>

DET indicates dipyridamole echocardiography test; HR, heart rate; bpm, beats per minute; DAP, diastolic blood pressure; SAP, systolic blood pressure; and RPP, rate-pressure product.

*P < .05 vs resting value; †P < .01 vs resting value; ‡P < .01 vs value of negative patients.

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**REGIONAL MYOCARDIAL BLOOD FLOW**

![Image](http://circ.ahajournals.org/)

**Fig 1.** Representative examples of coronary flow studies in patients with angiographically assessed coronary artery disease and either positive (top) or negative (bottom) dipyridamole-echocardiography tests. Two flow values for each myocardial wall are shown both at baseline (●) and after dipyridamole (○). In the positive tests, there is an obvious blunting of dipyridamole-induced flow at the level of the anterior (Ant) and septal regions, dependent on the stenotic left anterior descending coronary artery. Despite the limited spatial resolution of positron emission imaging (<10 mm), the impairment of perfusion appears more severe in the inner than in the outer portions of the anteroseptal walls. In the negative dipyridamole-echocardiography test, the blunting of flow increase is less pronounced, although still detectable in the anterior region compared with the regions supplied from non-stenotic arteries. Post-lat indicates posterolateral.
arteriography. Also, Salustri et al. found that patients with an ischemic response with stress echocardiography (either dipyridamole or dobutamine) had more severe coronary stenosis than did those with a nonischemic response.

In CAD patients, the dipyridamole time is also correlated with the rate-pressure product at peak exercise, which provides an indirect estimation of the physiological severity of coronary reserve impairment. Since it is known that the prognostic consequences of a stenosis are also related to the physiological impairment, the data showing a dramatic worsening of the prognosis in patients with low-dose positivity in comparison with high-dose positivity can also be considered consistent with the findings of the present study.

We have previously shown that the impairment in myocardial function after dipyridamole infusion identifies patients with a critical reduction in regional coronary reserve evaluated by the thermodilution technique. In comparison with the previous study, many substantial differences were introduced in experimental design and data analysis: (1) The regional coronary flow reserve was evaluated by PET measurements of $^{13}$NH$_3$ uptake. Although very sophisticated and expensive, this technique provides a reliable measurement of regional values of absolute myocardial flows. (2) The high-dose DET was considered, rather than the low-dose DET, which has a relatively low sensitivity and, therefore, a limited clinical appeal. (3) The test result was scored not only according to a binary (positive versus negative) response but also according to a multiparametric stratification of the DET positivity based on two separate parameters: (a) the timing and (b) the extent and severity (evaluated in an integrated fashion through the semiquantitative assessment of a wall motion score index) of the dyssynergy.

**Limitations of the Study**

The absence of correlation between wall motion score index and anatomic disease might be a result of the test protocol we used. According to our approach, the development of a new wall motion abnormality is an absolute end point of the test, chosen so as to prevent potential complications from severe or prolonged ischemia. The wall motion score index might have been more meaningful if a more aggressive protocol had been used, implying full-dose administration in all patients. However, we believe that this would probably have reduced the safety of the test.

The extraction of ammonia decreases with increasing flows. However, the decrease in extraction fraction occurs at flow values of $>2.5$ mL·min$^{-1}$·g$^{-1}$. Although this might hamper the measurement in normal subjects, it should not affect the measurement of maximal flow in the regions supplied by a stenotic coronary artery, which showed flow values of $>2$ mL·min$^{-1}$·g$^{-1}$ in only 3 of 18 patients (all with DET negativity). A potential limitation of our approach to the measurement of coronary reserve is the pharmacologic stimulus used. It is known that 0.56 mg/kg of dipyridamole over 4 minutes cannot guarantee a maximal vasodilation in all patients: this also provided the rationale for high-dose dipyridamole testing. Despite this potential drawback, the use of the standard dose for flow measurements in this particular study was convenient, since

**Discussion**

This study shows that in patients with single-vessel disease, DET positivity is associated with a greater reduction in regional perfusion reserve compared with DET negativity. In patients with DET positivity, different degrees of severity in coronary flow reserve impairment can be identified on the basis of the timing of the dyssynergy and of the severity of the induced dyssynergy (with shorter ischemia-free stress time and more severe dyssynergy being associated with more severe coronary reserve impairment).

**Comparison With Previous Studies**

The results of the present study are consistent with previous evidence obtained in our laboratory concerning the anatomic, functional, and prognostic correlates of dipyridamole stress results. Low-dose DET positivity is frequently associated with multivessel coronary disease, whereas high-dose DET positivity is more often linked to less extensive coronary disease. Within the subset of patients with limited CAD, the dipyridamole time is inversely related to the anatomic/geometric severity of the lesion estimated by quantitative coronary
reference values in normal subjects were already available with this dosage,\textsuperscript{20,29} and the same stimulus was administered in all patients. Otherwise, patients with low-dose positivity would have been exposed to a lower pharmacologic stimulus than the remaining study patients, and the interpatient comparison of flow values would have been difficult.\textsuperscript{1}

The degree of correlation between severity of coronary arterial stenosis and coronary reserve was lower than the one reported by other authors using different approaches, such as Doppler catheter.\textsuperscript{30} The occurrence of ischemia and its hemodynamic sequelae might have variably affected the maximal flow in the stenotic region. Moreover, it should be emphasized that the myocardial perfusion reserve, as measured by PET, can be affected by other factors beyond the hydraulic effects of epicardial stenosis, such as the extension of the perfusion field of the stenotic artery, the degree of collateral circulation, and its vasodilating capability.\textsuperscript{27} As a matter of fact, four of five patients with complete occlusion showed a residual coronary reserve—a phenomenon that has not been reported by measurements of flow in the epicardial coronary artery.

The conclusions of this study apply to a strictly defined population with single-vessel CAD and no previous myocardial infarction. Obviously, such information should not be inappropriately extrapolated to patients with either resting dyssynergies, left ventricular hypertrophy, or other exclusion criteria of the present study.

This study confirms that one of the limitations of DET is the inability to detect less severe, although anatomically and hemodynamically significant, coronary obstructions in patients with single-vessel disease.\textsuperscript{5-7} In the present study, patients with single-vessel stenosis and negative DET averaged 77\% stenosis and a regional coronary flow reserve of 2.35, outlining anatomic and physiological profile of moderate coronary disease, limiting maximal flow but unable to elicit ischemia under maximal vasodilation. This physiological feature may have a clinical counterpart in the high prognostic power of DET, which has been shown in different patient subsets.\textsuperscript{17,24} By contrast, this study seems to support the extraordinary sensitivity of PET scanning with \textsuperscript{13}NH\textsubscript{3} for the detection of even milder forms of single-vessel CAD.\textsuperscript{27}

**Limited Sensitivity of DET in Single-Vessel Disease**

In the selected population of patients with single-vessel disease, DET showed an excellent specificity but a limited sensitivity (61\% in this study). The argument of DET sensitivity in single-vessel disease has been subject to controversial results, since it has been reported to be as high as 88\%\textsuperscript{6} and as low as 0\%.\textsuperscript{31} Apart from these striking differences—which might be explained, in part, by different selection criteria, different levels of expertise in stress echocardiography, and small sample size, making the value of absolute percentages rather unrepresentative—it is our experience, confirmed by several other groups,\textsuperscript{7,22-26} that a dipyridamole-induced transient dyssynergy is a diagnostic marker with an excellent specificity and also an excellent sensitivity in patients with multivessel disease, whereas its Achilles' heel remains, in our opinion, its limited sensitivity in single-vessel disease. In a series of 429 patients with no prior myocardial infarction studied in our Institute, the sensitivity in patients with single-vessel disease was 67\%.\textsuperscript{37} Although the sensitivity is comparable to that obtained with high-dose (40-\(\mu\)g \cdot kg\(^{-1}\) \cdot min\(^{-1}\)) dipyridamole echocardiography, as shown by experimental\textsuperscript{38} and clinical\textsuperscript{22,29-42} studies, it is certain that a higher sensitivity in single-vessel disease would improve the strength of noninvasive diagnosis by pharmacologic stress echocardiography. With dobutamine, this has been achieved with the addition of atropine, which increases the dobutamine test sensitivity, especially in populations taking \(\beta\)-blockers, as demonstrated by McNeill et al.\textsuperscript{43} With dipyridamole, it has been previously shown that a tremendous sensitivity step-up can be obtained by combined forms of stress testing, such as dipyridamole exercise,\textsuperscript{44} which raises myocardial oxygen demand in the presence of a plateau of inappropriate coronary vasodilation. However, this test increases the technical complexity of the examination and lowers the feasibility of the examination. More recently, the validation of dipyridamole-atropine stress testing allowed us to have an exercise-independent stress, which does not significantly increase the imaging time or the incidence of side effects in comparison with DET alone, expands the dynamic range of the test, and allows the documentation of relatively minor, although still hemodynamically significant, forms of CAD.\textsuperscript{45} Of interest, in a different study, we found that, in patients with single-
vessel disease, dipyridamole-atropine positivity is associated with an average stenosis of 74±16%—a severity comparable to that in the patients of the present study “missed” by DET (77±12%). Therefore, atropine addition may be necessary to overcome the problem—shared by conventional dipyridamole stress echo with other commonly used noninvasive tests—of limited sensitivity in single-vessel disease. Other forms of combined pharmacologic stresses, such as dipyridamole-dobutamine, might show an even greater sensitivity, but still with an excellent specificity.46

Clinical Implications

Since the single most important pathophysiological and clinical information yielded by dipyridamole test is the timing of the dyssynergy, rather than its site and extent, we believe it is important to combine this pharmacologic stress with a continuous monitoring of left ventricular mechanics. This allows assessing the time course of the sequence of events during stress, providing a “cinematographic” (rather than simply photographic, as is the case with nuclear medicine imaging) representation of the stress.47 Two-dimensional echocardiography seems ideally suited for continuous monitoring of the left ventricular mechanics during dipyridamole stress,32 in comparison with other less operator-dependent imaging techniques proposed in combination with dipyridamole, such as radionuclide ventriculography32 or magnetic resonance imaging.33 The echocardiographic monitoring potentially increases the safety of the test, which can be stopped as soon as the dyssynergy (an absolute end point) is detected, and also optimizes the pathophysiological, clinical, and prognostic information that can be derived by the test, since the time of appearance of a transient dyssynergy during the test is even more important than its presence, severity, or extent.

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