Transesophageal Doppler Echocardiography Evaluation of Coronary Blood Flow Velocity in Baseline Conditions and During Dipyridamole-Induced Coronary Vasodilation

Sabino Iliceto, MD; Vito Marangelli, MD; Cataldo Memmola, MD; and Paolo Rizzon, MD

Transesophageal echocardiography allows the evaluation of proximal coronary artery anatomy and coronary blood flow velocity (CBFV). To assess the potential of transesophageal echocardiography in evaluating CBFV and its variations induced by coronary-active drugs, we studied 15 patients by high-quality pulsed wave Doppler recordings of CBFV. In these patients, transesophageal Doppler evaluation of CBFV was performed before, 2 minutes after cessation of dipyridamole infusion (0.56 mg/kg in 4 minutes), and 2 minutes after aminophylline infusion (240 mg injected 4 minutes after cessation of dipyridamole infusion). The following CBFV parameters were evaluated at each of the three steps of the study protocol: maximal and mean diastolic velocities and maximal and mean systolic velocities. Furthermore, the following indexes of coronary flow reserve were evaluated: the ratio between maximal diastolic velocity recorded after and before dipyridamole administration and the ratio between mean diastolic velocity recorded after and before dipyridamole administration. Nine of the 15 patients had a normal left anterior descending coronary artery (group A), whereas the remaining six had significant (≥75%) stenosis (group B). In group A patients, all CBFV parameters increased significantly during dipyridamole infusion and returned to near baseline values after aminophylline infusion. In group B patients, on the other hand, none of the CBFV parameters increased after dipyridamole infusion. Dipyridamole/baseline maximal diastolic velocity and mean diastolic velocity ratios were, respectively, 3.22±0.96 and 3.04±0.88 in group A and 1.46±0.45 (p<0.01 versus group A) and 1.48±0.49 (p<0.01 versus group A) in group B patients. We conclude that transesophageal Doppler echocardiography evaluation of CBFV is feasible and makes possible the evaluation of the changes induced by coronary-active drugs. This new approach has potential in assessing coronary blood flow reserve. (Circulation 1991;83:61–69)

Severity of coronary stenosis is usually assessed by coronary angiography. However, simple anatomic evaluation is very often of limited value because coronary flow reserve, the real indicator of the functional importance of the stenosis, only modestly correlates with its anatomic severity. Therefore, interest has increased in methods that assess coronary blood flow reserve by measuring coronary blood flow before and after drug-induced increases in coronary blood flow.2–5 However, all of the proposed methods to date require cardiac catheterization and are, therefore, not without risks, thus preventing their large-scale adoption.

Transesophageal echocardiography is an emerging application of ultrasonography that provides high-quality Doppler echocardiography images. Previous reports showed that transesophageal echocardiography can image the proximal part of left coronary arteries6–8; furthermore, when pulsed wave Doppler is used, coronary blood flow velocity in the left anterior descending coronary artery can be evaluated.7,9,10

In view of the above, we decided to explore the potential of transesophageal Doppler echocardiogra-
phy in evaluating coronary blood flow reserve. We studied a series of patients by use of transesophageal Doppler echocardiography and evaluated coronary blood flow velocity before and during dipyridamole-induced coronary vasodilation.

Methods

Thirty-nine patients undergoing coronary angiography for diagnostic purposes were studied. All patients underwent transesophageal echocardiography examination within 3 days of coronary angiography. In each patient, a careful attempt was made to visualize the proximal left coronary artery and to obtain a pulsed wave Doppler measurement of coronary blood flow velocity in the left anterior descending coronary artery.

Twelve of the 39 patients (31%) were excluded because of inadequate echocardiographic recording of blood flow. Of the remaining 27 patients, only those having either a normal left coronary artery or a significant stenosis (≥75% narrowing), without angiographically detectable collateral vessels involving the left anterior descending coronary artery, were entered into this study. Fifteen patients met these criteria (11 men and four women; mean age, 56.6±7.7 years). In nine patients, coronary angiography showed normal coronary arteries (group A), whereas in the remaining six patients (group B), a proximal stenosis (≥75%) of the left anterior descending coronary artery was shown. None of the group B patients had an occlusive stenosis of the left anterior descending coronary artery.

None of these patients had valvular heart disease, mitral valve prolapse, cardiomyopathy, congenital heart disease, or left ventricular hypertrophy detectable by echocardiography or clinical stress-testing data suggestive of “X syndrome.”

Transesophageal Echocardiography

Transesophageal echocardiography was performed using a 5-MHz transesophageal probe connected to a Hewlett-Packard echocardiographic system (Sonos 500 or 1000, Palo Alto, Calif.). Transesophageal echocardiography was performed in each patient after sedation by intravenous injection of 1 mg diazepam. Examination was performed with the patient in the left lateral decubitus position. Coronary artery imaging was attempted after routine examination of the cardiac chamber and walls. The left main coronary artery was visualized by placing the transducer at a level just above the aortic leaflets, approximately 28 cm from the mouth.

The left main coronary artery, arising from the corresponding sinus, is seen as an echo-free space. Small adjustments in transducer orientation are usually necessary to visualize the vessel along its full length from the aortic root to its bifurcation. The bifurcation is usually Y shaped with a large branch caused by the left main coronary artery. The circumflex coronary artery appears as a continuation of the left main artery, whereas the left anterior descending coronary artery lies in a plane that is often almost perpendicular to that of the left main and circumflex.

**Figure 1.** Echocardiogram showing visualization of aortic root (AO) and left atrium (LA) (left panel). Left main coronary artery arises from the aorta at the 2 o’clock position. Bifurcation of the left coronary artery and the left anterior descending coronary artery are also visualized (on the left). Pulsed Doppler sample volume (arrow) is located at the beginning of the left anterior descending coronary artery. Obtained biphasic flow velocity pattern is shown (right panel).
arteries. Once the bifurcation is visualized, small adjustments in transducer orientation in space (up-down, right-left, retroflexion) are needed to optimize proximal visualization of the left anterior descending coronary artery (Figure 1).

Doppler Recording of Flow in the Left Anterior Descending Coronary Artery

Coronary blood flow velocity was evaluated by means of pulsed wave Doppler exploration of the very initial part of the left anterior descending coronary artery, therefore proximal to eventual stenosis (Figure 1). Because of cyclic cardiac movement, the left anterior descending coronary artery does not always lie in the same position throughout the entire cardiac cycle. However, during diastole, because of the absence of ventricular contraction, the position of the left anterior descending coronary artery is much more stable, thus making its ultrasound exploration much more feasible. Because of this, pulsed wave Doppler sample-volume positioning was performed by considering the diastolic position of the explored vessel. Only those patients in whom an adequate recording of both systolic and diastolic coronary blood flow velocities was obtained were entered into this study.

Study Protocol and Doppler Measurements

Doppler evaluation of left anterior descending coronary blood flow velocity was obtained in resting conditions, 2 minutes after completing the dipyridamole injection4 (0.56 mg/kg i.v. in 4 minutes), and 2 minutes after injecting aminophylline (250 mg i.v. in 1 minute, injected 4 minutes after cessation of dipyridamole infusion). Blood pressure and a one-lead electrocardiogram were monitored throughout the entire protocol. Every minute, 12-lead electrocardiography was performed.

Coronary blood flow velocity in the left anterior descending coronary artery has a biphasic pattern with a greater diastolic component and a smaller systolic one (Figures 1 and 2). The following parameters were evaluated (as an average of the measurements obtained in 5–7 consecutive cardiac cycles) by tracing the contour of the Doppler pattern by means of the computer inserted in the echocardiographic equipment: maximal systolic velocity, maximal diastolic velocity, mean systolic velocity, and mean diastolic velocity. As indexes of coronary blood flow reserve, the ratios of dipyridamole to rest maximal diastolic velocities and dipyridamole to rest mean diastolic velocities were considered. Interobserver variability was assessed in 15 velocity recordings obtained in seven patients by having two independent observers evaluate the measurements blind, whereas intraobserver variability was assessed by having the parameters evaluated twice by the same observer at 1-week intervals on 15 velocity recordings obtained in seven patients. Reproducibility was assessed in seven patients who underwent Doppler evaluations of coronary blood flow velocity twice, 10 minutes apart.

To determine whether the angle between the direction of the left anterior descending coronary artery and the exploring ultrasound beam changed during the dipyridamole phase of the protocol from that of baseline, we measured this angle in seven patients in the two above-mentioned conditions. This angle was measured on a frozen diastolic frame printed on dry silver paper. With a goniometer, the
angle was measured between the ultrasound beam direction (appearing as a series of equidistant points automatically printed) and left anterior descending coronary artery direction (assessed by evaluating vessel anatomy on the two-dimensional echocardiographic tomographic plane).

Coronary Angiography

Coronary angiography was performed using either the Seldinger or the Sones technique. A stenosis was evaluated using multiple projections and was classified as significant if it narrowed the lumen by 75% or more.

Statistical Analysis

To compare different conditions (baseline, dipyridamole, aminophylline), we used a Wilcoxon’s ranked-sum test analysis. A Mann-Whitney ranked-sum test was used to compare the differences of the velocity ratios between the two groups. According to Bonferroni’s method for multiple pairwise tests, a two-tailed probability value less than or equal to 0.016 (0.05/3) was considered significant.

Results

In a patient with a normal left anterior descending coronary artery, all the velocity parameters clearly increased during dipyridamole infusion and tended to return to baseline values immediately after aminophylline administration (Figure 3). On the other hand, in a patient with significant stenosis of the left anterior descending coronary artery, the coronary blood flow velocity pattern is only very slightly altered by dipyridamole and, of course, also by aminophylline (Figure 4).

In Table 1, the individual results in the whole study group are given. In Tables 2 and 3 and in Figures 5 and 6, Doppler-measured parameters of coronary blood flow velocity are summarized. In group A (patients with normal left anterior descending coronary artery), all velocity parameters (maximal and mean diastolic velocities, maximal and mean systolic velocities) increased significantly after dipyridamole infusion and reverted to values not significantly different from those at baseline after aminophylline infusion. On the other hand, in group B (patients with stenosis of the left anterior descending coronary
Table 1. Individual Results in the Whole Study Group

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>Group A (normal LAD)</th>
<th>Group B (LAD stenosis ≥75%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>PDV (cm/sec)</td>
<td>MDV (cm/sec)</td>
</tr>
<tr>
<td>1</td>
<td>48</td>
<td>F</td>
<td>R 35</td>
<td>D 94</td>
</tr>
<tr>
<td>2</td>
<td>47</td>
<td>M</td>
<td>R 50</td>
<td>D 112</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>F</td>
<td>R 32</td>
<td>D 94</td>
</tr>
<tr>
<td>4</td>
<td>52</td>
<td>M</td>
<td>R 46</td>
<td>D 115</td>
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<td>5</td>
<td>54</td>
<td>M</td>
<td>R 35</td>
<td>D 113</td>
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<tr>
<td>6</td>
<td>66</td>
<td>M</td>
<td>R 12</td>
<td>D 63</td>
</tr>
<tr>
<td>7</td>
<td>55</td>
<td>M</td>
<td>R 42</td>
<td>D 109</td>
</tr>
<tr>
<td>8</td>
<td>47</td>
<td>F</td>
<td>R 33</td>
<td>D 139</td>
</tr>
<tr>
<td>9</td>
<td>63</td>
<td>M</td>
<td>R 30</td>
<td>D 99</td>
</tr>
</tbody>
</table>

PDV, peak diastolic velocity; MDV, mean diastolic velocity; PSV, peak systolic velocity; MSV, mean systolic velocity; RR, RR interval; SBP, systolic blood pressure; D/R PDV, dipyridamole/rest peak diastolic; D/R MDV, dipyridamole/rest mean diastolic velocity; D, dipyridamole 0.56 mg b.w. in 4 minutes; A, Aminophylline 240 mg i.v.; R, rest; LAD, left anterior descending coronary artery.

artery), none of the velocity parameters changed significantly from baseline after dipyridamole or after aminophylline infusion.

The dipyridamole infusion to baseline ratios of maximal and mean diastolic velocities (indexes of coronary blood flow reserve) were significantly higher in patients with a normal left anterior descending coronary artery (group A) than in those with stenosis (group B) (Figure 7). Both ratios were greater than 2.0 in all patients in group A and in only one patient in group B.

Table 2. Results in the Whole Study Group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (Normal)</th>
<th>Group B (LAD stenosis ≥75%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Dipyridamole (0.56 mg/kg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>104±21</td>
</tr>
<tr>
<td>PDV (cm/sec)</td>
<td>35 (12,50)</td>
<td>35 (109,139)*</td>
</tr>
<tr>
<td>MDV (cm/sec)</td>
<td>28±9</td>
<td>79±17</td>
</tr>
<tr>
<td>PSV (cm/sec)</td>
<td>24±7</td>
<td>48±7</td>
</tr>
<tr>
<td>MSV (cm/sec)</td>
<td>20±6</td>
<td>39±5</td>
</tr>
<tr>
<td>RR (msec)</td>
<td>781±120</td>
<td>600±55</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>722 (622,1020)</td>
<td>585 (540,687)*</td>
</tr>
</tbody>
</table>

Results are mean±SD and median (minimum, maximum) value. Group A, n=9; group B, n=6.

PDV, peak diastolic velocity; MDV, mean diastolic velocity; PSV, peak systolic velocity; MSV, mean systolic velocity; RR, RR interval; SBP, systolic blood pressure.

*p≤0.05/3=0.016 (rest vs. dipyridamole by Wilcoxon's ranked-sum test with p value adjusted according to Bonferroni's method for multiple pairwise tests); tp≤0.05/3=0.016 (dipyridamole vs. aminophylline by Wilcoxon's ranked-sum test with p value adjusted according to Bonferroni's method for multiple pairwise tests).
TABLE 3. Results in the Whole Study Group

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>LAD stenosis ≥75%</td>
</tr>
<tr>
<td>D/R PDV</td>
<td>3.22±0.96</td>
<td>1.46±0.45</td>
</tr>
<tr>
<td></td>
<td>2.94 (2.24,2.52)</td>
<td>1.46 (1.01,2.26)</td>
</tr>
<tr>
<td>D/R MDV</td>
<td>3.04±0.88</td>
<td>1.48±0.49</td>
</tr>
<tr>
<td></td>
<td>2.87 (2.15,4.89)</td>
<td>1.50 (0.94,2.31)</td>
</tr>
</tbody>
</table>

Results are mean±SD and median (minimum, maximum) value. Group A, n=9; Group B, n=6. D/R PDV, dipyridamole/peak mean diastolic velocity; D/R MDV, dipyridamole/rest mean diastolic velocity. p value by Mann-Whitney ranked-sum test.

Discussion

Visual inspection of the anatomic severity of a coronary stenosis does not adequately predict its physiological importance.1

The functional impairment of a coronary vessel can be better assessed by measuring its "flow reserve," that is, its capacity to increase the blood flow when needed. The concept of coronary flow reserve is receiving increasing attention because of its great clinical and physiopathological relevance.11

Coronary flow reserve is usually calculated by means of invasive techniques (thermodilution, Doppler catheters, digital coronary angiograms, and so on) capable of measuring blood flow (or blood flow velocity) in baseline conditions as well as during maximal or submaximal vasodilation induced pharmacologically (intravenous dipyridamole, intracoronary papaverine, and so on).2-5 Studies performed using these techniques have shown that when maximal or submaximal coronary dilatation is induced, blood flow (or blood flow velocity) increases much more in normal coronary vessels than in those affected by a significant stenosis.4,5 However, even if attractive, these methods, being invasive, cannot be used in a large proportion of patients in serial studies or for studying cardiac diseases where cardiac catheterization is very often not justified.

Measurement of Coronary Blood Flow by Transesophageal Echocardiography

Transesophageal echocardiography provides high-quality images of the heart and the great vessels.12 Previous studies by various groups including our own have also demonstrated that visualization of the coronary arteries is possible.6-8 In this study, we have

![FIGURE 5. Plot of changes induced in diastolic velocity parameters by dipyridamole (DIP) and aminophylline (AMF). In group A patients (without significant stenosis), both peak and mean diastolic velocities increased after dipyridamole administration and reverted to baseline values after aminophylline administration. On the other hand, in group B patients (with significant stenosis), diastolic parameters slightly increased, but not significantly, after dipyridamole infusion.](http://circ.ahajournals.org/.../1991)
shown the following: 1) Blood flow in the left anterior descending coronary artery can be adequately recorded in 69% of patients. 2) Short-term reproducibility is good, as shown by the small velocity changes observed in the two baseline evaluations. Of course, we are not able to define the source of the blood flow changes observed in the two consecutive studies; this source may be due to either technical aspects of Doppler or real physiological changes (heart rate, blood pressure, and preload) or both. However, the velocity changes were small (95% confidence interval of absolute difference was 0.9–2.7 cm/sec for peak diastolic velocity and 0.7–3.2 cm/sec for mean diastolic velocity) and well within those caused by dipyridamole in the control subjects. Recently, McGinn and colleagues\textsuperscript{13} showed that coronary blood flow reserve parameters, in the absence of major changes of heart rate, blood pressure, and preload, are reproducible even after 1 year. 3) Variations in coronary blood flow velocities caused by coronary-active drugs can also be appreciated. These results support previous data obtained in our laboratory in an unselected group of patients studied by transesophageal echocardiography.\textsuperscript{9} As expected from this study concerning the effects of dipyridamole and aminophylline on coronary blood flow, we found that in patients without significant coronary stenosis blood flow velocity increased significantly after dipyridamole infusion and reverted to baseline values just 2 minutes after amnophylline (a powerful dipyridamole antagonist) infusion. The results of this study have also revealed different flow responses to dipyridamole in patients with and without significant coronary artery stenosis. Unlike patients without significant stenosis of the left anterior descending coronary artery, patients with significant stenosis showed a significant increase in the blood flow velocity in the coronary artery during dipyridamole infusion, which obviously continued to remain at the same values after aminophylline administration. These different patterns of blood flow velocity response to this drug are similar to those obtained in other studies in which other techniques were used.\textsuperscript{4,5,14} In patients with stenosis of the left anterior descending coronary artery, coronary flow reserve is already exhausted so that blood flow velocity obviously cannot further increase during dipyridamole infusion. We used dipyridamole/baseline ratios of maximal and mean diastolic velocities as indexes of coronary blood flow reserve. As expected from the results of studies in which similar, though invasively obtained, parameters were considered,\textsuperscript{4,5,14} these ratios were greater in patients without stenosis of the left anterior descend-

TABLE 5. Doppler Echocardiographic Angle Difference

<table>
<thead>
<tr>
<th>Doppler angle (degrees)</th>
<th>Rest</th>
<th>Dipyridamole</th>
<th>Absolute difference of angles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>29.4±11.8</td>
<td>32.5±9.6</td>
<td>5.1±2.3</td>
</tr>
</tbody>
</table>

Values are mean±SD.

FIGURE 6. Plot of changes induced in peak and mean systolic velocities by dipyridamole (DIP) and aminophylline (AMF) administration. Behavior of systolic parameters was similar to that of the diastolic parameters in the two groups of patients (see Figure 3). Peak and mean systolic velocities increased after dipyridamole infusion in group A but remained constant in group B patients.
ing coronary artery than in those with stenosis. In particular, these ratios were greater than 2.0 in only one patient with stenosis, whereas the same ratios were greater than 2.0 in all patients without stenosis.

**Limitations of the Study**

The attractiveness of the technique presented in this study lies in its semi-invasiveness and consequently in its relative ease of application and repetition. However, it does have certain limitations: 1) Transesophageal echocardiography cannot be considered noninvasive because it entails a certain discomfort for the patient. However, it is definitely safer than cardiac catheterization, it does not require complex and costly apparatus or special organization, and it can easily be performed even in ambulatory patients. Consequently, it can also be used in serial studies. 2) The feasibility of transesophageal Doppler evaluation of coronary blood flow is not very high. In our laboratory, we are able to obtain adequate Doppler recordings in approximately 70% of our patients. However, even currently available invasive approaches for evaluating coronary blood flow reserve (Doppler catheters, thermodilution, digital angiography) are not without technical difficulties and limitations. 3) Because of the angle between the exploring ultrasound beam and vessel direction, blood flow velocities measured by this approach can be lower than the real velocities. However, because the main interest of this sort of evaluation is the assessment of coronary blood flow reserve (i.e., the ratio of two measured velocities) the effect of the angle between blood flow direction and ultrasound beam is eliminated; this is so because the underestimating factor is present, without changing its value (as our angle reproducibility evaluations have demonstrated) in the numerator and in the denominator of the ratio. 4) Doppler techniques measure velocities and not blood flow. Blood flow calculation requires the lumen cross-sectional area to be evaluated. However, dipyridamole only modestly increases lumen area, and as a consequence, as shown by Wilson et al., changes in coronary blood flow velocities induced by dipyridamole closely reflect changes in coronary blood flow. This problem is also present when using Doppler catheters that, like the technique presented in this study, measure velocity and not flow. The absolute velocity values obtainable by these two techniques are not comparable because of different modalities in Doppler analysis. In fact, although transesophageal Doppler uses the fast Fourier transform approach, Doppler catheters use the zero-crossing approach. A recent study questioned the accuracy of absolute velocity values obtained by 20-MHz Doppler catheters. Compared with the Doppler catheter technique, transesophageal Doppler has the advantage of not requiring a catheter to be placed inside the coronary lumen, which causes the lumen itself to become artificially narrowed. 5) In our study, the decrease in vascular resistance may have been submaximal for two reasons. First, we used standard dipyridamole dosage (0.56 mg/kg in 4 minutes), and as demonstrated by Rossen et al., this dosage may not be high enough to induce maximal vasodilation. A higher dosage or handgrip adjunction can increase the efficacy of the test. Second, we recorded Doppler signals between the second and fourth minutes after infusion interruption, after which aminophylline was immediately administered. A longer period of Doppler monitoring would have, in some patients, detected a greater and a delayed increase in blood flow velocity. However, we decided to interrupt the dipyridamole effect by injecting aminophylline 2 minutes after cessation of dipyridamole infusion to reduce the duration of examination (not exceeding 20 minutes in any patient of this series) and because previous observations demonstrated that a maximal dipyridamole effect is usually achieved between 6 and 8 minutes after the beginning of infusion (i.e., 2–4 minutes after cessation).

**Clinical Implications**

Transesophageal echocardiography can be used to evaluate coronary blood flow velocity. Our study also shows that transesophageal Doppler echocardiography can be used to assess the effects of vasoactive drugs and to evaluate coronary blood flow reserve. Even if this approach only allows the evaluation of
blood flow characteristics of the left anterior descending coronary artery, it does have some interesting potential uses. Transesophageal Doppler evaluation of coronary blood flow reserve appears to be particularly useful for physiopathological studies requiring serial evaluations of coronary flow reserve; for assessing pharmacological interventions on coronary blood flow velocity; for evaluating coronary flow reserve in cardiac diseases (left ventricular hypertrophy, cardiomyopathies, X syndrome) which, unlike coronary artery disease, are not regional and, therefore, flow reserve in the left anterior descending coronary artery can be considered an expression of overall coronary flow reserve; and, last, for the immediate and later evaluation of the functional effects of angioplasty on the left anterior descending coronary artery.

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References


KEY WORDS • echocardiography, Doppler • echocardiography, transesophageal • coronary blood flow
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