Transmitral Flow Changes during Dipyridamole-Induced Ischemia*  
A Doppler-Echocardiographic Study  
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Myocardial ischemia results in altered left ventricular (LV) diastolic compliance, reflected by an abnormal mitral inflow pattern on Doppler echocardiography. To investigate the relationship of Doppler echocardiography and regional myocardial systolic function during dipyridamole infusion, we evaluated transmitral flow changes detected by pulsed Doppler technique during a high-dose dipyridamole echocardiography test (DET, two-dimensional echo monitoring with dipyridamole infusion, up to 0.84 mg/kg over 10 min). The DET response produced two groups: group 1 (34 patients) with negative DET, and group 2 (35 patients) with positive DET, defined as the development of a newly onset LV regional asynergy. The E/A values overlapped at baseline (1.07 ± .32 vs .92 ± .22; p = NS) but differed at peak changes (.92 ± .26 vs .75 ± .25; p < .01). Heart rate changes could not account for the observed Doppler changes, since the values of R–R interval were similar in the groups, both basally (.927 ± .226 vs .867 ± .143 s; p = NS) and at peak dipyridamole (.754 ± .100 vs .681 ± .112; p = NS). Transient myocardial ischemia induced by dipyridamole administration is accompanied by changes in transmitral flow, which consist of an increase in the relative atrial contribution to LV filling, possibly owing to an acute impairment in LV relaxation. (Chest 1989; 95:1037-42)

| DET = dipyridamole echocardiography test; WMS = wall motion score; E = peak velocity of early diastolic rapid inflow (cm/s); A = peak velocity of late diastolic inflow due to atrial contraction (cm/s); E/A = ratio of peak early to peak late velocity; Acc = acceleration of early diastolic rapid inflow (cm/s²); Dec = deceleration of early diastolic rapid inflow (cm/s²) |

A transient regional asynergy owing to the induction of myocardial ischemia is the diagnostic end point of the dipyridamole echocardiography test (DET).1,2 This regional systolic dysfunction is an early and sensitive marker of the ischemic event. Both contraction and relaxation are active processes requiring energy; however, compared with the former, relaxation seems to be more sensitive to small changes in energetics.3 Recently, clinical studies have shown that mitral inflow velocity curve, observed noninvasively in man by Doppler technique, is an index of left ventricular (LV) diastolic function in resting conditions.4,6 Alterations in the mitral inflow velocity curve are associated with an acute impairment in LV relaxation owing to myocardial ischemia.7,8 Biventricular hemodynamic monitoring during dipyridamole infusion has shown that the dP/dt of relaxation, an invasive index of LV diastolic function, provides a sensitive marker of dipyridamole-induced ischemia.9 It seems appealing to monitor noninvasively myocardial diastolic function by Doppler techniques. Unfortunately, the mitral valve velocity curve, although easy to obtain and to analyze, is not dependent on only relaxation, but also on heart rate, myocardial contractility, blood pressure, preload, and passive compliance.11-13 These values may change during dipyridamole stress independent of the possible induction of ischemia.1,2

The aim of this work was to evaluate the presence and clinical significance of transmitral flow changes detected by pulsed Doppler technique during dipyridamole-induced ischemia. Doppler monitoring of transmitral flow, combined with two-dimensional echocardiographic (2D echo) monitoring, was attempted in 94 patients undergoing DET.

**MATERIAL AND METHODS**

Ninety-four patients (73 men, 21 women; age range, 36 to 71 years) with a presumptive diagnosis of coronary artery disease characterized by a history of either typical or atypical chest pain, on effort or at rest, were enrolled for the study. All had 2D echo images of acceptable quality in resting conditions and had to undergo DET for diagnostic purposes.

Exclusion criteria were the presence of LV hypertrophy (diagnosed on the basis of echo criteria), valvular or pericardial disease, and atrial fibrillation, since these conditions are known to affect the Doppler mitral inflow velocity curve.10 Patients entering the study had discontinued treatment with antianginal medications for at least 48 h.

**Dipyridamole Echocardiography Test**

Two-dimensional echocardiographic and 12-lead ECG monitoring were performed in combination with a dipyridamole infusion:9 0.56 mg/kg over 4 min, followed by 4 min of no dose, then 0.28 mg/kg in 2 min. The cumulative dose, therefore, was 0.84 mg/kg over 10 min.

Aminophylline (240 mg), which promptly reverses the effects of...
dipyridamole, was readily at hand. During the procedure, the blood pressure and the ECG were recorded each minute. Two-dimensional echocardiograms were continuously recorded during and up to 30 min after dipyridamole administration. We used a commercially available wide-angle, phased-array imaging system (Hewlett-Packard model 77020; 2.5- and 3.5-MHz transducers). Because we needed to obtain a wall motion score (WMS) and to combine 2D echo with Doppler monitoring, we relied primarily on the apical approach (four- and two-chamber views).

Wall motion abnormalities were evaluated both at rest and at peak dipyridamole dose in each patient. The evaluation was based on the subjective impression of the inward motion of the endocardial echo toward the center of the left ventricle and the degree of thickening of the myocardium. For the purpose of wall motion analysis, the left ventricle was divided into nine segments, one segment for the apex and two segments for each of the four LV walls (septal, anterior, lateral, and inferoposterior), so that each wall was divided into basilar third, middle third, and apex.

A WMS was derived by adding the score assigned to each segment. The WMS was graded +2 (normokinetic), +1 (hypokinetic), 0 (akinetic), and −1 (dysskinetic). The score of a normokinetic left ventricle was thus 18.

The videotapes were analyzed by two independent observers. Positivity of the test was linked to detection of a transient asynergy of contraction. When there was a disagreement about the results (positively vs negativity), a third observer reviewed the study, and the subsequent majority judgment was binding in all cases, the WMS was assigned through a consensus decision. None of the three observers had access to angiographic findings before interpretation of the videotapes.

When required, patients received IV aminophylline (50 to 240 mg) at the end of the test.

**Pulsed Doppler Examination**

The transducer was oriented to obtain an apical four-chamber view of the heart that provided good visualization of the LV cavity and maximal excursion of the mitral valve leaflets. The cursor line was positioned through a plane traversing the left ventricle from the apex to the mitral valve annulus. Great care was taken to achieve the smallest possible angle between the presumed direction of diastolic blood flow and the orientation of the ultrasound beam (cursor), this angle was estimated to be 0° or less than 20° in each patient. The sample volume was positioned in the inflow area of the left ventricle, usually 1 to 2 cm inferior to the mitral valve annulus, and its position along the cursor line was adjusted until the highest peaks of diastolic flow velocity were recorded, and the Doppler waveform was optimal. The position of the sample volume was kept as steady as possible throughout the test. The Doppler diastolic flow velocity waveform was recorded in resting conditions and every 1 min during dipyridamole challenge. All recordings were made during expiratory apnea.

For each test, two time points were considered for quantifiable evaluation: basal state and peak dipyridamole effect, when the maximal changes in transmirtal flow were recorded. This usually occurred at peak ischemia (just before aminophylline injection) in positive tests, and at 1 to 6 min after the administration of the full dipyridamole dose in negative tests.

For each time point in each test, LV diastolic flow velocity waveforms from at least three cardiac cycles were characterized quantitatively and the values averaged. For each tracing, the following measurements were obtained: (1) peak velocity of early diastolic rapid inflow (E, in cm/s); (2) peak velocity of late diastolic inflow due to the atrial contraction (A, in cm/s); (3) the ratio of the peak early to peak late velocity ratio (E/A); (4) acceleration of early diastolic rapid inflow (Acc, in cm/s²), and (5) deceleration of early diastolic rapid inflow (Dec, in cm/s²).

**Reproducibility of Doppler Measurements**

To assess the interobserver variability, two observers independently interpreted the same sets of cardiac cycles at rest (ten sets) and during dipyridamole administration (ten sets). To determine intraobserver variability, the same set of cardiac cycles was again evaluated by one observer at least one month after the first interpretation and without knowledge of his first evaluation. The average percentage of difference was calculated as the difference between the two values divided by the value of the first observation (Table 1).

**Angiographic Study**

Patients underwent biplane left ventriculography and selective right and left coronary arteriography, using either the Judkins or the Sones technique. Multiple views of each coronary artery were obtained, including cranio-caudal views. Two independent observers, blind to clinical data, analyzed the coronary angiograms. A vessel was considered to have significant obstruction if its diameter was narrowed by 70 percent or more with respect to the prestenotic tract.

During the examination, the left ventricular end-diastolic pressure (LVEDP) was measured with a fluid-filled catheter. Left ventricular ejection fraction was calculated on end-diastolic and end-systolic ventriculographic frames with the Dodge method.

**Statistical Analysis**

For each value the mean and SD are given. Differences were tested for significance by paired and unpaired Student's t test. Feasibility data and coronary artery disease (CAD) extent were evaluated by χ² test. A p value <0.05 was considered statistically significant.

**RESULTS**

**Feasibility of Doppler Study**

The Doppler study was attempted in the 94 patients enrolled for DET. Four patients had to be excluded because of a poor apical window, which precluded the Doppler examination during 2D echo study; two more patients had to be excluded because of resting tachycardia in baseline conditions, which precluded the acquisition of readable resting Doppler tracings. Another 19 patients, with dipyridamole-induced tachycardia, were excluded for the same reason. Interpretable Doppler tracings during control and during DET could be obtained in the remaining 69 patients.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Intraobserver and Interobserver Variability of Doppler Parameters*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E (peak velocity of A wave)</td>
</tr>
<tr>
<td>E</td>
<td>A</td>
</tr>
<tr>
<td>4.2±3.6</td>
<td>3.3±2.2</td>
</tr>
</tbody>
</table>

* = peak peak of A wave; Acc = acceleration rate of E wave; Dec = deceleration rate of E wave; E = peak velocity of E wave.
Table 2—Clinical Findings in the Patients of Each Study Group

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>M</th>
<th>F</th>
<th>Age, yr</th>
<th>OMI</th>
<th>EF</th>
<th>LVEDP</th>
<th>1VD</th>
<th>2VD</th>
<th>3VD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>13</td>
<td>6</td>
<td>44±7</td>
<td>7</td>
<td>60±9</td>
<td>8±5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>12</td>
<td>3</td>
<td>53±8</td>
<td>7</td>
<td>57±8</td>
<td>7±4</td>
<td>8</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>30</td>
<td>5</td>
<td>52±10</td>
<td>13</td>
<td>49±8</td>
<td>11±5</td>
<td>17</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>3A</td>
<td>23</td>
<td>20</td>
<td>3</td>
<td>51±9</td>
<td>8</td>
<td>48±6</td>
<td>10±5</td>
<td>12</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>3B</td>
<td>12</td>
<td>10</td>
<td>2</td>
<td>54±12</td>
<td>5</td>
<td>52±8</td>
<td>11±5</td>
<td>5</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

*CAD = coronary artery disease; OMI = old myocardial infarction; VD = vessel disease.

overall feasibility of Doppler was therefore 69/94 vs a feasibility of 2D echo of 94/94 (73 vs 100 percent; p<.01).

Clinical Findings

The 69 patients with interpretable Doppler tracings were arbitrarily divided, on the basis of angiographically assessed CAD and echocardiographically documented ischemia during dipyridamole stress, into three groups: group 1, no CAD, negative DET; group 2, CAD, negative DET; and group 3, CAD, positive DET. The clinical findings for each group of patients are summarized in Table 2 and the blood pressure response to dipyridamole infusion in Table 3.

Doppler Observations

The values of E and A waves, E/A ratio, acceleration and deceleration rates, and R-R intervals for each study are summarized in Table 4. The R-R interval showed a significant decrease at peak dipyridamole in all groups. The A wave rose significantly in all groups during stress; E/A decreased significantly in groups 1 and 3. Acceleration rose significantly in groups 2 and 3, while deceleration rose only in group 3. An example of Doppler findings in a positive DET is reported in Figure 1. For each study patient, the E/A value at peak dipyridamole was also expressed as percentage of variation of the baseline value, arbitrarily taken as 100 percent (Fig 2). Figure 2 shows a wide overlap in values among the three groups.

No significant differences could be recorded for any considered measurement between groups 1 and 2 (Table 5), which were pooled in the subsequent analysis. The E/A decrease was more pronounced in group 3 (positive DET) than in the pooled groups 1 and 2 (patients with negative DET; Fig 3). On the contrary, the values of the R-R interval were similar in the two groups, both basally and at peak dipyridamole (Fig 3).

To establish whether the extent of dipyridamole-induced ischemia might affect Doppler indices, two subsets were arbitrarily identified within group 3 according to the extent of dipyridamole-induced ischemia: those with a decrease during DET in WMS less than 5 (group 3A, 23 patients) and those with a decrease in WMS greater than 5 (group 3B, 12 patients). Clinical data of patients of these two subgroups are shown in Table 2. No significant differences in parameters concerning the clinical data or the baseline LV global and regional performance were recorded, while a significant difference (p<.01) was present considering the CAD extent of groups 3A and 3B. (The E/A values of the two subsets were similar in baseline conditions, while the group with greater impairment in LV contraction after dipyridamole stress showed a significantly lower value at peak dipyridamole (Fig 4).

Intraobserver and Interobserver Variability

For each Doppler index, the values of interobserver, and intraobserver variability are reported in Table 1.

The measures of E and A wave show a good reproducibility, while the acceleration and deceleration values have a high variability, which obscures their significance and reliability after the dipyridamole challenge.

DISCUSSION

The findings of this study show that dipyridamole-induced ischemia is characterized by an increase in the atrial contribution to transmural inflow velocity curve. These changes are more pronounced when a more extensive systolic dysfunction is found in a positive DET. However, a pseudoischemic pattern in transmural inflow velocity curve can be found even in the absence of CAD or dipyridamole-induced systolic dysfunction.

These findings are best understood if we remember that transmural inflow velocity curve is affected by many variables besides LV relaxation.11-15

In particular, pulsed Doppler derived indices of LV...
Table 4—Variation in Doppler Parameters and Heart Rate During DET in the Three Groups*

<table>
<thead>
<tr>
<th>Group</th>
<th>E Bas</th>
<th>E Dip</th>
<th>A Bas</th>
<th>A Dip</th>
<th>E/A Bas</th>
<th>E/A Dip</th>
<th>Acc Bas</th>
<th>Acc Dip</th>
<th>Dec Bas</th>
<th>Dec Dip</th>
<th>R-R Bas</th>
<th>R-R Dip</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64.9 ± 17.7</td>
<td>69.6 ± 14.9</td>
<td>59.3 ± 13.7</td>
<td>74.9± 21.8</td>
<td>1.10 ± .29</td>
<td>7.95± .29</td>
<td>737 ± 207</td>
<td>754 ± 205</td>
<td>367 ± 129</td>
<td>403 ± 140</td>
<td>687 ± 155</td>
<td>.71 ± .098</td>
</tr>
<tr>
<td>2</td>
<td>55.1 ± 18.1</td>
<td>66.1 ± 14.7</td>
<td>53.3 ± 7.0</td>
<td>7.28± 13.9</td>
<td>1.03 ± .36</td>
<td>.98± .21</td>
<td>688 ± 263</td>
<td>828± 221</td>
<td>366 ± 227</td>
<td>398± 180</td>
<td>.959 ± .269</td>
<td>.734± .103</td>
</tr>
<tr>
<td>3</td>
<td>57.1 ± 15.6</td>
<td>62.1 ± 17.0</td>
<td>62.6 ± 18.5</td>
<td>83.5± 20.1</td>
<td>.92 ± .22</td>
<td>.75± .25</td>
<td>644 ± 256</td>
<td>785± 318</td>
<td>306 ± 106</td>
<td>394± 142</td>
<td>.867 ± .143</td>
<td>.661± .112</td>
</tr>
</tbody>
</table>

*A = peak velocity of A wave (cm/s); Acc = acceleration rate of E wave (cm/s²); Bas = basal; Dec = deceleration rate of E wave (cm/s²); Dip = after dipyridamole (ischemia or peak changes); E = peak velocity of E wave (cm/s); E/A = ratio; R-R = R to R interval on ECG (s).

† = p<0.001.
‡ = p<0.01.

Doppler indices such as E/A ratio cannot be directly correlated to variations in the R-R interval.

mimic those previously reported with the impairment of LV diastolic function,15 in spite of the increased LV relaxation rate induced by dipyridamole infusion.10-16 The stress-induced tachycardia is also the limiting factor for the recording of interpretable Doppler tracings, since at over 90 to 95 beats/min, a fusion of E and A waves occurs.

There is some direct evidence that during dipyridamole stress the development of significant myocardial ischemia can provoke a decrease of the LV dP/dt of relaxation.10 This can explain the increase of the atrial contribution in ventricular filling recognized in several models of ischemia.9,3,17 This mechanism is
Table 5—Variation in E/A Doppler Value and Heart Rate During DET in Patients with Negative and Positive Test

<table>
<thead>
<tr>
<th>Group</th>
<th>E/A</th>
<th>R-R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bas</td>
<td>Dip</td>
<td>Bas</td>
</tr>
<tr>
<td>1 and 2 (DET -) (n = 34)</td>
<td>1.07 ± .32</td>
<td>.92 ± .26</td>
</tr>
<tr>
<td>3 (DET +) (n = 35)</td>
<td>.92 ± .22</td>
<td>.75† ± .25</td>
</tr>
</tbody>
</table>

*Bas = basal; Dip = dipyridamole; E/A = E, A ratio; R-R = R to R interval (S); + = positive; − = negative.
†p < 0.01.

also the most likely explanation of the more pronounced decrease in E/A value in patients with positive DET than in patients with a negative DET. In fact, the heart rate changes are similar in patients with different responses to DET. In patients with dipyridamole-induced ischemia, impaired LV relaxation, increase in heart rate, and compensatory hyperactivity of left atrial contraction may synergistically increase relative atrial contribution to LV filling.

These combined effects override the increased LVEDP that is secondary to ischemia and, through a rise in left atrial afterload, should increase the relative atrial contribution to LV filling.

Clinical Implications

From the theoretical viewpoint, Doppler-derived diastolic indices might have a clinical appeal as useful markers of myocardial ischemia. They proved early and sensitive indicators of acute ischemia in other clinical models, such as coronary angioplasty or coronary vasospasm. Also, with dipyridamole stress, myocardial ischemia can contribute to the recorded changes in Doppler indices of diastolic myocardial function. Two lines of evidence support this conclusion: (1) significant E/A changes, although also detec-

![Figure 2. Perceptual variation of E/A ratio in the three groups after dipyridamole infusion. If one takes a 23 percent reduction of E/A as a criterion of myocardial ischemia (horizontal dashed line), the sensitivity for prediction of angiographically assessed CAD is 36 percent, with a specificity of 69 percent.

![Figure 3. E/A and R-R interval variations during dipyridamole test in patients with negative (groups 1 and 2) and positive (group 3) DET.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21593/ on 06/27/2017)
able in patients with negative DET, were more pronounced in the group with documented systolic dysfunction provoked by dipyridamole-induced ischemia; and (2) in patients with positive DET, a more marked alteration in Doppler indexes was found in the presence of more pronounced ischemia, as independently assessed by the evaluation (through the WMS) of the entity and extent of systolic ischemic dysfunction.

This information, representing a feasible noninvasive window on diastolic events during dipyridamole stress, is of potential pathophysiologic interest. However, the clinical appeal of Doppler-derived measurements during dipyridamole-echocardiography test is severely limited by the poor feasibility and diagnostic accuracy. The information on LV diastolic function, which is present in transmitral flow-velocity curves, requires a large sample population. In the individual patient, it remains virtually buried by hemodynamic changes triggered by dipyridamole infusion, which may very well mimic or mask the effect of LV ischemia on transmitral flow pattern.

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REFERENCES

Figure 4. E/A and wall motion score (WMS) variations in patients with positive dipyridamole echocardiography tests (group S).