Relation between Doppler transmitral flow and wall motion abnormalities during dipyridamole echocardiography in coronary artery disease

Carluccio E, Bentivoglio M, Biagioli P, Corea L, Prociutti L, Tommasi S

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Relation Between Doppler Transmitral Flow and Wall Motion Abnormalities During Dipyridamole Echocardiography in Coronary Artery Disease

E. Carluccio, St. Tommasi, M. Bentivoglio, P. Biagioli, L. Prosciutti, L. Corea

Myocardial ischemia impairs left ventricular relaxation phase and diastolic function. Pulsed wave Doppler transmitral flow velocities have been proposed as a useful non-invasive tool to examine left ventricular diastolic function. With the present study we sought to evaluate whether changes in Doppler transmitral flow profile are related to the severity and extent of dipyridamole-induced wall motion abnormalities in patients with coronary artery disease.

Thirty-five patients (mean age 61.3 ± 12 years, 21 men) with known coronary artery disease (≥ 75 % in one or more vessels) underwent Dipyridamole Stress Echocardiography (DSE). Doppler-derived transmitral flow velocities were recorded at rest and immediately after drug infusion. At the same times wall motion score index (WMSI) was also calculated. E/A ratio decreased during dipyridamole infusion in 20 patients (group A) and increased in 15 patients (group B). The 2 groups resulted homogeneous with respect to demographic, echocardiographic and angiographic variables; however in group A 16 patients (80 %) had a positive DSE compared to 3 patients (20 %, p < 0.001) in group B. In group A time to ischaemia was lower (7.6 ± 3 vs. 10.1 ± 0.4 minutes, p < 0.001) and WMSI at peak was greater (1.43 ± 0.29 vs. 1.12 ± 0.15, p < 0.001) than in group B. The WMSI at peak was also lower in those 3 patients with positive DSE and increased E/A ratio compared to the positive DSE patients with reduced E/A ratio (1.27 ± 0.03 vs. 1.51 ± 0.27, p < 0.05). Finally, 8 patients (40 %) in group A and none in group B had an ischaemic response to low dose dipyridamole infusion (p < 0.01). A significant negative correlation was observed between the induced changes in wall motion abnormalities and the decrease in E/A ratio during dipyridamole infusion (r = -0.72, p < 0.0001).

In patients with coronary artery disease a reduced E/A ratio during dipyridamole stress echocardiography is often associated with a positive ischaemic response and is related to the severity and extent of induced wall motion abnormalities. J Clin Basic Cardiol 2000; 3: 47-51.

Key words: dipyridamole echocardiography, Doppler transmitral flow, myocardial ischaemia

It is well known that left ventricular diastolic dysfunction precedes systolic dysfunction during myocardial ischaemia [1]. Pulsed wave Doppler transmitral flow velocities have been proposed as a non-invasive useful tool to examine left ventricular diastolic function [2, 3] in several clinical settings such as dilated cardiomyopathy [4], essential hypertension and ischaemic heart disease [5, 6]. The results of most previous studies showed that myocardial ischaemia causes a pattern of abnormal left ventricular relaxation including a dominant atrial wave and an unmodified or reduced early rapid filling wave (with consequently reduced ratio of peak flow velocity in early diastole in respect to that in atrial systole-E/A ratio) [7–13]. High dose dipyridamole infusion is a recognized test able to induce myocardial asynergies in patients with coronary artery disease (CAD) as demonstrated by echocardiographic monitoring [14, 15]. This test has a good sensitivity and high specificity [16, 17]. However, the studies regarding the behaviour of left ventricular filling pattern during dipyridamole stress echocardiography in patients with known coronary artery disease have shown contrasting results. Actually, some authors did not find any changes in transmitral flow velocities and E/A ratio in patients with myocardial ischaemia in respect to those without it [18]. In particular, whether the extent and severity of ischaemic myocardium during stress could affect diastolic left ventricular pattern is still unknown. Therefore, the aim of this study was to evaluate whether changes in Doppler transmitral flow velocities are related to the extent and severity of dipyridamole-induced wall motion abnormalities in patients with known coronary artery disease.

Methods

Study patients

We studied 35 patients (mean age 61.3 ± 12 years, 21 men) with coronary artery disease (luminal diameter narrowing ≥ 75 % in one or more vessels) undergoing dipyridamole stress echocardiography (DSE). The patients were enrolled in the study if the following criteria were satisfied: 1) no signs of congestive heart failure; 2) no valvular regurgitation and stenosis at rest; 3) absence of bundle branch block on the baseline electrocardiogram (ECG); 4) presence of sinus rhythm; 5) echocardiographic evidence of normal left ventricular systolic function; 6) adequate transthoracic acoustic window for echocardiographic examination; 7) absence of asthmatic diseases which represent a contraindication to the dipyridamole stress test; 8) no history of myocardial revascularization procedures and, 9) written informed consent.

Cardioactive drugs were withdrawn 72 hours before the study. Nine patients had a history of essential hypertension but their blood pressure values did not exceed 150/90 mmHg after pharmacological wash-out and none of them had an increased echocardiographic left ventricular mass index. Seven patients had a history of acute myocardial infection. Nineteen patients had 1-vessel coronary disease, 11 patients had 2-vessel disease, and 5 patients had 3-vessel disease.

Dipyridamole stress test

Dipyridamole was infused at a rate of 0.56 mg/kg body weight in 4 minutes, followed by 4 minutes of interval (no dose) and then 0.28 mg/kg in 2 minutes. The cumulative dose was therefore 0.84 mg/kg over 10 minutes.
Echocardiographic examination
After routine preparation for dipyridamole stress, two-dimensional echocardiography was performed using a commercially available imaging system (ATL UltraMark 9, and 2.5 MHz transducers). The patients were studied in the left lateral decubitus position and standard parasternal long and short axis and apical four and two chambers views were continuously monitored during the study. Twelve-lead ECGs, heart rate and blood pressure values were obtained at rest, every 2 minutes during the test, and up to 10 minutes after the end of drug infusion. Each echocardiogram was recorded on video-tape and subsequently analyzed by two echocardiographers, who were unaware of the clinical and angiographic data. Dipyridamole-induced ischaemia was defined by the appearance of new or worsening of pre-existing dysynesies of contraction in at least to adjacent segments as the primary endpoint. The appearance of angina and/or ischaemic electrocardiographic changes alone were not used to define a positive test in the absence of induced wall motion abnormalities. According to the American Society of Echocardiography [19], a 16 segment model of the left ventricle was used. The wall motion of each segment was graded from 1 = normokinetic to 4 = dyskinetic and the Wall Motion Score Index (WMSI), an index of global ventricular function, was obtained by adding the score of all examined segments and thus dividing it by the number of the segments scored both at rest and at the end of drug infusion. If a segment was not visualised because of echo dropout or technical reasons its score was not given and the segment was excluded from the analysis of the WMSI. Disagreements in interpretation were resolved by consensus. For interobserver reproducibility, 30 echocardiograms were subsequently randomly analyzed: the concordance between observer 1 and observer 2 was 95%, with a k value of 0.58. Criteria for interruption of the test were: 1) achievement of peak dose; 2) appearance of evident wall motion abnormalities; 3) down-sloping ST segment depression > 2 mm in two consecutive leads; 4) anginal pain and/or dyspnoea; 5) appearance of limiting side effects (hypotension, bradycardia, severe dyspnoea, complex arrhythmias).

Left ventricular mass was calculated by means of Devereux's formula [20] and subsequently normalized by body weight. The partition value to identify left ventricular hypertrophy formula [20] and subsequently normalized by body weight.

Doppler flow analysis
Left ventricular diastolic function was evaluated immediately before and at the end of drug infusion, or at the time of the appearance of new or worsening of pre-existing wall motion abnormalities, by pulsed-wave Doppler interrogation of the left ventricular inflow tract from the apical four-chamber view. The sample volume was placed first at the middle of the line connecting the two margins of mitral valve and thereafter at the leaflet tips and its location was adjusted to obtain optimal signal. After obtaining a stable signal of the transmitral flow velocity, the Doppler cursor was moved toward the left ventricular outflow tract in the apical five-chamber view to record both mitral and aortic signals. The Doppler transmitral flow and aortic images were recorded on video-tape at a speed of 100 mm/s, with the patients in held expiration. The average value of three cycles was used for analysis. Peak early diastolic flow velocity (E), peak flow velocity of atrial contraction (A), and the deceleration time of E velocity were measured at the tips of mitral leaflets at the maximum amplitude of E velocity. Deceleration time was measured as the time from peak E velocity to the time when the E wave descent intercepted the zero line. Isovolumic relaxation time (IVRT) was calculated as the time from the end of aortic flow to the onset of mitral flow during the continuous wave interrogation of the left ventricular inflow-outflow tract. The percent changes in E/A ratio and in peak A velocity at the end of drug infusion were also calculated. All Doppler images were subsequently analyzed by two different echocardiographers without any knowledge of test results. Baseline inter- and intraobserver variability analysis was performed apart in a sample of 20 randomly chosen patients from those referred to our laboratory and was found to be less than 5% for all echocardiographic variables. Because aminophylline has positive inotropic and vasodilator properties and it could determine a fusion of peak E with peak A for tachycardia, it was administered, when necessary, after the last Doppler evaluation.

Statistical analysis
Data are presented as mean ± 1 standard deviation (SD). The statistical significance of the difference between the values of the two groups was tested with unpaired-t test for independent samples, and Mann Whitney U test when appropriate. Comparison between resting and peak values in each group was performed using a paired-t test and Wilcoxon rank test for non parametric data. Bivariate correlation between values was made with simple linear regression analysis. Multiple logistic regression model was used to identify which clinical, echocardiographic and haemodynamic variable could predict a reduced E/A ratio at peak of the DSE; variables analyzed were body mass index, age, peak heart rate, hypertension, previous myocardial infarction, left ventricular diastolic wall thicknesses, peak systolic and diastolic blood pressure values, relative wall thickness, time to ischaemia and percent increase in wall motion score index. Results were considered significant at a p value < 0.05.

Results

Study population
Patients were classified into two groups on the basis of changes in the ratio of peak flow velocity in early diastole to that in atrial systole (E/A ratio) during DSE. Group A consisted of 20 patients who had a decrease in E/A ratio at the end of DSE, whereas group B consisted of 15 patients who had an increase in E/A ratio. The two groups of patients tested homogeneous for clinical, echocardiographic, and angiographic variables, and showed a good left ventricular function at rest (Table 1). As shown in Table 2, at rest peak early diastolic velocity (PEV) was lower in group B than group A (p < 0.05), while peak velocity of atrial contraction (PAPV), their ratio (E/A), deceleration time of peak E (DT), and isovolumic relaxation time did not differ significantly between the two groups. Heart rate, systolic and diastolic blood pressure values at rest were also similar between group A and group B.

Transmitral flow profile during dipyridamole echocardiography test
Adequate Doppler transmitral flow recordings were obtained both at rest and at the end of dipyridamole infusion in all patients. The reduced E/A ratio at the end of dipyridamole infusion in group A was mainly due to a significant increase in peak A velocity (p < 0.0001) whereas peak E velocity did not significantly change (Figure 1). Deceleration time slightly increased in group A, while isovolumic relaxation time showed a significant increase in respect to resting conditions (p < 0.0001) (Table 2). In group B patients, the increased E/A ratio was associated with a slight increase in peak A velocity and to a more significant increase in peak E velocity (p < 0.0001, Figure 1). Deceleration time was slightly reduced (p = 0.09), while isovolumic relaxation time did not significantly increase at the end of DSE in group B (Table 2).
Doppler Determination During Dipyridamole Echocardiography Test

**ORIGINAL PAPERS, BASIC**

**Dipyridamole stress echocardiography results**

Sixteen patients of group A (80 %) had a positive DSE defined by the appearance of new or worsening of preexisting wall motion abnormalities during dipyridamole infusion, while DSE was positive in only 3 patients (20 %) of group B (p < 0.001) (Table 1). Resting WMSI did not significantly differ between group A and group B (1.14 ± 0.22 vs. 1.07 ± 0.14, p = ns respectively) however, at the end of drug infusion, group A showed a higher increase in peak WMSI than group B.

**Haemodynamic changes**

As shown in Table 2, heart rate increased from 72.5 ± 9 beats/min at rest to 94.7 ± 22 beats/min (p < 0.0001) at peak DSE in group A, and from 73.6 ± 12 beats/min to 95 ± 15 beats/min (p < 0.0001) in group B. There was no significant difference in heart rate between the two groups either at rest or at the end of drug infusion. Systolic and diastolic arterial pressure did not change significantly throughout the test in either group. During DSE all patients maintained the sinus rhythm.

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**Table 1. Characteristics of the study groups**

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 20)</th>
<th>Group B (n = 15)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.6 ± 12</td>
<td>62 ± 11</td>
<td>0.72</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>11/9</td>
<td>10/5</td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>9 (45)</td>
<td>6 (40)</td>
<td>0.96</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>2 (10)</td>
<td>1 (7)</td>
<td>0.72</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>11 (55)</td>
<td>10 (67)</td>
<td>0.71</td>
</tr>
<tr>
<td>Previous myocardial infarction (%)</td>
<td>7 (35)</td>
<td>4 (27)</td>
<td>0.80</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>113.5 ± 32</td>
<td>109.8 ± 35</td>
<td>0.75</td>
</tr>
<tr>
<td>1-vessel disease (%)</td>
<td>11 (55)</td>
<td>8 (53)</td>
<td>0.82</td>
</tr>
<tr>
<td>2-vessel disease (%)</td>
<td>6 (30)</td>
<td>5 (33)</td>
<td>0.85</td>
</tr>
<tr>
<td>3-vessel disease (%)</td>
<td>3 (15)</td>
<td>2 (12)</td>
<td>0.74</td>
</tr>
<tr>
<td>Positive DSE (%)</td>
<td>16 (80)</td>
<td>3 (20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak WMSI</td>
<td>1.43 ± 0.29</td>
<td>1.12 ± 0.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low dose ischaemia (%)</td>
<td>8 (40)</td>
<td>(–)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Time to ischaemia (minutes)</td>
<td>7.6 ± 3</td>
<td>10.1 ± 0.4</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

DSE = dipyridamole stress echocardiography; LVMI = left ventricular mass index; WMSI = wall motion score index

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**Table 2. Doppler indices and haemodynamic changes during dipyridamole stress echocardiography**

<table>
<thead>
<tr>
<th></th>
<th>Group A Rest</th>
<th>Group A Peak</th>
<th>Group B Rest</th>
<th>Group B Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEV (m/sec)</td>
<td>0.74 ± 0.18</td>
<td>0.72 ± 0.15</td>
<td>0.60 ± 0.145</td>
<td>0.70 ± 0.14*</td>
</tr>
<tr>
<td>PAV (m/sec)</td>
<td>0.72 ± 0.19</td>
<td>0.83 ± 0.19*</td>
<td>0.73 ± 0.14</td>
<td>0.78 ± 0.19**</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.05 ± 0.22</td>
<td>0.89 ± 0.19*</td>
<td>0.98 ± 0.34</td>
<td>0.96 ± 0.35**</td>
</tr>
<tr>
<td>DT (msec)</td>
<td>152.7 ± 33</td>
<td>163.7 ± 26</td>
<td>51.3 ± 52</td>
<td>131 ± 38</td>
</tr>
<tr>
<td>IVRT (msec)</td>
<td>95 ± 15</td>
<td>106.9 ± 19*</td>
<td>89.7 ± 13</td>
<td>90.2 ± 13</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>72.5 ± 9</td>
<td>94.7 ± 22</td>
<td>73.6 ± 12</td>
<td>95 ± 15*</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>134.5 ± 15</td>
<td>136.7 ± 16</td>
<td>132.3 ± 19</td>
<td>135.8 ± 10</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>79.7 ± 8</td>
<td>79.4 ± 7</td>
<td>81 ± 11</td>
<td>78.6 ± 6</td>
</tr>
</tbody>
</table>

* p < 0.0001 vs. rest; ** p < 0.01 vs. rest; $ p < 0.05 vs. group A; DT = deceleration time of peak E; HR = heart rate; DBP = diastolic blood pressure; IVRT = isovolumic relaxation time; PEV = peak E velocity; PAV = peak A velocity; SBP = systolic blood pressure

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**Figure 1. Changes in Doppler indices during dipyridamole stress echocardiography.**

- In group A (top panel) the reduction in E/A ratio was mainly due to a significant increase in peak A velocity at the end of dipyridamole infusion. In group B (bottom panel) the increased E/A ratio was due to a significant increase in peak E velocity and only a slight increase in peak A velocity.

**Figure 2. Wall motion score index (WMSI) at rest and peak of dipyridamole stress echocardiography in patients who had a reduction (group A) or an increase (group B) in E/A ratio at the end of drug infusion.** Group A patients showed a higher increase in peak WMSI than group B.
Correlations between variables and logistic regression results

A negative correlation between the percent decrease in E/A ratio and changes in WMSI was found in all patients in the study (beta = 0.72, p < 0.0001): more severe and extensive wall motion abnormalities were associated with a greater reduction in E/A ratio (Figure 3). A positive correlation was observed between changes in WMSI and the percent increase in peak late diastolic velocity (beta = 0.57, p < 0.001): the severity and extent of dipyridamole-induced wall motion abnormalities were associated with a greater increase in the atrial contribution to left ventricular filling. A weak positive correlation was noticed between changes in WMSI and the percent increase in isovolumic relaxation time (beta = 0.48, p < 0.01). Furthermore, no correlation was found between the percent decrease in E/A ratio and increase in heart rate. The multiple logistic regression model revealed that the percent increase in WMSI and time to ischaemia were the only variables independently related to a reduced E/A ratio during the dipyridamole echocardiography test (–2 Log Likelihood ratio = 10.12, p = 0.001, and 6.5, p = 0.01, respectively). Other selected clinical, haemodynamic and echocardiographic variables were not found to be predictive of a reduction in E/A ratio at the end of dipyridamole infusion.

Discussion

Left ventricular filling abnormalities are thought to be among the earliest signs of cardiac dysfunction and have been described in various cardiac diseases such as coronary artery disease, dilated cardiomyopathy, hypertensive heart disease, and acute ischaemia induced by any means [7–13]. The present study shows that changes in Doppler transmural flow pattern during dipyridamole echocardiography are related to the extent and severity of ischaemia-induced wall motion abnormalities in patients with coronary artery disease. In particular, patients with a reduced E/A ratio at the end of dipyridamole infusion frequently (80 %) had a positive DSE testing (defined as appearance of new or worsening of preexisting wall motion abnormalities) also at low doses of dipyridamole (40 %), and a reduced time to ischaemia. On the contrary, patients with an increased E/A ratio frequently (80 %) had a negative DSE testing, and the few patients (20 %) with positive DSE showed a lower WMSI in respect to the DSE positive patients who had a reduction in E/A ratio (p < 0.05). Finally, the induced changes in wall motion score index showed a good negative correlation with the percent reduction in E/A ratio (beta = 0.72, p < 0.0001).

Mechanism of induced changes in E/A during dipyridamole echocardiography test

The mechanisms of left ventricular filling are complex and remain poorly defined. Results of previous studies have shown that many factors may affect left ventricular diastolic filling, such as age [21, 22], heart rate [23], preload [24], afterload, and left ventricular wall thickness [5]. Age did not significantly differ between group A and group B, therefore we do not think that age affected our Doppler results in the present study. Heart rate significantly increased at the end of drug infusion in both groups of patients, however no differences in heart rate or systolic and diastolic blood pressure between the two groups were observed either at rest or at peak of DSE. Furthermore we did not find any correlation between changes in heart rate and the percent increase in peak A velocity or the percent decrease in E/A ratio; therefore it is unlikely that our results depend on some haemodynamic effect. Another factor able to affect transmural flow pattern is mitral regurgitation which was absent in all patients studied both at rest and at the end of dipyridamole infusion. Finally, all patients in the study showed a pattern of normal geometry of the left ventricle defined by a normal left ventricular mass and a relative wall thickness < 0.45. The E/A ratio has been used as an indicator of the left atrial contribution to left ventricular filling [25]. In our group A patients, the reduced E/A ratio at the end of dipyridamole infusion was essentially due to an increase in peak A velocity, whereas peak early diastolic velocity did not significantly change in respect to resting conditions. Therefore a dipyridamole-induced decrease in E/A ratio is thought to indicate an increase in the atrial contribution to a considerable extent. An interesting result of our study is the positive correlation between the induced changes in wall motion score index and the percent increase in peak A velocity at the end of dipyridamole infusion (beta = 0.57, p < 0.0001): the severity and extent of dipyridamole-induced wall motion abnormalities were associated with a greater increase in the atrial contribution to left ventricular filling. Because isovolumic relaxation time increased significantly in group A, it is possible that the results of our study reflect an ischaemia-induced impairment in left ventricular relaxation phase during dipyridamole infusion, resulting in less reduction and slower fall of intraventricular diastolic pressure and reduction of atrioventricular pressure gradient [26, 27]. In such a context the atrial contraction occurs when the atria are less empty than in normal conditions, so that blood is quickly pushed into the ventricle with consequent increase in peak late diastolic velocity, possibly because of an atrial Frank-Starling mechanism [27]. These alterations in diastolic dysfunction occur early during myocardial ischaemia, precede the systolic dysfunction, and seem to be a better index of ischaemia than systolic dysfunction itself [9]. The ischaemic cascade, beginning with heterogeneity of perfusion and metabolic alterations, identifies diastolic disorders of the left ventricle as an early phenomenon, before systolic dysfunction, electrocardiographic changes, or chest pain occur [1]. Group A patients showed a higher wall motion score index at peak of DSE, a lower time to ischaemia, and a higher prevalence of myocardial ischaemia at low doses of dipyridamole than group B. The greater extent and severity of dipyridamole-induced ischaemia in group A caused a greater impairment in left ventricular relaxation. In group B only 3 patients (20 %) had a positive DSE test, however their peak WMSI was lower than the WMSI of DSE positive patients who had a reduction in E/A ratio at the end of
dipyridamole infusion. We believe that in these 3 patients the increase in E/A ratio could be due to a minor impairment in left ventricular relaxation because of a lighter myocardial ischemia and a greater compensatory hyperkinesia of the nonischaemic myocardial segments in response to dipyridamole infusion.

Study limitations
Fifteen patients in our study were found to have essential hypertension which has been shown to augment the atrial component of left ventricular filling, however the hypertensive patients were well matched in the two groups and there was no significant difference in blood pressure values between the two groups either at rest or at peak DSE. Despite a significant increase in heart rate in both groups of patients after dipyridamole infusion, no patient had a fusion of E wave with A wave, and all patients had adequate transmitial flow patterns at peak of DSE. It is well known that the velocity of the transmitial volume is highly dependent from the position of the sample volume which varies with the breathing: small shifts of the sample volume from the annulus toward the tip of the mitral leaflets induce marked variations of the E/A ratio, with progressive attenuation of the atrial contribution. Transmitial flow recordings in the present study were obtained at the maintained endExpiration in all patients. Therefore we do not believe that our results are affected by breathing.

Conclusions
Results of our study show that in patients with coronary artery disease there was a variable change in diastolic filling indices which may be attributed to the degree of dipyridamole-induced myocardial ischemia: a reduction in E/A ratio during dipyridamole stress echocardiography was associated with more severe and extensive wall motion abnormalities, suggesting a higher increase in the atrial contribution to left ventricular filling. On the contrary, an increased E/A ratio was associated with a negative stress test or positive dipyridamole stress echocardiography with a lesser degree of induced ischemia.

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