Left ventricular transient ischemic dilation during dobutamine stress echocardiography predicts multi-vessel coronary artery disease

Nagwa El-Mahalawy (MD), Zainab Abdel-Salam (MD), Ayman Samir (MD), Waleed Mohasseb (MSc), Wail Nammas (MD)

Cardiology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt

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KEYWORDS
Stress echocardiography; Ventricular function; Coronary artery disease

Summary
Background: We sought to explore the value of stress-induced transient ischemic dilation (TID) of the left ventricle during dobutamine stress echocardiography, to predict the presence of multi-vessel coronary artery disease as seen by coronary angiography.

Methods: We enrolled 60 patients referred to our stress echocardiography labs with ischemic-type chest pain or other symptoms suggestive of myocardial ischemia. All patients underwent resting and stress echocardiography employing the standard dobutamine stress protocol. TID ratio was defined as the ratio of left ventricular end-diastolic volume or end-systolic volume measured at peak stress, to that measured at rest (EDV ratio and ESV ratio, respectively). We enrolled 20 consecutive patients with normal response (control group) who were subsequently evaluated to develop normal limits for TID ratio, and 40 patients with ischemic response (study group) that comprised 20 consecutive patients without TID (group A) and 20 consecutive patients with TID (group B). Patients then underwent coronary angiography.

Results: Both EDV ratio and ESV ratio were significantly higher in groups A and B as compared to the control group \( (P < 0.01 \text{ for both}) \). Analysis of the receiver operating characteristic (ROC) curves identified the 1.12 cutoff value as the optimal cutoff value of TID ratio that best predicts three-vessel disease. Using this cutoff value, the ESV ratio was able to predict three-vessel disease with a sensitivity of 90%, specificity 84%, positive and negative predictive values of 85% and 89%, respectively. The mean number of vessels affected by significant stenosis was \( 1.8 \pm 0.83 \) in group A in comparison with \( 2.45 \pm 0.69 \) in group B \( (P < 0.05) \). Among group B, both EDV ratio and ESV ratio were higher in female patients as compared to male ones.

* Corresponding author at: Cardiology Department, Ain Shams University Hospitals, Faculty of Medicine, Ain Shams University, P.O. 11381, Abbassia, Cairo, Egypt. Tel.: +20 124063718; fax: +20 224820416.
E-mail address: wnammas@hotmail.com (W. Nammas).

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Conclusions: In patients undergoing dobutamine stress echocardiography, the occurrence of TID is both sensitive and specific to predict underlying three-vessel coronary artery disease. © 2009 Japanese College of Cardiology. Published by Elsevier Ireland Ltd. All rights reserved.

Introduction

Pharmacological stress echocardiography is widely acknowledged for evaluation of patients with known or suspected coronary artery disease, essentially because it is feasible and safe, with a high diagnostic and prognostic accuracy [1,2]. Typically, stress-induced myocardial ischemia is identified by regional wall motion abnormalities in the distribution of the affected vessels. Reasonably, more extensive stress-induced wall motion abnormalities may predict a higher probability of underlying multi-vessel coronary artery disease [3]. Nevertheless, few data have been reported about the significance of stress-induced transient ischemic dilation (TID) of the left ventricle demonstrated by stress echocardiography [4].

Several reports employing radio-isotope myocardial perfusion single photon emission computed tomography (SPECT) imaging, have demonstrated that TID is a sensitive and highly specific marker for detection of severe and extensive coronary artery disease [5], and a strong independent predictor of cardiac events [6]. In a prospective study design, we tried to explore the value of stress-induced TID during dobutamine stress echocardiography, to predict the presence of multi-vessel coronary artery disease as seen by coronary angiography.

Patients and methods

Population

We included 60 patients referred to our stress echocardiography labs during the period from July 2007 to December 2008. Patients were considered eligible for inclusion if they had ischemic-type chest pain or other symptoms suggestive of myocardial ischemia and were considered for evaluation by dobutamine stress echocardiography. We excluded patients with unstable angina or myocardial infarction within the preceding 4 weeks, those with a protruding fresh left ventricular thrombus, those with significant valvular or congenital heart disease or any myocardial disease apart from ischemia, those with contraindication to dobutamine (for example, history of complex ventricular arrhythmias, uncontrolled hypertension with blood pressure >180/110 mmHg), and patients with limited life expectancy due to coexistent disease (for example, malignancy). Before inclusion, informed consent was obtained from each patient and the study protocol was reviewed and approved by our local institutional human research committee as it conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 2002.

Definition of risk factors

The presence of hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, previously recorded by repeated non-invasive office measurements, which led to life-style modification or antihypertensive drug therapy. The presence of diabetes mellitus was defined as fasting plasma glucose ≥126 mg/dl, and/or 2 h post-glucose load ≥200 mg/dl, or specific anti-diabetic drug therapy. Dyslipidemia was defined as LDL cholesterol >100 mg/dl, and/or serum triglycerides >150 mg/dl, and/or HDL cholesterol <40 mg/dl and <50 mg/dl in women.

Methods

Assessment of regional and global left ventricular systolic function was performed in all patients by transthoracic echocardiography using a Hewlett Packard Sonos 5500 cardiac ultrasound machine (Hewlett Packard, Andover, MA, USA) equipped with harmonic imaging capabilities. A 2.5 MHz phased array probe was used to obtain standard 2D, M-mode, and Doppler images. Patients were examined in the left lateral recumbent position using standard parasternal and apical views. Images were digitized in cine-loop format and saved for subsequent playback and analysis. Views were analyzed by a single echocardiographer employing the software program of the echocardiography machine. Biplane global left ventricular systolic function was assessed in apical 4-chamber and 2-chamber views using the modified Simpson’s rule. Regional wall motion was assessed according to the standard 16-segment model as recommended by the American Society of Echocardiography [7]. Regional
wall motion was visually assessed for each segment individually, considering both endocardial excursion and systolic thickening, and each segment was graded according to the semiquantitative scoring system described by Knudsen et al. [8]. Segments with poorly defined endocardial borders for 50% or more of their length were considered non-visualized and assigned a score of 0 [9]. Wall thickening was assessed at a distance of at least 1 cm from the adjacent segment to minimize the effect of tethering [10].

Dobutamine stress echocardiography protocol

Dobutamine was administered by intravenous infusion starting at a dose of 5 μg/kg/min and raised incrementally every 3 min up to a maximum of 40 μg/kg/min, or until a study end point was reached. In patients not achieving 85% of their age-predicted maximal heart rate, atropine was administered intravenously in 0.25–0.5 mg increments up to a maximum dose of 2.0 mg, while dobutamine was continued.

End points for terminating the test were attainment of the maximum dose, greater than 85% of age-predicted maximal heart rate, echocardiographic detection of wall motion abnormality not present at baseline, symptoms judged to be unacceptable by the attending cardiologist, serious arrhythmia detected by electrocardiogram, systolic blood pressure >220 mmHg or diastolic blood pressure >120 mmHg or a decrease in systolic blood pressure >20 mmHg.

Standard views were recorded at baseline, during each stage of the infusion protocol, as well as during recovery. Visual assessment of wall motion and thickening was performed as before.

Definitions of response

Normal response to stress was defined as normal wall motion at rest with increase in wall thickening and excursion during stress. Ischemic response was defined as deterioration in segmental wall thickening and/or excursion in at least two contiguous segments during stress (increase in wall motion score by ≥1 grade). Left ventricular volumes were evaluated according to the biplane modified Simpson’s rule. Measurements were averaged from three cardiac cycles. TID ratio was defined as the ratio of left ventricular end-diastolic volume or end-systolic volume measured at peak stress, to that measured at rest (EDV ratio and ESV ratio, respectively).

According to the above definitions, we enrolled 20 consecutive patients with normal response (control group) who were subsequently evaluated to develop normal limits for TID ratio, and 40 patients with ischemic response (study group) that comprised 20 consecutive patients without TID (group A, TID ratio <1 for both EDV ratio and ESV ratio) and 20 consecutive patients with TID (group B, TID ratio >1 for EDV ratio and/or ESV ratio).

Coronary angiography

All patients in the study group underwent selective left and right coronary angiography using the standard technique, and the angiographic data were individually analyzed by an independent expert interventionalist, blinded to both the clinical and the echocardiographic findings. The procedure was performed within 2 weeks after the stress echocardiography study. Significant coronary stenosis (assessed by visual estimation) was defined as 70% or more luminal obstruction of at least one sizable epicardial coronary artery (measuring 2.5 mm or more in diameter), seen in two different projections, or at least 50% luminal obstruction of the left main coronary artery. Patients with significant stenosis of the left main coronary artery were considered to have two-vessel disease and those with significant stenosis of the left main coronary artery and right coronary artery were considered to have three-vessel disease. Patients with previous coronary artery bypass surgery were assessed regarding the patency of the grafts and the non-grafted sizable native vessels.

Statistical analysis

All continuous variables were presented as mean ± SD, if they were normally distributed. Differences in the normally distributed variables were assessed using the t-test and the paired t-test for dependent variables. Categorical variables were described with absolute and relative (percentage) frequencies. Comparisons between the three individual groups were performed using the unpaired t-test (parametric) and Mann Whitney test (non-parametric) for continuous variables, and Pearson’s χ²-test for categorical variables. Finally, to determine the criterion for abnormal TID ratio, we generated receiver operating characteristic (ROC) curves to identify the optimal cutoff value of TID ratio that best predicts three-vessel coronary artery disease. All tests were two-sided and a probability value of P < 0.05 was considered statistically significant. Analyses were performed
Table 1  Baseline characteristics of the whole cohort and the three individual groups.

<table>
<thead>
<tr>
<th></th>
<th>Total cohort (N = 60)</th>
<th>Control group (N = 20)</th>
<th>Group A (N = 20)</th>
<th>Group B (N = 20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.9 ± 13</td>
<td>49.7 ± 10</td>
<td>55.6 ± 6</td>
<td>53.5 ± 8</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Males</td>
<td>32 (53.3)</td>
<td>8 (40)</td>
<td>11 (55)</td>
<td>13 (65)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Diabetes</td>
<td>26 (43.3)</td>
<td>3 (15)</td>
<td>9 (45)</td>
<td>14 (70)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hypertension</td>
<td>38 (63.3)</td>
<td>5 (25)</td>
<td>15 (75)</td>
<td>18 (90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>17 (28.3)</td>
<td>4 (20)</td>
<td>7 (35)</td>
<td>6 (30)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>17 (28.3)</td>
<td>2 (10)</td>
<td>7 (35)</td>
<td>8 (40)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Previous MI</td>
<td>5 (8.3)</td>
<td>0 (0)</td>
<td>2 (10)</td>
<td>3 (15)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>5 (8.3)</td>
<td>0 (0)</td>
<td>2 (10)</td>
<td>4 (20)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>6 (10)</td>
<td>0 (0)</td>
<td>2 (10)</td>
<td>3 (15)</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean ± SD, while categorical variables are presented as numbers (percentage). MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

Table 2  Echocardiographic data of the three individual groups.

<table>
<thead>
<tr>
<th></th>
<th>Control group (N = 20)</th>
<th>Group A (N = 20)</th>
<th>Group B (N = 20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDV rest (ml)</td>
<td>91 ± 21</td>
<td>135 ± 42</td>
<td>130 ± 40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EDV stress (ml)</td>
<td>66 ± 22</td>
<td>124 ± 39</td>
<td>149 ± 40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESV rest (ml)</td>
<td>53 ± 13</td>
<td>84 ± 29</td>
<td>78 ± 35</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ESV stress (ml)</td>
<td>38 ± 15</td>
<td>82 ± 33</td>
<td>101 ± 40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EF rest (%)</td>
<td>54 ± 4</td>
<td>38 ± 12</td>
<td>35 ± 12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EDV ratio</td>
<td>0.73 ± 0.17</td>
<td>0.93 ± 0.16</td>
<td>1.17 ± 0.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESV ratio</td>
<td>0.72 ± 0.2</td>
<td>0.96 ± 0.15</td>
<td>1.38 ± 0.49</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

All variables are presented as mean ± SD. EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction.

Results

A total of 60 patients were enrolled in the current study, which comprised 20 patients with normal response to stress echocardiography (control group), 20 others with ischemic response without TID (group A), and 20 with ischemic response with TID (group B). Table 1 shows the baseline clinical characteristics of the whole cohort, as well as the three individual groups. The mean age of the whole study cohort was 52.3 ± 13 years, 32 (53.3%) being males. The three individual groups were statistically matched regarding age, sex, smoking, dyslipidemia, prior myocardial infarction, prior percutaneous coronary intervention, and prior coronary artery bypass surgery. However, patients in the control group were less likely to have diabetes mellitus as compared to those in groups A and B [3 (15%), 9 (45%), and 14 (70%), respectively, P < 0.001]. Moreover, patients in the control group were less likely to have hypertension as compared to those in groups A and B [5 (25%), 15 (75%), and 18 (90%), respectively, P < 0.01].

Table 2 shows the echocardiographic findings of the three individual groups. All ventricular volume measurements (both end-diastolic and end-systolic) were significantly higher in groups A and B as compared to the control group (P < 0.01 for all). Resting left ventricular ejection fraction was significantly higher in the control group as compared to groups A and B (P < 0.01). Both EDV ratio and ESV ratio were significantly higher in groups A and B as compared to the control group (P < 0.01 for both).

Fig. 1  Receiver operating characteristic (ROC) curves to identify the optimal cutoff value of transient ischemic dilation (TID) ratio that best predicts three-vessel disease. EDV, end-diastolic volume; ESV, end-systolic volume.
Table 3  Angiographic data of the two study groups.

<table>
<thead>
<tr>
<th></th>
<th>Group A (N = 20)</th>
<th>Group B (N = 20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-vessel disease</td>
<td>9 (45)</td>
<td>2 (10)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Two-vessel disease</td>
<td>6 (30)</td>
<td>7 (35)</td>
<td></td>
</tr>
<tr>
<td>Three-vessel disease</td>
<td>5 (25)</td>
<td>11 (55)</td>
<td></td>
</tr>
</tbody>
</table>

All variables are presented as numbers (percentage).

Analysis of the ROC curves identified the 1.12 cutoff value as the optimal cutoff value of TID ratio that best predicts three-vessel disease (Fig. 1). Using this cutoff value, the EDV ratio was able to predict three-vessel coronary artery disease with a sensitivity of 85%, specificity 72%, positive and negative predictive values of 80% and 85%, respectively. Meanwhile, the ESV ratio was able to predict three-vessel coronary artery disease with a sensitivity of 90%, specificity 84%, positive and negative predictive values of 85% and 89%, respectively.

Table 3 shows the angiographic findings of the two individual study groups (A and B). Three-vessel coronary artery disease was significantly more prevalent in group B as compared to group A [11 (55%) versus 5 (25%), respectively] while single vessel disease was more prevalent in group A as compared to group B [9 (45%) versus 2 (10%), respectively, P < 0.05]. The mean number of vessels affected by significant stenosis was 1.8 ± 0.83 in group A in comparison with 2.45 ± 0.69 in group B (P < 0.05).

Among group B, both EDV ratio and ESV ratio were higher in female patients (1.25 ± 0.11 and 1.58 ± 0.81, respectively) as compared to males (1.13 ± 0.17 and 1.28 ± 0.14, respectively).

The dobutamine stress echocardiography protocol was well-tolerated by all patients with no major side effects during or after the test. Moreover, no patient reported any clinical events during the period from the stress echocardiography study to the time of coronary angiography.

Analysis of intra-observer variability revealed a close correlation between repeated measurements of regional wall motion by the single operator, with a correlation coefficient r = 0.92.

Discussion

Left ventricular TID was originally demonstrated in myocardial perfusion imaging studies and was regarded as a useful parameter to detect extensive "balanced" myocardial ischemia in patients with normal myocardial perfusion scans [11]. Regardless of the agent used in myocardial perfusion imaging or the type of stress employed, TID has become accepted as a marker of severe and extensive coronary artery disease, as well as a predictor of poor outcome [5,6,12,13]. The mechanisms underlying TID are still an issue of controversy; however, likely explanations may include subendocardial ischemia, systolic left ventricular dysfunction, and actual physical left ventricular dilation [4].

Our results demonstrated that patients with TID induced by dobutamine stress echocardiography have a higher likelihood of having extensive (three-vessel) coronary artery disease. It was formerly shown that patients with three-vessel coronary disease (even with preserved systolic function) have a higher mortality at 5 years follow-up as compared to those with single-vessel disease [14]. In the study by Perez de Isla et al., TID predicted survival free of acute myocardial infarction and was an independent predictor of long-term prognosis by multivariate analysis [15]. These data suggest that the presence of TID should be integrated among the high-risk criteria of a positive dobutamine stress echocardiography, and should be carefully evaluated in every stress echocardiography study. Assessment of TID during dobutamine stress echocardiography provides a simple, inexpensive, readily available and non-invasive means of appropriately triaging patients at "high risk" to coronary angiography with potential revascularization.

Our data suggest a cutoff value of 1.12 for either the EDV ratio or the ESV ratio, to best predict the presence of multi-vessel coronary disease. In defining a cutoff value, an approach that better identifies "risk" would be the preferred one. Thence, we adopted the cutoff value that best discriminates the "higher risk" group. Using this criterion, the ESV ratio predicted multi-vessel disease with a high sensitivity and a relatively high specificity (90% and 84%, respectively). In the study by Yao et al., a cutoff value of 1.17 for left ventricular volume ratios, was considered abnormal and predicted underlying "severe and extensive" coronary artery disease with a high sensitivity (100%) yet, at the expense of a low specificity (54%) [4]. They employed treadmill exercise as a stress test in 61% of their patients, while dobutamine stress was used in only 39%. In myocardial perfusion imaging...
in patients with TID (1.38 in group B as compared with 0.72 in the control group) was much greater than the change observed for the mean EDV ratio (1.17 in group B as compared with 0.73 in the control group). Several myocardial perfusion imaging studies reported this finding [17—19]. Possible explanations include the physiologic demand for an increased cardiac output after stress which depends on both heart rate and stroke volume [17] and transient stress-induced left ventricular dysfunction [4].

It was evident from our findings that female patients had higher mean values of TID as compared to male ones (EDV ratio 1.25 ± 0.11 versus 1.13 ± 0.17, ESV ratio 1.58 ± 0.81 versus 1.28 ± 0.14). Two former myocardial perfusion imaging studies supported this finding [20,21]. The fact that women are less physically conditioned may account for this gender difference. A female’s heart has to dilate more during stress as compared to a male’s heart (as a compensatory mechanism). Yet, it might be merely ascribed to a technical error created by smaller absolute left ventricular volumes in women [20].

Left ventricular ejection fraction was significantly lower in groups A and B as compared to the control group (Table 2). However, it was comparable between groups A and B (37.7 ± 11.8 and 35.2 ± 12.5, respectively). Accordingly, patients without multi-vessel disease are less likely to develop TID even if they have impaired baseline left ventricular systolic function. Hence, it seems that TID depends chiefly upon the extent of myocardial ischemia rather than baseline ejection fraction.

Limitations of the study

Our findings are based on a single center study with a relatively small sample size of the cohort, a fact that makes it difficult to generalize our results to all patients undergoing dobutamine stress echocardiography. Multicenter studies using the same protocol and examining a larger number of patients are needed. Moreover, the study group (40 patients) was composed of symptomatic patients referred for evaluation by stress echocardiography. This referral bias may have contributed to a high prevalence of multi-vessel disease. Another limitation of the study is the lack of quantitative methods for measuring systolic thickening; instead, the operator adopted visual assessment only.

Conclusions

We conclude that the occurrence of TID in patients undergoing dobutamine stress echocardiography, is both sensitive and specific to predict underlying three-vessel coronary artery disease, and can be used reliably to triage patients to coronary angiography with potential revascularization. A TID ratio of 1.12 would provide the best cutoff value to identify this patient category. In this regard, ESV ratio appears more valuable than EDV ratio. Finally, female patients have higher TID indices as compared to males.

Acknowledgments

We deeply appreciate the faithful efforts and sincere collaboration of all members of staff of the echocardiography lab in Ain Shams University Hospital, who have rigorously participated to the production of this work.

References


studies, it was noted that the cutoff value of TID is variable for different protocols, thus each cutoff value is protocol specific and should not be directly extrapolated to all patients undergoing myocardial perfusion study [16]. Using a single cutoff value for two different stress protocols might be responsible for the low specificity reported by Yao et al.

In our series, the change in the mean ESV ratio in patients with TID (1.38 in group B as compared with 0.72 in the control group) was much greater than the change observed for the mean EDV ratio (1.17 in group B as compared with 0.73 in the control group). Several myocardial perfusion imaging studies reported this finding [17—19]. Possible explanations include the physiologic demand for an increased cardiac output after stress which depends on both heart rate and stroke volume [17] and transient stress-induced left ventricular dysfunction [4].
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