Dobutamine Stress Tissue Doppler for Detection of Myocardial Viability

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Abstract

Objective: Investigate the rule of Dobutamine stress Tissue Doppler in viability assessment.

Methods: 25 patients with coronary stenosis >50%, EF <45%, and SWMA's were included. Pulsed wave-Tissue Doppler were applied to basal and mid myocardial segments with measuring of S, E' and A' velocities at rest, low dose dobutamine (LDD: 10mic/Kg/min), and peak stress.

Results: After exclusions of apical segments, 200 segments were analyzed, 100 were normal, 79 hypokinetic and 21 akinetic by visual interpretation at rest. At LDD: 62 (78%) of hypokinetic segments showed improvement in contractility, the others were considered non viable. At peak stress: Hibernating segments developed biphasic response, continuous improvement or worsened while non viable segments showed no change.

Using Pulsed TD: At rest, akinetic segments had significantly lower S and E' velocities than hypokinetic ones (p<0.05). At LDD and peak stress, S was higher and E' was higher in hibernating than non viable segments (p<0.05). No difference in A' in all segments at different stages of stress.

Cutoff Values for Viability: An increase of S by 2.9cm/s and E' by 1.5cm/sec during LDDSB (sensitivity 90%, 96% and specificity 87%, 97% respectively).

Conclusion: LDD-Pulsed TDI is a reliable tool for detection of viability.

Key Words: Dobutamine stress echocardiography – Pulsed Tissue Doppler – Ischemic cardiomyopathy – Viability.

Introduction

CORONARY Artery Disease (CAD) remains a principal cause of morbidity and mortality worldwide [1]. It makes up more than half of all cardiovascular events in men and women <75 years of age [2].

In many patients with CAD, resting Left Ventricular (LV) dysfunction is a consequence of myocardial hibernation [3]. Detection of myocardial viability or hibernation is important in patients with ischemic cardiomyopathy. Restoration of blood flow to viable myocardium is associated with improved left ventricular function and improved patient prognosis [4].

A variety of non-invasive imaging techniques have been developed to detect viable myocardium in patients with ischemic heart failure. The different imaging techniques target different characteristics of viable myocardium [5].

Several studies demonstrated the potential role of tissue Doppler imaging during dobutamine stress echocardiography to quantify myocardial velocity and deformation, instead of or in addition to traditional evaluation of the Wall Motion Score Index (WMSI) [6-8]. However, its application during stress echocardiography remains controversial [9].

Aim of the work:

Investigate the rule of Dobutamine stress Tissue Doppler in viability assessment.

Patients and Methods

Patient selection and study design:

Prospectively, we enrolled 25 consecutive patients with known ischemic heart disease who were subjected to elective diagnostic coronary angiography. The study was performed from September 2011 to July 2013 in the Critical Care Department, Cairo University and Cardiology Department, Fayoum University.

Patients were considered eligible for inclusion if they had coronary stenosis >50%, Left Ventricular Ejection Fraction % (LVEF%) <45%, and...
presence of Segmental Wall Motion Abnormalities (SWMAs) at rest by echocardiography.

Excluded from this study patients with: Significant left main coronary artery stenosis, severe valvular lesions, serious atrial or ventricular arrhythmias, atrial fibrillation, bundle branch block, active ischaemia, non ischaemic cardiomyopathy, suspected or known aortic dissection or acute pulmonary embolism, those with severe systemic hypertension (more than 180/110mmHg), technically inadequate echocardiographic imaging and any other contraindications to dobutamine stress echocardiography.

Before inclusion, informed written consent was obtained from each patient after full explanation of the study protocol. Finally, the study protocol was reviewed and approved by the ethical committee. After full history, complete clinical examination, and routine laboratory investigations; all patients were subjected to the following:

Coronary angiography: Selective coronary angiography was performed with the standard Judkins approach. The equipment used was the digital Siemens Hicor 1000 system. Quantitative coronary angiography was considered the reference standard for the detection of coronary artery stenosis. Significant coronary artery stenosis was identified in the presence of a >50% reduction in lumen diameter.

Baseline echocardiographic assessment: Assessment of regional and global left ventricular systolic function was performed by trans-thoracic echocardiography. Patients were examined in the left lateral recumbent position using standard parasternal and apical views. Measurement of LV End-diastolic (LVED), and LV End-Systolic (LVES) diameters and calculation of LVEF% was obtained in M-mode parasternal view. Regional wall motion was assessed according to the standard 16-segment model recommended by the American Society of echocardiography [10].

Stress echocardiographic protocol:
All patients underwent DSE using a standard protocol [11] with an incremental dobutamine infusion rate of 5, 10, 20, 30, and 40µg/kg/min every 3 minutes and up to 1mg of atropine if the target heart rate (85% of the age-predicted maximal heart rate) was not achieved. Heart rate, blood pressure, 12-lead electrocardiography and symptoms during DSE were recorded at each DSE stage. Beta-blockers and calcium channel blockers (non-dihydropyridines) were discontinued at least two days prior to the test. Criteria for terminating the test were completion of the protocol, development of new WMA, severe chest pain, Systolic Blood Pressure (SBP) >220mmHg or Diastolic Blood Pressure (DBP) >120mmHg, symptomatic hypotension and serious ventricular or supraventricular arrhythmias. The examinations were performed in the left supine position with Siemens system equipped with TDI technology with 2.5MHz transducer. Standard views were recorded at baseline, low dose and high dose dobutamine. Images were digitized in cine-loop format and saved for subsequent playback and analysis.

The following was measured:
1- Wall Motion Score (WMS) was analyzed at rest and peak stress using a 4-point scale as follows: (1=normal or hyperkinesia, 2=hypokinesia, 3=akinesia and 4=dyskinesia). The WMSI was calculated by dividing the wall motion score by the number of segments. Normal contraction results in a WMSI of 1; a higher score index is indicative of wall motion abnormalities. Ischemic response defined as Dobutamine new or worsening wall thickening (or motion) abnormalities at any dobutamine (or atropine) stage in more than one segment of the same region.
2- Pulsed Tissue Doppler: Pulsed wave TD sampling velocities was done on eight myocardial segments (basal and mid septum, basal and mid lateral, basal and mid inferior and basal and mid anterior walls). Apical segments were not interrogated because previous work has shown myocardial Doppler velocity in these regions to be too low to accurately identify ischemia [12].

Systolic S wave (maximum systolic velocity of ejection phase), diastolic E’ wave (diastolic early filling velocity), and A’ wave (diastolic late filling velocity) measurements were performed individually for each segment, at baseline, low dose and at the end of dobutamine infusion. Measurements were obtained from three cardiac cycles and an average was taken. Cardiac cycles associated with extra-systolic, post-extra-systolic beats, or any other rhythm disturbances were excluded from analysis.

Statistical methods:
SPSS (Statistical Package for Social Sciences) version 12.0 was used for data analysis. Mean and standard deviation are descriptive values for quantitative data with median and range for non-normally distributed data. Student t-test and non-parametric t-test (Mann Whitney test) were used for comparing means of two independent groups and Kruskal Wallis ANOVA (analysis of variance)
for comparing means of more than 2 groups. Paired t-test and non parametric paired t-test (Wilcoxon signed rank test) was used for comparing means of two dependent groups. Chi-square-Fisher exact test were the tests for proportion independence. *p*-value is significant at 0.05 levels.

**Results**

**Patient characteristics:**

This study was conducted on 25 consecutive patients with known IHD who had significant coronary stenosis and impaired LV systolic function (Table 1). Represents their baseline characteristics.

**Angiographic data:**

The following table summarizes the angiographic results in the study group.

**Dobutamine stress echo:**

1- Stress endpoints and complications:

48% of patients needed atropine administrations. 64% reached target HR, chest pain developed in 20%, new or worsening WMAs in 8%, ST depression in 4%, VT in 4% and severe epigastric pain in 4%.

2- 2-D echocardiography:

200 segments were analyzed (100 normal, 79 hypokinetic and 21 akinetic) with WMSI=1.6±0.2 which reached 1.8±0.2 at peak stress.

The analysis was done at 2 stages:

- Low Dose Dobutamine (LDD): 62 of hypokinetic segments showed improvement in contractility at 10mic/Kg/min; which described as hibernating segments and all akinetic segments (21 segments) and the remaining 17 severely hypokinetic segments did not improve with LDD and described as non viable segments (total non viable segments =37).
- High dose dobutamine: Hibernating segments developed biphasic response, continuous improvement or worsened and non viable segments showed no change.

3- Tissue Doppler velocities:

A- S velocities:

At rest: Mean systolic velocity was 4.8±1.2 cm/sec in abnormal (dysfunctioning) segments with lower velocities in akinetic than hypokinetic segments (3.0±0.9 vs 5.4±1.4, respectively), *p*<0.05.

With stress: Statistically higher S velocities in hibernating than non viable segments at LDD and peak stress (LDD: 9.7±2.3cm/sec vs 3.1±0.9cm/sec and with peak stress 10.0±3.3cm/sec vs 3.3±1.4 cm/sec, respectively), *p*<0.05.

**Percentage difference:** It defines the degree of change in velocities between rest and stress and calculated as follow; (stress-rest/rest).

A statistical significance in percentage difference between rest and LDD (79%) and rest and peak stress (84.4%) in hibernating segments, (Table 3).

No statistical significance in percentage difference between rest and LDD (1.3%) or peak stress (9.3%) among non viable segments, (Table 3).

B- E’ velocities:

At rest: Mean E’ velocities in dysfunctional segments was 6.1±2.4cm/sec.

The reduction was more prominent in akinetic than hypokinetic segments (4.0±1.2cm/sec vs 6.5±2.2cm/sec, respectively) (*p*<0.05).

With stress: Statistically higher E’ velocities in hibernating than non viable segments at LDD and peak stress (LDD: 10.6±2.7cm/sec vs 4.1±1.9 cm/sec and peak stress 10.8±3.6cm/sec vs 4.4±2.1 cm/sec, respectively) (*p*<0.05).

**Percentage difference:** A statistical significance in percentage difference between rest and LDD (63.1%) and rest and peak stress (66.8%) in hibernating segments (Table 4). No statistical significance between rest and LDD (2.5%) or peak stress (11.9%) among non viable segments, (Table 4).

C- A’ velocities:

No significant difference between hypokinetic and akinetic segments at rest, LDD or peak stress (rest: 6.7±2.6cm/sec vs 5±1.6cm/sec, LDD: 8.6±3.6 cm/sec vs 5.4±1.6cm/sec and peak stress 8.5±5 cm/sec vs 5.4±1.9cm/sec, respectively), P. NS.

**Percentage difference:** No statistical significance in percentage difference between rest and LDD (27.9%) and rest and peak stress (66.8%) in hibernating or non viable segments.

4- Cutoff values for viability assessment:

Using ROC curves, the optimal cutoff value for S velocity was an increase of 2.9cm/s during LDD (90% sensitivity and 87% specificity), Fig. (1).

The optimal cutoff value for E’ velocity was an increase of 1.5cm/s during LDD (96% sensitivity and 97% specificity) in predicting recovery of myocardial function, Fig. (2).
Follow-up after revascularization:

We were able to follow 15 patients, 1 to 2 months post revascularization (12 patient underwent PCI and 3 patients underwent CABG) and were able to follow viability of dysfunctional segments in those patients.

- Before revascularization, the numbers of dysfunctional segments in those patients were 56 segments, 37 were described as hibernating and 19 segments were described as non viable segments. S and E’ velocities were statistically higher in hibernating segments than non viable segments (S: 4.3±1.3 vs 3.1±0.6 cm/sec E’: 6.4±2.2 vs 3.99±1.7 cm/sec).

- Post revascularization, the hibernating segments showed improvement of contractility with statistically higher S and E’ velocities than segments described to be non viable with LDD (S: 7.83±1.3 vs 3.36±0.8 cm/sec E’: 8.69±1.9 vs 4.36±1.3 cm/sec).

Regarding A’ there were no statistically significant difference between hibernating segments than non viable segments pre and post revascularization.

- Percentage difference:
  - Hibernating segments showed statistically higher percentage difference compared to non viable segments regarding S velocities (82.1% vs 8.1%, respectively), and E’ velocities (35.8% vs 9.3%, respectively) between pre and post revascularization regarding, (p:<0.05).
  - No statistical significance in percentage difference between hibernating and non viable segments (7.6% vs 4.2%, respectively) pre and post revascularization regarding A’ velocities, (p:<0.05).

Table (1): Baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Mean age (years)</th>
<th>Males</th>
<th>DM</th>
<th>HTN</th>
<th>Smoking</th>
<th>Dyslipidemia</th>
<th>Family history of IHD</th>
<th>LVEDD (cm)</th>
<th>LVESD (cm)</th>
<th>LVEF%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>53.8±11.3</td>
<td>21 (84%)</td>
<td>9 (36%)</td>
<td>7 (28%)</td>
<td>9 (36%)</td>
<td>8 (32%)</td>
<td>5 (20%)</td>
<td>5.9±3.6</td>
<td>3.8±3.2</td>
<td>44±4.2</td>
</tr>
</tbody>
</table>

Table (2): Angiographic data.

<table>
<thead>
<tr>
<th>Vessel affected</th>
<th>Number of affected vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel affected</td>
<td>24 (96%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of affected vessels</th>
<th>Single vessel</th>
<th>Two vessels</th>
<th>Three vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of affected vessels</td>
<td>12 (48%)</td>
<td>10 (40%)</td>
<td>3 (12%)</td>
</tr>
</tbody>
</table>

Table (3): Percentage difference in S velocities.

<table>
<thead>
<tr>
<th>TD</th>
<th>Hibernating segments</th>
<th>Non viable segments</th>
</tr>
</thead>
<tbody>
<tr>
<td>S (rest)</td>
<td>5.4±1.4</td>
<td>3.0±0.9</td>
</tr>
<tr>
<td>p&lt;0.05 A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S (LDD)</td>
<td>9.7±2.3</td>
<td>3.1±0.9</td>
</tr>
<tr>
<td>p&lt;0.05 A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S (peak stress)</td>
<td>10.0±3.3</td>
<td>3.3±1.4</td>
</tr>
<tr>
<td>p&lt;0.05 A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% difference LDD</td>
<td>79.0% (p&lt;0.05) B</td>
<td>1.3% (NS) B</td>
</tr>
<tr>
<td>% difference peak</td>
<td>84.4% (p&lt;0.05) C</td>
<td>9.3% (p: NS) C</td>
</tr>
</tbody>
</table>

Table (4): Percentage difference in E’ velocities.

<table>
<thead>
<tr>
<th>TD velocities</th>
<th>Hibernating segments</th>
<th>Non viable segments</th>
</tr>
</thead>
<tbody>
<tr>
<td>E’ (rest)</td>
<td>6.5±2.2</td>
<td>4.0±1.2</td>
</tr>
<tr>
<td>p&lt;0.05 A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E’ (LDD)</td>
<td>10.6±2.7</td>
<td>4.1±1.9</td>
</tr>
<tr>
<td>p&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E’ (peak stress)</td>
<td>10.8±3.6</td>
<td>4.4±2.1</td>
</tr>
<tr>
<td>p&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% difference LDD</td>
<td>63.1% (p&lt;0.05) B</td>
<td>2.5% (NS) B</td>
</tr>
<tr>
<td>% difference peak</td>
<td>66.8% (p&lt;0.05 ) C</td>
<td>11.9% (NS) C</td>
</tr>
</tbody>
</table>

A: Indicate significance between hibernating and non viable.
B: Indicate significance of % difference between rest and LDD.
C: Indicate significance of percentage difference between rest and peak stress.

A: Indicate significance between hibernating and non viable segments.
B: Indicate significance of percentage difference between rest and LDD.
C: Indicate significance of percentage difference between rest and peak stress.
Discussion

Coronary Artery Disease (CAD) is one of the top 10 leading causes of death all over the world (1) with the resulting Left Ventricular (LV) dysfunction an important complication. The distinction between viable and non-viable myocardium in patients with LV dysfunction is a clinically important issue among possible candidates for myocardial revascularization. Several available non-invasive techniques are used to detect and assess ischemia and myocardial viability. These techniques include echocardiography, radionuclide images, cardiac magnetic resonance imaging and recently myocardial computed tomography perfusion imaging [13].

Dobutamine stress echocardiography is widely used in the clinical setting because it is a safe and accurate method for the detection of myocardial viability; however, its subjective nature remains one of its major limitation [14]. Several studies demonstrated the potential role of tissue Doppler imaging during dobutamine stress echocardiography to quantify myocardial velocity and deformation, instead of or in addition to traditional evaluation of the Wall Motion Score Index (WMSI) [6-8]. However, its application during stress echocardiography remains controversial since no clear advantage in terms of both test interpretation and objective quantification has been demonstrated [9].

In our study we measured TDI velocities (S, E’ and A’) in dysfunctional myocardial segments as assessed by standard wall motion analysis at rest, during LDD and peak stress and we found that S and E’ velocities were statistically lower in akinetic than hypokinetic segments (p<0.05). This finding was consistent at rest, LDDD, or peak stress. Regarding A’, there was no statistically difference between all segments either at rest or stress.

Using ROC curves, the optimal cutoff values for viability assessment were an increase of 2.9cm/s in S velocity and 1.5cm/sec in E’ during LDDSE with sensitivity 90% and 96% and specificity 87% and 97%; respectively.

Our results were in agreement with Ageli et al., [15], who examined 41 patients with CAD and LV dysfunction (EF 40%), already scheduled for revascularization, underwent echocardiographic assessment of viability at rest and during LDD infusion (up to 10micro/kg/min), 2 days before and 3 months after revascularization. TDI was performed at rest and during LDDSE; S, pre-Ej (pre ejection) and diastolic velocities (E’, A’) were recorded at rest and at 10mic/kg/min dobutamine infusion. S, pre-Ej and E’ velocities increased significantly during LDDSE in viable segments, while A’ velocity did not change significantly. The optimal cutoff values for viability assessment were an increase of 0.5cm/s in S (80% sensitivity and 88% specificity), >0.6cm/s in pre-Ej (91 % sensitivity and 90% specificity), and 0.44cm/s E’ velocity (80% sensitivity and 81% specificity) during LDDSE. However, in their study the pre-Ej wave velocities had higher sensitivity and specificity than S velocity.

Similar results were also found by Schneider et al., [16]. They assessed myocardial viability in 56 patients with previous MI (mean EF 42%) using LDDSE (5mic/kg/min) combined with analysis of S wave by TDI. They found that increase of S >1cm/s during dobutamine stimulation allowed
the identification of viable myocardium with a sensitivity of 82% and specificity 82% (DSE: 77% and 80%).

Our results were in accordance with Bountioukos et al. [17], who demonstrated that no statistical difference regarding S in dysfunctional viable and nonviable regions at rest (6.3±1.9cm/s vs. 6.3±2.0cm/s, respectively, \(p=0.93\)), however, at LDD, S was significantly higher in viable regions (8.5±2.7 cm/s vs. 7.8±2.4cm/s, \(p=0.002\)). Viable regions had higher E’ at rest compared with nonviable regions (8.4±2.5cm/s vs. 7.5±2.8cm/s, \(p=0.003\)). They demonstrated that quantification of systolic velocity by TDI (at LDD) is markedly improved in viable myocardium, indicating the presence of contractile reserve in viable regions [20]. They also concluded that superior early diastolic filling at rest can also differentiate viable from nonviable myocardium, and that myocardial velocities were significantly higher in patients > or = 65 years old, both in viable and nonviable regions.

Other studies assessed the velocity at the mitral annular velocities as a marker for viability. Darahim et al. [18] examined 42 patients with previous MI referred for CA and revascularization. They used pulsed TD on 6 mitral annular sites (anteroseptal, posterior, postero septal, lateral, anterior and inferior walls) during LDD (5mic/kg/min) measuring velocities of pre-ejection wave (pre-Ej) and S wave at rest and during LDD. Echo was done after 1 month for follow-up. They found that the optimal cut-off value for viability assessment was an increase of 1.75cm/s in both pre-Ej wave and S wave during LDD. They concluded that viable LV myocardium could be identified easily and quantitatively with pre-Ej and S velocities at mitral annul during dobutamine infusion but the pre-Ej wave showed greater sensitivity and specificity than S wave, (66.15% and 67.94%, vs 56.92%, 64.12%), for the prediction of myocardial viability [18].

Ciampi et al. [19] studied sixty-four HF patients (age 67±9 years, 58% with an ischaemic aetiology, and a mean value of the ejection fraction 29±7%) underwent high-dose DSE. The mean value of the TD mitral annulus septal-lateral Sm change was analysed at rest and at peak DSE. All patients underwent also the cardiopulmonary exercise test. With a receiver operating characteristic analysis, a value of 2.02cm/s obtained as a stress-rest difference in a mean value of the peak systolic velocity of the mitral annulus (Sm) was the best value for diagnosing the myocardial contractile reserve [area under the curve 0.69 (95% CI 0.56-0.80), sensitivity 69% (95% CI 54-81), specificity 80% (95% CI 45-97)].

Schinkel A. et al. [20] who studied 70 patients with reduced LV function caused by chronic CAD to differentiate between stunned, hibernating, and scarred myocardium. TDI was done close to the mitral annulus; S and the difference in S between LDD and the resting values were assessed. At rest, S in stunned, hibernating, and scar tissue was, (6.3±1.8, 6.6±2.2, and 5.5±1.5cm/s, respectively) \(p=0.001\). With LDD infusion S was higher in stunned than hibernating than scar tissue (8.3±2.6 vs 7.8±1.5 vs 6.8±1.9cm/s, respectively, \(p=0.001\)). They concluded that quantification of TDI could differentiate between stunned, hibernating, and scar tissues.

In the previous three studies, mitral annular not regional velocities were evaluated. In spite of its simplicity and correlation with global LV function [21], the measured values might be influenced by the infarcted area or wall motion in the non-infarcted regions. Moreover, left atrial hemodynamics might influence mitral annular motion in patients with markedly elevated LV end diastolic pressure or left atrial dilatation. The differences in the mean velocities values, cutoff values, specificity and sensitivity of TD parameters between studies may be attributed to the degree of LV dysfunction and the dose of dobutamine used and the area used for obtaining measurements.

**Study limitations:** The small number of the study population could limit the strength of the findings obtained from the study, large scale studies are recommended. We were not able to follow all patients in our study post-revascularization, however the followed patients had evidence of improved systolic S and diastolic E’ velocities post revascularization. The recording of myocardial velocities during dobutamine stress is a time-consuming technique. The need to acquire all values on-line within a limited time margin at peak stress is a limitation of this modality. The measurement of myocardial velocities is sometimes affected by the translocation and rotation of the left ventricle throughout the cardiac cycle.

**Conclusion:**

Dobutamine stress TDI is a reliable, safe and accurate non-invasive test in evaluation of myocardial viability. We recommend its use to guide treatment options, estimate and improve clinical outcome.
References


