Dobutamine Stress Tissue Dopler For Detection Of Myocardial Viability

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Objective: To investigate the role of dobutamine stress Tissue Doppler in assessment of myocardial viability.

Methods: 25 patients with coronary stenosis > 50%, EF < 45%, and SWMAs 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: 10 mic/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 & E' velocities than hypokinetic ones ($P < 0.05$). At LDD and peak stress, S was higher & 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 2.9 cm/s & E' by 1.5 cm/sec during LDDSE (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) is considered a principal cause of morbidity and mortality worldwide [1] accounting for more than half of all cardiovascular events in less than 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 hibernation or viability or is crucial in patients with ischemic cardiomyopathy. Restoration blood flow to the viable myocardium is mostly associated with improved left ventricular function and more favorable patient outcome. [4]

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

The potential role of tissue Doppler imaging during dobutamine stress echocardiography for quantification of myocardial velocity and deformation, instead of or in addition to traditional evaluation of the wall motion score index (WMSI) has been demonstrated by different studies. [6-8] However, its application during stress echocardiography remains controversial. [9]

Aim of the work:

To investigate the role of dobutamine stress Tissue Doppler in assessment of myocardial viability.

Patients & Methods

Patient Selection and Study Design

Twenty five consecutive patients with known ischemic heart disease who were subjected to elective diagnostic coronary angiography were enrolled in this study. 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 180/110 mmHg), technically inadequate echocardiographic imaging and any other contraindications to dobutamine stress echocardiography.

Written consent was obtained from all patient after explanation of the research protocol. Full history, complete clinical examination, and routine laboratory investigations were assessed for all patients. All studied patients were subjected to the following:

Coronary Angiography: Selective coronary angiography as 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:

Regional and global left ventricular systolic function assessment 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 calcualation of LVEF% was obtained in M-mode parasternal view. Assessment of regional wall motion was done according to the standard 16-segment model recommended by the American Society of Echocardiography [10].

Stress Echocardiographic Protocol

DSE were studied in all patients using a standard protocol [13]. Dobutamine infusion with doses of 5, 10, 20, 30, and 40 µg/kg/min given in incremental rate every 3 minutes was applied to all patients and up to 1 mg of atropine was administered if the target heart rate was not achieved (85% of the age-predicted maximal heart rate). We recorded heart rate, 12-lead electrocardiography, blood pressure, as well as relevant symptoms at each DSE stage. Beta-blockers as well as calcium channel blockers were discontinued at least two days preceding the test. Terminating criteria for the test included: completion of the test protocol, occurence of severe chest pain, development of new WMA, elevation of either systolic blood pressure (SBP) > 220 mmHg or diastolic blood pressure (DBP) > 120 mmHg, serious ventricular or supraventricular arrhythmias or symptomatic hypotension and. The examinations were performed in the left supine position with Siemens system equipped with TDI technology with 2.5 MHz 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:

- ***Wall motion score Index (WMSI):***

Wall motion score (WMS) was analyzed at rest and peak stress in both groups using a 4-point scale as follows: (*normal or hyperkinesia: 1, hypokinesia: 2, akinesia:3 and dyskinesia:4)*. Calculation of the WMSI was done by dividing the wall motion score by the number of segments. Normal contraction is represented as a WMSI of 1; whereas a higher score index was indicative of wall motion abnormalities. Definition of ischaemic response was

achieved when dobutamine new or worsening wall thickening or motion abnormalities were developed at any dobutamine or atropine stage in more than one segment of the same region.

- ***Pulsed Tissue Doppler:***

Pulsed wave TD sampling velocities was done on eight myocardial segment (basal and mid septum, basal and mid lateral, basal and mid inferior and basal and mid anterior walls)[14]. The following tissue measurements for each interrogated segment included S wave *(maximum systolic velocity of ejection phase),* E' wave *(diastolic early filling) velocity, and* A' wave *(diastolic late filling velocity).*

All previous velocities were performed at rest and peak stress in *both groups* and were taken in a good signal cycle with averaging its value in 3 different cycles. We excluded cardiac cycles with rhythm disturbance extrasystolic or post extrasystolic beats.

Statistical methods:

Data was statistically described in terms of range and mean ± standard deviation (SD) for quantitative variables. Frequencies and relative frequencies were used for categorical variables. Comparison of quantitative variables was assessed by using Student t test for independent samples if they were normally distributed and Mann Whitney U test for independent samples if they were not normally distributed.

Chi square test was performed for comparing categorical data. Exact test was used instead when the expected frequency is less than 5.

Pearson correlation coefficient was used for correlation between continuous variables. ROC curve (Receiver operator characteristic) curve was used to determine the cut-off point in which highest sensitivity and specificity of studied parameters. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel version XP (Microsoft Corporation, NY, and USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 19 for Microsoft Windows.

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

Table 1. Baseline characteristics

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

Angiographic data

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

Table 2. Angiographic data

Vessel affected • LAD • LCX • RCA	 24 (96%) 11 (44%) 8 (32%)
Number of affected vessels • Single vessel • Two vessels • Three vessels	 12 (48%) 10 (40%) 3 (12%)

Dobutamine stress echo

- ***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 epigasric pain in 4%.

- ***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 10 mic/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.

- ***Tissue Doppler velocities***
- *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±2.3 cm/sec vs 3.1±0.9 cm/sec & with peak stress 10.0±3.3 cm/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%) & rest and peak stress (84.4%) *in hibernating* segments, table 3.

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

Table 3. Percentage difference in S velocities

TD	***Hibernating segments***	***Non Viable segments***
S (rest)	5.4±1.4	3.0±0.9
	P<0.05 [A]	
S (LDD)	9.7±2.3	3.1±0.9
	P<0.05 [A]	

S (peak stress)	10.0±3.3	3.3±1.4
	P<0.05 [A]	
% difference LDD	79.0 % (<0.05) [B]	1.3 % (NS) [B]
% difference peak	84.4 % (P<0.05) [C]	9.3 % (P: NS) [C]

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

- *E' velocities:*

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

The reduction was more prominent in *akinetic* than *hypokinetic segments (4.0±1.2 cm/sec vs 6.5±2.2 cm/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 & peak stress 10.8±3.6 cm/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%) & rest and peak stress (66.8%) *in hibernating* segments. table 4. No statistical significance between rest & LDD (2.5%) or peak stress (11.9%) among *non viable* segments, table 4.

Table 4. Percentage difference in E' velocities

TD velocities		
	Hibernating segments	*Non Viable segments*
E' (rest)	6.5±2.2	4.0±1.2
	P<0.05 [A]	
E' (LDD)	10.6 ±2.7	4.1±1.9
	P<0.05	
E' (peak stress)	10.8±3.6	4.4±2.1
	P<0.05	
% difference LDD	63.1 % (P<0.05) [B]	2.5 % (NS) [B]
% difference peak	66.8 % (P<0.05) [C]	11.9 % (NS) [C]

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

- *A' velocies:*

No significant difference between *hypokinetic* and *akinetic segments at rest, LDD or peak stress (rest: 6.7±2.6 cm/sec vs 5±1.6 cm/sec, LDD: 8.6±3.6*

cm/sec vs 5.q±1.6 cm/sec & peak stress 8.5±5 cm/sec vs 5.4±1.9 cm/sec, respectively), P. NS.

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

- *Cutoff values for viability assessment:*

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

The optimal cutoff value for E' velocity was an increase of 1.5 cm/s during LDD (96% sensitivity and 97% specificity) in predicting recovery of myocardial function, figure 2.

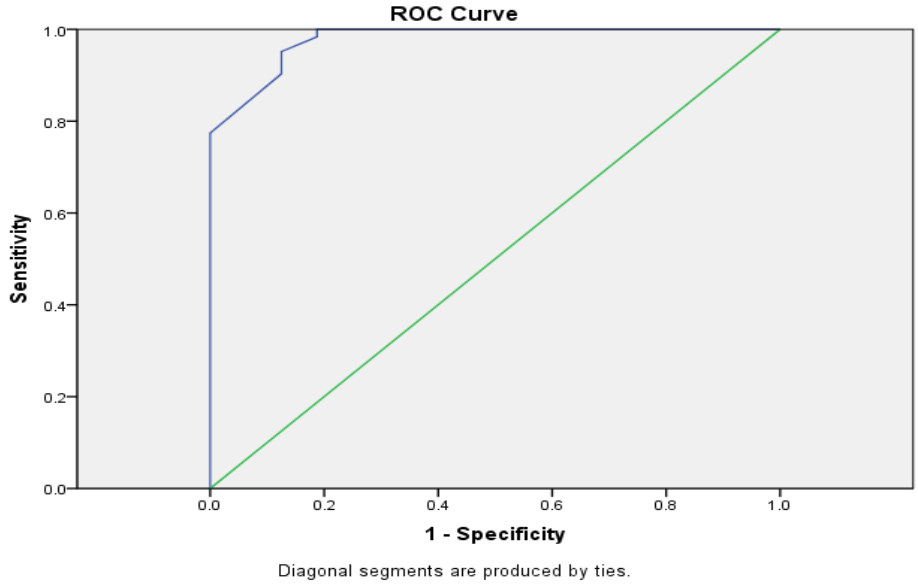

Figure 1. Sensitivity and specificity for ΔS in myocardial viability detection

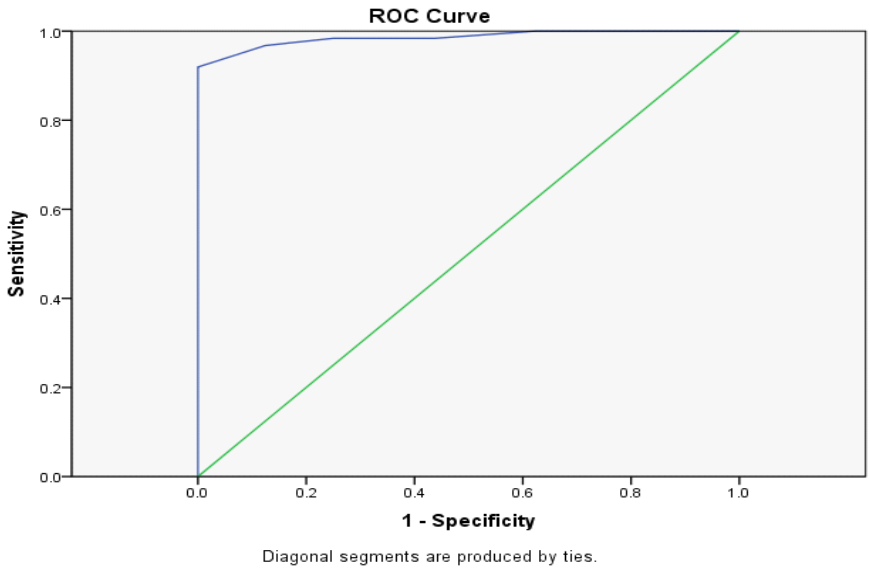

Figure 2. Sensitivity and specificity for ΔE' in myocardial viability detection

Follow up after revascularization

We were able to follow15 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 vs3.1±0.6 cm/sec E': 6.4±2.2 vs3.99± 1.7cm/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±1.3vs 3.36±0.8cm/sec E': 8.69±1.9 vs4.36±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).

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 as a common complication. The distinction between viable and non-viable myocardium in patients with LV dysfunction is a clinically important issue especially among patients planned for myocardial revascularization. Several non-invasive techniques are used to detect and assess myocardial viability and ischemia. These techniques include echocardiography and various cardiac imaging including radionuclide, magnetic resonance and myocardial computed tomography perfusion imagings (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 in quantification of myocardial velocity and deformation, instead of or hand in hand with the traditional evaluation of the wall motion score index (WMSI).(6-9)

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 2.9 cm/s in S velocity and 1.5 cm/sec in E' during LDDSE with sensitivity 90% and 96% & specificity 87% and 97%; respectively.

Our results were in agreement with *Ageli C. 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 10 micro/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 10 mic/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 cut-off values for viability assessment were an increase of 0.5 cm/s in S (80% sensitivity and 88% specificity), >0.6 cm/s in pre-Ej (91% sensitivity and 90% specificity), and 0.44 cm/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 C 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 >1 cm/s during dobutamine stimulation has 82% sensitivity and 82 specificity in identification of viable myocardium.

Our results were in accordance with *Bountioukos M et al* (17), who demonstrated that no statistical difference regarding S in dysfunctional viable and nonviable regions at rest (6.3 ± 1.9 cm/s vs. 6.3 ± 2.0 cm/s, respectively, P = 0.93), however, at LDD, S was significantly higher in viable regions (8.5 ±2.7 cm/s vs. 7.8 ± 2.4 cm/s, P = 0.002). Viable regions had higher E' at rest compared with nonviable regions (8.4 ± 2.5 cm/s vs. 7.5 ±2.8 cm/s, P = 0.003). They demonstrated that quantification of systolic velocity by TDI (at LDD) is markedly improved in viable myocardium, indicating that the viable regions have contractile reserve. ***[20]***

Other studies assessed the velocity at the mitral annular velocities as a marker for viability. *Darahim K 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, posteroseptal, 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 assessment of myocardial viability was 1.75 cm/s increase of 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 annuls 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 Q et al (19) studied sixty-four HF patients with 58% had an ischaemic aetiology and underwent high-dose DSE. And found that a value of 2.02 cm/s obtained as a stress–rest difference in a mean value of the peak systolic velocity of the mitral annulus (Sm) was the best for diagnosing the myocardial contractile reserve with 69% and 80% specificity.

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± 1.5 cm/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± 1.9 cm/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 is suggested to be influenced by the infarcted region 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 need to acquire all values in a limited time of the test is another limitation. 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.

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