Dobutamine Stress Tissue Doppler For Evaluation Of Myocardial Ischemia

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ABSTRACT

Objective: To study the role of dobutamine stress-tissue Doppler in detection of myocardial ischemia.

Material & Methods: 35 patients with known or suspected CAD were divided into: ischemic group (15 pts) with coronary stenosis ≥ 50%, normal echocardiography and control (20 patients) with normal coronary angiography and echocardiography. Dobutamine stress-Tissue Doppler was applied to basal and mid myocardial segments with measuring S, E' and A' velocities at rest and peak stress.

Results: At rest: No statistical difference in S between ischemic group and control (7.9±1.4 vs 9±2 cm/sec, respectively, P: NS). E' was statistically lower in ischemic group than control (8.7±2.1 vs 11.8±3.2 cm/sec, respectively, P<0.05).

With stress: the increase in S and E' were statistically lower in ischemic segments than control (S: 15.4±2.4 vs 23.5±4.4 cm/sec & E': 15.2±3.7 vs 23.3±4.9 cm/sec, respectively, P<0.05).

No difference between both groups regarding A' velocities at rest or peak stress.

Cut-off values for ischemia: Δ S ≤ 115% and Δ E' ≤ 104% (Δ the increase from rest to peak stress) with sensitivity 83%, 79% and specificity 84%, 79% respectively.

Conclusion: TDI provided objective quantitative information about myocardial ischemia.

Keywords: Dobutamine stress echocardiography, Pulsed-Tissue Doppler, coronary angiography, ischemia.

Introduction:

Coronary artery disease (CAD) is the third cause of death in the developing countries the leading cause of death in the developed countries accounting for about one third of all deaths in subjects over 35. [1] Along with history and risk factors, clinicians use noninvasive testing for early detection of CAD, risk stratification of the patients, and safely guide treatment options. [2, 3] Stress echocardiography is a widely used and reliable physiological non invasive technique for the detection of myocardial ischaemia with high sensitivities and specificities (80 and 85% respectively) in patients with CAD. [4-6] The major limitations of stress echocardiography are related to the subjective nature and experience in visual interpretation of endocardial excursion and myocardial thickening. Besides, it is documented that the human eye has limitations in the ability to resolve rapid, short-lived motion. [7] Currently much attention is being paid to new echocardiographic techniques such as tissue Doppler imaging (TDI). [8] One of the most important fields of the supposed application of TDI is an objective evaluation of myocardial contraction. [9, 10] TDI allows the quantification of intramural myocardial velocities by the detection of consecutive phase shifts of the ultrasound signal reflected from the contracting myocardium. [11]

Aim of the work:

To investigate the role of dobutamine stress-tissue Doppler in detection of myocardial ischemia.

Patients & Methods:

Patient Selection and Study Design

Prospectively, we enrolled 35 consecutive patients with known or suspected to CAD who were subjected to elective diagnostic coronary angiography and divided into: ischemic group (15 pts) with coronary stenosis ≥ 50%, normal echocardiography and control (20 patients) with normal coronary angiography and echocardiography. The study was performed from September 2011 to July 2013 in the Critical Care Department, Cairo University and Cardiology Department, Fayoum University.

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.

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 calcualation 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 [12].

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.

Vascular territories: Vascular territories of the left ventricular wall segments were assigned according to the following schema: Left anterior descending artery (LAD): basal and mid anteroseptal, basal and mid anterior walls mid posterior septum, the entire apex;Left circumflex artery (LCx): basal and mid lateral and posterior walls; Right coronary artery (RCA): basal and mid inferior walls and basal posterior septum.

- ***Tissue Doppler imaging (TDI):***

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. The percentage of difference from rest to peak stress was determined. Using ROC curves, the optimal cutoff values for ischaemia assessment were determined.

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 35 consecutive patients with known or suspected CAD subjected to elective diagnostic coronary angiography. Table 1 represents their baseline characteristics

Table (1): Baseline characteristics

	Control group	***Ischemic group***	***P***
Mean Age (y.)	٩.٤±٤٩	١١.٦±٥٥	NS
Males	(%٥٠) ١٠	(%٦٦) ١٠	NS
Females	(%٥٠) ١٠	(%٣٣) ٥	NS
DM	(%٤٠) ٨	(%٥٣) ٨	NS
HTN	(%٣٠) ٦	(%٥٣) ٨	٠.٠٥>
smoking	(%٢٥) ٥	(%٤٧) ٧	٠.٠٥>
Dyslipidaemia	(%٢٠) ٤	(%٣٣) ٥	NS
IHD	(%٢٠) ٤	(%٣٣) ٥	NS
FH	(%٢٥) ٥	(%٢٧) ٤	NS
LV ED (cm)	4.8± 2.1	4.8± 2.9	NS
LV ES (cm)	2.9± 1.9	2.8± 1.6	NS
EF (%)	63.8±6.2	60.4±5.7	NS
Rest RWMA	1	1	NS
Stress RWMA	1	1.47±0.19	<0.05
Resting HR(/min)	75.4±13.9	65.7±13.5	NS
Target HR(/min)	٧.٨±١٤٥	٩.٦±١٤٠.٥	NS
peak HR(/min)	٧.٤±١٤٧	١٣.٩±١٤٠.٦	NS
Resting SBP(mmgh)	١٢±١٢٢.٧	١١.١±١٢٦.٦	NS
peak SBP(mmgh)	١٠.٤±١٢٦.٥	٢٢.٧±١٤٢	NS
Resting DBP(mmgh)	٦.٩±٧٢	١١.٨٠٢±٧٠	NS
Peak DBP(mmgh)	٩.٤±٧٤	١١.١±٨٢.٣	NS

Angiographic data

The angiographic results in the ischemic group are summarized in table (2).

Table (2): Angiographic data

Vessel affected	
• LAD	*11 (73%)*
• RCA	*7 (47%)*
• LCX	*3 (20%)*
Number of affected vessels	
• Single vessel	10 (67%)
• Two vessels	4 (27%)
• Three vessels	1 (7%)

Dobutamine stress echo:

- *Stress endpoints and complications:*

Regarding group II 53% of patients needed atropine administrations, 60% reached target HR, chest pain developed in 27%, new or worsening WMAs in 8%, ST depression in 13%, severe hypertension in 6.7%, dyspnea in 5% and PVCs in 7%.

Results:

Tissue Doppler analysis:

At rest: No statistical difference in S between ischemic group and control (7.9±1.4 vs 9±2 cm/sec, respectively, P: NS). E' was statistically lower in ischemic group than control (8.7±2.1 vs 11.8±3.2 cm/sec, respectively, P<0.05), table (3).

With stress: the increase in S and E' were statistically lower in ischemic group than control (S: 15.4±2.4 vs 23.5±4.4 cm/sec & E': 15.2±3.7 vs 23.3±4.9 cm/sec, respectively, P<0.05), table (3).

On the contrary there was no significant difference between the 2 groups regarding A' velocity with rest *(ischemic group:* 9.3±2*cm/sec, vs control group:* 9.5±2.2*cm/sec respectively P:* NS) or stress *(ischemic group: 13±3cm/sec vs control group I: 12.5±5.5 cm/sec, respectively; P: NS)*, table (3).

Percentage differences were calculated as the changes in global myocardial systolic and early diastolic velocities from rest to peak stress; (peak stress-rest/rest values). It was all significantly lower in ischemic group when compared control group follow *(S: 94.9% vs 161.2% & E': 74.3% vs96.7%)*, table (3).

Using ROC curve, the cutoff values with best validity criteria (sensitivity and specificity) was determined for each TDI parameter for prediction of obstructive CAD in patients, Cut-off values for ischemia: Δ S $\leq$ 115% and Δ E' $\leq$ 104% (Δ the increase from rest to peak stress) with 83% ,79% sensitivity and

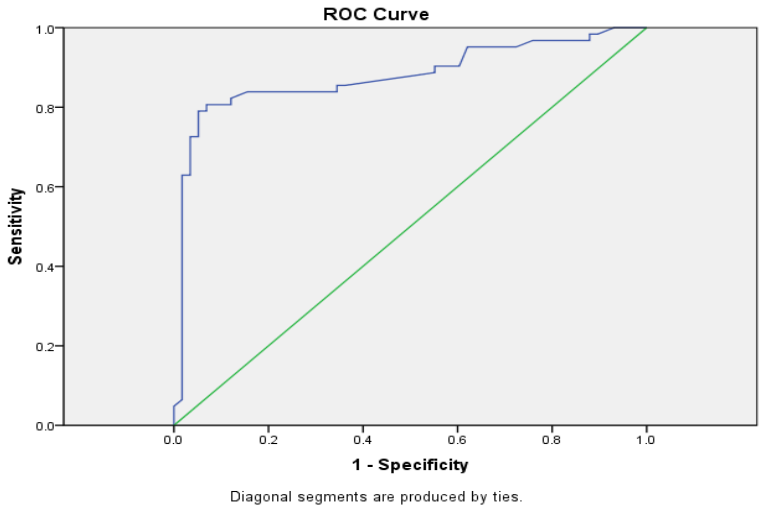
84%, 79% specificity respectively.) (i.e.: an increment (Δ changes) less than 115% in S or 104% in E from rest to peak stress identified CAD), table (4), fig 1 & fig 2.

Table (3): Myocardial velocities response to dobutamine stress

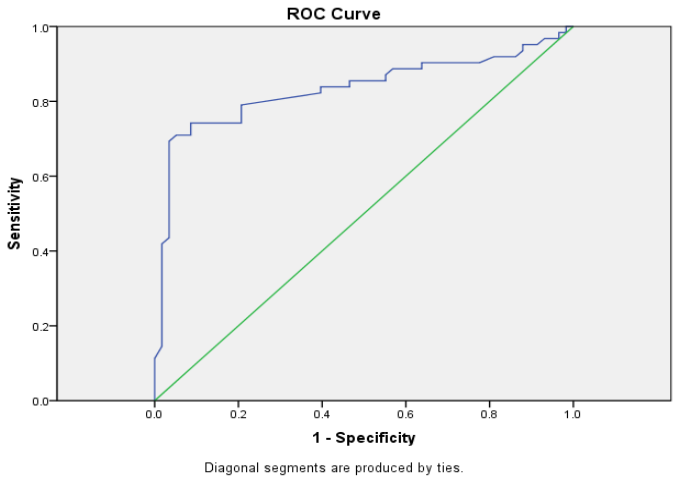
velocities		***Control Group***	***Ischemic Group***	***P***
S (cm/sec)	Rest	٢±٩	١.٤±٧.٩	NS
	Stress	٤.٤±٢٣.٥	٢.٤±١٥.٤	٠.٠٥>
	% difference	161.2 %	94.9 %	<0.05
E' (cm/sec)	Rest	٣.٢±١١.٨	٢.١±٨.٧	٠.٠٥>
	Stress	٤.٩±٢٣.٣	٣.٧±١٥.٢	٠.٠٥>
	% difference	% ٩٦.٧	% ٧٤.٣	٠.٠٥>
A' (cm/sec)	Rest	٢.٢±٩.٥	٢±٩.٣	NS
	Stress	12.5±5.5	٢.٧± .١٣	NS
	% difference	30.1 %	% ٤٠.٩	NS

Table (4): Cutoff values of tissue Doppler parameters in diagnosis of CAD

	ΔS	ΔE'
Cutoff value	115%	104%
Sensitivity	83%	79%
Specificity	84%	79%



detection ischemia ΔS in myocardial sensitivity and specificity for :(Figure (1



detection ischemia ΔE' in myocardial sensitivity and specificity for :(Figure (2

Discussion:

Our study was designed to investigate the role of quantitative information obtained using TDI during DSE in detection of myocardial ischemia.

In our study we found that TDI is a promising technique could used in quantification of myocardial ischaemia when used during DSE and help us to detect the appropriate cut off values during peak stress that differentiate between patients with obstructive (group II) and normal or non obstructive (group I) CAD (ΔS ≤ 115% and for ΔE ≤104%).

The following 3 studies (*Elnoamany M. et al,Zagatina A. et al and MYDISE Study)* were concordant with our study regarding methodology (they assessed velocities at different myocardial segments) and results; with some differences as described below:

Elnoamany M. et al in 2011examined 46 diabetic patients with suspected CAD underwent DSE with TDI and CA was the standard reference. They found that global S and global E' were significantly lower in diabetics with positive CA (>50%) compared to diabetics with negative CA at peak stress (11.3 ± 3.7 cm/sec vs 14.5 ± 2.2 cm/sec, $p < 0.01$) and (11.3 ± 1.6 cm/sec

vs. 13.1 ± 2.1 cm/sec, $p<0.01$) respectively. The cutoff values for global S and global E' to detect obstructive CAD in diabetics were an increment (Δ changes) less than 0.56 in S or 0.26 in E' from rest to peak stress identified CAD with 78.8 %, 89.3% sensitivity and 94.7%, 90.7% specificity respectively[15]. The difference in the mean velocities and cut-off values for ΔS and Δ E' between their study and our study was attributed to type of studied population (they studied diabetics only) and the methods of the statistical analysis (they assessed velocities globally), however in our study, myocardial segments were analysed according to regional wall motion abnormalities (RWMAs) which might be better estimation of segmental ischaemia.

Zagatina A. et al in 2007evaluated regional systolic and diastolic myocardial functions of 123 patients by pulsed TDI in eight segments (basal and mid segments of septum, lateral, inferior and anterior walls) during *exercise stress testing*, and described that patients with LAD and LCx disease without previous MI had lower values of post stress than normal patients. They found that the best discriminators for diseased LAD was post stress S_{mean} (mean systolic) velocity in basal anterior wall segment which was more lower in stenosed LAD group than normal LAD group (3.39 cm/s ± 1.16 vs 5.55 cm/s ±1.42, respectively, cut-point 4.9 cm/s, P<0.05) and the best discriminators for diseased LCx group was post stress S_{mean} in mid lateral wall which was more lower in stenosed LCx group than normal LCx group (3.01 cm/s± 1.25 Vs 5.34cm/s± 1.81, respectively , cut- point 3.1 cm/s, P<0.005,).There were no criteria for the detection of RCA disease in this study.[16] The difference in the values between this study and our study was related to using different stressor (they used exercise but we used dobutamine), inability to asses RCA related segments in their study (we assessed all territories in our study).

MYDISE Study in 2003 was the first multicenter study assessed TDI applied to DSE. The study enrolled 289 patients separated in 3 groups: group 1 (n = 92) patients with normal coronary arteries, group 2 (n = 48) patients with

known CAD and group 3 (n = 149) consecutive patients with suspected CAD and compared the results with CA. They acquired tissue systolic velocities during dobutamine stress, and measured myocardial responses by off-line analysis of 11 LV (basal posterior, mid posterior, and mid anterior septum, basal septal, basal anterior, basal lateral, and basal inferior, mid septal, mid anterior, mid lateral and mid inferior segments), five segments (apical segments and basal anterior septum) were not used because off-line velocities in these segments are unreliable). [17]

They demonstrated that, at peak stress, patients with CAD reached a lower PSV (peak systolic velocity) than did normal subjects (PSV increased >100% in healthy subjects compared with 50-75% in patients with CAD).They used logistic regression models for statistical analysis, using systolic velocities at maximal stress adjusting for independent correlations directly with heart rate and inversely with age and female gender [17]. Our study was better than MYDISE study as they neglected the effect of stress on diastolic velocities and they used a very difficult statistical technique to reach the cutoff values (logistic regression models).

The following 4 studies (*Sharif D. et al, Rosenstein U. et al, Badran HM et al, and Jelena et al)* were matched with our study regarding results but they assessed TD velocities at mitral annulus not at myocardial segments as described bellow:

Sharif D. et al in 2011 examined 50 subjects with suspected CAD and chest pain, using DSE, as well as TDI at mitral annulus at the septal, lateral, inferior, anterior, posterior regions and the proximal anteroseptal region from the apical views, before and immediately after DSE. They found that systolic velocity in normals was higher than in those with WMA (19.2 ± 3.8 cm/sec vs 14.6 ± 2.5 cm/ sec, P < 0.0003). [18]

Rosenschein U. et al in 2011studied 59 subjects, (15 with RWMA), underwent DSE and measurement of annular systolic displacements and

velocities before and immediately after DSE and described that no significant difference in annular systolic velocity at rest in those with and without WMA, (9.7 ± 1.8 cm/sec vs 11.25 ± 2.7 cm/sec, P>0.05) and in both groups the velocity increased after DSE but velocities were lower in those with WMA than those without WMA, (14.5 $\pm$ 4.5 cm/sec vs 17.8 $\pm$ 3.2 cm/sec, p = 0.025).[19]

Badran HM et al in 2007 studied 62 patients with left bundle branch block (LBBB) with suggested CAD underwent DSE, in addition to wall motion analysis, pulsed TD sampling of mitral annulus was performed at rest and peak stress. They found that no significant difference between LBBB with CAD and LBBB without CAD in global WMSI at rest. In the LBBB with CAD group, S velocity increased during peak stress to a smaller extent (rest: 6.3±1.1& stress: 7.2 ±2.0 cm/s, % difference: 24%, P <0.03) than in non CAD group (rest: 6.8 ±1.0& stress: 9.6 ±2.7 cm/s, % difference 46% P <0.01). Similarly, E' velocity increased to a lesser extent in CAD group (ΔE'1.6 ±1.7 vs 2.8 ±1.7 cm/s, 25% vs 42%, P <0.0001).There were no significant difference in A' between LBBB and control groups. They concluded that S and E' velocities with DSE allows a quantitive diagnostic benefit in the detection of CAD in patients with LBBB where subjective wall motion analysis failed.[20]

Jelena et al in 2004examined 60 patients without previous MI who underwent DSE and pulsed TD at the mitral annulus. S and E' were measured at rest and during stress and demonstrated a reduced increase of Sand E' in ischaemic group in comparison with non ischaemic segments during stress (S: 8.0→12.7 vs 9.3→16.4 cm/s, E': 6.5→10.2 vs 7.9→13.2 cm/s, P < 0.05) [21]. The difference in velocities values between our study and the previous4 studies was related to the measurement of velocities at mitral annulus and not at different segments (neglecting heterogeneity of segmental ischaemia).Another difference with *Badran HM. et al* that they studied only patients with LBBB.

Theodore P et al reported in 2007 that tissue Doppler velocities are reduced in ischemia and infarction. Systolic tissue velocities increase with dobutamine stimulation in the normal subject. This response is blunted in areas with induced ischemia and described that changes in systolic tissue velocity during dobutamine stress may help to identify false positive WMA. [22]

Our results were not matched with *Celutkiene J. et al* in 2012 who studied 151 patients with known or suspected CAD or symptomatic chest pain, who underwent DSE (excluding patients with previous MI). S, post-systolic, E' and A', strain and strain rate parameters were obtained at rest and at peak dobutamine challenge. Coronary angiography was chosen as reference method. They failed to find single powerful quantitative parameter applicable in each myocardial segment for prediction of coronary stenosis. They concluded that visual assessment are more accurate than strain/strain rate markers and single velocity in the diagnosis of CAD. [23]

Study Limitations:

Although CA is widely accepted as the reference standard, the relationship between physiological reduction of coronary flow and stenosis severity is markedly variable. Hence other methods (like radionuclide, FFR…) providing information about the perfusion of myocardium may be more accurate than CA in identifying ischaemic regions. The limited number of patients is another limitation of this the study. Rotation as well as apicobasal movement of the heart may affect the assessment of regional function. Exclusion of myocardial apical segments during the study. The recording of myocardial velocities during dobutamine stress echo was time consuming technique. Offline analysis of tissue velocities may be a solution. Our results were obtained in patients in sinus rhythm, and they will need to be tested separately in patients with atrial fibrillation.

Conclusions:

Tissue Doppler imaging is a promising objective technique allowing accurate quantification of *ischemia* induced regional diastolic and systolic dysfunction when used during dobutamine stress echo. Generally, the addition of tissue Doppler to dobutamine stress echo has the advantage of making the procedure easy, quantitative, with high sensitivity, specificity, and reproducibility than standard WMSI analysis alone.

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