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ORIGINAL ARTICLE

Diagnostic value of dobutamine stress Doppler tissue imaging in diabetic patients with suspected coronary artery disease

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KEYWORDS

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Abstract *Background:* Coronary artery disease (CAD) is often silent in diabetic patients, and it is typically in advanced stages of development by the time it manifests. Various forms of stress testing have been investigated to detect obstructive CAD in diabetes mellitus.
Objectives: To assess the diagnostic value of dobutamine stress pulsed-wave Doppler tissue imaging (DTI) compared with standard wall motion analysis in detection of myocardial ischemia in diabetic patients with suspected CAD.
Methods: The study comprised 46 diabetic patients with suspected CAD who underwent dobutamine stress echocardiography (DSE) with DTI within 4 weeks before coronary angiography (CA). Dobutamine infusion started at 5 μ/kg/min and increased up to 40 μ/kg/min with additional atropine during submaximal heart rate responses. In addition to wall-motion score index (WMSI) analysis, pulsed-wave DTI examination of basal and mid segments of posteroseptal, lateral, anterior, inferior and anteroseptal walls was performed. Myocardial velocities were measured at rest in the apical 4, 3 and 2-chamber views. The measurements were repeated at low dose (10–15 μ/kg/min) and at peak stress (40 μ/kg/min). DTI measurements included peak systolic velocity (*S*), peak early diastolic velocity (*E*) and peak late diastolic velocity (*A*) and the results were compared to WMSI

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analysis. Patients were classified into two groups according to CA results; group (I) diabetics with positive CA ($n = 27$) and group (II) diabetics with negative CA ($n = 19$).

Results: There was no significant difference between the two groups in duration of diabetes, global WMSI at rest or the Δ changes (stress-rest/rest) of WMSI ($p > .05$). Global S and global E were significantly lower in group I compared to group II at peak stress (11.3 ± 3.7 cm/s vs. 14.5 ± 2.2 cm/s, $p < 0.01$) and (11.3 ± 1.6 cm/s vs. 13.1 ± 2.1 cm/s, $p < 0.01$) respectively. The cutoff points for global S and global E to detect obstructive CAD in diabetics were 11.3 cm/s and 11.2 cm/s respectively with 75.7%, 73.4% sensitivity and 94.7%, 89.47% specificity respectively. 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. The accuracy of DTI parameters during peak stress was higher than WMSI analysis (sensitivity 74.1% vs. 59.3% and specificity 90% vs. 79%, $p < 0.01$ for each). In multivariate regression analysis, only ΔS and ΔE were independent predictors of obstructive CAD in diabetics (odd ratio: 36.16, 95% CI, 1.34–532.01 and 63.77, 95% CI, 3.19–721.47) respectively.

Conclusion: Quantitative analysis, using DTI during DSE, adds new dimension in diagnosis of myocardial ischemia. It is more sensitive, specific, accurate and reproducible compared with standard wall motion analysis for recognition of significant CAD in diabetic patients.

1. Introduction

Diabetes mellitus (DM) has recently been classified as a major independent risk factor for development of coronary artery disease (CAD). Epidemiologic data also indicate that, patients with diabetes have increased cardiovascular morbidity and mortality.[1] Diabetic patients without previous myocardial infarction have outcomes similar to those of nondiabetic patients who had a prior infarction. These data support aggressive risk factor modification and early noninvasive identification of coronary artery disease in diabetic patients.[2]

Exercise electrocardiography (ECG) is the standard noninvasive technique used for diagnostic and prognostic assessment of nondiabetic patients with known or suspected CAD.[3] In diabetic patients the accuracy of exercise ECG may be lowered as a result of several factors such as blunted response of blood pressure and heart rate with exercise, previous silent infarctions, high frequency of conduction abnormalities, left ventricular hypertrophy, and reduced exercise capacity resulting from peripheral vascular disease.[3] Because of the reduced diagnostic accuracy of exercise ECG, exercise or pharmacologic stress with myocardial perfusion scintigraphy has been recommended for diagnostic and prognostic assessment of diabetic subjects.[4]

In nondiabetic subjects, stress echocardiography has been found to enhance diagnostic and prognostic accuracy compared with exercise ECG.[5] The absence of ischemia on a stress echocardiogram identifies patients at low risk for future cardiovascular events.[6]

Doppler tissue imaging (DTI) is a relatively recent noninvasive technique that records myocardial wall motion velocities during different phases of the cardiac cycle. It evaluates global and regional systolic and diastolic LV function.[7]

The combination of pulsed-wave tissue Doppler (PWDTI) during dobutamine stress echocardiography (DSE) may provide quantitative component to myocardial function assessment by measuring the contraction and relaxation velocities of myocardial fibers from the base to the apex.[8–11]

2. Aim of the work

To assess the diagnostic value of dobutamine stress pulsed-wave DTI compared with standard wall motion analysis in detection of myocardial ischemia in diabetic patients with suspected CAD.

3. Patients and methods

3.1. Study population

The present study included 46 patients with known history of DM. It was performed prospectively in Menoufyia University Hospital in the period from June 2007 to February 2009.

The study was approved by the appropriate Institutional Review Board and Institutional Ethical Committee for Human Research. All study subjects provided written informed consent regarding study procedures.

Diabetes mellitus (DM) was diagnosed according to World Health Organization (WHO) and the American Diabetes Association (ADA)[12–14] as fasting blood glucose ⩾126 mg/dL (⩾7.0 mmol/L) or 2 h post-load plasma glucose ⩾200 mg/dL (⩾11.1 mmol/L) or random plasma glucose ⩾200 mg/dL.

3.2.1. Inclusion criteria

The study included all diabetic patients who have one or more of the following criteria:

- Known diabetic patients with 15 years duration in Type I or 10 years duration in Type II or 5 years with one or more risk factor for CAD.[15]
- Resting ECG changes suggestive of ischemic heart disease.
- Positive exercise stress ECG.
- Regional wall motion abnormalities in resting echocardiography.

3.2.2. Exclusion criteria

Patients with one or more of the following were excluded from the study: (1) prior history of acute coronary syndrome; (2)

valvular heart disease; (3) suspected or known aortic dissection; (4) acute pulmonary embolism; (5) acute myocarditis, endocarditis; (6) severe systemic hypertension (more than 180/110 mmHg); (7) pregnancy; (8) hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy; (9) ventricular aneurysm; (10) serious arrhythmias.

3.2.3. For each patient the following was done

1. Detailed history taking.
2. Full clinical examination.
3. Standard 12-lead resting ECG.
4. Complete two-dimensional echocardiographic examination was done using Acuson XP10 C (Acuson, Mountain view, Calif) system equipped with DTI technology with 2.5 MHz transducer. Examination was performed in the left lateral decubitus position for:

   A. Measurement of wall thickness, dimensions, ejection fraction and resting wall motion abnormality.
   B. Dobutamine stress echocardiography.

Dobutamine stress echocardiography (DSE) requires two-dimensional echocardiography with Doppler and an infusion pump to deliver dobutamine. The area where DSE is performed is equipped with resuscitation equipment (defibrillator, endotracheal intubation, etc.).[16]

3.2.4. Preparation for examination

The patients abstain from all oral intakes for at least 3 h before the procedure. β-Blockers were withheld 48 h before testing. The procedure as well as side effects and potential complications were explained to the patient. If baseline echocardiographic images are adequate for assessment of regional wall motion, an intravenous cannula was placed in an arm vein for administration of medications. An infusion solution that consists of 100 mg of dobutamine in 100 mL of 5% dextrose was prepared, and the appropriate infusion rates in milliliters per minute, based on the patient's body weight, to provide dosages from 5 μg/kg/min were determined. Atropine (1 mg/10 mL) was available if needed to increase the heart rate. The short-acting β-blocker, propranolol was available to be administrated, if necessary, to reverse the β-adrenergic effects of dobutamine. Nitroglycerin was available for sublingual administration as needed. Lidocaine hydrochloride was also available for treatment of ventricular arrhythmias.[16]

3.2.5. Examination procedure

Dobutamine was administrated intravenously by an infusion pump at a starting dosage of 5 μg/kg/min. At 3-min intervals, the dosage is increased to 10, 20, 30, and 40 μg/kg/min until a predetermined endpoint was reached. If neither target heart rate (85% of age-predicted maximal heart rate) nor any of the other endpoints was reached, the infusion rate was increased up to 50 μg/kg/min, or atropine was administrated intravenously. A dose of 0.25–0.5 mg of atropine was repeated at 1 min intervals to a maximal dose of 2 mg or until an endpoint was reached and dobutamine infusion is continued during atropine administration.[17] Throughout the dobutamine infusion the ECG was continuously monitored and recorded at 1 min intervals and BP is recorded every third minute. End-points for interruption of the test were[11]: (1) achievement of target heart rate; (2) maximal dose of both dobutamine and atropine; (3) extensive new wall motion abnormalities; (4) horizontal or downsloping ST-segment depression (0.2 mV 80 ms after the J-point compared with the baseline); (5) severe angina; (6) symptomatic reduction in systolic blood pressure >40 mmHg from baseline; (7) hypertension (blood pressure $>240/120$ mmHg); (8) significant arrhythmias or (9) any serious side effect regarded as being due to dobutamine infusion.

3.2.6. Doppler tissue imaging (DTI)

Pulsed-wave DTI examination was performed after activation of the DTI mode of the same machine. The gain was set to an optimal level to minimize noise. A 5 mm sample volume was used and Doppler signals were recorded at sweep speed 100 mm/s.

The left ventricle was divided into 16 segments according to the recommendation of American society of Echocardiography.[18] As previous studies have already indicated that, the apex is fairly stationary and velocities obtained in that region are negligible; so myocardial velocity was not measured in that region.[19,20] The resulting 12 LV segments were combined to reflect the territories of the coronary arteries: midseptum, anteroseptal, and anterior segments were assigned to the left anterior descending artery (LAD), basal septum and inferior segments to the right coronary artery (RCA), and lateral and posterior segments to the left circumflex (LCX).[18]

In each patient, echocardiographic velocities were obtained from the apical 4, 3, 2 chambers views. These views provided visualization of septal and lateral walls (apical 4), anterior and inferior walls (apical 2) anteroseptal wall (apical 3). The basal and mid segments of each wall were examined.

During systole, a major positive velocity wave (S) was recorded when the annulus moves toward the cardiac apex. During diastole, when the annulus moves toward the base away from the apex, 2 major negative velocity waves were recorded: one during the early phase of diastole (E) and another during the late phase of diastole (A).[21]

The regional myocardial velocity waveforms measured were systolic velocity (S) (Fig. 4), peak early diastolic filling velocity (E) (Fig. 5) and peak late diastolic filling velocity (A) (Fig. 6).[22] The isovolumic contraction time (IVCT) was calculated from the beginning of QRS in ECG till the beginning of S (Fig. 1) wave while the isovolumic relaxation time (IVRT) was calculated from the end of S wave till the beginning of E wave. (Fig. 3) Time to peak S wave was measured from the beginning of QRS in ECG till peak of S wave (Fig. 2). Time to peak E was measured from the beginning of QRS in ECG till peak of E wave. All measurements were obtained at baseline, low-dose, and peak stress and were taken in a good-signal cycle with averaging its value in three different cycles. Cardiac cycles with extrasystolic, post extrasystolic beats, or rhythm disturbance were excluded.[19]

Wall motion score index (WMSI) also was determined at rest and peak stress. Using a four-point scale as follows: normal (1), hypokinetic (2), akinetic (3), dyskinetic (4). 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.[18]

Dobutamine stress test was considered to be positive in cases of new or worsening wall thickening (or motion) abnormalities at any dobutamine (or atropine) stage in more than one segment of the same region (Fig. 7), the condition of akinesia becoming dyskinesia was not considered.[11,23]

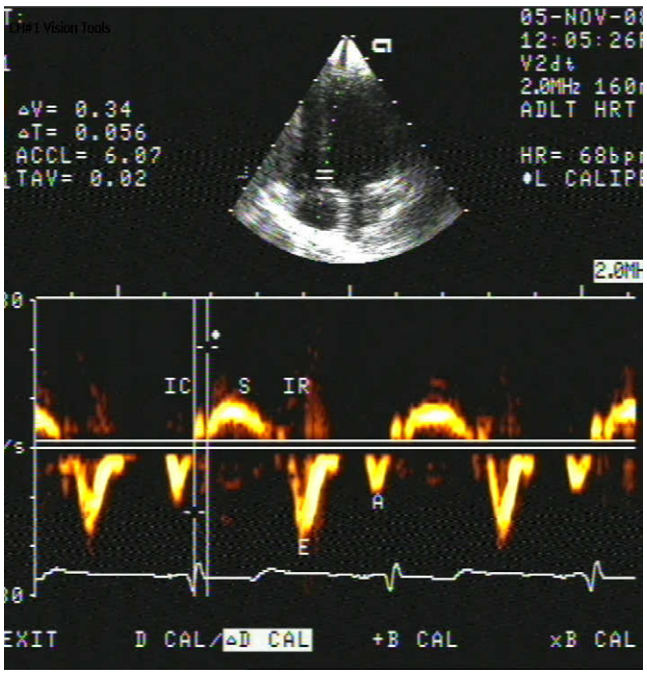

Figure 1 Measurement of isovolumic contraction time at the basal posterior septal wall in apical four chambers view at rest (56 ms) in one patient of group II.

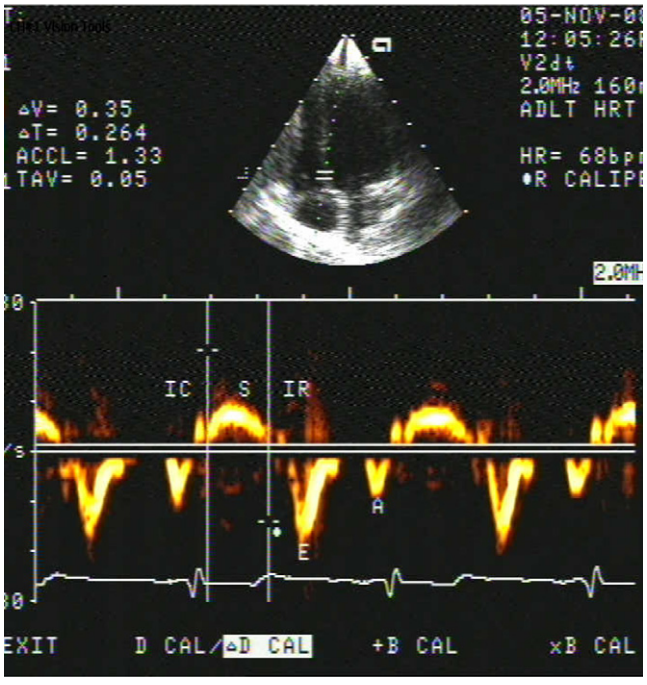

Figure 2 Measurement of duration of S wave (contraction time) at the basal posterior septal wall in apical four chamber view at rest (264 ms) in one patient of group II.

3.3. Coronary angiography

Selective coronary angiography was performed with the standard Judkins approach within 1 month from DSE. The equipment used was the digital Siemens Hicor 1000 system. All coronary angiograms were interpreted by two experienced cardiologists who were unaware of the results of DSE. No cardiac events occurred for any of the studied patients in the interval between the time of DSE study and coronary angiography.

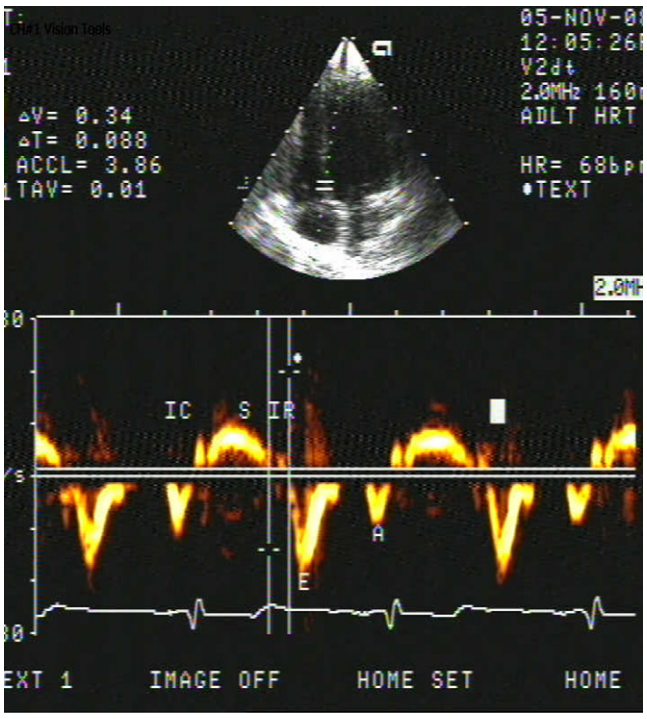

Figure 3 Measurement of isovolumic relaxation time at the basal posterior septal wall in apical four chambers view at rest (88 ms) in one patient of group II.

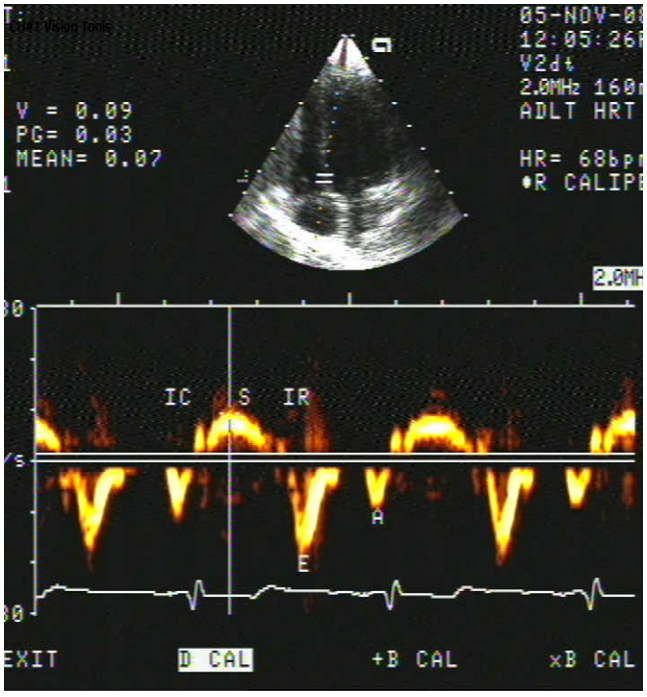

Figure 4 Measurement of peak velocity of S wave at the basal posterior septal wall in apical four chamber view at rest (9 cm/s) in one patient of group II.

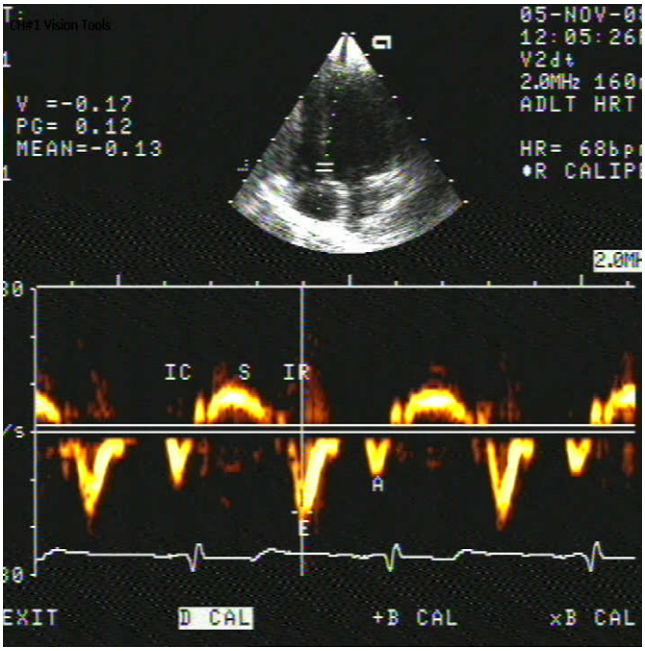

Figure 5 Measurement of peak velocity of E wave at the basal posterior septal wall at rest (measured 17 cm/s) in one patient of group II.

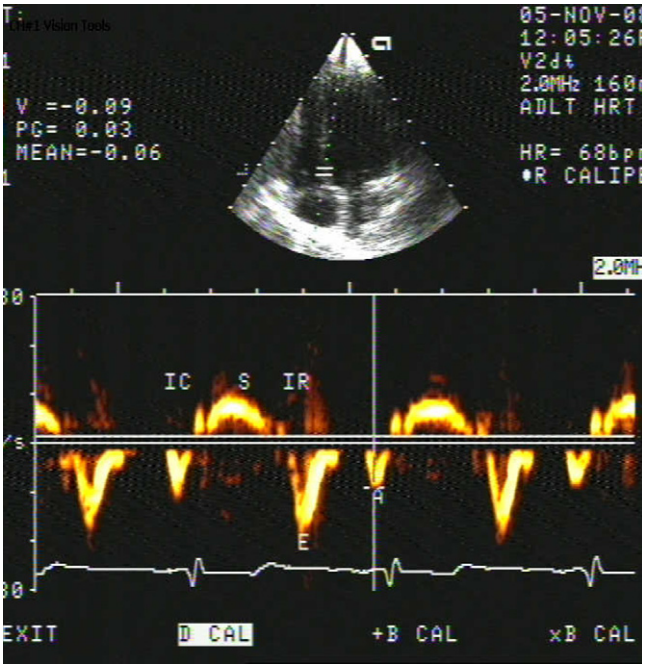

Figure 6 Measurement of peak velocity of A wave at the basal posterior septal wall at rest (measured 9 cm/s) in one patient of group II.

Significant CAD was defined as the presence of $\geqslant 50\%$ luminal diameter narrowing of one or more major epicardial arteries or its major branches localized in the first or middle segments of the coronary arterial tree, observed in two orthogonal angiograms.[11,24] For CAD location, left main stenosis was regarded as disease of the LAD and the LCX. A "diffuse disease" was defined by the presence of significant stenosis in $\geqslant 2$ coronary vessels with stenosis in $\geqslant 2$ segments of each vessel. The results of coronary angiography were compared to those of dobutamine stress with standard wall motion analysis and DSE with DTI.

According to the results of the coronary angiography, the patients were divided into two groups: group (I); DM with CAD comprised 27 patients with significant ($>50\%$) coronary stenosis and group (II); DM without CAD comprised 19 patients with normal findings or non-significant lesions in coronary arteries.

4. Statistical analysis

Data were analyzed by SPSS statistical package version 16.0 (SPSS INC, Chicago, IL, USA). Quantitative data expressed as mean and standard deviation (SD). Student-*t* test was used for comparison of the means of two groups of quantitative variables. Qualitative data expressed as number and percentage and analyzed by Chi-square (χ^2) or Fisher exact test when appropriate.

Diagnostic performance of DSE tested by measuring sensitivity, specificity, positive predicative value (PPV), negative predicative value (NPV) and accuracy.

The diagnostic performance of global *S*, Delta (Δ) *S*, global *E*, Delta (Δ) *E* or the ability to discriminate diseased cases from normal cases is evaluated using receiver operating characteristic (ROC) curve analysis to determine the appropriate cut-off points.

Multivariate logistic regression was used to assess independent predicators of positive coronary angiography (ischemia) among patients using clinical, laboratory and echocardiographic variables. Level of significance was set as p value <0.05.[25]

5. Results

From 56 diabetic patients recruited for the study, 46 patients were included for the study analysis (10 patients did not undergo coronary angiography). According to coronary angiographic results diabetic patients were classified into two groups; group I diabetic patients with positive coronary angiography included 27 patients (16 males and 11 females with mean age 64.52 $\pm$ 6.6 years) and group II diabetic patients with negative coronary angiography included 19 patients (11 males and 8 females with mean age 59.11 $\pm$ 6.5 years).

By comparing both groups, no significant difference was found between group I and group II as regards the age, gender difference, diabetes duration, prevalence of hypertension, systolic or diastolic blood pressure levels, resting heart rate, total cholesterol or triglycerides levels ($p > 0.05$). The percentage of smokers was significantly higher in group I than group II ($p < 0.05$) (Table 1).

Concerning conventional echocardiographic parameters, no significant difference was found between the group I and group II except in WMSI with stress which was significantly higher in group I in comparison to group II ($p < 0.05$) (Table 1).

There was a significant difference between group I and group II as regards response of systolic (*S*) velocity and early diastolic (*E*) velocity measured during dobutamine DTI from rest to peak stress ($p < 0.001$ for each). On the contrary there was no significant difference between the two groups regarding the response of late diastolic (*A*) velocity ($p > 0.05$) (Table 2).

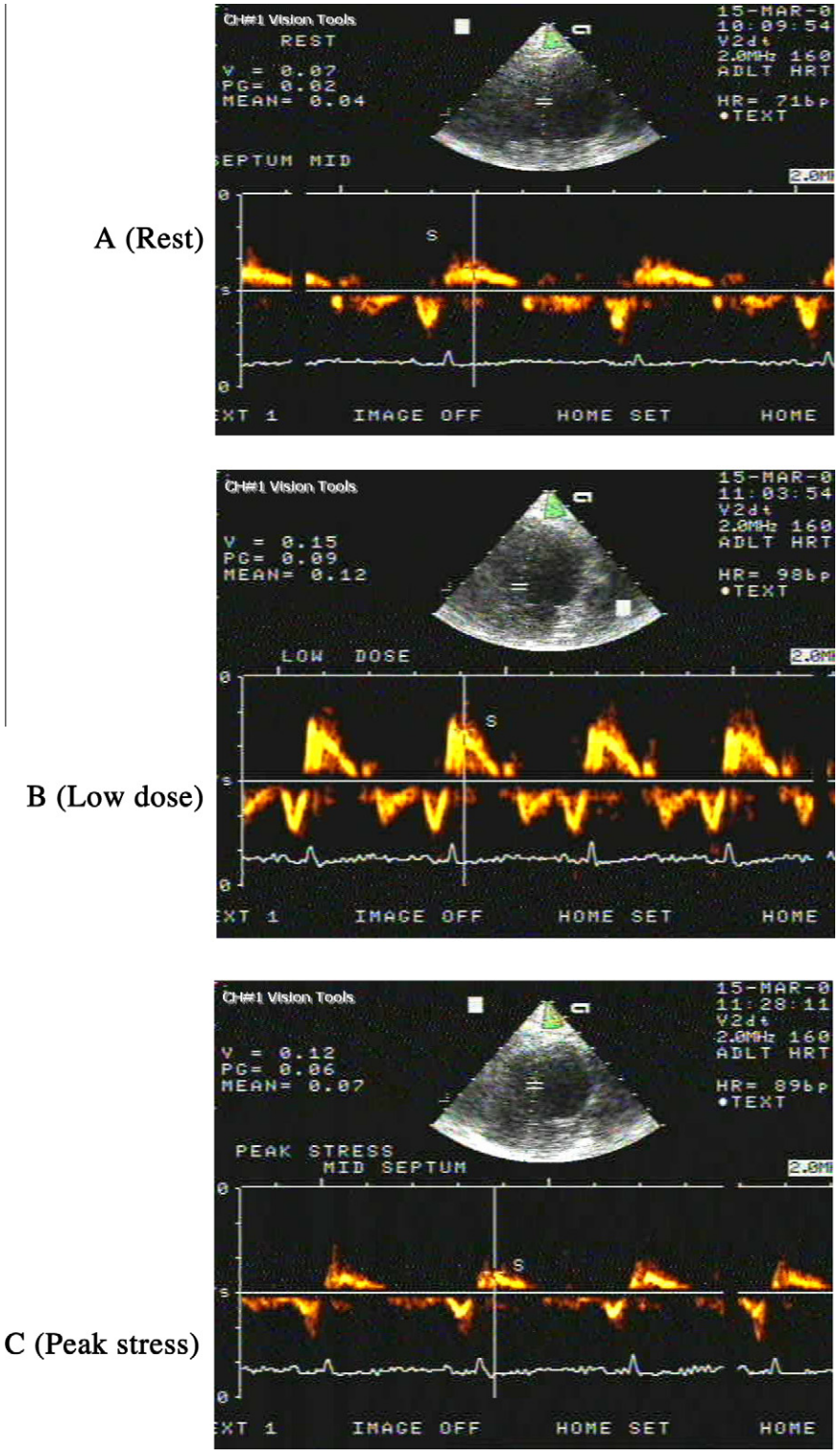

Figure 7 Example of biphasic response of S wave velocity indicating ischemia in one patient of group (I). The peak velocity of S wave measured at mid posterior septal wall at rest, *panel A* (7 cm/s), low dose, *panel B* (15 cm/s) and peak stress, *panel C* (12 cm/s).

Comparative analysis of dobutamine stress DTI parameters at different LV walls demonstrated that, isovolumic contraction time (IVCT), contraction time (CT), time to peak *S* and time to peak *E* were significantly prolonged in all walls at peak stress in group I compared to group II, while *S* and *E* velocities were significantly lower in group I when compared to the values of the corresponding walls in group II. The isovolumic relaxation time measured at peak stress was found to be more prolonged in all LV walls in group I compared to group II, however the difference did not reach the statistically significant

Table 1 Baseline demographic, clinical, laboratory & echocardiographic data of the studied groups.

	Group I Positive CA (n = 27)	Group II Negative CA (n = 19)	T test	p value
Age (mean ± SD)	64.52 ± 6.6	59.11 ± 6.5	1.29	> 0.05
Gender				
Male	16 (59.3%)	11 (57.9%)	χ^2 = 2.24	> 0.05
Female	11 (40.7%)	8 (42.11%)		
BMI (kg/m^2)	30.24 ± 5.5	31.5 ± 5.8	0.71	> 0.05
Hypertension (%)	19 (70.4%)	15 (78.9)	χ^2 = 0.42	> 0.05
DM duration (years)	10.82 ± 5.82	9.28 ± 5.14	2.11	> 0.05
Smoking (%)	11 (40.7%)	4 (21.1%)	χ^2 = 1.96	< 0.05
SBP (mmHg)	135.19 ± 14.24	135.26 ± 15.76	0.01	> 0.05
DBP (mmHg)	87.04 ± 9.12	84.74 ± 7.72	0.89	> 0.05
HR (b/min)	75.70 ± 7.28	79.84 ± 7.41	1.88	> 0.05
Total cholesterol bn(mg/dL)	232.41 ± 40.36	224.32 ± 46.20	1.48	> 0.05
Triglycerides (mg/dL)	160.93 ± 37.30	155.53 ± 33.19	0.50	> .0.05
IVS (mm)	10.41 ± 1.9	11.21 ± 2.3	1.28	> 0.05
LVEDD n(mm)	48.26 ± 4.9	48.21 ± 3.9	0.03	> 0.05
LVESD n(mm)	10.74 ± 3.8	11.89 ± 5.2	0.86	> 0.05
LVPW (mm)	29.78 ± 6.0	28.21 ± 5.6	0.89	> 0.05
FS%	35.59 ± 4.3	37.05 ± 5.8	0.98	> 0.05
EF%	65.93 ± 5.5	67.68 ± 5.8	1.04	> 0.05
WMA (%)	2 (7.4%)	1 (5.3%)	Fisher exact	> 0.05
WMSI				
At rest	1.05 ± 0.18	1.05 ± 0.23	0.01	> 0.05
With stress	1.52 ± 0.49	1.18 ± 0.38	2.59	< 0.05

BMI, body mass index; DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; IVS, Interventricular septum; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LVPW, left ventricular posterior wall; FS, fractional shortening; EF%, ejection fraction; WMA, wall motion abnormality; WMSI, wall motion score index.

level. As regards the late diastolic velocity (A), no significant difference was detected between the two groups at peak stress (Table 3).

Changes in global myocardial systolic and early diastolic velocities measured from rest to peak stress and (Δ) change in these velocities (measured as the difference between the peak stress-rest values) were all significantly lower in group (I) when compared group (II) (Table 4).

Using ROC curve, the cutoff points with best validity criteria (sensitivity and specificity) were determined for each DTI parameter for prediction of obstructive CAD in diabetic patients. The cutoff points for global S and global E were 11.3 cm/s and 11.2 cm/s with 75.7%, 73.4% sensitivity and 94.7%, 89.47% specificity respectively. For ΔS and ΔE the cutoff points were 0.56, 0.26 with 78.8%, 89.3% sensitivity and 94.7%, 90.7% specificity respectively (Table 5).

Comparing the validity criteria of WMSI and DTI dobutamine stress in detection of CAD in diabetic patients, the latter was found to be more sensitive (74.1% vs. 59.3%) and more specific (90% vs. 79%).

Moreover, dobutamine stress DTI had higher positive predictive value (91% vs. 80%), higher negative predictive value (71% vs. 57.7%) and better accuracy (80.4% vs. 67.4%) in detection of CAD in the studied patients (Table 6).

In multivariate logistic regression analysis of all clinical, laboratory and echocardiographic variables for prediction of obstructive CAD in patients with DM, only $\Delta E \leqslant 0.26$ was the most significant powerful independent predictor followed by $\Delta S \leqslant 0.56$, ($p < 0.01$, < 0.05 respectively) (Table 7).

In analyses testing the reproducibility, the interobserver and intraobserver variabilities were compared in 40 consecutive measurements and were 2.1% and 3.3%, respectively, for the measurement of ΔS and for measurement of ΔE were 3.9% and 3.7%, respectively. Accordingly, each parameter has good limits of interobserver and intraobserver variabilities accounting for good reproducibility. Validation had been confirmed in previous studies.[11,26]

6. Discussion

Coronary artery disease (CAD) is the leading cause of death in patients with DM. Patients often present with advanced and asymptomatic disease.[27] Although mortality from cardiovascular disease has declined in the general population, the decline is much less in diabetic men and in diabetic women there is actually an increase in cardiovascular mortality.[28] These data emphasize the importance of accurate risk stratification of diabetic patients to identify diabetic patients with subclinical disease at a high risk of future cardiac events.

In the present study, diabetic patients were investigated for CAD using dobutamine stress DTI. To the best of our knowledge this is the first study to assess the diagnostic accuracy of dobutamine stress DTI in diabetic patients with suspected CAD.

In our study, the validity of DTI parameters during peak stress was higher than WMSI analysis (sensitivity 74.1% vs. 59.3% and specificity 90% vs. 79%, $p < 0.01$ for each). Moreover, dobutamine stress DTI had higher positive predictive

Table 2 Myocardial velocities response to dobutamine stress in studied groups.

Peak systolic velocity (S)	Group I Positive CA ($n = 27$)		Group II Negative CA ($n = 19$)		χ^2	p
	No	%	No	%		
Decreased	10	37.04	0	0.0	9.05	<0.001
Biphasic	10	37.04	3	15.8		
Increased	7	25.9	16	84.2		
Early diastolic velocity (E)						
Decreased	18	66.67	4	21.1	10.98	<0.001
Biphasic	2	7.41	0	0.0		
Increased	7	25.9	15	78.9		
Atrial diastolic velocity (A)						
Decreased	3	11.1	2	10.5	0.73	>0.05
No change	1	3.7	0	0.0		
Increased	23	85.2	17	89.5		

values (91% vs. 80%), higher negative predictive values (71% vs. 57.7%) and better accuracy (80.4% vs. 67.4%) in detection of CAD in diabetic patients.

Doppler tissue imaging (DTI) provides a quantitative analysis of regional myocardial function through its excellent ability to quantify regional myocardial contraction and relaxation velocities and has good temporal resolution allowing accurate estimation of the very short time intervals during the cardiac cycle.[29] In our study, addition of DTI to DSE has the advantage of quantitative analysis that enables to detect the appropriate cut off values during peak stress that differentiate between patients with obstructive (group I) and normal or nonobstructive (group II) CAD (global $S \leqslant 11.3$ cm/s, global $E \leqslant 11.2$ cm/s, $\Delta S \leqslant 0.56$ and $\Delta E \leqslant 0.26$). Furthermore, in multivariate logistic regression analysis of predictors of obstructive CAD in patients with DM, only $\Delta E \leqslant 0.26$ was the most significant powerful independent predictor followed by $\Delta S \leqslant 0.56$ ($p < 0.01$, <0.05 respectively).

6.1. Conventional DSE and WMSI in diagnosis of CAD among diabetics

The prognostic value of DSE in diabetic patients with known or suspected CAD has been previously demonstrated.[30,31] However, given their high-risk status for the development of cardiovascular diseases, diabetic patients present with a substantially increased pretest likelihood of adverse outcome. Thus, to verify whether the test conveys similar prognostic information in diabetic and nondiabetic patients is of primary clinical relevance.[32]

In our study, despite WMSI measured during peak dose DSE was higher in diabetic patients with obstructive CAD, it has lower sensitivity, specificity and predictive power compared to dobutamine stress DTI.

In agreement with our findings, Masoor et al.[28] postulated that, diabetic patients with negative DSE were twice as likely to have cardiac events and four times more likely to have nonfatal infarctions compared with nondiabetic subjects. They suggested that, the absence of ischemia is a less reliable predictor of event-free survival in diabetic patients. The cause of the reduced predictive value of a negative DSE in diabetic patients is unknown. One possibility is that, diabetic patients are more likely to have diffuse distal vessel disease. In this setting, regional wall motion abnormalities may be more difficult to detect with stress because of global rather than regional reduction of perfusion reserve.[28]

Furthermore, Anne et al.[33] reported that, diabetic patients with normal DSE appear to have a greater risk for subsequent cardiovascular events than nondiabetic patients, particularly beyond 2 years. Similarly, Kamalesh et al.[34] found increased incidence of cardiac events despite negative DSE in DM cohort (6% vs. 2.9% yearly).

6.2. Additional role of DTI to DSE in diagnosis of CAD among diabetics

In our study, application of DTI during DSE makes the procedure easy, quantitative, with higher sensitivity, specificity, accuracy and reproducibility than standard WMSI analysis. This superiority helps to diagnose obstructive CAD in diabetics more accurately without additional risk or cost.

In agreement with our findings, Pellikka[26] demonstrated that, DTI is promising technique to reduce intraobserver and interobserver variabilities for the interpretation of stress echocardiograms. Moreover, this technique offers the potential to quantify the extent of ischemia. In addition to assessment of indices of contractile function, distinct patterns of diastolic function can be depicted during ischemia with an accuracy which probably cannot be appreciated by the naked eye.[26]

Fraser et al.[35] in the MYDISE (Myocardial Doppler in Stress Echocardiography) study, used myocardial Doppler velocities during DSE for diagnosis of CAD comparing its results with coronary angiography. They demonstrated that, CAD can be diagnosed accurately and objectively, from offline measurements of myocardial velocities recorded non-invasively by DTI during DSE. Furthermore the accuracy of DTI in diagnosis of CAD is much more than conventional analysis of wall motion abnormalities.[35]

Wall motion analysis of the inferobasal segment of the left ventricle is a common problem during DSE and may be a cause for unnecessary coronary angiography. Even resting imaging of the inferobasal segment often demonstrates abnormal motion as a result of close proximity of the mitral valve and atrioventricular groove. During DSE, this impairment may become more prominent and can be interpreted incorrectly as ischemia.[36] Leitman et al.[36] investigated changes of

Table 3 Comparison of myocardial velocities and time intervals between diabetic groups at peak stress.

Items		IVCT (ms)	*S* (cm/s)	CT (ms)	Time to peak *E* (ms)	Time to peak *S* (ms)	*E* (cm/s)	*A* (cm/s)	IVRT (ms)
Posterior Septal wall	Group I	57.48 ± 20.99	10.94 ± 4.247	206.00 ± 47.86	440.93 ± 75.34	99.00 ± 31.31	10.37 ± 2.02	14.09 ± 2.41	107.56 ± 35.9
Dobutamine DTI at peak stress	Group II	47.37 ± 9.54	13.31 ± 3.587	180.21 ± 34.21	385.74 ± 40.79	81.89 ± 19.15	13.68 ± 3.01	14.684 ± 2.21	91.58 ± 34.04
	p	< 0.05	< 0.05	< 0.05	< 0.01	< 0.05	< 0.05	> 0.05	> 0.05
Lateral wall	Group I	62.96 ± 23.28	10.75 ± 4.41	210.33 ± 48.65	430.63 ± 79.37	118.93 ± 45.13	11.85 ± 2.20	13.89 ± 2.57	90.59 ± 27.39
Dobutamine DTI at peak stress	Group II	44.63 ± 7.45	14.97 ± 2.42	172.53 ± 28.28	371.95 ± 41.06	90.32 ± 21.71	14.05 ± 2.70	15.34 ± 2.08	80.53 ± 21.34
	p	< 0.001	< 0.001	< 0.01	< 0.01	< 0.01	< 0.01	> 0.05	> 0.05
Anterior wall	Group I	66.67 ± 23.53	10.85 ± 4.276	209.85 ± 46.36	440.96 ± 79.99	114.37 ± 38.84	10.24 ± 2.39	13.91 ± 2.54	91.85 ± 25.79
Dobutamine DTI at peak stress	Group II	43.58 ± 9.03	14.05 ± 3.55	178.82 ± 32.30	376.89 ± 55.34	86.74 ± 21.37	13.29 ± 2.53	15.684 ± 2.78	84.00 ± 26.73
	p	< 0.001	< 0.05	< 0.05	< 0.01	< 0.01	< 0.01	> 0.05	> 0.05
Inferior wall	Group I	59.70 ± 20.93	12.05 ± 3.91	206.59 ± 43.87	428.07 ± 73.45	105.00 ± 30.64	11.481 ± 2.37	15.333 ± 2.56	95.41 ± 37.18
Dobutamine DTI at peak stress	Group II	40.63 ± 7.45	15.73 ± 2.06	167.37 ± 29.46	369.21 ± 48.07	83.37 ± 26.67	13.9 ± 2.16	15.684 ± 1.96	82.53 ± 29.00
	p	< 0.001	< 0.01	< 0.001	< 0.01	< 0.05	< 0.05	> 0.05	> 0.05
Anterior septal wall	Group I	58.94 ± 21.08	11.90 ± 4.48	206.44 ± 54.46	429.56 ± 78.71	107.56 ± 32.97	11.44 ± 2.44	16.074 ± 10.05	98.52 ± 33.41
Dobutamine DTI at peak stress	Group II	39.16 ± 7.00	15.36 ± 2.54	169.47 ± 24.52	367.42 ± 42.71	82.95 ± 25.18	13.98 ± 2.07	15.789 ± 2.11	81.89 ± 28.29
	p	< 0.001	< 0.01	< 0.01	< 0.001	< 0.05	< 0.05	> 0.05	> 0.05

IVCT, isovolumic contraction time; *S*, systolic velocity; CT, contraction time; *E*, early diastolic velocity; *A*, late diastolic velocity; IVRT, isovolumic relaxation time; DTI, Doppler tissue imaging.

the inferobasal segment during DSE with DTI in 50 patients with more than 70% stenosis of RCA and compared the results with coronary angiography. They reported that, conventional stress echocardiography was falsely positive in 10.3% and falsely negative in 27.3%. When DTI was combined with conventional stress echocardiography, it enhances the diagnosis of inferior ischemia during DSE and it improves sensitivity and specificity up to 81.8% and 97.4% respectively and accordingly can be added to conventional imaging protocol in those patients.[36]

6.2.1. Changes in myocardial velocities and time intervals during dobutamine stress – DTI

In our study, comparing measurements of dobutamine stress DTI parameters at different walls in the two studied groups with results of coronary angiography revealed that, peak systolic velocity (*S*) and early diastolic velocity (*E*) become significantly lower in all walls at peak stress in group I compared to group II. Regarding late diastolic velocity (A), there was no significant difference between the two groups.

These results are in agreement with data reported by Von Bibra et al.[37] using pulsed Doppler myocardial mapping of 12 left ventricular segments during DSE, and reported, a stress-induced reduction of peak lengthening of early diastolic velocity which was accurate and superior to peak systolic tissue Doppler recordings for detecting coronary artery stenosis.[37]

Several investigators had shown Doppler myocardial velocity imaging to be a sensitive alternative to the conventional echocardiographic and scintigraphic imaging techniques to evaluate stress tests. The peak velocity response for both systole and diastole has been shown to be significantly lower during dobutamine stress in mal-perfused myocardial regions compared to normal.[37,38]

Jelena et al.[39] examined 60 patients without previous myocardial infarction who underwent DSE. Peak systolic, early and late diastolic velocities were measured at rest and during stress and they found that, there was no significant difference between ischemic and non-ischemic groups in systolic and both diastolic velocities at rest. However, pronounced differences developed during stress in all segments, peak systolic velocity in the ischemic group during stress was lower than in the non-ischemic group ($p < 0.05$). Furthermore clear difference between the two groups was found in the magnitude of early diastolic filling wave (E') during stress ($p < 0.04$).[39]

Concordant to our findings, Ofelia et al.[40] studied 63 patients for CAD by measuring regional diastolic velocities using DTI during DSE and comparing it to results of coronary angiography they concluded that, E velocity in patients with CAD showed a lower value at peak stress compared with control ($p < 0.001$). On the other hand, the A velocity in both groups did not show any significant difference at baseline and peak stress.[40] Similarly, Yamada et al.[38] reported blunting of the *E* velocity from baseline to peak stress in ischemic compared with nonischemic segments.

In our study, the isovolumic contraction time, contraction time, time to peak *S* and time to peak *E* showed significant prolongation during peak stress in group I compared with group II. These parameters represent more deterioration of myocardial function (both systolic and diastolic) during peak stress. Although the isovolumic relaxation time measured at peak stress was found to be more prolonged in group I

Table 4 Changes of global myocardial systolic velocity (*S*), early diastolic velocity (*E*) and Δ change from rest to stress in studied patients.

	Group I ($n = 27$)	Group II ($n = 19$)	*T* test	*p* value
Global *S* (cm/s)	11.30 ± 3.66	14.48 ± 2.16	3.69	<0.01
Global *E* (cm/s)	11.27 ± 1.63	13.12 ± 2.10	3.16	<0.01
Δ*S*	0.50 ± 0.51	0.93 ± 0.30	3.56	<0.01
Δ*E*	0.21 ± 0.16	0.42 ± 0.16	4.40	<0.001

S, systolic velocity; *E*, early diastolic velocity; Δ, Delta.

Table 5 Cutoff points of Doppler tissue parameters in diagnosis of CAD in diabetic patients.

	Sens. (95% CI)	Spec. (95% CI)
Global $S \leqslant 11.3$ (cm/s)	75.7 (55.4–94.3)	94.7 (73.9–99.1)
Global $E \leqslant 11.2$ (cm/s)	73.4 (54.6–93.1)	89.47 (66.8–98.4)
$\Delta S \leqslant 0.56$	78.8 (54.3–95.7)	94.7 (73.9–99.1)
$\Delta E \leqslant 0.26$	89.3 (68.7–105.9)	90.7 (71.4–101.4)

S, systolic velocity; *E*, early diastolic velocity; Δ, Delta; CI, confidence interval.

compared to group II, the difference did not reach the statistically significant level.

Similar to our data, Jun et al.[41] reported prolongation of isometric contraction time and ejection time in ischemic patients using pulsed-wave DTI with DSE.

Kugacka et al.[42] reported that, the value of isovolumic relaxation time corrected for heart rate (IVRTc) = 80 ms at peak dobutamine infusion is able to discriminate patients with residual ischemia from those without with a sensitivity of 80% and a specificity of 70%.

However, these time intervals are not so reliable due to different variabilities of its measurement especially at a higher heart rate when both systolic and diastolic time intervals are getting shorter.

6.3. Study limitations

The limited number of patients could limit the strength of the findings obtained from the study; future large scale studies are recommended for more validation of the results. The difficulty of quantifying the apical segments using myocardial Doppler velocities is because of the relatively immobile nature of the

Table 6 Criteria of the validity of DSE with Doppler tissue imaging versus standard wall motion analysis in diagnosis of CAD in Diabetes mellitus.

Doppler tissue imaging	Coronary angiography		Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
	Group I ($n = 27$)	Group II ($n = 19$)					
Positive	20	2	74.1	90	91	71	80.4
Negative	7	17					
WMSI							
Positive	16	4	59.3	79	80	57.7	67.4
Negative	11	15					

PPV, positive predictive value; NPV, negative predictive value; WMSI, wall motion score index.

Table 7 Multivariate logistic regression analysis of predictors of obstructive CAD in diabetes mellitus.

Variables	*B*	SE	Wald χ^2	*p*	OR	95.0% CI for OR	
						Lower	Upper
Age	0.22	0.12	3.11	>0.05	1.25	0.97	1.61
Male sex	1.29	1.75	0.54	>0.05	3.65	0.11	113.36
Hypertension	0.29	1.33	0.04	>0.05	1.34	0.09	18.46
Smoking	−0.52	1.85	0.07	>0.05	0.59	0.01	22.43
DM (year)	0.13	0.11	1.53	>0.05	1.14	0.92	1.42
TC > 200 mg/dl	1.608	1.23	1.69	>0.05	4.99	0.44	56.20
WMSI > 1	−0.39	1.32	0.08	>0.05	0.67	0.05	9.00
$\Delta S \leqslant 0.56$	3.58	1.68	4.55	<0.05	36.16	1.34	532.01
$\Delta E \leqslant 0.26$	4.15	1.52	7.39	<0.05	63.77	3.19	721.47
Constant	−16.56	8.56	3.84	<0.05			

DM, diabetes mellitus; TC, total cholesterol; WMSI, wall motion score index; *S*, systolic velocity; *E*, early diastolic velocity; Δ, delta; CI, confidence interval; OR, odds ratio; SE, standard error.

apex, and therefore an inherent limitation of the assessment of base–apex axis function. However, despite the inability of the test to identify apical wall motion abnormalities, this did not emerge as a major impediment to overall sensitivity in this study. When using the pulsed wave-DTI technique, the procedure is relatively time consuming because of the large number of measurements needed to be recorded from the standard myocardial segments. Doppler tissue imaging measurements are affected by cardiac translational movements, tethering effect and angulations, however these could be minimized by using more relatively recent DTI techniques and choosing myocardial regions of interest within 15–20° of the axis of Doppler interrogation.

7. Conclusion

Doppler tissue imaging is a promising technique allowing accurate quantification of ischemia induced regional diastolic and systolic dysfunction and when used during dobutamine stress echocardiography, it adds new dimension to the diagnosis of myocardial ischemia in diabetic patients. It is more sensitive, specific, accurate and reproducible than standard wall motion analysis for recognition of significant CAD in such category of patients.

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