Original Article

Predictive Accuracy of Dobutamine Stress Echocardiography in Detection of Presence and Extent of Coronary Artery Disease

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Abstract

Introduction*: Exercise tolerance test (ETT) is an established screening test for coronary artery disease (CAD), but not feasible in 30−40% of patients. Dobutamine stress echocardiography (DSE) is an excellent alternative. Traditionally, inducible worsening of wall motion by 1 grade from baseline provides an index of CAD; worsening by 2 grade or more theoretically represents a more severe perfusion abnormality. The present study represents the inaugural experience of DSE at the National Institute of Cardiovascular Disease, Dhaka.* ***Objective****: To assess the predictive accuracy of DSE results with the presence and extent of CAD in subjects with suspected stable angina pectoris.* ***Materials and Methods****: In this prospective observational study, 35 subjects with intermediate to high probability of CAD were subjected to DSE followed by coronary angiography (CAG) within one month. Comparison of DSE results and predicted coronary artery involvement with angiographic findings were done. Overall sensitivity, specificity, accuracy as well as accuracy by arterial territory involvement were calculated.* ***Results****: DSE identified 82 abnormal segments, 66 with 1 grade change in 23 subjects (Group A) and 16 with 2 grade change in 8 subjects (Group B). CAG detected 54 significant lesions, 23 (42.59%) in left circumflex (LCX), 18 (33.33%) in left anterior descending (LAD), 11 (20.37%) in right coronary (RCA) and 2 (3.7%) in left coronary (LCA) artery. DSE had a sensitivity of 93.1% and a specificity of 66.7%. The accuracy was 88.57% overall, 94.29% for LAD and 91.43% for both LCX and RCA territories. Group B subjects had significantly higher number of coronary stenosis per patient (2.63 versus 1.38, p<0.001), triple vessel (62.5% versus 8.6%, p=0.003) and lower single vessel CAD (0% versus 47.8%, p=0.005).* ***Conclusion****: This study shows that DSE is a reliable test for prediction of the presence and extent of CAD.*

Keywords*: Dobutamine stress echocardiography; Coronary artery disease; Ischemia*

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Introduction

One of the cardinal features of heart is its dynamism and our survival depends as much on its dynamic response to environmental challenges as to its basal function. Accordingly, responses of the cardiovascular system to stress are important measures of cardiovascular health and stress testing such as treadmill exercise stress testing (ETT/TMT etc.) has become a key component of cardiovascular diagnosis and prognosis with respect to coronary artery disease.[1] The coronary artery vasodilatory reserve is such that ischemia occurs at rest only at critical (~90% coronary diameter) narrowing. During stress, however, the demand for flow may outstrip the maximal hyperemic flow at lesser degrees of stenosis. This phenomenon of inducible ischemia is the underlying principle of cardiovascular stress testing for ischemia.[2]

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The provocation of ischemia gives rise to a continuum of pathophysiological responses, referred to as "ischemic cascade/pyramid" – starting with reduced perfusion (detectable by perfusion scintigraphy and contrast echocardiography), leading to metabolic changes (detectable by Positron Emission Tomography scanning techniques). Prolongation of this phenomenon leads to initial diastolic dysfunction followed by systolic dysfunction detectable by Nuclear Ventriculographic and Echo-cardiographic techniques. ECG changes of provoked ischemia lie only at the tip of the pyramid – a very delayed phenomenon detected by exercise electrocardiography (ETT).[3] Transient regional myocardial wall motion abnormality is a more proximate response to ischemia than ECG changes and this echo-cardiographically detectable response was shown experimentally more than 40 years ago. Although ETT is of established value in the clinical detection of provocable myocardial ischemia as a screening test, in 30−40% of patients it is not feasible due to various reasons.[4] Stress combined with echocardiographic imaging of induced transient wall motion abnormality provides an excellent alternative – the spectrum includes physical stress, pharmacological (exercise-simulating) and vaso-active agents. Dobutamine stress echocardiography is a good modality combining a widely available pharmacological agent with a widely available imaging modality, costing less than scintigraphic or nuclear scanning techniques.[5] Traditionally, inducible worsening of regional wall motion during dobutamine stress echocardiography (DSE) by one grade or more from baseline provides an accurate index of coronary artery disease (CAD), and the degree and magnitude of induced dyssynergy correlates significantly with angiographic severity of CAD.[6] Deterioration of wall motion by two grades during DSE theoretically represents more severe ischemia in terms of more severe and extensive perfusion defect.

The present study represents the inaugural experience of DSE as a screening test of suspected CAD at National Institute of Cardiovascular Diseases, Dhaka, Bangladesh. The aim of the study was to assess the correlation of DSE results with the presence and extent of angiographic coronary artery stenosis in patients with suspected stable angina pectoris.

Materials and Methods

This prospective, observational study was conducted in the department of Cardiology at the National Institute of Cardiovascular Diseases, Sher-E-Bangla Nagar, Dhaka. The protocol was approved by the institutional review board and informed consent was obtained from all the subjects. A total of 35 subjects with suspected stable angina with a Dobutamine Stress Echocardiography as a screening test who subsequently underwent invasive coronary angiography were included in the final analysis.

Subjects included were those with suspected coronary artery disease based on symptoms of stable angina pectoris who i) were unable to perform adequate ETT, ii) had inconclusive/equivocal ETT results, iii) had baseline ECG abnormalities precluding a conclusive ETT, iv) were referred for DSE by physician preference and v) had an available coronary angiographic result performed within one month of the DSE test were included in the study. Patients with significant valvular heart disease, significant resting arrhythmias, uncontrolled systemic hypertension (systolic BP ≥160 mm Hg and/or diastolic BP ≥110 mmHg); subjects with symptomatic congestive heart failure, known cardiomyopathies or previous coronary interventions/ surgeries were excluded.

A full history was taken and clinical evaluation was done prior to the test and DSE was performed in the Echocardiography department using the Mayo Clinic Foundation Protocol[7] – briefly, betablockers and non-dihydropyridine calcium channel blockers were stopped at least 24 hours before the test; the patients were positioned supine in a semi-left lateral decubitus and under continuous 3-lead ECG monitor connected to a defibrillator monitor. Standard 12 lead ECG was set up for ECG at the end of every 3-minute stage. A baseline echocardiography with segmental wall motion assessment was recorded. Dobutamine was infused intravenously by a continuous syringe pump at an initial dose of 5 micrograms/kg/minute, with stepwise increase every 3 minutes to 10-, 20-, 30- and 40 micrograms/kg/minute, with continuous chronotropic monitoring and blood pressure measurement at the beginning of the last minute of each 3 minute stage until i) age predicted target heart rate {calculated as THR = (220 − age in completed years) × 0.85} was reached, or ii) SBP of ≥180 mm

Hg and/or DBP of ≥120 mm Hg was reached, or iii) patient asked to stop because of undue symptoms. If the maximum dose of dobutamine infusion failed to achieve the desired heart rate, augmentation at a dose of 0.25 mg atropine intravenously every 1 minute up to a total of 1 mg (total 4 doses) with continued dobutamine infusion was done.

In the last minute of each stage, echocardiographic assessment of segmental wall motion and left ventricular global systolic function were recorded on a VingMed System Five Cardiac Ultrasound Machine (GE Medical Systems, Germany) through four standard echo windows (parasternal long axis, parasternal short axis at the papillary muscle level, apical four chamber and apical two chamber views). Regional wall motion was scored using the 16-segment model of ASE (American Society of Echocardiography), using a four point scale of – 1=normal, 2=reduced, 3=absent inward motion and wall thickening in systole and 4=paradoxical outward motion during systole (dyskinesia). Ischemia was defined as new or worsening wall motion abnormality and the severity of worsening was calculated as the difference between rest score and the worst score during the test. The patients and the segments with 1 grade change from baseline and those with ≥2 grade changes were identified and a wall motion score index (sum of scores in 16 segments/16) were calculated at the end of the test. From the identified abnormal segments, predicted arterial involvement was identified according to the scheme depicted in Fig 1.[8]

All subjects underwent selective coronary angiography by standard Judkins technique with multiple standard projections as per institutional practice and the angiographies were analyzed by a quantitative analysis program native to the Siemens Angiography machines (HICOR, Siemens Medical Systems, Germany). Significant coronary stenosis was defined as a ≥50% reduction in diameter or an absolute lumen diameter of ≤1 mm in a major epicardial coronary artery and its first order branch with a healthy lumen diameter of ≥2 mm. The number of arteries with significant stenosis and location by arterial territory and position for each patient were recorded.

Comparison of DSE results and predicted coronary artery involvement with angiographic findings were done. Overall sensitivity, specificity, accuracy as well as accuracy by arterial territory involvement were calculated. Patients with only 1 grade change from baseline and those with 2 or more grade changes of wall motion during DSE in at least one myocardial segment during DSE were compared in terms of angiographic findings. Statistical analysis was done with SPSS (Statistical Package for Social Sciences) version 11.0.

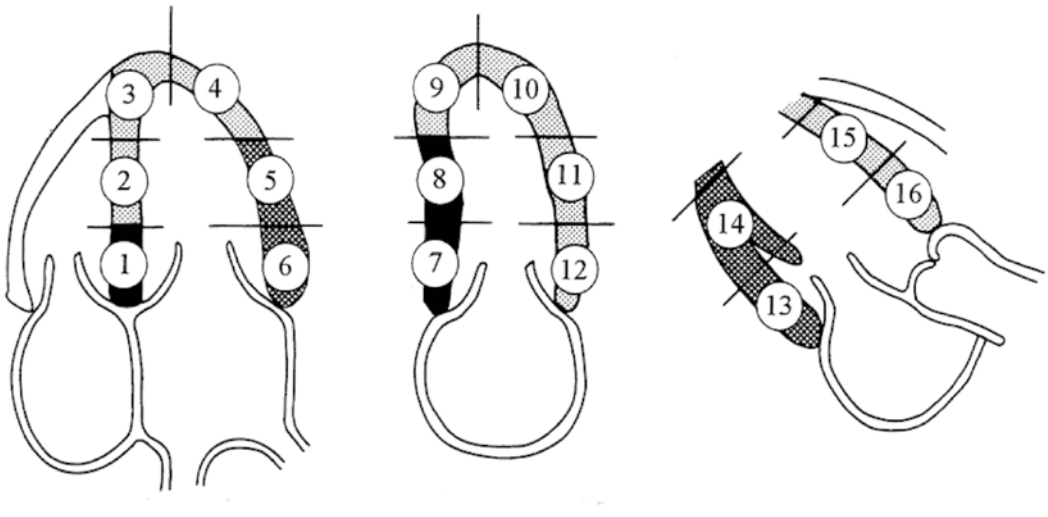

Fig 1. Diagrams showing the 16 wall segments and distribution of coronary perfusion

Left, apical four-chamber view; **middle,** apical two-chamber view; **right,** long-axis view. **Dotted areas** (segments 2, 3, 4, 9, 10, 11, 12, 15 and 16) = left anterior descending coronary artery; **cross-hatched areas** (segments 5, 6, 13 and 14) = left circumflex artery; **solid areas** (segments 1, 7 and 8) = right coronary artery

After Geleijsn ML, Fioretti PM, Roelandt JRTC. J Am Coll Cardiol 1997; 30(3): 596.

Results

Demographic and clinical profiles of subjects (Table I)

The mean age of the subjects was 53.11 years, with females representing only 11.7%. Roughly half of the subjects were in the overweight or obese category. Smoking was the most prevalent hard risk factor for CAD, followed by hypertension in frequency. However, over two-thirds of the subjects had typical angina. In all, 14 (40%) of the subjects were sent for DSE by referring physicians – at the time when there was great enthusiasm for this novel diagnostic technique, and physicians tended to prefer the added information about the coronary territorial involvement from DSE.

Dobutamine Test results (Table II)

Significant heart rate and blood pressure were achieved in the majority of the subjects. However, in 12 subjects age-predicted THR were not achieved – including 3 with significant wall motion abnormality before THR, 2 with high peak BP before THR, and two who failed to achieve THR even after atropine augmentation. The mean dobutamine dose required was close to the highest dose permitted in the protocol. Side effects developed in 37.1% of the subjects and all were considered minor. The most frequent side effect was chest discomfort/pain, occurring in 9 (25.7%) of the subjects.

Abnormal segmental wall motion developed in 82 myocardial segments in 46 arterial territories, most commonly in the left coronary territories − 43.48% in left circumflex (LCX) and 39.13% in left anterior descending (LAD) territories. Of these, 66 segments (76.74%) in 23 subjects had a change of 1 grade (Group A) and 16 (23.26%) segments in 8 subjects had 2 grade changes (Group B) from baseline. Comparison between these two groups in terms of angiographic findings are presented in Table IV and discussed later.

Table I: Demographic and clinical characteristics of the subjects (N=35)

Characteristics	Values*
Age in years – Range; Mean (SD)	37−66; 53.11 (7.44)
Sex	
Male Number (%)	31 (88.6)
Female Number (%)	4 (11.4)
Body Mass Index (BMI) – Range; Mean (SD)	19.47−32.04; 24.42 (3.014)
Normal	18 (51.4)
Overweight	15 (42.9)
Obese	02 (05.7)
Smokers (current and ex-smoker)	21 (60.0)
Dyslipidemic	13 (37.1)
Diabetic	07 (20.0)
Hypertensive	16 (45.7)
Family history of coronary artery disease	05 (14.3)
Symptoms	
Typical angina	27 (77.1)
Atypical angina/non-anginal symptom	08 (22.9)
Indications for DSE	
Unable to perform ETT	17 (48.6)
ETT inconclusive	04 (11.4)
Preference by referring physicians	14 (40.0)

* Continuous variables are presented as range, mean and standard deviation; categorical variables are expressed as number and percentage in parenthesis. DSE, dobutamine stress echocardiograpgy; ETT, exercise tolerance test

Table II: Dobutamine Stress Test results

Parameters	Values*
Peak heart rate achieved (beats/min) − Range; Mean (SD)	94−157; 133.46 (18.87)
Peak systolic blood pressure achieved (mm Hg) − Range; Mean (SD)	130−220; 167 (22.6)
Peak rate-pressure product (RPP) − Range; Mean (SD)	13160−29600; 22360.29 (4583)
Peak dobutamine dose (microgram/kg/min) − Range; Mean (SD)	20−40; 38.57 (43)
Subjects who achieved target heart rate	23 (65.7)
ECG − ST segment changes of ischemia	08 (22.9)
Side effects	13 (37.1)
Headache and nausea	03 (8.6)
Chest discomfort/pain	09 (25.7)
Atrial ectopics	02 (05.7)
Ventricular ectopics	04 (11.4)
Wall motion analysis results	
Total segments with abnormal response	82
Grade 1 change from baseline	66 (76.74)
Grade 2 change from baseline	16 (23.26)
Predicted coronary artery territories of segments with abnormal response	
Total arterial territories	46
Left anterior descending artery	18 (39.13)
Left circumflex artery	20 (43.48)
Right coronary artery	08 (17.39)

* Continuous variables are presented as range, mean and standard deviation; categorical variables are expressed as number and percentage in parenthesis.

Coronary angiographic findings (Table III)

Of the 35 subjects, 6 (17.14%) had no significant coronary lesions; 29 (82.9%) had 54 significant coronary artery lesions – most of them (79.63%) in the left coronary territories, with LCX lesions having the highest frequency (23 lesions, 42.59%) and 02 (3.7%) in the left main coronary artery (LMCA). Single vessel disease (SVD) was found in 11, LCX again representing the most frequent one involved (5, 14.29%). Although LAD represented the least frequent artery in the SVD category, it had the second highest frequency overall.

Table III: Coronary angiographic findings in subjects (N=35)

Parameters	Values*
Distribution of lesions by coronary arteries – 29 (82.9%) subjects with total lesions 54.	
Left main coronary artery	02 (3.71)
Left anterior descending (LAD)	18 (33.33)
Left circumflex (LCX)	23 (42.59)
Right coronary (RCA)	11 (20.37)
Distribution of subjects by presence and extent of coronary artery disease (N= 35)	
No significant disease	06 (17.14)
Single vessel disease (SVD)	11 (31.42)
LAD	02 (05.70)
LCX	05 (14.29)
RCA	04 (11.43)
Double vessel disease (DVD)	11 (31.42)
Triple vessel disease (TVD)	07 (20.00)

*Categorical variables are expressed as number and percentage in parenthesis

Overall, we could achieve a sensitivity of 93.1% and a specificity of 66.7%, with an overall accuracy of 88.57% (Table IVa). In terms of specific vessel territories (Table IVb), the DSE performed best for the LAD territory (accuracy rate of 94.29%), and the overall accuracy level was good (>90%) in all three vessel territories.

Comparison of the severity of DSE test results with the angiographic findings (Table IVc) show that those with a change of 2 grades in terms of wall motion from baseline (Group B subjects) compared to those with a change of 1 grade (Group A subjects) had a higher peak wall motion score index (1.371 ± 0.082 versus 1.15 ± 0.071, p<0.001), average number of coronary artery stenosis (2.63 ± 0.518 versus 1.38 ± 0.81, p<0.001), and triple vessel CAD frequency (62.5% versus 8.6% of the total 7 TVD subjects detected, p=0.003). The presence of double vessel CAD was higher among Group A subjects, but not statistically significant. All of the single vessel coronary artery disease patients were in Group A (11 versus 0 in Group B, p<0.001) suggesting that individual coronary artery lesions reflect poorly on the corresponding wall segments if other coronary arteies provide sufficient collateral support.

Table IV: Performance and accuracy of Dobutamine Stress Echocardiography in prediction of coronary artery disease (N=35)

a. Performance

Sensitivity	− 93.1%
Specificity	− 66.7%
Accuracy	− 88.57%

b. Performance according to coronary artery territory

Territory	Predicted diseased	Predicted disease-free	Missed	Accuracy (%)
LAD	16	17	02	94.29
LCX	20	12	03	91.43
RCA	08	24	03	91.43

c. Comparison of DSE and CAG findings between subjects with 1 grade (Group A) and 2 grade (Group B) worsening of regional wall motion during stress echocardiography

Variables	Group A (n=21)*	Group B (n=08)*	p values**
Peak Wall Motion Score Index	1.152 (0.071)	1.371 (0.082)	<0.001
Average number of coronary lesions	1.38 (0.81)	2.63 (0.518)	<0.001
Single vessel CAD	11 (47.8)	0 (0)	<0.001
Double vessel CAD	06 (26.0)	03 (37.5)	0.893
Triple vessel CAD	02 (08.6)	05 (62.5)	0.003

* Continuous variables are presented as mean and standard deviation in parenthesis; categorical variables are expressed as number and percentage in parenthesis.** p values were calculated by Student's t test for continuous and Chi-square test for categorical variables.

Discussion

According to the age range and mean age of the patients together with their ischemic symptoms (typical and atypical angina) the patients of the present study had intermediate to high pre-test likelihood of coronary artery disease.[9]

The dobutamine dosage schedule that was followed in the study allowed achievement of a high peak dose, probably contributing to the high diagnostic yield. Yet the side effect profile consisted mostly of minor complaints. Mathias et al[10] reported the occurrence of headache in 2% and nausea in 4% subjects (n=4033) whereas in the present study they occurred in 8.6% subjects. Their meta-analysis cited an 11% incidence of chest pain whereas Secknus & Marwick[11] reported chest pain in 24% of subjects and Geleijnse et al[8] reported a figure of about 20%. In the current study

it occurred in 25.7% of subjects, but none of them required treatment other than 2 puffs of GTN and all of them were associated with significant wall motion abnormality. The authors cited above-reported incidence of atrial and ventricular ectopics in around 10%[8] and 15%[11] compared to our result (17.1%). Atrial and ventricular tachycardias were not observed in the current study. Symptoms such as dyspnea or vomiting occurred in 0.3% and 0.1% of subjects in the series of Mathias et al[10], but were not seen in the current study.

The mean peak heart rate, rate pressure product and the peak of systolic blood pressure achieved in the study of Mazeika et al[12] were 116 ± 20 beats/minute, 18845 ± 4156 and 172 ± 22 mm Hg, respectively. In the current study, the heart rate achieved was higher than that of Mazeika et al[12] and closer to the study of Elhendy et al[13] in which an aggressive dobutamine stress protocol comparable to the current study was used. The rate pressure product of the current study was higher than Elhendy et al study[13] but comparable to the study of Mazeika et al[12]. Therefore, significant hemodynamic and peak stress was consistently achieved in the present study.

Elhendy et al[13] reported the occurrence of ST segment depression in 38% of patients, but did not find any relation between these changes with severity of coronary lesions. In the present study, the occurrence of this change was lower in frequency, but was associated with multi-vessel coronary lesions.

The coronary territory distribution of the myocardial segments with abnormal wall motion in the present study is different than that of Segar et al.[14] In their sample of 85 patients, RCA had the highest territory of abnormal segments, followed by LAD and LCX. In the study of Elhendy et al[13], LAD was the most frequent territory involved, followed by LCX and RCA. In the series of Beleslin et al[15], LAD was the most frequent territory identified, followed by RCA and LCX. Tousolis et al[16] identified LAD as the most frequently (21 patients, n=30) involved territory. The present study identified highest number of diseased segments in the LCX territory, followed by LAD and RCA territories.

There is clear preponderance of LAD territory involvement in the published reports. The findings of the present study differ in this respect, which is also reflected in the angiographic findings in our study. In 23 (42.59%) subjects the lesion was located in the left circumflex territory. This territory is the most difficult one to be visualized and assessed by stress echocardiography, and dobutamine stress echocardiography has advantage over other stress modalities in that it creates less motion artefacts. Our subjects also had high proportion of multi-vessel disease (51.4%), compared to the series of Daigianti et al[17] (25% [n=60] patients with suspected CAD). Elhendy et al[13] however reported a higher frequency (70%, n=147), but their study consisted of a high proportion of patients with known myocardial infarction (65%).

The present study indicated a high sensitivity and low specificity of DSE in detecting CAD. Segar et al[14] reported detection rates of 88% for LAD stenosis, 82% for LCX stenosis and 86% for RCA lesions. Bigi et al[18] in their review cited the following sensitivity figures: 69% for LAD lesions, 43% for RCA lesions and 69% for LCX lesions. These figures are from subjects with single vessel disease. In subject with single vessel disease, apparently stress test has lower sensitivity and specificity. Sawada et al[19] found that sensitivity and specificity of DSE in patients with multi-vessel disease are higher – 89% and 85% respectively.

In our study, Group B patients were characterized by a significantly higher peak wall motion score index and a lower baseline EF (p=0.063). These two variables, together with the greater deterioration of wall motion at peak stress, identified subjects who had high risk angiographic profiles. They had significantly higher number of coronary artery stenosis ($p<0.001$), a higher incidence of triple vessel coronary artery disease. Only 3 (37.5%) of these Group B patients had double vessel disease, involving both LAD and LCX in all three subjects. Therefore, our study identified a subset of patients with severe coronary artery disease by the severity of induced wall motion abnormality during dobutamine stress. Elhendy et al[13] in a similar study explored the DSE test variables with perfusion studies as well as coronary angiography. They identified similar sets of variables predictive of severity of disease, together with presence of wall motion abnormality in LAD territory. Hoffman et al[6] reported that the severity of wall motion deterioration improved the sensitivity and positive predictive value of the test but did not comment on the predictive role of

such finding. A pilot study has found that measurement of high sensitivity troponin T during DSE identifies patients with CAD even if DSE is negative and also improves the sensitivity and specificity of DSE in detecting severe CAD when combined with positive DSE results.[20]

This study achieved a good sensitivity but low specificity in DSE compared to previously reported studies.[6,13,20] Among the reasons suggested by American Society of Echocardiography for lower specificity in DSE are hypertensive responses during stress, inexperienced personnel/interpreter bias, circumflex coronary territory disease etc., which may have occurred in the present study.[21] The study however showed that severe worsening of regional function, defined as an increase of wall motion score of 2 grade, occurs in patients with anatomical coronary abnormality with poor prognosis – extensive coronary artery disease as assessed by mean number of stenotic arteries and a greater prevalence of multi-vessel disease. This can be explained by more severe reduction in coronary flow reserve with more extensive coronary artery disease. Additionally, the impairment of flow to the ischemic regions may be more profound in the presence of more extensive coronary artery disease owing to diminished flow reserve in the adjacent coronary artery beds resulting in poor collateral support. In our study, patients with more severe deterioration of regional wall motion had a greater prevalence of multiple territory involvement associated with more severe impairment of perfusion. This by itself is an indicator of poor prognosis.

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