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Cardiac Image

Acute Beta Blockade at Peak Stress: Will It Alter the Sensitivity of Dobutamine Stress Echocardiography in Patients with Normal Resting Wall Motion?

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Background: We compared the accuracy of recovery phase images following administration of intravenous propranolol with peak stress images, for detection of coronary artery disease in patients with no resting wall motion abnormalities undergoing dobutamine stress echocardiography.

Methods: We enrolled 100 consecutive patients with no resting wall motion abnormalities who underwent dobutamine stress echocardiography. Propranolol was injected after termination of dobutamine infusion. Positive peak stress images were defined as the induction of wall motion abnormalities at any stage before propranolol injection. Positive recovery phase images were defined as maintenance or worsening of wall motion abnormalities induced at peak stress, or the appearance of new wall motion abnormalities during recovery phase. Significant coronary stenosis was defined as ≥ 50% obstruction of ≥ 1 sizable artery by coronary angiography.

Results: Seventy-two patients (72%) had significant coronary artery disease. Analysis of peak stress images revealed sensitivity, specificity, positive and negative predictive values of 80.6%, 85.7%, 93.5%, and 63.2%; the overall accuracy was 82%. Analysis of the recovery phase images revealed sensitivity, specificity, positive and negative predictive values of 91.7%, 75%, 90.4%, and 77.8%; here, the overall accuracy was 87%.

Conclusions: In patients with no resting wall motion abnormalities, acute beta blockade during dobutamine stress echocardiography improved the sensitivity of recovery phase images for detection of significant coronary artery disease versus peak stress images, but with reduced specificity.

Key Words: Accuracy • Beta blocker • Coronary artery disease • Dobutamine stress echocardiography • Recovery phase images

INTRODUCTION

Dobutamine stress echocardiography (DSE) is widely acknowledged as a procedure used for diagnostic evaluation of patients with known or suspected coronary artery disease (CAD).[1] However, a wide range of procedural sensitivity (from 54% to 96%) and specificity (from 62% to 93%) was reported in the literature due to variation of baseline clinical characteristics, angiographic selection bias, and several echocardiographic and angiographic technical factors.[2,3] The presence of resting wall motion abnormalities (WMA) has a particular influence on the accuracy of DSE: in a meta-analysis of 62 studies, sensitivity tended to be lower ($p = 0.14$) and specificity higher ($p < 0.01$) in studies that excluded patients with resting WMA, compared with studies that enrolled such a patient subset.[3]

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Evidence from prospective cohorts suggested that rapid injection of beta blockers at peak dobutamine stress improves the sensitivity for detection of CAD, without compromise of the specificity.[4,5] Yet, such cohorts did not exclude patients with resting WMA. The value of acute beta blockade during DSE in patients with normal resting wall motion remains unclear. Hence, we sought to compare the diagnostic accuracy of recovery phase images following rapid intravenous injection of propranolol during peak dobutamine stress, versus peak stress images, for detection of angiographically significant CAD in patients with normal baseline resting wall motion.

MATERIALS AND METHODS

Patient selection

Prospectively, we enrolled 100 consecutive patients referred to our stress echocardiography labs for diagnostic evaluation of CAD during the period from December 2011 to June 2012. Patients were considered eligible for inclusion if they had ischemic-type chest pain or other symptoms suggestive of myocardial ischemia, and were considered for non-invasive stress testing. We excluded patients with previously diagnosed CAD, those with resting WMA, those with a significant valvular or congenital heart disease, those with congestive heart failure, left ventricular hypertrophy or bundle branch block, those with a protruding fresh left ventricular thrombus, those with a contraindication to dobutamine (for example: history of complex ventricular arrhythmia, uncontrolled hypertension defined as blood pressure > 180/110), those with a contraindication to beta blockers (for example: history of bronchial asthma, peripheral arterial disease), and patients with limited life expectancy due to a coexistent disease (for example: malignancy). Before inclusion, informed written consent was obtained from each patient, and the study protocol was reviewed and approved by our Institutional Human Research Committee as it conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 2013.

Resting echocardiographic assessment

Assessment of regional and global left ventricular systolic function was performed in all patients by transthoracic echocardiography using a Hewlett Packard Sonos 5500 cardiac ultrasound machine (Hewlett Packard, Andover, Massachusetts, USA) equipped with harmonic imaging capabilities. A 2.5 MHz phased array probe was used to obtain standard 2-D, M-mode and Doppler images. Patients were examined in the left lateral recumbent position using standard parasternal and apical views. Images were digitized in cine-loop format and saved for subsequent playback and analysis. Views were analyzed by a single expert observer employing the software of the echocardiography machine. Regional wall motion was assessed according to the standard 16-segment model as recommended by the American Society of Echocardiography.[6] Regional wall motion was visually assessed for each segment individually, considering both endocardial excursion and systolic thickening, and each segment was graded according to the semi-quantitative scoring system described by the American Society of Echocardiography.[6]

Dobutamine stress echocardiography protocols

Patients who were receiving beta blockers or non-dihydropyridine calcium antagonists for whatever indication had to discontinue these medications at least 48 hours before DSE. Dobutamine (Dobutrex®, Eli Lilly and Company, Indianapolis, USA) was administered by intravenous infusion starting at a dose of 10 ug/kg/min for three minutes, and raised incrementally by 10 ug/kg/min every three minutes up to a maximum of 40 ug/kg/min, or until a study endpoint was reached. In patients not achieving 85% of their age-predicted maximal heart rate at the end of the final stage, atropine was administered intravenously in 0.25 to 0.5 mg increments at one-minute intervals up to a maximum dose of 2.0 mg, while dobutamine infusion was continued. Immediately following the acquisition of peak stress images, a bolus of 5 mg propranolol hydrochloride (Inderal®, AstraZeneca, London, UK) was injected intravenously within one minute of termination of dobutamine infusion.[7] Regional wall motion was assessed at peak dobutamine stress (peak stress images), as well as during the recovery phase 2-3 minutes after injection of propranolol (recovery phase images). Visual assessment of endocardial excursion and systolic thickening was performed individually for each segment by the same observer as

before. The observer was blinded to the clinical and angiographic data. Positive peak stress images were defined as the induction of WMA in at least 2 contiguous non-overlap segments at any stage of dobutamine infusion before the injection of propranolol. Positive recovery phase images were defined as maintenance or worsening of WMA induced at peak stress, or appearance of new WMA only during the recovery phase.

Monitoring

All patients had continuous heart rate, electrocardiogram (ECG), and pulse oximetry monitoring. Heart rate and blood pressure readings were recorded at baseline, at the end of each stage of dobutamine infusion, and during the recovery phase. A 12-lead ECG was recorded at baseline and during the recovery phase. Patients were questioned at the end of the test regarding any symptoms or adverse drug reactions.

Test termination endpoints

Endpoints for terminating the test included attainment of the maximum dose of dobutamine and/or atropine, achievement of target heart rate (greater than 85% of age-predicted maximal heart rate), echocardiographic detection of WMA, symptoms judged to be unacceptable by the attending cardiologist, serious arrhythmia detected by ECG, ST segment elevation > 0.1 mV at 80 milliseconds from the J point, systolic blood pressure > 200 mm Hg, diastolic blood pressure > 110 mm Hg, or a decrease in systolic blood pressure > 30 mm Hg from the baseline value.

Coronary angiography

All patients underwent selective left and right coronary angiography using the standard technique, and the angiographic data were individually analyzed by an independent interventional cardiologist, blinded to both clinical and echocardiographic findings. The procedure was performed within one week after DSE evaluation. Reference vessel diameter and the percent diameter stenosis were measured using quantitative coronary analysis (Inturis Allura, Phillips Medical Systems, Netherlands). Significant coronary stenosis was defined as 50% or more luminal obstruction of at least one sizable epicardial coronary artery (measuring 2.5 mm or more in diameter), seen in two different projections. Multi-vessel disease was defined as significant stenosis of more than one sizable coronary artery, or significant stenosis of the left main coronary artery.

Statistical analysis

Continuous variables were presented as mean ± SD, if they were normally distributed. Data were tested for normal distribution using the Kolmogorov-Smirnov test. Categorical variables were described with absolute and relative (percentage) frequencies. Taking the results of coronary angiography as the 'gold standard' for diagnosis, the sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy were calculated according to the standard definitions, individually for the peak stress images and the recovery phase images: in the whole cohort, in patients with single-vessel disease, and in those with multi-vessel disease. Twenty cases were randomly selected for analysis of intra-observer variability of the single observer. Similarly, ten cases were randomly selected and analyzed by a second observer (W.N.) for analysis of inter-observer variability between the 2 observers. Intra-observer and inter-observer variability were tested using Spearman's correlation. All tests were two-sided and a probability value of $p < 0.05$ was considered statistically significant. Analyses were performed with the SPSS version 16.0 statistical package (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline clinical characteristics

We excluded 10 patients for poor acoustic window, or poor image quality. We enrolled 100 consecutive patients with suspected CAD and no resting WMA, who were referred for evaluation by DSE. The mean age of the study cohort was 53.4 ± 8.4 years; 56% were males, 36% diabetic. Table 1 shows the baseline clinical characteristics of the study cohort.

Test protocol data

The mean test duration was 15.0 ± 1.2 minutes. All patients achieved target heart rate, and atropine was needed in 56 (56%) patients. The mean heart rate was 81 ± 11 beats.min^{-1} at rest, 157 ± 28 beats.min^{-1} at peak stress, and 112 ± 17 beats.min^{-1} during the recovery

Table 1. Baseline clinical characteristics of the study cohort

Character	Study cohort (N = 100)
Age (years)	53.4 ± 8.4
Male gender	56 (56)
Diabetes mellitus	36 (36)
Hypertension	45 (45)
Smoking	45 (45)
Dyslipidemia	26 (26)
Family history of CAD	39 (39)
CCS class	
Class I	56 (56)
Class II	44 (44)
Medications	
Beta blockers	33 (33)
Aspirin	57 (57)
Statins	49 (49)
ACEI/ARB	43 (43)

Continuous variables are presented as mean ± SD, whereas categorical variables are presented as number (percentage). ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CAD;coronary artery disease; CCS, Canadian Cardiovascular Society.

phase. The mean systolic blood pressure was 126 ± 15 mm Hg at rest, 153 ± 23 mm Hg at peak stress, and 131 ± 21 mm Hg during the recovery phase. The mean diastolic blood pressure was 78 ± 12 mm Hg at rest, 89 ± 23 mm Hg at peak stress, and 80 ± 13 mm Hg during the recovery phase. Eighteen patients (18%) developed hypertensive response to DSE: in 13 patients (13%) diastolic, and in 5 (5%) both systolic and diastolic. The mean rate pressure product was 10206 ± 2093 beats.mm Hg.min^{-1} at rest, 24021 ± 5431 beats.mm Hg.min^{-1} at peak stress, and 14672 ± 3265 beats.mm Hg.min^{-1} during the recovery phase. Fifteen patients (15%) with negative test result at peak stress developed new WMA during the recovery phase. In these 15 patients, significant CAD was confirmed in 10: multi-vessel CAD in 4 and single-vessel CAD in 6 (3 affected in the right coronary artery, 2 in the left anterior descending, and 1 in the left circumflex artery). In the other 5 patients, the result during the recovery phase was false positive (1 had 40% stenosis of the right coronary artery, 1 had 30-40% stenosis of the left anterior descending artery, 2 had corkscrew vessels, and 1 had ectatic changes with slow flow in the left anterior descending and right coronary artery). Forty-eight patients (48%) had augmented (more profound) WMA in the recovery phase images, confirming the results of acute phase images (peak stress).

Accuracy of DSE to detect significant CAD

Seventy-two patients (72%) had significant CAD by coronary angiography, of whom 40 (55.6%) had multi-vessel disease. At peak stress images, there were 58 true positive, 24 true negative, 4 false positive, and 14 false negative results compared with coronary angiography. Analysis of peak stress images revealed sensitivity, specificity, positive and negative predictive values of 80.6%, 85.7%, 93.5%, and 63.2%, with an overall accuracy of 82%. During the recovery phase, there were 66 true positive, 21 true negative, 7 false positive and 6 false negative results compared with coronary angiography. Analysis of the recovery phase images revealed sensitivity, specificity, positive and negative predictive values of 91.7%, 75%, 90.4%, and 77.8%; the overall accuracy was 87% (Table 2). Analysis of intra-observer variability of the single observer (Z.A.) revealed high agreement between repeated assessments of regional wall motion at peak stress (r = 0.92), and during the recovery phase (r = 0.95). Similarly, analysis of inter-observer variability between 2 observers revealed good agreement between repeated assessments of regional wall motion at peak stress (r = 0.90), and during the recovery phase (r = 0.91).

Accuracy of DSE to detect single-vessel CAD

Of 72 patients with significant CAD, 32 (44.4%) had single-vessel disease. At peak stress images, there were 24 true positive, 24 true negative, 2 false positive, and 8 false negative results compared with coronary angiography. Analysis of peak stress images revealed sensitivity, specificity, positive and negative predictive values of 75%, 92.3%, 92.3%, and 75%, with an overall accuracy of 82.8%. During the recovery phase, there were 28 true positive, 21 true negative, 4 false positive and 4 false negative results compared with coronary angiography. Analysis of the recovery phase images revealed sensitivity, specificity, positive and negative predictive values of 87.5%, 84%, 87.5%, and 84%; the overall accuracy was 85.9% (Table 2).

Accuracy of DSE to detect multi-vessel CAD

Of 72 patients with significant CAD, 40 (55.6%) had

Table 2. Accuracy parameters of the peak stress images and recovery phase images for the whole cohort, the subgroup with single-vessel disease, and the subgroup with multi-vessel disease

Group	Sensitivity	Specificity	PPV	NPV	Accuracy
Whole cohort – peak stress	80.6	85.7	93.5	63.2	82
Whole cohort – recovery phase	91.7	75	90.4	77.8	87
Single-vessel disease – peak stress	75	92.3	92.3	75	82.8
Single-vessel disease – recovery phase	87.5	84	87.5	84	85.9
Multi-vessel disease – peak stress	85	92.3	94.4	80	87.9
Multi-vessel disease – recovery phase	95	87.5	92.7	91.3	92.2

All variables are presented as percentages.
NPV, negative predictive value; PPV, positive predictive value.

multi-vessel disease. At peak stress images, there were 34 true positive, 24 true negative, 2 false positive, and 6 false negative results compared with coronary angiography. Analysis of peak stress images revealed sensitivity, specificity, positive and negative predictive values of 85%, 92.3%, 94.4%, 80%; the overall accuracy was 87.9%. During the recovery phase, there were 38 true positive, 21 true negative, 3 false positive and 2 false negative results compared with coronary angiography. Analysis of the recovery phase images revealed sensitivity, specificity, positive and negative predictive values of 95%, 87.5%, 92.7%, and 91.3%; the overall accuracy was 92.2% (Table 2).

Safety of DSE protocol

No major complications were observed at peak stress or during the recovery phase. Two patients (2%) developed supraventricular tachycardia at peak stress that was effectively terminated by injection of propranolol in the standard dose defined by the protocol. No major side effects were reported following propranolol injection. Moreover, no patient reported any clinical events during the period from DSE evaluation to coronary angiography.

DISCUSSION

Major findings

The current study demonstrated that in symptomatic patients with suspected CAD referred for evaluation by DSE who have no resting WMA, rapid intravenous injection of propranolol at peak dobutamine stress resulted in improved sensitivity but reduced specificity of the recovery phase images for detection of angiographically significant CAD compared with peak stress images only. Similarly, the sensitivity improved – and the specificity decreased – during recovery phase images, both in patients with single-vessel disease, and in those with multi-vessel disease. Both the sensitivity and specificity were better in patients with multi-vessel disease compared with the whole cohort in peak stress images, as well as in recovery phase images.

Accuracy parameters of DSE for diagnosis of CAD

Accuracy parameters of DSE are influenced by many patient and test-related factors; among these are baseline patient characteristics, angiographic referral bias, and technical factors.[3] The inclusion of patients with resting WMA or those with prior myocardial infarction increases the sensitivity but decreases the specificity of DSE, primarily because those patients more often have more extensive CAD.[3] Likewise, angiographic referral bias increases the sensitivity at the expense of decreased specificity of DSE. Similarly, the definition of positive results based on the presence of preexisting WMA at rest, rather than dobutamine-induced new WMA increases the sensitivity, but reduces the specificity.[3] Routine early administration of atropine during DSE, rather than conventional administration at peak stress only in patients who do not achieve their target heart rate, slightly improved the sensitivity and decreased the specificity in diabetic patients with suspected CAD.[8]

Acute beta blockade during DSE

Evidence suggested that acute beta blockade at peak dobutamine stress during DSE improves the sensi-

tivity for detection of CAD, with little effect on specificity.[4,5] However, the issue remains controversial due to the limited number of prior studies, and small sample size.[9] Moreover, these studies enrolled patients with resting WMA, and this may limit the interpretation of peak stress images. In the current study, we opted to exclude patients with resting WMA, in order to improve the visual detection of new WMA in response to dobutamine stress, both at peak stress, and during the recovery phase. Enrollment of patients with normal resting wall motion avoids confusion in recognizing dobutamine-induced WMA. Ongoing with our results, Mathias et al. demonstrated increased sensitivity (from 84% to 92%) of DSE, with a slight reduction of specificity (from 92% to 89%), for diagnosis of CAD with intravenous administration of metoprolol at peak stress.[4] Similarly, they reported improved sensitivity in patients with single-vessel disease (from 73% to 88%), and slightly so in those with multi-vessel disease (from 92% to 95%).[4] In contrast to our study, they included patients with resting WMA (16%). Moreover, they conducted their study in patients referred for coronary angiography, and this may have introduced selection bias. This may possibly explain the higher sensitivity of DSE at peak stress images in their study, compared with ours, in the whole cohort (84% versus 80.6%), as well as in patients with multi-vessel disease (92% versus 85%).[4] Interestingly, both studies reported a similar sensitivity of recovery phase images in the whole cohort (92% versus 91.7%), as well as in patients with multi-vessel disease (95% versus 95%).[4] Yet, the specificity of DSE was higher in their study both in peak stress images (92% versus 85.7%), and in recovery phase images (89% versus 75%).[4] Similarly, Karagiannis et al. studied 200 patients with known or suspected CAD who received intravenous metoprolol at peak stress during DSE. They reported increased sensitivity for detection of CAD of recovery phase images after metoprolol (from 88% to 97%), with no change in specificity (65%) compared with peak stress images.[5] Similarly, they reported improved sensitivity in patients with single-vessel disease (from 81% to 99%), and slightly so in patients with multi-vessel disease (from 85% to 89%).[5] Compared with our study, the sensitivity of DSE in the whole cohort was higher in their study at peak stress images (88% versus 80.6%), as well as in recovery phase images (97% versus 91.7%).[5] Nevertheless, the specificity of DSE was lower in their study both in peak stress images (65% versus 85.7%), and in recovery phase images (65% versus 75%).[5] The fact that 80% of their patients had resting WMA might underlie these differences.

During DSE, the detection of dobutamine-induced new WMA might be hindered by tachycardia, as well as by beta receptor-mediated hyperkinesia of non-ischemic segments. Moreover, since most of the ischemic effect occurs in the subendocardial layer of the myocardium, WMA of an individual segment might be masked by hypercontractility of its mid- and epicardial layers.[10] Rapid intravenous administration of a beta blocker at peak stress during DSE may serve to reduce tachycardia, and improve visualization of new WMA, enhancing the sensitivity of the test. On the other hand, acute blockade of beta 1 and beta 2 receptors during DSE leaves unopposed the alpha receptor-mediated effect of dobutamine on the coronary vascular resistance, further contributing to myocardial ischemia.[11,12] This increases the sensitivity, but decreases the specificity of the test for detection of CAD.

Clinical implications

The added value of acute beta blockade at peak stress during DSE resides in its ability to enhance the visualization of new WMA, and therefore, to improve the diagnostic accuracy of the test in patients with a low pretest probability of CAD. One such example is patients with single-vessel CAD. Indeed, the current study demonstrated that DSE with acute beta blockade was able to detect patients with single-vessel disease with a high sensitivity and specificity (87.5% and 84%, respectively) in the recovery phase images. Similarly, patients with normal resting wall motion have a lower pretest probability of CAD. Another potential implication of DSE with acute beta blockade is patients whose DSE test result was inconclusive/equivocal at peak stress images as a result of unclearly seen WMA. In such a case, acute beta blockade would serve to confirm or rule out doubtful WMA detected at peak stress.

Limitations of the study

Our findings are based on a single-center study with a relatively small sample size. Multi-center studies employing the same protocol in a larger number of patients

are needed. The rather small study population with a high prevalence of significant CAD (72%) – 55.6% of whom had multi-vessel disease – could bias the results, and limits the generalization of the results to groups with different risk characteristics. Moreover, the study cohort consisted of patients who had no resting WMA. Therefore, it is difficult to extrapolate our results to patients with prior myocardial infarction, or baseline resting WMA. Furthermore, the use of propranolol (a non-cardioselective beta blocker) during the recovery phase of DSE is much less common than the cardioselective metoprolol. However, no serious side effects were reported following propranolol injection. Finally, the precise mechanism underlying the variety of responses to propranolol during DSE remains largely unclear.

CONCLUSIONS

In symptomatic patients with suspected CAD referred for evaluation by DSE who have no resting WMA, acute beta blockade at peak dobutamine stress improved the sensitivity of the recovery phase images for detection of angiographically significant CAD, compared with peak stress images alone; however, the specificity was reduced.

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DISCLOSURES

The authors declare that there is no conflict of interest.

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