Dobutamine Stress Echocardiography for the Evaluation of Coronary Artery Disease in Thai Population: Siriraj Experience

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Objective: *No previous report of dobutamine stress echocardiography in the Thai population has been available. The present study seeks to document the protocol, indications, results and safety of dobutamine stress echocardiography performed at Siriraj Hospital.*
Material and Method: *The authors studied 421 [mean age 67.7 ± 11.0 years, 179 (43%) men] consecutive Thai patients undergoing dobutamine stress echocardiography at Siriraj Hospital. The protocol, indications and echocardiographic analysis were described. Clinical characteristics, hemodymanics, results and adverse effects were recorded at the time of dobutamine stress echocardiography.*
Results: *Dobutamine stress echocardiography was performed for preoperative assessment before non-cardiac surgery in 212 patients (50%), for the diagnosis of suspected Coronary Artery Disease (CAD) in 179 patients (43%), for risk stratification of CAD in 24 patients (6%), and for other reasons in six patients (1%). The results were normal and positive for inducible ischemia in 276 (66%) and 80 (19%) patients, respectively. Limiting side effects were observed in 3%. No death, myocardial infarction or life-threatening arrhythmias occurred. Transient stress-associated tachyarrhythmias, such as atrial fibrillation, nonsustained ventricular tachycardia or supraventricular tachycardia, occurred in 3.5% of patients.*
Conclusion: *Dobutamine stress echocardiography was considered a safe and tolerable technique for the evaluation of CAD in Thai population.*

Keywords: *Dobutamine, Coronary artery disease, Safety, Stress echocardiography*

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Coronary artery disease (CAD) has increasingly become a worldwide major health concern. Prompt diagnosis remains a challenge and subsequent appropriate management leads to better outcomes. Traditionally, coronary angiography is a gold standard in the diagnosis of CAD. However, it cannot be used as a screening tool because of limited availability, high cost, need for hospitalization, and relatively high risk of complications associated with the invasive procedure. These limitations are overcome with the application of noninvasive stress testing, such as exercise treadmill testing, stress echocardiography and myocardial perfusion imaging. While coronary angiography provides anatomical information, the noninvasive stress testing shares a common pathophysiological basis and functional approach to CAD - stress-induced myocardial ischemia and the detection of ischemic myocardium demonstrated via electrocardiogram (ECG), two-dimensional echocardiographic or nuclear imaging.

Over the past decade, stress echocardiography, exercise or pharmacological, has been accepted as a reliable tool in the diagnosis and prognostic implication of CAD in various patient populations[1-10]. It

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provides useful information on the key issues of CAD such as a diagnostic accuracy for the noninvasive detection of CAD, identification of myocardial viability, risk stratification in patients after acute myocardial infarction or patients undergoing non-cardiac surgery, and its prognostic significance. This fact has been documented by numerous publications. Because of its high specificity, relatively low cost, versatility, convenience, and safety, stress echocardiography has the potential to become one of the ideal imaging techniques in virtually any clinical arena.

Although two-dimensional and Doppler echocardiography has been widely performed in Thailand for decades and dobutamine stress echocardiography has increasingly become a well-accepted technique worldwide, not many echocardiographic laboratories in Thailand perform stress techniques. Several important limitations exist, such as complex machine set-up, various stress protocols, duration of procedure, requirement of skill and expertise by those who administer the technique and concerns regarding procedural-associated complications especially catecholamine-induced cardiac arrhythmias[11-13]. Data regarding safety and feasibility of stress echocardiography have been well established in several studies [4,14-19]. Nevertheless, most are studies from overseas centers, which may be populated by patients with different characteristics, comorbidities, indications, hemodynamic responses to stress, and test results. This leads to the question whether those available data are also applicable to the Thai population. Interestingly, no previous reports have addressed any aspects of dobutamine stress echocardiography in a Thai population. Dobutamine stress echocardiography has been routinely performed at Siriraj Hospital and to establish more fully its role, the authors, therefore, describe herein the method, indications, stress hemodynamics and results of dobutamine stress echocardiography and evaluate its safety in a consecutive series of patients undergoing this technique at Siriraj Hospital.

Material and Method

Study population

The present study was approved by the institutional ethical committee. All patients gave informed consent to undergo dobutamine stress echocardiography. Clinical characteristics, indications, stress hemodymanics, results and adverse effects were recorded at the time of dobutamine stress echocardiography. From September 2004 through November 2006, 430 patients were referred for dobutamine stress echocardiography. Nine patients were excluded from the analysis due to inadequate echocardiographic images. The remaining 421 patients constituted the study population.

Hypertension was defined as either systolic blood pressure $\geq$ 140 mmHg, diastolic blood pressure $\geq$ 90 mmHg, or the use of antihypertensive medication. Patients were diagnosed as having diabetes mellitus according to the criteria set by the American Diabetes Association [20]. Patients were considered to have hypercholesterolemia if their total cholesterol was $\geq$ 200 mg/dl or if they were receiving lipid-lowering medication.

Dobutamine stress protocol

Dobutamine stress echocardiography was performed [21]. The procedure, possible adverse effects, and potential complications were explained to the patient. Beta-blockers and other antianginal medications were not routinely withheld before the test. Heart rate, blood pressure, 12-lead ECG, and two-dimensional echocardiogram were recorded at rest and at the end of each stage of dobutamine stress protocol. Cardiac rhythm was continuously monitored by the 6-lead ECG throughout the test. Dobutamine was administered in-

Table 1. Baseline characteristics

Characteristics	n = 421
Age (years)	67.7 ± 11.0
Male	179 (43)
Body mass index (kg/m^2)	25 ± 5
Hypertension	328 (78)
Diabetes mellitus	184 (44)
Hypercholesterolemia	241 (57)
Smoking	31 (7)
Family history of premature coronary artery disease	4 (1)
History of coronary artery disease	44 (10)
Prior coronary revascularization	27 (6)
Prior myocardial infarction	21 (5)
History of stroke	28 (7)
Abnormal rest electrocardiogram	181 (43)
Concurrent medications	
Beta-blocker	243 (58)
ACEI / ARB	195 (46)
Digoxin	10 (2)

Results are expressed as mean ± SD or number (%) of patients

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers

travenously by an infusion pump, starting at 5 mcg/kg/min and increasing to 10, 20, 30 and 40 mcg/kg/min every 3 minutes. If the predetermined endpoint was not achieved and the patient had inadequate heart rate response, atropine, in 0.25 mg increments every 1 minute to a total dose of 2 mg, was administered intravenously as needed to augment the heart rate while dobutamine infusion was continued. In the event of serious adverse effects, intravenous propranolol, to reverse beta-adrenergic effects of dobutamine, and sublingual nitroglycerin were available as needed. The predetermined endpoints for the test termination were extensive new or worsening wall motion abnormalities (WMA), the completion of stress protocol, achieving target heart rate, severe angina, positive stress ECG, ST-segment elevation in ECG leads without significant Q wave, hemodynamically significant arrhythmias, hypertension (> 220/110 mmHg), hypotension (> 20 mmHg reduction in systolic blood pressure from the previous stage), and intolerable symptoms. All adverse effects and arrhythmias during dobutamine stress echocardiography were recorded, regardless of clinical significance.

Table 2. Rest and stress hemodynamic and echocardiographic data

Characteristics	
Heart rate (beats/minute)	
Rest	72 ± 14
Peak	132 ± 16
Systolic blood pressure (mmHg)	
Rest	139 ± 24
Peak	146 ± 37
Ejection fraction (%)	
Rest	63 ± 10
Peak	70 ± 14
Impaired ejection fraction at rest	32 (8)
Presence of rest wall motion abnormality	108 (26)
Positive stress electrocardiogram	30 (7)
Abnormal stress left ventricular end-systolic volume	62 (15)
Failure to achieve target heart rate	70 (17)
Presence of fixed wall motion abnormality	79 (19)
Test result	
Normal	276 (66)
Ischemic or positive	80 (19)
Wall motion score index	
Rest	1.2 ± 0.4
Peak	1.3 ± 0.5
% Abnormal segments	
Rest	15.3 ± 30.3
Peak	16.8 ± 30.2

Results are expressed as mean ± SD or number (%) of patients

Echocardiographic Analysis

Two-dimensional echocardiography was performed with the patient in the left lateral decubitus position. Echocardiographic images in parasternal long- and short-axis, apical four- and two-chamber views were obtained at rest, during the final minute of each stage of dobutamine infusion, and in the recovery. For the purpose of analysis, echocardiographic images at baseline and at each stage were continuously stored on videotape and, in addition, digitized images were required to obtain quad-screen format (baseline, low dose at 5 to 10 mcg/kg/min, peak dose and recovery images) for a side-by-side comparison. Dobutamine stress echocardiography was reviewed by a cardiologist experienced in the interpretation of regional ventricular wall motion. Wall motion was assessed and scored 1 through 5 in each of 16 segments, according to a previously described recommendation by the American Society of Echocardiography[22] where 1 = normal, 2 = hypokinesis, 3 = akinesis, 4 = dyskinesis, and 5 = aneurysm. Left ventricular wall motion score index was calculated, at rest and peak stress, by summing the scores and dividing by the number of visualized segments. The development of new or worsening WMA, including a deterioration of wall motion after an improvement at low-dose dobutamine, was considered inducible ischemia and positive dobutamine stress echocardiography. A resting WMA unchanged with dobutamine infusion or an akinetic segment that became dyskinetic was defined as fixed abnormality. The percentage of abnormal segments was calculated at rest and stress as the number of abnormal segments divided by the number of visualized segments, multiplied by 100. The percentage of ischemic and fixed segments was similarly derived. Normal dobutamine stress echocardiography was defined if there were no WMA at rest or stress. Abnormal dobutamine stress echocardiography was defined if there was inducible ischemia or fixed WMA. Target heart rate was defined as 85% of age-predicted maximal heart rate (220-age in years). The dose of dobutamine and heart rate at which the deterioration of wall motion first occurred were recorded. Ischemic threshold was defined as the heart rate at which new or worsening WMA occurred, divided by the age-predicted maximal heart rate, multiplied by 100%. Ejection fraction was

evaluated by a modification of the method of Quinones et al[23] combined with visual estimation. Impaired left ventricular systolic function was defined as an ejection fraction < 50%. The change in left ventricular end-systolic volume (LVESV) from rest to peak stress was recorded as either normal (decrease in LVESV) or abnormal (increase or absence of a decrease). Dynamic intracavitary obstruction during dobutmaine infusion, indicating an excessive hyperdynamic left ventricular function, was defined as either an obliteration of left ventricular cavity at peak stress or an increase in intracavitary pulse-wave Doppler peak velocity of at least 2 m/sec. The stress ECG was positive for ischemia if there was horizontal or downsloping ST-segment depression of ≥ 1 mm at 80 ms after the J-point in the absence of baseline ST-segment deviation.

Statistical analysis

Categorical variables were summarized as percentages and continuous variables as mean ± standard deviation (SD). Comparison between groups was based on the Student's *t* test for continuous variables and Pearson's chi-square test for categorical variables. A p-value of <0.05 was considered statistically significant.

Results

Clinical data

All patients were referred, as clinically indicated, for dobutamine stress echocardiography primarily by cardiologists who were responsible for clinical management. The study population consisted of 421 consecutive patients [mean age 67.7 ± 11.0 years (range

Table 3. Clinical, electrocardiographic, baseline and stress echocardiographic characteristics for ischemic and non-ischemic dobutamine stress echocardiography

Variables	Ischemic n = 80	Non-ischemic n = 341	p-value
Age (years)	69 ± 9	68 ± 11	0.429
Male	44 (55)	135 (40)	0.013
Hypertension	64 (80)	263 (77)	0.608
Diabetes mellitus	40 (50)	143 (42)	0.198
Hypercholesterolemia	58 (73)	182 (53)	0.001
Smoking	13 (16)	18 (5)	0.002
Prior myocardial infarction	4 (5)	17 (5)	1.000
Prior revascularization	9 (11)	18 (5)	0.051
Beta-blocker therapy	57 (71)	185 (54)	0.005
Abnormal rest electrocardiogram	51 (64)	129 (38)	<0.0001
Positive stress electrocardiogram	12 (15)	18 (5)	0.006
Achieving target heart rate	59 (74)	291 (86)	0.011
Rest ejection fraction (%)	55 ± 13	65 ± 9	<0.0001
Impaired LV systolic function	16 (20)	16 (5)	<0.0001
Angina during the test	25 (31)	10 (3)	<0.0001
Abnormal stress LV end-systolic volume	53 (66)	9 (3)	<0.0001
Heart rate (beats/minute)			
Rest	69 ± 13	73 ± 14	0.028
Peak	131 ± 18	133 ± 15	0.263
Systolic blood pressure (mmHg)			
Rest	140 ± 21	139 ± 25	0.613
Peak	147 ± 39	146 ± 37	0.897
Wall motion score index			
Rest	1.5 ± 0.5	1.1 ± 0.4	<0.0001
Peak	1.9 ± 0.6	1.1 ± 0.3	<0.0001
% Abnormal segments			
Rest	35 ± 37	11 ± 2	<0.0001
Peak	60 ± 30	77 ± 20	<0.0001

Results are expressed as mean ± SD or number (%) of patients
LV = left ventricle

30 to 95), 179 men (43%)]. Dobutamine stress echocardiography was performed for preoperative assessment before non-cardiac surgery in 212 patients (50%), for the diagnosis of suspected CAD in 179 patients (43%), for risk stratification of CAD in 24 patients (6%), and for other reasons in six patients (1%). Reasons for inability to exercise were debility or aging in 286 patients (67.9%), orthopedic limitations in 60 patients (14.3%), peripheral vascular disease in 33 patients (7.8%), pulmonary disease in 13 patients (3.1%), and others in 29 patients (6.9%). No patient had unstable CAD, significant tachyarrythmias, or uncontrolled hypertension before the test. Table 1 summarizes the clinical characteristics of patients undergoing dobutamine stress echocardiography. History of chest pain was reported in 138 (33%) patients; among these, 21 had typical angina.

Hemodynamic and stress echocardiographic data

Hemodynamic and stress echocardiographic data are shown in Table 2. The mean peak dose of dobutamine infusion was 36 ± 8 mcg/kg/min. Atropine, mean dose 0.5 ± 0.6 mg, was administered in 240 (57%) patients. The mean rate-pressure product and peak heart rate achieved were 19,202 ± 5520 MTTI and 87 ± 10 % of age-predicted maximal heart rate, respectively. The mean heart rate increase was 60 ± 20 beats/minute. Among 70 patients who failed to achieve target heart rate, 53 (76%) were receiving beta-blockers and 21 (30%) patients had inducible ischemia. The reasons for test termination were achieving target heart rate in 312 patients (74.1%), detection of inducible ischemia in 53 patients (12.6%), completion of the protocol in 44 patients (10.5%), intolerable symptoms in 5 patients (1.2%), hypotension in 3 patients (0.7%), and hypertension in 4 patients (0.9%). The reasons for failure to achieve target heart rate were completion of the protocol in 63% of the patients, inducible ischemia in 21% of the patients, and side effects in 16% of the patients. Among 108 patients with rest WMA, prior myocardial infarction was reported by history in 15 patients and by significant Q wave on ECG in 37 patients. Among patients with ischemic dobutamine stress echocardiography, ischemic threshold was 75 ± 16 % of age-predicted maximal heart rate. The clinical, electrocardiographic, baseline and stress echocardiographic findings for the ischemic and non-ischemic test result are shown in Table 3. Patients with inducible ischemia were more likely to be male, current smokers, on beta-blocker therapy and to have hypercholesterolemia, have a history of coronary revascularization, an abnormal rest ECG, impaired left ventricular systolic function at rest, angina during dobutamine infusion, a positive stress ECG, and abnormal LVESV response to stress ($p < 0.05$). As expected, the percentages of abnormal segments and wall motion score index at rest and peak stress were significantly greater in patients with ischemic than with nonischemic test results ($p < 0.0001$).

Table 4. Adverse effects during dobutamine stress echocardiography

Adverse effects	No. (%)
Palpitation	161 (38)
Dyspnea	45 (11)
Chest pain	35 (8)
Headache	11 (3)
Nausea	11 (3)
Lightheadedness	7 (2)
Hypertension	4 (0.9)
Hypotension	3 (0.7)
Atrial fibrillation	5 (1)
Supraventricular tachycardia	7 (2)
Nonsustained ventricular tachycardia	2 (0.5)

Adverse effects and safety of dobutamine stress echocardiography

The dobutamine infusion was well tolerated by most patients, even though mild adverse effects, such as palpitation, dyspnea and chest pain, were common (Table 4). There was no life-threatening complication during the present study. Specifically, neither fatal event nor myocardial infarction was observed. No patient required an intravenous betablocker to reverse adverse effects. The majority of adverse effects were mild and resolved spontaneously after the discontinuation of dobutamine infusion. Dobutamine extravasation was not reported. Atropine was well tolerated, but it appeared to prolong the heart rate recovery period. Intracavitary obstruction without an evidence of inducible ischemia developed in 10 patients, but led to the interruption of the test due to hypotension with lightheadedness in three patients. These resolved quickly with heart rate recovery and intravenous fluid resuscitation. Palpitation was the most common symptom reported (38%) in the present study and, in all patients, related to stress-induced tachycardia, which resolved quickly after the discontinuation of dobutamine infusion. Chest pain or angina occurred in 38 patients, but none had severe angina necessitating test termination. Asymptomatic arrhythmias were common; isolated

premature atrial and ventricular contractions occurred in 62 (15%) and 128 (30%) patients, respectively. Hemodynamically significant tachyarrhythmias, including ventricular fibrillation, were not reported. Stress-associated tachyarrhythmias, such as atrial fibrillation, nonsustained ventricular tachycardia or supraventricular tachycardia, were transient and resolved following the discontinuation of dobutamine. The occurrence of adverse effects was not associated with any clinical or echocardiographic variables.

Discussion

The clinical implications of dobutamine stress echocardiography in the evaluation and risk stratification of CAD have been widely accepted in several patient subgroups. The present study showed the experience at Siriraj Hospital on dobutamine stress echocardiography in a Thai population. Even in the setting of high-dose dobutamine-atropine protocol as reported in the present study, dobutamine stress echocardiography was considered tolerable and safe without any serious adverse effects, such as death, myocardial infarction or sustained arrhythmias. Among 430 consecutive patients referred for dobutamine stress echocardiography in the present study, 9 (2%) were excluded because of an inadequate acoustic window. In previous reports, an inadequate echocardiographic window precluded the test performance in approximately 5% of patients, slightly higher than that of the present study[4,10,15,21]. The proportion may not be comparable because of different body habitus between Thais and Caucasians. As shown in Table 1, the population in the present study had the mean body mass index of 25 ± 5 kg/m^2 and this may allow the better echocardio-graphic images.

Safety of dobutamine stress echocardiography in Thai population

No death, myocardial infarction or ventricular fibrillation occurred in the authors' experience, which is in agreement with several previous studies[4,8,10,15]. Serious complications, such as ventricular fibrillation or myocardial infarction, after dobutamine stress echocardiography are rare (<0.1%)[15,17-19]. No fatal event has ever been reported. With the trend toward high dose protocols and co-administration of higher maximal dose of atropine to achieve the diagnostic test (presence of inducible ischemia or absence with a maximal heart rate response), the incidence of serious adverse effects remained acceptably low, as shown both in the present study and others[15,16,24]. These increase the confidence in the safety of the dobutamine stress echocardiography protocol.

Although, the adverse effects of dobutamine stress are theoretically related to the intense sympathomimetic stimulation, most reported events were well-tolerated and did not necessitate test termination. The most commonly reported cardiovascular adverse effects were angina, hypotension and cardiac arrhythmias[17-19]. The majority of arrhythmias were premature ventricular / atrial contractions and supraventricular or ventricular tachycardia, which responded promptly to termination of the test and rarely required medical intervention. Atrial fibrillation, supraventricular tachycardia and nonsustained ventricular tachycardia occurred in 4% of patients in the present study, a rate similar to that of Mertes et al. (4.3%)[17] and Poldermans et al. (3.6%)[19]. The frequency of dobutamine stress-induced hypotension varied from 5-37%, depending on its definition in each study, and most events resolved after test termination and intravenous fluids (if necessary)[15,16,19,25]. Symptomatic hypotension leading to the test termination occurred only rarely.

Conclusion

Dobutamine stress echocardiography is a safe and tolerable test for the evaluation of CAD in the Thai population. This is also true despite the use of aggressive high-dose dobutamine-atropine protocol.

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การทดสอบหัวใจโดยการตรวจคลื่นเสียงสะท้อนหัวใจ ร่วมกับการกระตุ้นหัวใจด้วยยาโดบูทามีน เพื่อประเมินโรคหลอดเลือดหัวใจตีบตันในประชากรไทย : ประสบการณ์จากโรงพยาบาลศิริราช

นิธิมา เชาวลิต, เดโช จักราพานิชกุล, กมล อุดล, บุษกร กิจรัตนา

ภูมิหลัง: *การทดสอบสมรรถภาพหัวใจ โดยการตรวจคลื่นเสียงสะท้อนหัวใจร่วมกับการกระตุ้นหัวใจด้วยยาโดบูทามีน เพื่อประเมินโรคหลอดเลือดหัวใจตีบตัน เป็นวิธีที่ใช้กันแพร่หลายทั่วโลก อย่างไรก็ตามยังไม่เคยมีรายงานเกี่ยวกับการตรวจวิธีนี้ในประเทศไทย*

วัสดุและวิธีการ: *การศึกษารวบรวมผู้ป่วยที่เข้ารับการตรวจคลื่นเสียงสะท้อนหัวใจ ร่วมกับการกระตุ้นหัวใจด้วยยาโดบูทามีนที่โรงพยาบาลศิริราช จำนวน 421 คน (อายุเฉลี่ย 67.7 11.0 ปี, ผู้ชาย 43%) ซึ่งมีการบันทึกข้อมูลในวันที่ผู้ป่วยมาตรวจ*

ผลการศึกษา: *ข้อบ่งชี้ในการตรวจ ได้แก่ ประเมินความเสี่ยงก่อนผ่าตัดที่ไม่ใช่การผ่าตัดหัวใจ 179 (50%) ราย วินิจฉัยโรคหลอดเลือดหัวใจตีบตัน 179 (45%) ราย ประเมินความเสี่ยงในผู้ป่วยที่เป็นโรคหลอดเลือดหัวใจตีบตัน 24 (6%) ราย และเหตุผลอื่นใน 6 (1%) ราย ผลการทดสอบปกติ 276 (66%) ราย และผลบวกใน 80 ราย (19%) พบผลข้างเคียง 3% โดยไม่พบการเสียชีวิต ภาวะกล้ามเนื้อหัวใจตาย หรือหัวใจเต้นผิดจังหวะแบบรุนแรง อาการข้างเคียงที่พบส่วนใหญ่เป็นแบบไม่ร้ายแรง เช่น ใจสั่น, เหนื่อย, เจ็บหน้าอก และหัวใจเต้นผิดจังหวะที่ไม่มีอาการ ส่วนภาวะหัวใจเต้นเร็วผิดจังหวะแบบ atrial fibrillation, nonsustained ventricular tachycardia หรือ supraventricular tachycardia พบได้ 3.5% ของผู้ป่วย*

สรุป: *การทดสอบหัวใจโดยการตรวจคลื่นเสียงสะท้อนหัวใจร่วมกับการกระตุ้นด้วยยาโดบูทามีนเป็นวิธีที่ปลอดภัยในการประเมินโรคหลอดเลือดหัวใจตีบตันในประชากรไทย*