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ORIGINAL ARTICLE

# Accelerated dobutamine stress testing: Feasibility and safety in patients with moderate aortic stenosis

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**KEYWORDS**

Dobutamine stress echocardiography;
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Safety

**Abstract** *Objective:* A continuous infusion of a single high dose of dobutamine was suggested as a simple protocol of dobutamine stress echocardiography (DSE). The present study explores the feasibility and safety of an accelerated DSE protocol in patients with calcific moderate valvular aortic stenosis undergoing DSE for evaluation of suspected coronary artery disease.

*Methods:* Eligible patients ($n = 100$) were prospectively enrolled. They were randomly assigned to undergo either the accelerated (group A, 50 patients) or the conventional protocol (group B, 50 patients). Group A received a continuous infusion of 40 μg/kg/min ± 1–2 mg atropine. Patients were monitored for adverse drug effects. Test duration was recorded. Patients with positive stress results underwent coronary angiography (CA).

*Results:* Mean age of the study cohort was 62.29 ± 9.8 years, 62 (62%) being males. Mean pressure gradient across the aortic valve was recorded (group A: 32.2 mmHg and group B: 31.16 mmHg, $P < 0.05$). Group B showed a longer mean test duration (17.9 ± 2.3 vs. 8.9 ± 1.9 min, $P < 0.001$) and higher mean weight-adjusted cumulative dobutamine dose (385 ± 115 vs. 350 ± 110.24 μg/kg, $P < 0.05$). The two groups received a similar total dose of atropine. Group A patients showed significantly lower incidence of extra-systoles, non-sustained ventricular tachycardia and severe hypotension ($P < 0.05$). CA results yielded almost similar diagnostic outcomes in both groups.

*Conclusion:* In patients with calcific moderate aortic stenosis undergoing DSE; adopting the described accelerated protocol is associated with shorter test duration, lower weight-adjusted cumulative dobutamine dose for target heart rate achievement and fewer adverse effects, while maintaining a comparable diagnostic value.



## 1. Introduction

Dobutamine stress echocardiography (DSE) is widely used for the diagnosis of coronary artery disease (CAD). Data regarding the diagnosis of CAD in patients with moderately elevated maximal gradient across the stenosed aortic valve (AV) are limited. However, the diagnostic value of DSE for the diagnosis of CAD in patients with stenosed AV is high.[1] Safety of

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DSE for ischemia detection has been extensively evaluated. The most frequent side effects are hypotension and arrhythmia.[2] Currently, in patients with suspected or known CAD, most laboratories use stepwise increments of dobutamine at three-minute intervals, which had evolved from the commonly used exercise treadmill protocols. However, steady-state dobutamine levels during dobutamine infusion are not obtained for up to ten minutes.[3–5] Consequently, the full effect of any infusion rate of dobutamine is not obtained before the dobutamine dose had advanced to the next level[6] and plasma dobutamine concentrations increase rapidly and non-linearly during the test.[7–9] Shortening the time of infusion of dobutamine would increase the feasibility and the cost effectiveness of DSE.[10] Therefore, a continuous infusion of a single high dose of dobutamine has been suggested as a simple and effective protocol of DSE.[7,11] It is worth mentioning that an "accelerated" dipyridamole infusion protocol had been already used[12] and validated in a large study.[10]

The current study prospectively sought to explore the feasibility and safety of infusion of a fixed high dose of dobutamine i.e. accelerated DSE protocol in achieving the target heart rate compared to the conventional DSE protocol, in a series of patients suffering from calcific moderate valvular aortic stenosis, being evaluated for suspected CAD.

## 2. Materials and methods

### 2.1. Study design and data collection

A total number of 100 consecutive patients suffering from calcific moderate valvular aortic stenosis were prospectively enrolled in the present study. They were referred to the stress echocardiography lab in the Cardiology department of Ain Shams University (Cairo, Egypt) in the period between February 2011 and August 2013. Patients were considered eligible for inclusion if they exhibit normal resting left ventricle ejection fraction (LVEF%) and suffer from symptoms suggestive of myocardial ischemia, requiring evaluation by DSE. Exclusion criteria included; prior history of unstable angina or myocardial infarction (MI), previous percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery, other etiologies of aortic stenosis or significant aortic regurgitation, presence of other significant valvular disease, congenital heart disease or any myocardial disease apart from ischemia. Also, patients with contraindications to dobutamine infusion (for example; with a history of complex ventricular arrhythmias or uncontrolled hypertension with blood pressure $>180/110$ mmHg), with contraindications to atropine intake (for example; with a history of narrow-angle glaucoma or obstructive uropathy) and patients with limited life expectancy due to coexistent disease (for example; malignancy), were excluded. After enrollment, patients were randomly assigned in 1:1 fashion to undergo either; accelerated DSE protocol (group A) or conventional DSE protocol (group B) according to a computer-generated random series of numbers. Randomization was performed by block randomization (blocks of 10 patients). All included patients were subjected to detailed history taking including drug-intake, continuous electrocardiogram (ECG) monitoring, in addition to baseline transthoracic echocardiogram (TTE) assessment before stress testing. All included patients stopped beta blocker and calcium antagonist therapies 48 h before stress testing, while nitrate therapy was stopped 24 h before it. Before inclusion, informed written consent was obtained from each patient and the study protocol was reviewed and approved by our local institutional human research committee; as it conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 2008.

### 2.2. Definition of risk factors of coronary artery disease

The presence of hypertension was defined as systolic blood pressure $\geqslant 140$ mmHg and/or diastolic blood pressure $\geqslant 90$ mmHg, previously recorded by repeated non-invasive office measurements, which led to life-style modification and/or intake of antihypertensive drug therapy.[13] The presence of diabetes mellitus was defined as fasting plasma glucose $\geqslant 126$ mg/dl and/or 2 h post-glucose load $\geqslant 200$ mg/dl, or specific anti-diabetic drug therapy intake.[14] Dyslipidemia was defined as LDL cholesterol $>100$ mg/dl, and/or serum triglycerides $>150$ mg/dl, and/or HDL cholesterol $<40$ mg/dl ($<50$ mg/dl in women).[15]

### 2.3. Baseline echocardiographic assessment

Assessment of regional and global LV systolic functions was performed in all patients by TTE using a General Electric Vivid 7 cardiac ultrasound machine (General Electric, Horten, Norway), equipped with harmonic imaging capabilities. A 2.5 MHz phased array probe was used to obtain standard 2D, 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 echocardiographer blinded to the study protocol, employing the software program of the echocardiography machine. All patients suffered from calcific moderate valvular aortic stenosis defined echocardiographically by having aortic valve area of 1–1.5 $cm^2$ (measured using continuity equation) and recorded mean pressure gradient (PG) of 25–40 mmHg (across the valve).[16] Regional wall motion was assessed according to the standard 17-segment model as recommended by the American Society of Echocardiography.[17] That was achieved through visual assessment for each segment individually, considering both endocardial excursion and systolic thickening. Each segment was graded according to the semi-quantitative scoring system described by Knudsen et al.[18] Segments with poorly-defined endocardial borders for 50% or more of their length were considered non-visualized and assigned a score of 0.[19] Wall thickening was assessed at a distance of at least 1 cm from the adjacent segment, to minimize the effect of tethering.[20]

### 2.4. Dobutamine stress echocardiography protocols

Once eligible, patients were randomly assigned to undergo one of the following two DSE protocols:

#### 2.4.1. Accelerated DSE protocol (group A, 50 patients)

Dobutamine (Dobutamine MYLAN®, MYLAN S.A.S, France) was administered by intravenous (IV) infusion using a high fixed dose from the start (40 μg/kg/min). Infusion duration was assigned to be 10 min. In patients not achieving