Accuracy and safety of low-dose dobutamine stress echocardiography early after acute anterior myocardial infarction.

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Abstract

OBJECTIVES: We sought to explore the safety and prognostic accuracy of low-dose dobutamine stress echocardiography (DSE), performed early in the course of acute anterior ST elevation myocardial infarction (STEMI), in patients who received thrombolytic therapy.
METHODS: We enrolled 73 consecutive patients presenting with first acute anterior STEMI, who had significant coronary stenosis/occlusion of the culprit artery amenable for revascularization. Low-dose DSE was performed within 2-7 (3.8±1.8) days of the index hospitalization. Patients underwent coronary revascularization. Follow-up echocardiography was carried out 2-3 months after revascularization to assess regional wall motion abnormality. Predicted viability by low-dose DSE was compared with actual contractility improvement seen at follow-up echocardiography.
RESULTS: Considering a per-patient analysis, low-dose DSE early after anterior STEMI predicted viability with a sensitivity of 88.9%, specificity of 75.7%, PPV of 78%, NPV of 87.5%. Built on a per-segment analysis, low-dose DSE achieved a sensitivity of 86.9%, specificity of 92.5%, PPV of 73.2%, NPV of 96.8%. Based on a per-segment analysis performed individually for hypokinetic segments, low-dose DSE achieved a sensitivity of 88%, specificity of 85.4%, PPV of 74%, NPV of 93.8%. For akinetic segments, low-dose DSE achieved a sensitivity of 82.4%, specificity of 97%, PPV of 70%, NPV of 98.5%.
CONCLUSION: Low-dose DSE performed early in patients presenting with acute anterior STEMI who received thrombolytic therapy, is safe with a high sensitivity but a modest specificity for predicting contractile improvement after revascularization, based on a per-patient analysis. However, based on a per-segment analysis, both sensitivity and specificity are high.

Keywords: dobutamine stress echocardiography; acute myocardial infarction; viability.

INTRODUCTION

Identification of viable myocardium after myocardial infarction (MI) has gained paramount importance with the latest progress in myocardial revascularization over the past two decades, especially in patients scheduled for coronary intervention [1]. Myocardial viability represents transient impairment of contractility with potential recovery when blood supply is restored [2]. Improving blood supply to viable myocardial segments following MI results in improvement of left

ventricular contractility, clinical heart failure, functional capacity, and reduces long-term mortality. Therefore, an important concern is whether hypokinetic or akinetic myocardial segments following MI represent viable myocardium - with severely reduced blood supply -or permanently damaged scar tissue [3]. This theme was supported by the results of a prior report, in which only those with severe left ventricular systolic dysfunction after MI - who harbored viable myocardium - improved by coronary revascularization [4].

Pharmacological stress echocardiography is widely acknowledged for the identification of viable myocardium in post-MI patients, chiefly because it is feasible, safe, with a high diagnostic and prognostic accuracy [5]. Low-dose dobutamine stress echocardiography (DSE) has emerged as an appealing tool for identifying viable myocardium through its ability to elicit a beta receptor-mediated increase in myocardial thickening. Low-dose dobutamine response accurately predicts potential recovery of dysfunctional - yet viable - myocardial regions and thus identifying a subset of patients whose left ventricular function will improve following successful coronary revascularization [6]. The problem of inter- and intra-observer variability can be minimized by stronger adherence to common and new methodological standards [7]. Dobutamine-responsive wall motion is specific for predicting reversible impairment of contractility; yet, its sensitivity remains suboptimal [8]. In a prospective study, we sought to explore the safety and prognostic accuracy of low-dose DSE, performed early in the course of acute anterior ST elevation MI (STEMI), in patients who received thrombolytic therapy.

METHODS

Patient selection and study design: we enrolled 73 consecutive patients admitted to our intensive care unit with first acute anterior STEMI, during the period from April 2012 to April 2013. Patients were considered eligible for inclusion if they had received thrombolytic therapy, had significant stenosis/occlusion of the culprit artery, and a culprit artery amenable for revascularization as evident from subsequent coronary angiography. Significant coronary stenosis was defined as at least 70% luminal obstruction of a sizable arterial segment (measuring 2.5 mm or more in diameter), seen in 2 different projections. Total coronary occlusion was defined as 100% luminal obstruction with Thrombolysis in Myocardial Infarction (TIMI) grade 0 forward flow distal to the site of obstruction. The diagnosis of STEMI was based on 12-lead electrocardiogram showing ST segment elevation of 1 mm or more in at least two contiguous leads plus one of the following: 1) prolonged chest discomfort typical of myocardial ischemia, 2) elevated cardiac biomarkers: creatine kinase-MB fraction and/or troponin more than twice the upper reference limit. We excluded patients with early post-MI angina or hemodynamic instability, congestive heart failure, protruding fresh left ventricular thrombus, significant valvular or congenital heart disease, any myocardial disease apart from ischemia, contraindication to dobutamine (such as history of complex ventricular arrhythmias, uncontrolled hypertension with blood pressure >180/110), and patients with limited life expectancy due to coexistent disease (such as malignancy). All patients received fibrinolytic therapy in the form of streptokinase given at a dose of 1 500 000 U, administrated by intravenous infusion for 30-60 minutes, started within 6 hours of the onset of chest pain. Before inclusion, informed written consent was obtained from each patient after full explanation of the study protocol, and the protocol was reviewed and approved by the our institutional Human Research Committee, as it conforms to the ethical guidelines of

the 1964 Declaration of Helsinki, as revised in 2013.

Baseline echocardiographic assessment of regional and global left ventricular systolic function was performed in all patients by trans-thoracic echocardiography within 48 hours of admission. Doppler echocardiography was performed using a General Electric Vivid 7 Pro cardiac ultrasound machine (General Electric, Horten, Norway) 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 observer (W. Adel) employing the software program of the echocardiography machine. Global left ventricular systolic function was assessed in apical 4-chamber view using the biplane modified Simpson's method. Regional wall motion was assessed according to the standard 16-segment model recommended by the American Society of Echocardiography [9]. Individual segments were then sub grouped, based on the known vascular distribution, into left anterior descending territory, left circumflex territory, right coronary artery territory, and overlap segments [9]. 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 Knudsen and associates [10]. Segments with poorly defined endocardial borders for 50% or more of their length were considered non-visualized and assigned a score of 0 [11]. Wall thickening was assessed at a distance of at least 1 cm from the adjacent segment in order to minimize the effect of tethering [12]. Wall motion in a vascular territory was considered abnormal if wall thickening was abnormal in at least two contiguous non-overlap segments [9]. Dividing the sum of individual segment scores by the number of interpretable segments derived wall motion score index.

Low-dose DSE Protocol: Dobutamine (Dobutrex®, Lilly, Eli and Company, Indianapolis, USA) was infused starting at 5 microgram/kg/min; the infusion rate was subsequently increased by 5 microgram/kg/min every 3 minutes (that is at 10, 15 and 20 microgram/kg/min) up to a maximal infusion rate of 20 microgram/kg/min. Standard views were recorded at baseline, during each stage of the infusion protocol, as well as during recovery. The same observer performed visual assessment of wall motion and thickening. Global left ventricular systolic function and wall motion score index were evaluated at rest and at the end of each stage. The presence of viability was defined by improvement of regional wall motion score by at least one grade in at least two contiguous non-overlap segments along with at least 20% reduction in global wall motion score index, compared with baseline evaluation [12]. Low-dose DSE protocol was performed with the patients on their full anti-ischemic medications.

Monitoring: All patients had continuous heart rate, ECG, and pulse oxymetry 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 recovery. Patients were questioned at the end of the test for any symptoms or adverse drug reactions.

Coronary revascularization: All patients underwent culprit artery revascularization within 2 weeks of hospital admission, by either percutaneous coronary angioplasty, or surgical bypass grafting, according to the operator's discretion. Operator's decision was based on the clinical presentation, and coronary

anatomy, but not on the presence or absence of viability by low-dose DSE.

Follow-up echocardiographic re-assessment was performed (by the same observer) 2-3 months after revascularization to evaluate regional and global left ventricular systolic function, as described before. The presence of myocardial contractile improvement was defined by improvement of regional wall motion score by at least one grade in at least two contiguous non-overlap segments along with at least 20% reduction in global wall motion score index, compared with baseline evaluation. During follow-up, patients were interrogated for the occurrence of new MI or congestive heart failure by clinical visits, telephone calls, hospital chart reviews, or personal communication with the referring physician.

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. The sensitivity, specificity, positive and negative predictive values and diagnostic accuracy were calculated according to the standard definitions for low-dose DSE protocol to predict viability (actual contractility improvement after revascularization). The accuracy parameters were calculated based on a per-patient analysis, then based on a per-segment analysis for all dys-synergic segments. Segments were then subdivided according to the severity of baseline dys-synergy into 3 subgroups, namely, hypokinetic, akinetic, and dyskinetic. The accuracy parameters were then calculated individually for each subgroup of segments based on a per-segment analysis. A probability value of $p < 0.05$ was considered statistically significant. Analyses were performed with SPSS version 16.0 statistical package (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 73 consecutive patients with first acute anterior STEMI were enrolled in the current study, and underwent revascularization of the culprit artery. Baseline clinical and echocardiographic characteristics are presented in table 1. Mean age was 49.8 ± 10.3 years and 85% of patients were males. Low-dose DSE was performed within 2-7 (3.8±1.8) days from the index hospitalization. Low-dose DSE protocol was well tolerated by all patients, with no major side effects during or immediately after the test. All patients completed 2-3 months of follow-up, and no patient reported any clinical events during the period from revascularization to follow-up echocardiography evaluation.

Table 1: Baseline clinical and echocardiographic characteristics

	Study Cohort (N=73)
Age (years)	49.8 ± 10.3
Male gender	62 (84.9)
Smoking	45 (61.6)
Diabetes	37 (50.7)
Hypertension	38 (52.1)
Dyslipidemia	43 (58.9)
FH of IHD	27 (36.9)
Medications	
Aspirin	71 (97.3)
Beta blockers	48 (65.8)
ACE inhibitors	54 (73.9)
Calcium antagonists	23 (31.5)
Diuretics	31 (42.5)
Echocardiographic data	
LV EF (%)	41.2 ± 8.7
WMSI	1.94 ± 0.5
Mitral regurgitation	16 (21.9)

Variables are presented as mean ± SD or numbers (%), as indicated. N = number of patients, ACE = angiotensin converting enzyme, FH = family history, IHD = ischemic heart disease, LV EF = left ventricular ejection fraction, WMSI = wall motion score index.

Per-patient analysis: Of 73 patients, 41 (56.2%) had a low-dose DSE positive for viability (of whom 32 improved after revascularization on subsequent follow-up echocardiography), whereas 32 (43.8%) had low-dose DSE negative for viability (of whom 4 improved after revascularization). Considering a per-patient analysis, low-dose DSE predicted viability (contractility improvement after revascularization) with a sensitivity of 88.9%, specificity of 75.7%, positive predictive value of 78%, negative predictive value of 87.5%, and a diagnostic accuracy of 82.2%.

Per-segment analysis for all dys-synergic segments: A total of 1168 segments were analyzed in 73 patients. Of the total, 923 (79%) were assigned as dys-synergic at baseline echocardiography. Dys-synergic segments included 443 (48%) hypokinetic, 438 (47.5%) akinetic, and 42 (4.6%) dyskinetic segments. Of the 923 dys-synergic segments, 209 were responsive to low-dose DSE (of which 153 improved after revascularization), whereas 714 were non-responsive to low-dose DSE (of which 23 improved after revascularization). Considering a per-segment analysis, low-dose DSE predicted viability with a sensitivity of 86.9%, specificity of 92.5%, positive predictive value of 73.2%, negative predictive value of 96.8%, and a diagnostic accuracy of 91.4%.

Per-segment analysis for individual dys-synergic segments: Of the 443 hypokinetic segments, 169 were responsive to low-dose DSE (of which 125 improved after revascularization), whereas 274 were non-responsive to low-dose DSE (of which 17 improved after revascularization). Per-segment analysis performed individually for hypokinetic segments revealed that low-dose DSE predicted viability in hypokinetic segments with a sensitivity of 88%, specificity of 85.4%, positive predictive value of 74%, negative predictive value of 93.8%, and a diagnostic accuracy of 86.2%. Of the 438 akinetic segments, 40 were responsive to low-dose DSE (of which 28 improved after revascularization), while 398 were non-responsive to low-dose DSE (of which 6 improved after revascularization). Per-segment analysis performed individually for akinetic segments revealed that low-dose DSE predicted viability in akinetic segments with a sensitivity of 82.4%, specificity of 97%, positive predictive value of 70%, negative predictive value of 98.5%, and a diagnostic accuracy of 95.9%. All 42 dyskinetic segments were non-responsive to low-dose DSE (none improved after revascularization).

DISCUSSION

The results of the current study suggest that low-dose DSE performed early (within 2 to 7 days) in patients presenting with acute anterior STEMI who received thrombolytic therapy, is safe with a rather high sensitivity (88.9%) but a modest specificity (75.7%) to predict the presence of myocardial viability, as compared to the 'reference standard' of actual contractility improvement after revascularization; based on per-patient analysis. On the other hand, based on per-segment analysis, specificity was high (92.5%) and sensitivity remained almost equally high (86.9%). Furthermore, prediction of contractile improvement in akinetic segments by low-dose DSE was highly specific (97%) but moderately sensitive (82.4%), whereas in hypokinetic segments, it was less specific (85.4%) but more sensitive (88%).

The finding that hypokinetic segments are more likely to manifest contractile improvement in response to low-dose DSE is consistent with histopathology studies showing that these segments harbor a mixture of scar tissue, normal and hibernating myocardium in variable proportions, where fibrosis is usually minimal and myocardial viability is more common [13]. Nevertheless, some hypokinetic segments that improved with

low-dose DSE did not recover contractile function following revascularization. This coincides with the hypothesis that hypokinetic segments may not always represent hibernating myocardium, but instead, they might be the result of a non-transmural infarction leaving a heterogeneous mixture of necrotic and functioning myocardium (already well perfused), that would not further improve its contractility after revascularization. Alternatively, hypokinetic segments may represent tethering of a severely dysfunctional region by an adjacent functioning segment [14]. These factors would contribute to a higher false positive response rate, and consequently, a lower specificity for predicting functional recovery in hypokinetic segments following revascularization.

In contrast, low-dose DSE demonstrated a lower sensitivity to predict viability in akinetic segments. This can be attributed to the finding that these segments are mostly supplied by critically stenosed or totally occluded coronaries with so exhausted coronary flow reserve, that even at low levels of pharmacological stress they fail to improve their contractility, despite the presence of viable myocardium that would eventually improve its contractility after revascularization [15]. Furthermore, prediction of reversible contractile dysfunction in akinetic segments might be difficult with the standard dosage of low-dose DSE, owing to the usual presence of a large infarct size in these regions [16,17].

Few previous studies segregated myocardial segments according to the severity of their baseline dys-synergy (hypokinesia, akinesia or dyskinesia) when reporting the prognostic power of low-dose DSE to predict contractile improvement after revascularization. Ongoing with our results, many reported that low-dose DSE exhibits a higher sensitivity and lower specificity for predicting functional recovery after revascularization in hypokinetic segments as compared with akinetic ones [17-21]. Our results showed a modest sensitivity for low-dose DSE for predicting contractile improvement after revascularization of akinetic segments (82.4%). Many previous reports observed an even 'worse' sensitivity (range from 11% to 47%) for predicting contractile improvement in akinetic segments by low-dose DSE [15,17, 22-24]. This wide divergence may be due to variations of baseline clinical characteristics, selection bias, several echocardiographic and angiographic technical factors, and different timing of revascularization and echocardiographic reassessment following revascularization.

Several diagnostic imaging modalities are well established for myocardial viability assessment; they are based on myocardial perfusion imaging. Single Photon Emission Computed Tomography (SPECT) has a higher sensitivity and lower specificity than diagnostic modalities that depend on residual contractile recovery [25]. Its main limitations include significant exposure to ionizing radiation, low spatial resolution, and attenuation artifacts. Positron Emission Tomography (PET) has superior spatial resolution and attenuation correction, compared with SPECT, and is currently considered the gold standard for viability assessment. It is limited mainly by lack of availability [26].

Clinical Implications: Identification of myocardial viability following STEMI is one of challenging fields in modern interventional cardiology. Primary angioplasty is the recommended treatment of choice in centers provided with facilities to perform emergency coronary angiography within 90 minutes of hospital presentation. In centers without these facilities, or when primary angioplasty cannot be performed ‘on-time’; however, thrombolytic therapy is still an alternative in patients presenting within the ‘appropriate’ time window. In these

patients, elective coronary angiography can still be performed 'early' enough within the index hospitalization, provided that they prove to have 'adequate' myocardial viability. Hence, an appealing strategy is to employ an 'adequately safe' and accurate method for identifying myocardial viability early after STEMI in patients who received thrombolytic therapy. The results of the current study suggest that low-dose DSE is a promising strategy for achieving this goal.

Study limitations:

Our findings are based on a single center study with a relatively small sample size of the cohort, a fact that makes it difficult to generalize our results to all patients presenting with acute STEMI who received thrombolytic therapy. Multi-center studies applying the same protocol and examining a larger number of patients are needed. Moreover, the follow-up period of 2-3 months might have been rather inadequate to allow recovery of some dys-synergic but viable segments, thereby underestimating the specificity of low-dose DSE for predicting contractile improvement after revascularization. Delayed recovery can further occur in a substantial number of segments up to a median of 14 months following revascularization, a fact that warrants repeated assessment after longer periods of follow-up. Finally, follow-up coronary angiography was not done, therefore, restenosis or re occlusion cannot be definitely excluded, something that would hazard the achieved functional improvement and again underestimate specificity. However, no patient reported any clinical events during the period from revascularization to follow-up echocardiographic evaluation.

CONCLUSION

Low-dose DSE performed early in patients presenting with acute anterior STEMI who received thrombolytic therapy, is safe with a high sensitivity but a modest specificity for predicting contractile improvement after revascularization, based on a per-patient analysis. However, based on a per-segment analysis, both sensitivity and specificity are high. Moreover, prediction of contractile improvement in hypokinetic segments was more sensitive but less specific than in akinetic ones.

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