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Prognostic significance of submaximal negative dobutamine stress echocardiography: A 3-year follow-up study

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Abstract

Background: *To estimate the prognostic value of submaximal negative dobutamine stress echocardiography (NDSE) on major cardiac events.*

Methods and results: *Patients with NDSE were analyzed in 2 cohorts based on predicted maximal heart rate (PMHR) (< 85% or ≥ 85% PMHR) and were assessed for major adverse cardiac events over 3 years. Of 756 patients with NDSE, 415 achieved ≥ 85% PMHR. Both groups had comparable ejection fractions (EF) > 50% (80.6%* vs. *81.9%, p = 0.66). The NsubDSE group had higher rates of atrioventricular nodal blocker use (58.7%* vs. *39.9%, p < 0.0001), and diabetes (38.7%* vs. *27.6%, p = 0.001). Kaplan-Meier survival analysis showed no differences in freedom from cardiac death (98%* vs. *98%, p = 0.88), nonfatal myocardial infarction (94%* vs. *94%, p = 0.85), or combined major cardiac events (81%* vs. *78%, p = 0.24). Diabetes and preserved ejection fraction were predictive of cardiac events in a multi-variate analysis (p = 0.005).*

Conclusions: *In our study, NsubDSE carried a favorable prognosis. Diabetics were more likely to have an NsubDSE and suffer from a cardiac event despite a preserved ejection fraction. Hence further evaluation for coronary artery disease in this high risk cohort should be pursued.* (Cardiol J 2008; 15: 237–244)

Key words: dobutamine stress echocardiography, target heart rate, prognosis, double product, beta-blockers

Editorial p. 207

Introduction

Dobutamine stress echocardiography (DSE) is well established as a safe, feasible, and accurate modality for detection of myocardial ischemia and prognostication in patients with known or suspected coronary artery disease, particularly when they have limited exercise capacity [1–3]. Although the adverse prognosis of chronotropic incompetence is well established with exercise testing [4], the prognostic value of negative submaximal DSE (NsubDSE), defined as achieving < 85% predicted maximal heart rate achieved (PMHR) has varied implications. Some studies have suggested that patients with NsubDSE have adverse outcomes similar to patients with inducible ischemia in selected populations [5, 6]; others have reported that patients

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undergoing major noncardiac surgery with NsubDSE have excellent immediate outcomes (< 1–2% annual events rates), comparable to patients with negative maximal DSE (NmaxDSE), as long as resting wall-motion abnormalities are not present [7]. Since published studies assessing long-term prognostic significance of NsubDSE have tended to either exclude patients on beta-blockers [5], or have studied selected high-risk populations [6], the prognostic implications of NsubDSE in an unselected patient population on beta-blockers or rate-slowing calcium-channel blocker therapy is unknown. Also, although double product has been felt to be unimportant with DSE, we are not aware of specific studies addressing this in patients with NsubDSE. Thus, whether this parameter carries a different connotation in this subset is unclear. Consequently, we sought to determine the prognostic value and outcomes following NsubDSE in an unselected population.

Method

Population

This study was carried out at a large tertiary care center involving an unselected patient population including patients on beta-blocker and calcium-channel blocker therapy. Between January 1, 1999, and December 31, 1999, consecutive patients who underwent DSE were screened retrospectively. Patients with a positive DSE, younger than 18 years-old, pregnant, mentally impaired, or who refused to provide consent were excluded. Patients who underwent very early revascularization (< 2 months) after index-negative DSE were excluded, as in these cases the clinical suspicion and/or ancillary testing likely influenced the decision for angiography. Moreover, the outcomes were altered early in these patients by intervention, thus precluding long-term analysis of NsubDSE in this subset. Only the first event data was used for patients with more than one event. After applying exclusion criteria, 756 patients with negative DSE formed the initial screening group. The study was approved by and the ethical standards were in accordance with the Henry Ford Hospital Institutional Review Board (Detroit, MI).

Dobutamine stress echocardiography protocol

Images were obtained in the parasternal long axis and short axis, apical 4-axis, 2-axis, and apical long axis at baseline, and after each incremental dose of dobutamine. Images were digitally stored at baseline, low, intermediate, and high doses to facilitate quad screen display and analysis. Recovery images were also obtained and stored on videotape. In case of suboptimal digital capture quality, a tape review was performed for interpretation. Heart rate, blood pressure, and 12-lead electrocardiograms were recorded at baseline and monitored through each stage. Dobutamine was initiated at a dose of 10 μg/kg/min and increased at 3-min intervals to 20, 30, and up to a maximum of 40 μg/ /kg/min. Per our lab protocol, atropine is injected (observing standard precautions and contraindications at 0.2 mg dose increments every minute, up to a total dose of 2 mg) if a ≥ 85% age-PMHR or an absolute heart rate of ≥ 100 has not been reached after a 3-min infusion of dobutamine at 20 μg/ /kg/min. The test was terminated at the completion of the protocol or with the development of significant ischemic ST-segment shifts, intolerable symptoms, ventricular tachycardia, symptomatic hypotension (or SBP < 90 mm Hg), or severe hypertension (> 220/110 mm Hg). A normal DSE was defined as having a normal contractile response with dobutamine regardless of resting wall-motion abnormalities. An NsubDSE was defined by failure to achieve a PMHR of ≥ 85%, but showing normal segmental augmentation with dobutamine regardless of the presence or absence of resting wall-motion abnormalities. Visual assessment of wall motion was accomplished using the following format: normal, hypokinetic, akinetic, and dyskinetic. The ASE standard 16-segment models were used for the reporting of wall motion. Ejection fraction (EF) estimation was based on visual assessment and an EF ≥ 50% was defined as normal.

Electrocardiograms were designated as ischemic with the presence of ≥ 1 mm of horizontal or downsloping ST-segments 80 ms after the J-point, or if there was ≥ 1 mm ST-segment elevation in leads without significant Q-waves at baseline. Patients with a positive stress EKG but normal peak wall motion were considered to have negative DSE, and were part of the study group.

Endpoints and definitions

Individual major adverse cardiac events (MACE) assessed were cardiac death, nonfatal myocardial infarction (MI), and revascularization. Individual endpoints and combined MACE utilizing all 3 events were assessed. Patients were also followed up for unstable angina (USA). The follow-up period for reporting outcomes was 36 months. MI was defined by CK elevation more than twice the upper limit of normal, or troponin elevation above the upper limit of normal in the setting of chest pain,

Table 1. Baseline characteristics of NsubDSE and NmaxDSE patients.

Variable	NsubDSE (n = 341) (PMHR < 85%)	NmaxDSE (n = 415) (PMHR ≥ 85%)	Group comparison (p)
Age (mean ±SD)	69.4 ± 12.9	73.0 ± 11.1	< 0.0001*
Gender (male)	42.2% (144/341)	40.7% (169/415)	0.68
Prior MI	24.6% (84/341)	19.3% (80/415)	0.08
Prior CABG	9.7% (33/341)	8.7% (36/415)	0.63
Prior PCI	14.7% (50/341)	8.7% (36/415)	0.01*
CAD	32.6% (111/341)	28.0% (116/415)	0.17
Tobacco use	28.4% (97/341)	23.4% (97/415)	0.11
Hypertension	91.5% (312/341)	86.3% (358/415)	0.02*
Hypercholesterolemia	52.8% (180/341)	49.6% (206/415)	0.39
History of HF	22.3% (76/341)	15.9% (66/415)	0.03*
Diabetes mellitus	39.0% (133/341)	27.7% (115/415)	0.001*
EF ≥ 50%	80.6% (275/341)	81.9% (339/414)	0.66
Beta-blockers/Ca-blockers	58.4% (199/341)	39.5% (164/415)	< 0.0001*

*Statistically significant, $p < 0.05$; MI — myocardial infarction, CABG — coronary artery bypass grafting, PCI — percutaneous coronary intervention, CAD — coronary artery disease, HF — heart failure, EF — ejection fraction, PMHR — predicted maximal heart rate

or other clinical signs/symptoms suggesting cardiac ischemia. Cardiac death was documented as death related to MI (ST-elevation myocardial infarction or non-ST-elevation myocardial infarction), congestive heart failure, sudden cardiac death, arrhythmias, or any event that was felt related to a cardiac cause. Revascularization included any percutaneous intervention or coronary artery bypass graft (CABG) surgery. USA was defined as an accelerated pattern of chest pain, with increased frequency, longer duration, decreased response to medical therapy, occurrence at rest, or new onset chest pain.

Hypertension was defined as office visit documentation of history of hypertension, or being on antihypertensive therapy. Diabetes mellitus (DM) was present if there was documentation of DM in an office note, or the patient was on antihyperglycemics (oral medication or insulin). Hypercholesterolemia was present if office notes mentioned history of hyperlipidemia or if the patient was on an anti-lipid medication. Heart failure (HF) was defined as the presence of a history of systolic or diastolic HF and/or left ventricular EF < 50% in the medical record. Coronary artery disease (CAD) was defined as a history of previous MI/angina or history of percutaneous coronary intervention (PCI) or CABG.

The study was approved by the local bioethical committee and all patients gave their informed consent.

Statistical analysis

A descriptive analysis was performed, comparing baseline clinical and demographic characteristics between the NmaxDSE (≥ 85% PMHR) and NsubDSE (< 85% PMHR) patient groups. The two-sample t-test for continuous variables and χ^2 test for categorical variables were used. Kaplan-Meier analysis was used to create freedom-from-event curves for individual major clinical outcomes (nonfatal MI, cardiac death, revascularization), and combined MACE. Cox regression analysis was used to determine predictors of cardiac death or nonfatal MI for both the NsubDSE and NmaxDSE cohorts. All the statistical analyses were performed using the SAS software (version 8.2).

Results

Patient characteristics

A total of 756 patients had a negative DSE in the specified time period, of which 341 patients (45%) had NsubDSE studies and formed the study population. The mean overall age was 71.4 ± 2.1 years and the mean overall follow-up time was 39.0 ± 18 months. About 80% of the patient population including both the NDSE groups had preserved left ventricular function (Table 1). Patients in the NsubDSE groups were younger, with a higher incidence of diabetes, hypertension, history of heart failure and prior percutaneous intervention, and were more often on beta-blockers or calcium-channel blockers (Table 1). Primary indications for performing DSE included chest pain, preoperative clearance and evaluation for CAD. Reasons for DSE termination included protocol completion and achievement of maximum heart rate. The peak doses of dobutamine achieved during the study were:

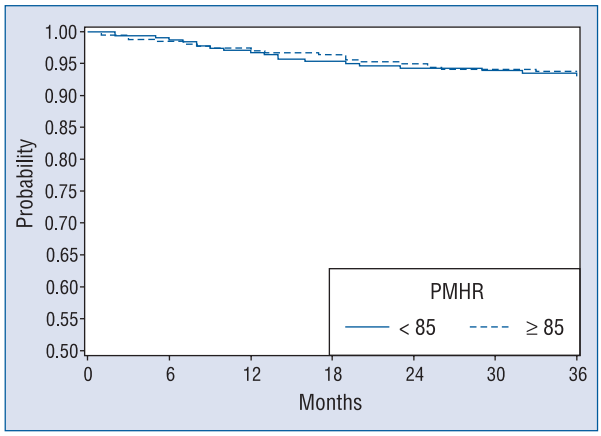

Figure 1. Kaplan-Meier curves for freedom from non-fatal myocadrial infarction based on achievement or lack thereof at least 85% PMHR in negative DSE patients (log rank p-value = 0.84); DSE — dobutamine stress echocardiography, PMHR — predicted maximal heart rate.

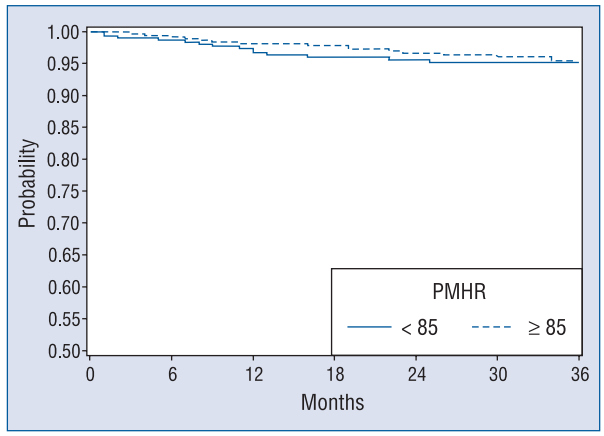

Figure 3. Kaplan-Meier curves for freedom from revascularization based on achievement or lack thereof at least 85% PMHR in negative DSE patients (log rank p-value = 0.54); DSE — dobutamine stress echocardiography; PMHR — predicted maximal heart rate.

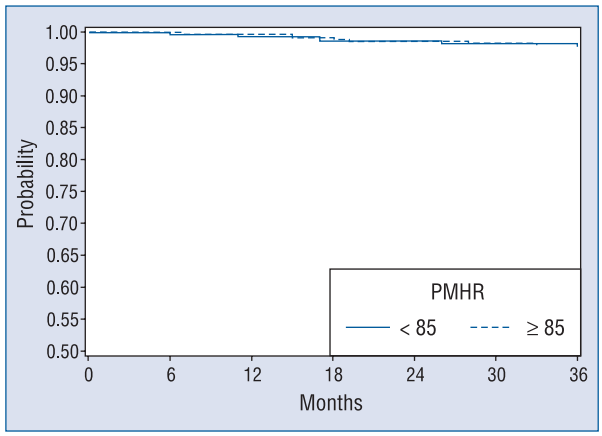

Figure 2. Kaplan-Meier curves for freedom from cardiac death based on achievement or lack thereof at least 85% PMHR in negative DSE patients (log rank p-value = 0.88); DSE — dobutamine stress echocardiography, PMHR — predicted maximal heart rate.

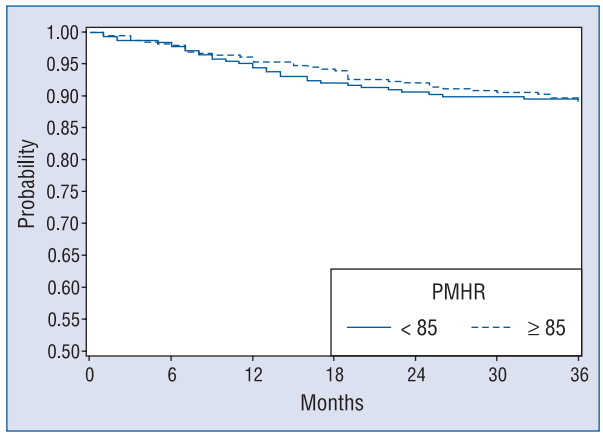

Figure 4. Kaplan-Meier curves for freedom from any major adverse cardiac events based on achievement or lack thereof at least 85% PMHR in negative DSE patients (log rank p-value = 0.81); DSE — dobutamine stress echocardiography; PMHR — predicted maximal heart rate.

4 patients received under 20 μg, 33 received 20 μg, 61 — 30 μg, and 238 patients received the peak dose of 40 μg at the conclusion of the test. Dosing was not specified in the stress reports in 5 patients. About half of the NsubDSE cohort (48%) received atropine based on the DSE protocol. The mean double product was significantly lower in the NsubDSE compared to NmaxDSE (16 473 ± 4901 *vs*. 19 230 ± 4648, $p < 0.0001$), and the mean maximum heart rate was also significantly different between the 2 groups (110.9 ± 19.1 *vs*. 136.6 ± ± 11.3, $p < 0.0001$).

Outcomes

Figures 1–3 show the Kaplan-Meier survival curves for freedom from non-fatal MI (93% *vs*. 94%, $p = 0.84$), cardiac death (98% *vs*. 98%, $p = 0.88$), and any revascularization (95% *vs*. 96%, $p = 0.54$) between the NsubDSE and NmaxDSE groups at 36 months of follow-up, respectively. The freedom from combined MACE rates between the 2 groups at 36 months was also nonsignificant (89% *vs*. 90%, $p = 0.81$) (Fig. 4). There were no significant event rate differences between NsubDSE and NmaxDSE patients who were subcategorized as those with an

Table 2. Cox regression results for predicting any cardiac event (cardiac death or non-fatal MI) in patients with NsubDSE.

Variable	Univariable p	Multivariable p	Multivariable hazard ratio	95% hazard ratio confidence limits	
Age	0.907	0.820	1.004	0.973	1.035
Gender (male)	0.251	0.266	1.570	0.710	3.470
History of MI/CABG/PCI/CAD	0.494	0.632	0.807	0.336	1.938
Tobacco use	0.557	0.621	1.240	0.530	2.900
Hypertension	0.496	0.656	1.596	0.205	12.429
Hypercholesterolemia	0.958	0.951	1.026	0.462	2.277
History of HF	0.069	0.310	1.569	0.657	3.748
Diabetes mellitus	0.009*	0.005*	3.209	1.436	7.173
Ejection fraction ≥ 50%	0.022*	0.035*	0.379	0.154	0.933
Beta-blockers/Ca-blockers	0.934	0.990	1.005	0.455	2.222

*Statistically significant, $p < 0.05$; MI — myocardial infarction, CABG — coronary artery bypass grafting, PCI — percutaneous coronary intervention, CAD — coronary artery disease, HF — heart failure

achieved PMHR < 70% versus those with a PMHR of 70–84% (freedom from nonfatal MI 92% *vs*. 93%, p = 0.83; cardiac death 98% *vs*. 98%, p = 0.36; revascularization 97% *vs*. 94%, p = 0.94). When NsubDSE patients were subcategorized as those with double products < or ≥ 15 000 they had similar rates of nonfatal MI, cardiac death, revascularization, and combined MACE at 36 months (freedom from nonfatal MI 94% *vs*. 92%, p = 0.30; cardiac death 98% *vs*. 98%, p = 0.72; revascularization 93% *vs*. 97%, p = 0.16).

There were 34 total all-cause deaths during follow-up. Cox regression analysis to identify predictors of hard cardiac MACE (cardiac death or nonfatal MI) was performed in both NsubDSE and NmaxDSE groups. Older age, male gender, and history of heart failure or coronary artery disease predicted events in NmaxDSE group whereas history of diabetes mellitus and EF ≥ 50% predicted events in the NsubDSE group.

A comparative analysis was performed between both the study groups (> or ≤ 85% PMHR) among patients who had cardiac events (cardiac death or NFMI). Younger patients (69 ± 14.8 years *vs*. 76.6 ± 8.7 years, p = 0.02) and those with diabetes mellitus were more likely not to achieve a PMHR of 85% or greater (63.0% *vs*. 32.4%, p = 0.015).

Discussion

This study shows that regardless of achieved percentage of PMHR or double product; patients with NsubDSE do not have increased MACE compared to NmaxDSE patients over a 36-month follow-up period. Overall, as long as there is a normal contractile response to dobutamine, these patients seem to have very low MACE rates (death, nonfatal MI) over a 36-month follow-up period. Nevertheless diabetics appear to be a distinct patient population with worse outcomes, higher MACE rates and an increased likelihood to have an NsubDSE (Table 2).

An important aspect of our study, which needs to be considered in drawing these conclusions, is that 80.6% of NsubDSE and 81.9% of NmaxDSE patients had a normal ejection fraction. Since EF is a powerful predictor of cardiac mortality in patients with coronary artery disease [8], it is not surprising that the annualized cardiac death rate in both the NsubDSE and NmaxDSE groups was about 0.6%, with a 3-year event rate of 2%, which is similar to prior published reports [9–11]. In our study, nonfatal MI rates were 6% to 7% in both study groups over 36 months, with annualized event rates of around 2%, which is also comparable to published reports [9–13] for DSE. Similarly, revascularization rates were comparably low over a 3-year follow-up (4–5% over 3 years for both respective groups, nonsignificant difference). We believe that the reason for an EF > 50% to be a multivariate predictor of cardiac events was likely confounding, due to the large percentage of patients in the entire study population with a normal ejection fraction.

Ballal et al. [5] reported that patients with NsubDSE had adverse cardiac event rates similar to positive DSE patients over a 28-month follow-up. Their study reported a 31% cardiac event rate in the NsubDSE group compared to a 36% event rate in the positive DSE groups (p = NS), thereby

concluding that an NsubDSE should be considered nondiagnostic, necessitating further evaluation. The key differences between their study and ours is that they had a much higher risk population (higher incidence of prior CAD, CABG, PCI), a much higher incidence of left ventricular dysfunction (56%), and exclusion of patients on beta-blockers, all of which makes the 2 studies incomparable.

Another study focusing on DSE and chronotropic incompetence (defined as < 85% PMHR) in patients with peripheral arterial disease, Chaowalit et al. [6] showed that NsubDSE was associated with higher all-cause mortality and cardiovascular morbidity, which is not surprising as this was a high-risk cohort given significant concomitant peripheral arterial disease [14]. However the study did not focus on cardiac mortality as an endpoint and studied a select high-risk patient population, much different to our study.

Our results show that despite being on beta--blockers or calcium-channel blockers, patients with NsubDSE tests have similar outcomes compared to patients with NmaxDSE. Previous studies have also demonstrated that beta-blockers attenuate the ischemic response in patients undergoing DSE, particularly when the degree of stenosis is not severe [15]. While withholding beta-blockers prior to stress testing would be ideal in terms of maximizing achievement of target heart rate, many referring physicians are hesitant to withhold beta-blockers. At our institution, withholding beta-blockers or rate slowing calcium-channel blockers prior to testing is not routine. This practice is consistent with other reported studies [16–18]. Published data indicating the safety, feasibility, and enhancement of DSE diagnostic accuracy by using adjunctive atropine during DSE can make physicians less inclined to routinely withhold atrioventricular nodal blockers. About 48% of our study patients received adjunctive atropine. This is likely due to the fact that over half the study population in our subDSE group was on atrioventricular-nodal blocking agents (58% on beta-blockers or nondihydropyridine calcium-channel blockers).

Race and dobutamine stress echocardiography

About half the study population comprised of African Americans (AA) (421/801, 50%) and as depicted in our recent study of negative DSE patients [19], AA patients had higher incidences of hypertension (92% *vs*. 86%, p = 0.01) and left ventricular hypertrophy (71% *vs*. 50%, p < 0.001) compared to Caucasian patients (CA). Stress variables showed that AA patients had more hypertensive responses (17% *vs*. 4%, p < 0.001), and fewer achieved target heart rates (50% *vs*. 60%, p = 0.003) despite a comparable rate of atrioventricular nodal blocker use (50% *vs*. 51%, p = 0.746). It has been shown that higher prevalence of diabetes mellitus, hypertension, and other risk factors in AA lead to dysfunction at the microvasculature level. Hence we postulate that racial differences might explain the higher frequency of subDSE in our study population. The role of race in beta-receptor sensitivity and response to chronotropic stimulus merits further research with an added focus on pharmacogenetics of response to dobutamine in AA and CA patients.

Although there is overwhelming evidence that poor functional capacity is linked to increased adverse outcomes, chronotropic incompetence with DSE in a setting of atrioventricular nodal blockers does not necessarily mean poor functional capacity and adverse prognosis. As illustrated by prior authors, being on beta-blocker therapy and having a subDSE might simply reflect the therapeutic bradycardic effect of these agents [7].

It is possible that NsubDSE can miss underlying CAD and underestimate ischemic burden due to decreased sensitivity from submaximal heart rate, and we believe this is the reason for trend for high rates of unstable angina and non-fatal MI in our study. Tables 2 and 3 lists the predictors for cardiac events (cardiac death or non-fatal MI) in the NsubDSE and NmaxDSE groups obtained by Cox regression analysis. As shown in Table 2, diabetes mellitus and EF ≥ 50% were predictors for cardiac events in the NsubDSE cohort.

Diabetes mellitus and dobutamine stress echocargiography

Consistent with prior literature [20], in our study diabetic patients were more likely to have a cardiac event despite a NDSE. This is not surprising given the fact that diabetics (considered equivalent to having CAD) are known to carry an increased cardiovascular risk particularly with documented CAD [21–23]. In our study, multivariate analysis performed revealed diabetes mellitus to be a significant predictor for any cardiac event in the NsubDSE cohort (Table 2). Furthermore this high risk cohort was more likely to have a subDSE secondary to under-achievement of PMHR of 85% or higher (Table 1). Also, amongst patients who had either cardiac death or non-fatal MI, diabetics were less likely to achieve a PMHR of 85% or greater (Table 4). Our results highlight the pitfalls of NsubDSE in effectively risk stratifying diabetics

Table 3. Cox regression results for predicting any cardiac event (cardiac death or non-fatal MI) in patients with NmaxDSE.

Variable	Univariable p	Multivariable p	Multivariable hazard ratio	95% hazard ratio confidence limits	
Age	0.027*	0.068	1.033	0.998	1.070
Gender (male)	0.047*	0.298	1.453	0.719	2.935
History of MI/CABG/PCI/CAD	< 0.001*	0.022*	2.427	1.135	5.189
Tobacco use	0.393	0.584	1.236	0.579	2.637
Hypertension	0.482	0.842	1.135	0.327	3.936
Hypercholesterolemia	0.801	0.466	0.774	0.389	1.540
History of HF	0.049*	0.525	1.327	0.555	3.178
Diabetes mellitus	0.566	0.897	1.049	0.511	2.151
EF ≥ 50%	0.100	0.920	0.957	0.404	2.265
Beta-blockers/Ca-blockers	0.262	0.583	1.212	0.611	2.406

*Statistically significant, $p < 0.05$; MI — myocardial infarction, CABG — coronary artery bypass grafting, PCI — percutaneous coronary intervention, CAD — coronary artery disease, HF — heart failure, EF — ejection fraction

Table 4. Characteristics of patients who had either cardiac death or non-fatal MI in both groups.

Variable	PMHR < 85% (n = 27)	PMHR ≥ 85% (n = 37)	p
Diabetes mellitus	17 (63.0%)	12 (32.4%)	0.015*
Hypertension	26 (96.3%)	34 (91.9%)	0.632
Hypercholesterolemia	15 (55.6%)	20 (54.1%)	0.905
Tobacco use	9 (33.3%)	11 (29.7%)	0.759
History of MI/CAD/CABG	12 (44.4%)	22 (59.5%)	0.235
Age	69.0 ± 14.8	76.6 ± 8.7	0.022*
Gender (male)	14 (51.9%)	20 (54.1%)	0.862
Race (black)	19 (79.2%)	24 (64.9%)	0.232
Beta-blocker	13 (48.1%)	13 (35.1%)	0.295
Ca-blocker	7 (25.9%)	8 (21.6%)	0.688
Baseline WMA	10 (37.0%)	12 (32.4%)	0.702
EF ≥ 50	18 (66.7%)	27 (73.0%)	0.586
Ischemic ECG change	4 (14.8%)	1 (2.7%)	0.153

*Statistically significant, $p < 0.05$; MI — myocardial infarction, CABG — coronary artery bypass grafting, CAD — coronary artery disease, WMA — wall-motion abnormalities, EF — ejection fraction, PMHR — predicted maximal heart rate

thereby emphasizing the need for considering an NsubDSE inconclusive in this patient subset and proceeding with alternative definitive evaluation for coronary artery disease.

Limitations of the study

This study had weaknesses inherent in retrospective analysis, which might include documentation inaccuracies and incomplete follow-up. The difficulty in determining true unstable angina from non-cardiac chest pain admissions in a retrospective chart review might also have likely contributed to the high rate of unstable angina in our patient population. Patients who underwent very early revascularization (< 2 months) after the index-negative DSE were excluded from the study; hence we would be unable to comment on this group of patients. A quantitative wall-motion scoring was not performed and assessments of echocardiograms were completed by multiple readers and based on visual analysis.

Conclusions

Our study shows that NsubDSE is associated with low MACE rate over a 36-month follow-up period, regardless of the achieved heart rate or double product. Since the majority of our patients had

normal resting ejection fractions, our study findings imply that unless clinically indicated, patients with NsubDSE and normal resting ejection fractions need not undergo further diagnostic evaluation, and can be followed closely with all the continued aggressive risk factor modification strategies. An exception to this strategy would be diabetics in whom an NsubDSE should be considered inconclusive and further evaluation of CAD be carried out as clinically indicated.

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