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Prognostic value of real time dobutamine stress myocardial contrast echocardiography in patients with chest pain syndrome

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Abstract

The aims of this study were (1) to evaluate the prognostic value of negative wall motion (WM) and myocardial perfusion during contrast-dobutamine stress echocardiography (DSE), (2) to determine whether WM-myocardial contrast echocardiography (MCE) had incremental prognostic value over just WM during DSE in patients with chest pain in the emergency room(ER), and (3) to compare the prognostic value of negative DSE-WM, and DSE-WM-MCE to nuclear-myocardial perfusion imaging (N-MPI) in a similar patient population over the same time period. We retrospectively studied 569 patients with real time contrast DSE, and 147 patients underwent N-MPI for evaluation of chest pain. Follow-up for cardiac events was obtained between 12 and 25 months. The cumulative cardiac event-free survival was 94.5% in negative DSE-WM, 97.1% in negative DSE-WM-MCE and 96.7% in negative N-MPI group. Cardiac event-free survival of the negative DSE-WM-MCE group was significantly higher than the DSE-WM group (log rank $P < 0.01$), and similar in the DSE-WM-MCE group compared to the N-MPI group. Combined WM and perfusion during DSE was the strongest independent predictor for cardiac events. The negative predictive power of DSE-WM-MCE is superior to that of just negative DSE-WM and is comparable to that of N-MPI. Myocardial perfusion and WM analysis during DSE provide independent information for predicting cardiac events in patients with chest pain syndrome in the ER.

Keywords

Dobutamine stress; Myocardial contrast; Echocardiography; Chest pain syndrome

Introduction

Dobutamine stress echocardiography (DSE) and nuclear myocardial perfusion imaging (N-MPI) are both useful in the triage of patients who present with chest pain to an emergency room (ER) [1–4]. They both have comparable positive predictive value for patients who come to the ER with chest pain syndrome showing chest pain from various causes and do not have typical electrocardiogram (ECG) changes or elevated cardiac enzymes [1–6]. The negative predictive value (NPV) for cardiac events is important since this improves the confidence of the ER physician to discharge rather than admit these patients. However, the NPV for cardiac events of N-MPI (0.6–0.7%/year) is superior to that of DSE (6–8%/year) [7–9]. The lower NPV for cardiac events with DSE-wall motion (WM) when compared to N-MPI suggest that obtaining perfusion information may provide incremental prognostic value to DSE-WM alone in patients with chest pain in the ER. Real time myocardial contrast echocardiography (MCE) has enabled the assessment of myocardial perfusion and WM simultaneously. It has been reported that real time DSE-MCE provides incremental prognostic information in higher risk patients with known or suspected coronary artery disease (CAD) in the non-ER setting [10]. However, to our knowledge, there has been no study that has examined the prognostic value of negative DSE-MCE for risk stratification in lower risk patients who present to the ER with chest pain. The purpose of this study were (1) to evaluate the prognostic value of negative WM and WM-MCE during contrast DSE, (2) to determine whether WM-MCE had incremental prognostic value over just WM during DSE in patients with chest pain in the ER, and (3) to compare the prognostic value of negative

DSE-WM and DSE-WM-MCE to N-MPI in a similar patient population during the same time period.

Methods

Patient population

We retrospectively studied a total of 569 patients (216 men; mean age 63 ± 12 years) who underwent contrast DSE for the evaluation of resting chest pain presenting to the ER between September 2005 and December 2006. This study also included an additional 147 patients who underwent adenosine gated N-MPI for evaluation of chest pain during the same period. None of these patients had evidence of acute coronary syndrome (elevated cardiac enzymes, acute ischemic ECG changes: ST-T segment elevation >1 mm, ST-T depression >1 mm, or acute T wave inversion). We calculated Framingham risk score (FRS) for the evaluation of 10 year coronary heart disease risk [11]. We excluded patients who did not achieve the target heart rate in DSE. Patients with known valvular heart disease, significant arrhythmia and patients who underwent revascularization after the stress test were also excluded. DSE was done with contrast for left ventricle opacification (LVO) in 569 patients and LVO was successful in all of these patients. This population was defined as the DSE-WM group ($n = 569$). MCE was successful at rest and peak in 94% (535/569) of the patients. This population was defined as the DSE-WM-MCE group ($n = 535$). DSE and N-MPI was performed when two sets of Troponin-I (6 and 12 h after patients arrived at ER) were negative for myocardial infarction. Stress echocardiography or radionuclide studies had been selected ER physician preference during same period.

Follow-up was completed in December 2008. Follow-up for overall and cardiac events were obtained between 12 and 25 months (average 18 months). Follow-up was not available in 26 patients (4.6%) in the DSE-WM, 22 patients (4.1%) in the DSE-WM-MCE, and 4 patients (2.7%) in the N-MPI group. Thus, the final study population consisted of 513 patients with successful DSE-WM and DSE-WM-MCE and at least 6 months follow-up and 143 patients with the N-MPI. The study was approved by the Institutional Review Board of the University of California, Irvine and Yeungnam University, Daegu, Korea.

Dobutamine stress echocardiography

Dobutamine was infused at a starting dose of $5 \mu\text{g/kg/min}$, followed by increasing doses of 10, 20, 30, and $40 \mu\text{g/kg/min}$ in 3- to 5-min stages [12]. Atropine (up to 2 mg) was administered intravenously if 85% of maximal predicted heart rate ($220 - \text{age}$) was not achieved solely with dobutamine. Blood pressure and cardiac rhythm were monitored before, during, and after the dobutamine infusion. 12-lead ECGs were obtained at 3-min intervals. The stress ECG was considered positive for ischemia in the presence of horizontal or down-sloping ST-segment depression >1 mm for 0.06 s after the J point. End points of the stress test were achievement of target heart rate (85% of age-predicted maximal heart rate), maximal dose of dobutamine and atropine, hypertension (blood pressure $>240/120$ mmHg), symptomatic decrease in systolic blood pressure, development of severe or extensive WM abnormalities, ST-segment elevation >2 mm in ECG leads, sustained arrhythmias, severe chest pain, or any intolerable side effects considered to be the result of

dobutamine or atropine. Metoprolol (1–5 mg) was injected intravenously to reverse the effects of dobutamine if these did not revert quickly after termination of the infusion [13, 14]. The DSE was considered positive if inducible abnormalities were detected by analysis of WM or myocardial perfusion. Baseline left ventricular ejection fraction (LVEF) was estimated by the biplane Simpson's formula in the apical 2- and 4-chamber views [15]. Patients were considered to have abnormal left ventricular function when LVEF was <50%.

Real time contrast echocardiography

Real time contrast echocardiography was performed using Sequoia C512 ultrasound Contrast Pulse Sequencing (CPS) algorithm on the Acuson platform (Siemens, Mountain View, CA, USA). The ultrasound scan width, imaging depth and system spatial temporal settings were optimized to achieve the highest possible frame rate. Contrast echocardiography was performed with the lipid-encapsulated microbubble echo contrast agent, Definity (Lantheus Medical Imaging, Billerica, MA, USA). As a slow intravenous bolus, 0.2–0.4 ml of Definity was given followed by 1–5 ml of normal saline flush [16, 17]. Definity was given at baseline and peak dobutamine stress. At both stages, first contrast LVO was obtained with a higher MI setting (0.5–0.7), and then LVO-MCE was obtained with a lower MI setting (0.1–0.3). More than one bolus injection were required to acquire LVO and MCE images. Perfusion images were obtained in the apical 4-, 2-chambers and apical long axis view at baseline and at peak stress. The real time MCE images were digitally acquired after reaching peak myocardial opacification and continued until disappearance of contrast from the myocardium. The gain was adjusted at the beginning of the rest study and kept unchanged throughout the study.

Gated nuclear myocardial perfusion imaging

Tc-99 sestamibi (20–30 mCi) was injected at rest and single photon emission computed tomography (SPECT) imaging was initiated 10 min later. A stress SPECT-MPI study was obtained after adenosine (0.14 mg/kg/min) infusion over 4 min. Acquisitions were performed using a SPECT camera with a high-resolution detector (ADAC-VXHR, Milpitas, CA, USA). Rest and stress images were reconstructed by back projection using a low pass ramp filter and reoriented in three orthogonal planes using standard techniques. Radioisotope uptake was graded by an independent observer without knowledge of other data.

Perfusion analysis

An independent experienced investigator blind to the clinical data interpreted WM and perfusion echocardiography using the 17-myocardial-segment model [15]. MCE was analyzed after attenuation from left ventricular cavity contrast was resolved. Resting images were compared side by side with stress images using digitally captured cardiac cycles for each apical view. A stress induced perfusion defect (positive) was considered present when two contiguous segments failed to exhibit contrast enhancement during the washout of contrast after the bolus injection as compared to other segments at the same depth in the same view, and as compared with contrast enhancement in the same segment at rest using a side by side image analysis. Artifacts resulting from contrast or lung interference were considered present if the endocardial and epicardial borders of a segment could not be

visualized and thus were not distinguishable from surrounding tissues [18]. Ten randomly chosen studies were reanalyzed for intraobserver and inter-observer variability.

For SPECT-MPI, perfusion was independently quantified by an experienced nuclear cardiologist blinded to clinical data. Composite reading of SPECT-MPI included an assessment of wall motion (gated SPECT) and attenuation correction. A normal response was defined as normal uptake ($>70\%$) at rest and stress; ischemia was defined as normal uptake at rest and reduced ($<70\%$) during stress.

Wall motion analysis

An independent observer who was not involved in MCE interpretation analyzed the WM of patients using acquired LVO images. WM was scored in each of the 17 segments as normal, hypokinetic, akinetic, or dyskinetic. A normal response was defined as normal or hyperdynamic function during exercise. A positive test for wall motion was defined as a new or worsening wall motion abnormality in two or more contiguous segments during dobutamine infusion. The intraobserver agreement of real-time MCE in our laboratory was 89% ($\kappa = 0.64$) for myocardial perfusion and 94% ($\kappa = 0.67$) for WM. The inter-observer agreement was 82% ($\kappa = 0.61$) and 90% for WM ($\kappa = 0.63$) analysis.

Follow up

A physician blinded to the result of the stress test determined the clinical status of each patient during the follow-up period. Overall events were defined as the composite of any sudden unexpected death or hospitalization. Cardiac events were defined as the composite of cardiac death (death in the presence of acute myocardial infarction [AMI], significant cardiac arrhythmia, or refractory congestive heart failure), cardiac arrest, myocardial infarction, hospitalization for unstable angina, hospitalization for congestive heart failure, or coronary revascularization. Nonfatal AMI was defined according to the World Health Organization criteria, including a typical history, defined changes on the ECG, and a rise in cardiac markers. Rehospitalization for unstable angina (UA) was defined as recurrent episodes of chest pain requiring hospital admission and intravenous treatment with heparin and nitrates to relieve symptoms.

Change in the clinical status or documentation of cardiac events was confirmed by review of the patients' hospital chart, electronic records, and telephone interview. The Overall event-free survival and cardiac event-free survival for patients with a negative test was calculated for each group separately.

Statistical analysis

Continuous variables were presented as mean and standard deviation, and were compared using the Student *t* test. Comparison of categorical variables was made by the Chi-square test. A *P* value <0.05 was considered statistically significant. The probability of cardiac events as a function of follow-up duration was estimated by the Kaplan–Meier method and compared between the three groups of different imaging modalities by the log rank test. Survival curves were developed using SPSS software package (SPSS v13.0, Chicago, IL, USA). For survival analysis, patients with more than one event were included until the date

of the first event and censored thereafter. Bivariate logistic regression analyses, as well as standard forward and backward stepwise logistic regressions were performed to identify predictors of subsequent cardiac events from clinical and demographic variables available for each patient in the DSE-MCE. Independent variables evaluated were age, ejection fraction, history of hypertension, diabetes mellitus, hypercholesterolemia, CAD, smoking, WM and perfusion responses to dobutamine. The variables associated with the end point in the univariate analysis were compared using multivariate stepwise logistic regression analysis. A value of $P < 0.05$ was considered significant.

Results

Study population

Clinical data for all patients is displayed in Table 1. The mean age of the DSE group was 62 ± 13 years, and 216 (38.0%) of 569 patients were men. The mean LVEF was $60 \pm 15\%$. There were 48 patients (8.4%) with baseline LVEF $< 50\%$. Clinical characteristics for the DSE group included hypertension ($n = 170$, 30%); diabetes ($n = 89$, 16%), history of CAD ($n = 75$, 13%), hypercholesterolemia ($n = 189$, 33%), and smoking ($n = 122$, 21%). Average FRS of the DSE group was 6.97 (10 year coronary heart disease risk; 14%). There was no significant difference in baseline characteristics between the DSE and N-MPI group.

Contrast DSE and N-MPI results

The mean maximal dose of dobutamine was $34 \pm 8 \mu\text{g/kg/min}$. Atropine was injected in 81% of patients with a mean cumulative dose of $0.8 \pm 0.5 \text{ mg}$. Heart rate increased from $73 \pm 12 \text{ bpm}$ at baseline to $139 \pm 15 \text{ bpm}$ at peak stress, and the rate-pressure product increased from $10,784 \pm 3,120 \text{ mmHg/min}$ at baseline to $22,204 \pm 4,172 \text{ mmHg/min}$ at peak stress. The mean percentage maximal predicted heart rate achieved at peak stress was $88 \pm 8\%$. Definity was used in all patients, and its mean cumulative dose was $1.3 \pm 0.6 \text{ ml}$.

For patients in the DSE-WM group, the stress echocardiogram was interpreted as normal for WM in 505 patients (89%) and abnormal in 64 patients (11%). For patients in the DSE-WM-MCE group, the stress echocardiogram based on WM and perfusion was interpreted as normal in 427 patients (80%) and abnormal in 108 (20%). N-MPI was negative in 123 (84%) and positive in 24 (16%) patients (Table 2).

Follow up and outcomes in negative stress tests

Follow-up was completed in 543 patients (95%) in the DSE-WM-group, 513 patients (94%) in the DSE-WMMCE group, and 143 patients (97%) in the N-MPI group. The mean follow-up period was 23 months (range: 12–30 months). For patients with a negative stress test, there were 58 overall events and 28 cardiac events in the DSE-WM group, 31 overall events and 12 cardiac events in the DSE-WM-MCE group, and 9 overall events and 4 cardiac events in the N-MPI group during the follow-up. Overall event rate was 11.8% (58/490) in patients with negative DSE-WM, 7.6% (31/408) in patients with negative DSE-WM-MCE, and 7.5% (9/120) in negative N-MPI (Fig. 1). The cardiac event rate was 5.7% (28/490) in negative DSE-WM, 2.9% (12/408) in negative DSE-WM-MCE and 3.3% (4/120) in

negative N-MPI (Fig. 2). The positive predictive value for cardiac events for DSE-WM, DSE-WM-MCE, and N-MPI was 28, 29, and 22%, respectively.

The cumulative overall event-free survival during the follow-up period was 88.5% in patients with negative DSE-WM, 92.4% in negative DSE-WM-MCE, and 92.5% in negative N-MPI. The cumulative cardiac event-free survival during the follow-up period was 94.5% in negative DSE-WM, 97.1% in negative DSE-WM-MCE and 96.7% in negative N-MPI. Overall event-free survival of the DSE-WM-MCE group was significantly higher than that of the DSE-WM group (log rank $P < 0.05$, Fig. 1). The cardiac event-free survival of the DSE-WM-MCE group was significantly higher than the DSE-WM group (log rank $P < 0.01$, Fig. 2). Both overall and cardiac event-free survival was similar in the DSEWM- MCE and N-MPI group (log rank $P = ns$).

Follow up and outcomes in contrast DSE

Of the 513 patients undergoing DSE-WM-MCE, 42 (8.2%) patients had cardiac events during the follow-up. Events occurred at a median of 10 months after the DSE and included death in 2 patients, non-fatal myocardial infarction and unstable angina in 44 patients in the DSE-WM group, 40 patients in the DSE-WM-MCE group and 9 patients in the N-MPI group (Table 3). The clinical characteristics of patients with and without subsequent events are presented in Table 4. No differences in age, sex, history of hypertension, diabetes, and smoking were observed between patients with or without events. In patients with cardiac events, there was a significantly higher incidence of hypercholesterolemia (45% vs. 30%, $P = 0.001$), history of CAD (29% vs. 13%, $P = 0.001$) and a significantly lower ejection fraction (52.5 ± 16 vs. 61.2 ± 11 , $P = 0.04$) compared to those without cardiac events (Table 4). Both WM and perfusion analyses were concordant in 463 patients (90%; $\kappa = 0.72$). Both tests were normal in 408 and abnormal in 55 patients. There were 50 patients (9.7%) with normal WM but abnormal perfusion. All patients with abnormal WM also had abnormal myocardial perfusion determined by MCE. The event-free survival rate was 97% in patients with normal WM and perfusion, 74% in patients with normal WM and abnormal perfusion, and 69% in patients with both WM and perfusion abnormality (log rank $P < 0.001$, Fig. 3).

Variables associated with outcome

Clinical variables associated with the end point (univariate analysis) during follow-up were hypercholesterolemia ($P = 0.02$), a history of CAD ($P = 0.01$), abnormal resting LVEF ($<50\%$) ($P < 0.001$), abnormal DSW-WM ($P = 0.005$), and abnormal DSE-WM-MCE ($P < 0.001$) (Table 5). A combination of abnormal WM and perfusion (DSE-WM-MCE) was a strong independent predictor for cardiac events (odds ratio (OR), 8.9; 95% confidence interval (CI). 2.2–21.8; $P < 0.001$). Abnormal resting LVEF was the only independent clinical predictor for the combined end point (OR, 2.8; 95% CI, 1.0–4.3; $P = 0.05$) (Table 6). After adjustment, hypercholesterolemia, a history of CAD, and abnormal WM were not significant.

Discussion

The present study is the first study to our knowledge that compared the value of negative WM and myocardial perfusion during DSE in patients presenting with chest pain. This study demonstrated that DSE-MCE had an independent prognostic value in relatively low-risk chest pain patients with a normal ECG and negative cardiac enzymes in the ER. The cardiac event rate was 5.5% (28/505) in negative DSEWM, 2.9% (12/408) in negative DSE-WM-MCE and 3.3% (4/120) in negative N-MPI. The incidence of cardiac events at 2-year follow-up was significantly lower in patients with negative WM and myocardial perfusion at DSE-MCE or negative N-MPI than those with negative DSE-WM alone. A combination of abnormal WM and perfusion (DSE-WM-MCE) data provided incremental prognostic information for cardiac events.

Although conventional DSE has proven value as a stress imaging modality, it has a number of limitations, including its dependence on the provocation of WM abnormalities for the diagnosis of ischemia, reliance on qualitative WM scoring, frequent non-diagnostic rate due to suboptimal image quality, and underestimation of the extent of CAD [19–21]. In consideration of these shortcomings of conventional DSE, a large number of studies have recently investigated the accuracy and prognostic implication of contrast DSE. They have reported that real-time DSE-MCE provides a high degree of diagnostic accuracy [14] and incremental prognostic information in patients with known or suspected CAD [10]. However, there has been no study evaluating the prognostic value of real-time DSE-MCE in relatively low-risk chest pain patients in the ER. In this study, the 2-year event rate of negative DSE-WM-MCE was 2.9%. The cardiac event rate was lower than in the study by Tsutsui et al. [10], which was targeted at patients with known or suspected CAD (4.5%). The event-free survival rate of our study was significantly higher in normal WM and perfusion (97%) than normal WM and abnormal perfusion group (74%). This result was also similar to that of the previous study in high risk patients [10].

N-MPI has a wealth of data on efficacy and safety for the evaluation of both high risk and low risk patients with chest pain syndrome [5]. Our 2-year cardiac event rate of 3.3% after negative N-MPI was relatively higher (1.78%) than what has been reported from meta-analysis of many studies in differing patient populations [7]. The event rate in our study included hospitalization for unstable angina, whereas the meta-analysis data included only cardiac death and non-fatal-MI. The discrepancy may be explained based on the population studied and inclusion of softer event criteria during follow-up in our study and the 2-year event rate of negative DSE-WM-MCE and N-MPI (2.9% vs. 3.3%), which was not statistically significant. Thus, DSE-WM-MCE offers a test as good as N-MPI for predicting prognosis with all the advantages of echocardiography, which include a relatively low cost, no radiation exposure, higher spatial resolution, applicability at bedside, shorter test duration, immediate availability of results, ability to perform stress and rest images in the same setting, and the ability to have real-time imaging of both myocardial perfusion and WM [2, 10, 22].

Stress WM echocardiography has comparable accuracy with N-MPI and obvious advantages [23–27]. It has been reported that DSE WM provides good prognostic value in higher risk

patients with known or suspected CAD [9, 22, 28–30], but very few studies have looked at lower risk patients with chest pain. One single-center study, which examined DSE-WM in low-risk ER chest pain patients, reported good results in terms of negative predictive value [31]. In this study, the event rate was 4% in negative DSE-WM patients which was lower compared to the 5.5% event rate in our study. However, this previous study had a smaller population (n = 377) and shorter follow-up duration (6 months) compared to the 2-year follow up in our study.

Clinical significance

This investigation is the first to evaluate the incremental prognostic value of combining WM and MCE during DSE in patients with relatively low-risk (FRS; 6.97) chest pain patients in the ER. Among the clinical parameters examined, abnormal resting LVEF, hypercholesterolemia, and history of CAD were found to be significant predictors of cardiac events in the univariate analysis. However, in the multivariate analysis, only abnormal resting LVEF was a significant clinical predictor of cardiac event during the follow-up period. In our study, abnormal WM and perfusion during DSE was the most significant independent predictor of cardiac events in low-risk chest pain patients in the ER.

Study limitations

In most of the previously published studies, the perfusion and WM data from DSE were derived from separate groups of patients. However, in our study WM and WM-MCE data was analyzed from the same cohort of 569 patients. This was done for a number of reasons including (1) many patients now get contrast during DSE for WM delineation, (2) advances in contrast technology means that it is now possible to obtain real-time MCE data in a significant number of patients who get contrast for LVO, and (3) by using data from the same cohort, we balanced the effect of other confounding risk factors which may have determined prognosis. We had only 147 N-MPI patients compared to 569 DSE patients. However, the N-MPI population in this study was to merely show that in our center, N-MPI has similar prognostic efficacy as that previously described in this population, and consequently not to establish the efficacy of N-MPI. In our study, the stressors used for DSE (dobutamine) and N-MPI (adenosine) were different. Dobutamine and adenosine have different hemodynamic effects, which may result in different sensitivity and specificity in this setting. However, the comparable accuracy of DSE-WM and N-MPI for detection of CAD has been established previously [3–5, 7–10]. Lastly, our results were based on the retrospective analysis of studies performed at a single center, and larger multi-center randomized prospective studies are necessary to confirm the feasibility and reproducibility of this technique.

Conclusion

The combined negative WM and myocardial perfusion response at contrast DSE in patients with chest pain in the ER predicts a good prognosis. The negative predictive power of DSE-WM-MCE is superior to that of negative DSE-WM alone and is comparable to that of N-MPI. Myocardial perfusion and WM analysis during DSE provides independent information

for predicting cardiac events in low-risk patients with chest pain in the ER. Further confirmatory prospective studies are necessary.

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Conflict of interest Mani Vannan—Research and Honorarium Support from Siemens and Bristol Myers Squibb Medical Imaging.

Abbreviations

DSE	Dobutamine stress echocardiography
N-MPI	Nuclear myocardial perfusion imaging
ER	Emergency room
ECG	Electrocardiogram
NPV	Negative predictive value
WM	Wall motion
MCE	Myocardial contrast echocardiography
CAD	Coronary artery disease
FRS	Framingham risk score
LVO	Left ventricular opacification
SPECT	Single photon emission computed tomography

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Fig. 1.

Kaplan–Meier survival curves for overall events in patients with negative DSE-WM, DSE-WM-MCE, and N-MPI. The difference between the DSE-WM and DSE-WM-MCE group was statistically significant (log rank $P < 0.05$). *DSE* dobutamine stress echocardiography, *WM* wall motion, *MCE* myocardial contrast echocardiography, *N-MPI* nuclear myocardial perfusion imaging

Fig. 2.

Kaplan–Meier survival curves for cardiac events in patients with negative DSE-WM, DSE-WM-MCE, and N-MPI. The difference between the DSE-WM and DSE-WM-MCE group was statistically significant (log rank $P < 0.01$). *DSE* dobutamine stress echocardiography, *WM* wall motion, *MCE* myocardial contrast echocardiography, *N-MPI* nuclear myocardial perfusion imaging

Fig. 3. Kaplan–Meier survival curves based on the combination of WM and perfusion. The difference between the three groups was statistically significant (log rank $P < 0.001$). WM wall motion

Table 1

Clinical characteristics of the study population

	DSE (n = 569)	N-MPI (n = 147)	P
Age (years)	62 ± 13	65 ± 11	NS
Male (%)	216 (38.0)	60 (40.8)	NS
EF (%)	60 ± 15	54 ± 16	NS
Risk factors			
Hypertension (%)	170 (30.0)	48 (32.7)	NS
Diabetes mellitus (%)	89 (15.6)	24 (16.3)	NS
CAD history (%)	75 (13.2)	27 (18.4)	NS
Hypercholesterolemia (%)	189 (33.2)	52 (35.3)	NS
Smoking (%)	122 (21.4)	33 (22.4)	NS
Framingham risk score	6.97	7.35	NS

Data are mean ± SD

DSE dobutamine stress echocardiography, *MCE* myocardial contrast echocardiography, *N-MPI* nuclear myocardial perfusion imaging, *EF* ejection fraction, *CAD* coronary artery disease

Table 2

Distribution of results in the study population

Results	DSE-WM (n = 569)	DSE-WM-MCE (n = 535)	N-MPI (n = 147)
Normal (%)	505 (88.8)	427 (79.8)	123 (83.7)
Abnormal (%)	64 (11.2)	108 (20.2)	24 (16.3)

DSE dobutamine stress echocardiography, *WM* wall motion, *MCE* myocardial contrast echocardiography, *N-MPI* nuclear myocardial perfusion imaging

Table 3

Clinical outcomes in the study population

	DSE-WM		DSE-WM-MCE		N-MPI	
	Positive (n = 53)	Negative (n = 490)	Positive (n = 105)	Negative (n = 408)	Positive (n = 23)	Negative (n = 120)
Cardiac event	18	28	30	12	5	4
Cardiac death	1	1	2	0	0	0
Nonfatal AMI	6	9	11	4	2	1
Rehosp-UA	11	18	17	8	3	3
Non cardiac event	8	30	18	19	3	5

DSE dobutamine stress echocardiography, *WM* wall motion, *MCE* myocardial contrast echocardiography, *Rehosp* rehospitalization, *UA* unstable angina

Table 4

Comparison of clinical variables in relation to cardiac event status

	Without cardiac events (n = 471)	With cardiac events (n = 42)	<i>P</i>
Age (years)	63 ± 13	61 ± 11	0.64
Male (%)	151 (31.9)	10 (24.4)	0.11
EF (%)	61.2 ± 11	52.5 ± 16	0.04
Risk factors			
Hypertension (%)	155 (32.9)	15 (35.7)	0.16
Diabetes (%)	81 (15.8)	8 (19.0)	0.12
CAD history (%)	63 (13.3)	12 (28.6)	0.001
Hypercholesterolemia (%)	140 (29.7)	19 (45.5)	0.001
Smoking (%)	113 (23.9)	9 (22.0)	0.89

Data are mean ± SD

EF ejection fraction, *CAD* coronary artery disease

Table 5

Predictors of cardiac events by univariate analysis

	Odds ratio (95% CI)	P
Hypercholesterolemia	2.655 (1.115–3.417)	0.02
CAD history	2.987 (1.381–4.141)	0.01
Ejection fraction	4.440 (2.241–8.799)	<0.001
Abnormal DSE-WM	3.207 (1.019–8.753)	0.005
Abnormal DSE-MCE-WM	17.873 (5.174–61.795)	<0.001

CAD coronary artery disease, *DSE* dobutamine stress echocardiography, *WM* wall motion, *MCE* myocardial contrast echocardiography

Table 6

Predictors of cardiac events by multivariate analysis

	Odds ratio (95% CI)	P
Hypercholesterolemia	1.051 (0.381–6.083)	0.944
CAD history	1.617 (0.589–5.907)	0.201
Ejection fraction	2.874 (1.011–4.285)	0.054
Abnormal DSE-WM	1.842 (0.475–7.147)	0.104
Abnormal DSE-MCE-WM	8.873 (2.174–21.795)	<0.001

CAD coronary artery disease, *DSE* dobutamine stress echocardiography, *WM* wall motion, *MCE* myocardial contrast echocardiography