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Prognosis after Change in Left Ventricular Ejection Fraction during Mental Stress Testing in Patients with Stable Coronary Artery Disease

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Abstract

Previous studies of patients with stable coronary artery disease (CAD) have demonstrated that decreases in left ventricular (LV) ejection fraction (EF) during acute mental stress are predictive of adverse clinical outcomes. The present study examined the prospective relationship of mental stress on clinical outcomes in a sample of 138 patients with stable CAD. Patients underwent mental stress testing and were followed for a median of 5.9 years to assess the occurrence of the combined endpoint of myocardial infarction or all-cause mortality. There were 32 events (17 nonfatal myocardial infarctions and 15 deaths) over the follow-up period. Of the 26 patients who exhibited myocardial ischemia during mental stress testing, 11 (42%) sustained a subsequent clinical event, compared to 21 (19%) of the 112 patients who showed no mental stress-induced ischemia. LVEF change during mental stress also was related to the clinical events in a graded, continuous fashion, with each 4 percentage point decrease from resting LVEF associated with an adjusted hazard ratio of = 1.7, 95% CI = 1.1, 2.6, p = .011. We conclude that reductions in LVEF during mental stress are prospectively associated with adverse clinical outcomes.

Keywords

Myocardial Ischemia; Mental Stress; Ejection Fraction; Coronary Artery Disease

Introduction

A decrease in left ventricular ejection fraction (LVEF) during mental stress (LVEF-MS) has been shown to identify patients at increased risk for adverse clinical events[1-4] in patients with documented coronary artery disease (CAD). Previously, we have shown that reductions in

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LVEF in response to mental stress[1] were associated with increased likelihood of subsequent clinical events, but these events were primarily revascularization procedures.[1] Because revascularization procedures may not always reflect extra-clinical factors as well as disease progression,[5] we reexamined this association using 'hard' endpoints of all-cause death and myocardial infarction in a sample of patients with stable CAD.

Methods

Data were available from baseline assessments of 138 of 144 patients with documented CAD who participated in a clinical trial of exercise and behavioral stress management.[6] In order to participate in the trial patients had to have documented CAD (by prior myocardial infarction, coronary artery bypass graft surgery, coronary angioplasty, and/or ≥75% stenosis in at least 1 major coronary artery), and a positive treadmill exercise test within the prior year. Informed consent was obtained for all participants and the study protocol was approved by the Institutional Review Board at Duke University Medical Center.

Unless medically contraindicated, patients were briefly withdrawn from anti-ischemic medications (e.g., beta blockers, calcium channel blockers, and long-acting nitrates) at least 48 hours prior to testing; the medication washout period was at least 5 half-lives of the anti-ischemic medication. Twenty-eight patients were unable to be withdrawn from their medications and were tested on their usual dosage of anti-ischemic medications. After a 40-minute rest period, mental stress testing was performed in which patients were presented with two mental stress tasks, Public Speaking and Mirror Trace, in counterbalanced order. The Speaking stressor required participants to give a speech on a controversial current events topic after 1 minute of preparation. The Mirror Trace required participants to outline the shape of a star from its reflection in a mirror. Each task lasted for 5 minutes, with a 10 minute rest period between each stressor. These tasks have been used in prior work and have been found to elicit ischemia in vulnerable patients.[7]

To determine the presence of myocardial ischemia, R-wave-synchronized, gated equilibrium radionuclide ventriculography (RNV) with Paragon PBR software (Medasys Inc., Ann Arbor, MI) was performed prior to and during each stressor at 20 frames per cardiac cycle using a gamma camera (Siemens Gammasonics Inc., Des Plaines, IL) equipped with a sodium iodide crystal and an all-purpose collimator. Images were obtained following the labeling of autologous red blood cells with technetium 99m pertechnetate using the *in vivo* technique.[8] Imaging was conducted during the last 2 minutes of the rest period, the first minute of speech preparation, at 2 min and 4 min for the Speaking and Mirror trace stressors with the camera in the left anterior oblique view. LVEF was obtained using the PBR software.

We defined LVEF-MS as the change from resting levels in LVEF, averaged across the Speaking and Trace tasks. We also classified patients who had a reduction in LVEF of at least 5% (e.g., from 55% during rest to an average of 50% or lower during the tasks) exhibiting mental stress-induced myocardial ischemia. Participants were assessed for clinical events 4 months after testing and annually thereafter through a combination of telephone and mail contact with participants, examination of medical records, and public sources of vital statistics. The primary outcome was the combined endpoint of all-cause mortality or myocardial infarction.

We used multivariable Cox proportional hazards models[9] to estimate the hazard associated with LVEF-MS, adjusting for age, gender, history of myocardial infarction, and LVEF at rest. LVEF-MS was modeled as a continuous variable and scaled such that the resulting hazard ratio represented the change in hazard for every 4% (the interquartile range of LVEF-MS) reduction in LVEF-MS. Resting LVEF and age also were modeled as continuous variables scaled to their

interquartile range (14% and 15 years, respectively). We examined the association between the continuous LVEF-MS measure and the endpoint for possible nonlinearity using a flexible non-parametric curve-fitting algorithm.[10,11] We also conducted a number of sensitivity analyses, adjusting for further potential confounders, including revascularization procedures that occurred during follow-up (modeled as a time-varying covariate). In addition, we evaluated whether the relation between LVEF-MS and the combined endpoint differed for patients who were tapered off their cardiac medication during the mental stress testing and those who were still on medication by testing an LVEF-MS by medication status (on versus off medication) interaction term in the Cox model. Finally, we re-estimated the primary Cox models for the separate endpoints of death and myocardial infarction.

Results

One-hundred thirty eight (138) participants (98%) had adequate RNV studies during mental stress testing. The average age of the sample was 62 years, with the majority being male and Caucasian. Twenty six patients (19%) of the sample exhibited mental-stress-induced ischemia. Patients with mental stress-induced ischemia were more likely to belong to an ethnic minority, to report a history of diabetes, and to have lower serum high density lipoprotein (HDL) levels at the time of testing compared to the non-ischemic patients (Table 1). The median follow-up time was 5.9 years (interquartile range = 4.8 – 7.2 years; range = 35 days – 8.8 years). There were 18 deaths and 17 non-fatal myocardial infarctions. Of the 18 deaths, 4 were known to be related to cardiac causes, 2 were known to be non-cardiac, and 12 were of unknown causes. In 3 cases death was preceded by myocardial infarction, so the initial myocardial infarction rather than death was used as the outcome. Thus, there were 32 unique events (15 deaths, 17 myocardial infarctions) available for analysis.

Among the 26 patients who exhibited mental-stress induced ischemia, 42% (n = 11) sustained a clinical event during the follow-up period, compared to 19% (n = 21) of the 112 patients who showed no ischemia. Figure 1 shows the unadjusted Kaplan-Meier curves for patients with and without mental stress-induced ischemia. The log rank test comparing the two curves was statistically significant, p = .020. Turning to the Cox regression results, LVEF-MS was significantly associated with the time to the combined endpoint (See Table 2), adjusting for age, gender, prior MI, and resting LVEF. We found no evidence that the association between LVEF-MS and the combined endpoint was nonlinear (p = .485).

Adjusting for revascularization procedures (as a time-varying covariate), diabetes, HDL, and ethnic minority status in the primary Cox model did not materially alter the estimate for LVEF-MS, HR = 1.8, 95% CI = 1.1, 2.9, p = .012. We also observed no evidence that the relation between LVEF-MS and the endpoint differed by medication status during the mental stress testing (p = .637). Considering only the 17 myocardial infarctions as the endpoint (censoring deceased patients at the time of death) the estimate for LVEF-MS remained similar to that in the primary analysis, HR = 1.8, 95% CI = 1.02, 3.2, p = .043. Using only the 18 deaths (including the 3 patients who had died after a myocardial infarction) as the endpoint, the HR for change in LVEF-MS was attenuated, HR = 1.6, but the confidence interval contained 1.0; 95% CI = 0.84, 2.9, p = .159. When we removed the 3 deceased cases with known MI from the analysis of deaths only, the HR was further attenuated and the confidence intervals became wider: HR = 1.5, 95% CI = 0.8-2.9, p = .221.

Discussion

Our finding of an association between clinical events and LVEF change during mental stress is consistent with several prior reports using a variety of methodologies to evaluate mental stress-induced changes in left ventricular function,[1-4] supporting the robustness of the

association across a relatively broad population of patients with stable CAD. In the present sample, the hazard ratio for every 4 percentage point decrease in LVEF during mental stress was 1.7, which is consistent with our prior study, in which the adjusted hazard ratio was about 1.5 for every 4 percentage point reduction in LVEF during mental stress.[1] We also found that the hazard estimate for LVEF-MS remained relatively unchanged after adjustment for a number of additional covariates, and also when examining myocardial infarction and all-cause mortality as a separate endpoint. The association of LVEF-MS with all-cause mortality alone was somewhat weaker, especially after the three overlapping MI cases were removed from among the deaths. This latter finding suggests that the inclusion of non-cardiac related death may have attenuated the association in the primary analysis of the combined endpoint. Sensitivity analyses also indicated that the present finding is unlikely explained by confounding baseline differences between patients with and without ischemic responses. We also found that although the conventional binary definition of ischemia during mental stress was related to the risk of an event, the continuous measures of LVEF change also was associated with clinical events. Indeed, given the relatively few patients (19%) with responses that met the definition of mental stress-induced ischemia, the association between LVEF change and prognosis was driven to a large extent by patients who did not have a fall in LVEF of at least 5%. We observed a similar continuous linear association in our previous study.[1] Because LVEF changes with stress may reflect hemodynamic responses that are not due to myocardial ischemia, other mechanisms may contribute to the relationship between LVEF change and subsequent cardiovascular events.

Despite the important diagnostic and prognostic utility of mental stress ischemia, the mechanisms underlying its occurrence are not well understood. Because mental stress typically elicits marked hemodynamic adjustments, including increased blood pressure and heart rate, as well as cardiac contractility, it results in increased myocardial oxygen demand.[12] Unlike normal coronary arteries, atherosclerotic vessels are prone to constrict rather than dilate, and constriction of the coronary arteries leads to reduced myocardial oxygen supply.[13] Myocardial ischemia is understood to be the manifestation of a myocardial O_2 supply/demand imbalance.[14] On the demand side, we have previously shown that mental stress-induced ischemia was associated with increases in systolic blood pressure and rate pressure-product, but not with increased heart rate.[7] We also observed that mental stress-induced ischemia was associated with elevated diastolic blood pressure and suggested that ischemia may result from reduced myocardial oxygen supply.[7] Indeed, increased systemic vascular resistance (SVR) during mental stress has been linked to myocardial ischemia in the PIMI study[15] and increased SVR may be considered to be a manifestation of arterial vasoconstriction and represent a marker of coronary vasoconstriction. Our previous work has shown that mental stress-induced increases in SVR are associated with vascular endothelial dysfunction, as indexed by low flow-mediated dilation (FMD).[16] Indeed, the occurrence of mental stress-induced myocardial ischemia has been found to be associated with impaired FMD in postmenopausal women with angina.[17] Acute mental stress may also result in unfavorable transient alterations in endothelial function. Ghiadoni and colleagues[18] found that exposure to a laboratory-based, simulated public speaking stressor, resulted in transiently impaired FMD (falling from 5% at rest to 2.8% post-stress) in 10 healthy middle-aged men. Gottdiener et al.[19] also documented that mental stress, associated with laboratory anger recall and mental arithmetic stressors, impaired FMD in a study sample comprised of 38 men and women. Findings of mental-stress related impairment of FMD have been replicated in several additional studies, which have utilized a variety of laboratory-based mental stressors, including mental arithmetic,[20] psychomotor reaction time tasks,[21] and cold pressor.[22,23] Therefore, mental stress ischemia may be a manifestation of increased myocardial demand, combined with impaired vascular regulation that may transiently compromise myocardial oxygen supply and increase vulnerability to adverse cardiac events.

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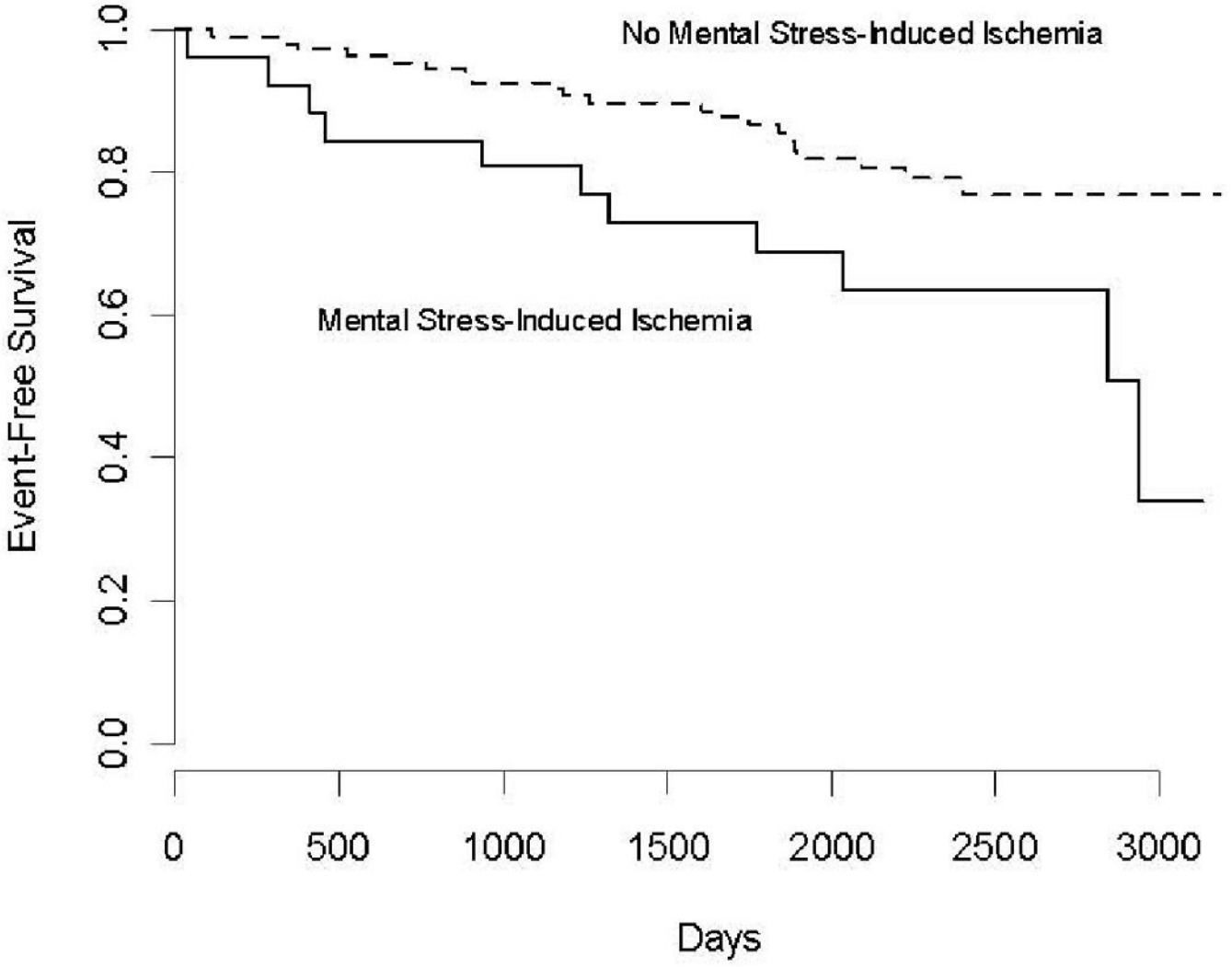

Figure 1.
Kaplan-Meier curves comparing patients with myocardial ischemia (LVEF decrease ≥ 5%) and those without myocardial ischemia (LVEF decrease < 5%) during mental stress. The log-rank test was statistically significant, p = .012.

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Table 1

Characteristics of patients with and without mental stress-induce myocardial ischemia (n = 138)

Variable	No Ischemia (N = 112)	Ischemia (N = 26)	All Participants (N = 138)	P-value comparing Ischemia to No Ischemia groups [a]
Age (years)	62.5 (55.8,71.2)	60.0 (51.2,69.0)	62.0 (55.0,70.0)	0.471
Men	79 (71%)	17 (65%)	96 (70%)	0.607
Ethnicity				0.030[b]
African America	17 (15%)	8 (31%)	25 (18%)	
Caucasian	91 (81%)	15 (58%)	106 (77%)	
Other Ethnicity	4 (4%)	3 (12%)	7 (5%)	
Education				0.391[b]
High School or Less	32 (29%)	7 (27%)	39 (28%)	
Some college	39 (35%)	6 (23%)	45 (33%)	
College or more	41 (37%)	13 (50%)	54 (39%)	
Body Mass Index (kg/m^2)	28.4 (25.8,32.3)	30.1 (25.5.,32.4)	28.9 (25.7, 32.3)	0.584
Hypertension	60 (54%)	15 (58%)	75 (54%)	0.704
Diabetes Mellitus	21 (19%)	10 (38%)	31 (22%)	0.030
Current Smoker	14 (12%)	3 (12%)	17 (12%)	0.893
Quit Smoking	72 (64%)	15 (58%)	87 (63%)	0.530
Past Myocardial Reinfarction	63 (56%)	15 (58%)	78 (57%)	0.894
Past Revascularization	50 (45%)	12 (46%)	62 (45%)	0.889
Total Cholesterol (mg/dL)	180 (160,205)	183 (166,197)	180 (161,201)	0.819
Low Density Lipoprotein (mg/dL)	97 (87,124)	114 (88,125)	98 (87,125)	0.539
High Density Lipoprotein (mg/dL)	45 (39,54)	40 (35,47)	44 (38,52)	0.016
Triglycerides (mg/dL)	141 (102,211)	138 (100,166)	140 (102,210)	0.888
Beta Blockade	81 (72%)	18 (72%)	99 (72%)	0.974
Nitrates	34 (30%)	8 (23%)	42 (31%)	0.872
Calcium Channel Blockade	25 (22%)	5 (20%)	30 (22%)	0.800
Anticoagulants	102 (91%)	22 (85%)	124 (90%)	0.326
Statins	87 (78%)	20 (77%)	107 (78%)	0.934
Left Ventricular Ejection Fraction at Rest (%)	57.5 (51.0,66.2)	56.2 (51.1,63.0)	57.2 (51.0,64.9)	0.729
Reduction in Left Ventricular Ejection Fraction during Mental Stress (%)	-0.75 (-2.25,0.75)	-6.50 (-7.19, -5.56)	-1.50 (-3.50, 0.50)	< .001

Variable	No Ischemia (N = 112)	Ischemia (N = 26)	All Participants (N = 138)	P-value comparing Ischemia to No Ischemia groups [a]
Medication During testing	21 (19%)	7 (27%)	28 (20%)	0.351

Data presented are median (interquartile range) or number (percent) of patients.

[a] Wilcoxon Test used for continuous variables, Pearson chi-square for categorical variables

[b] P-value is from global test of all categories.

Table 2

Cox regression results predicting time to combined endpoint of death (n = 15) or non-fatal myocardial infarction (n = 17)

Factor	Scale Value for Predictor	Hazard Ratio	p-value	Lower 95% Confidence Interval	Upper 95% Confidence Interval
Age	15	1.1	.718	0.6	1.9
Prior Myocardial Infarction	Yes vs. No	1.1	.824	0.5	2.4
Left Ventricular Ejection fraction at Rest	14	1.0	.820	0.6	1.6
Reduction in Left Ventricular Ejection Fraction During Mental Stress	4	1.7	.011	1.1	2.6

Continuous predictor variables age, LVEF at rest, and LVEF reduction during mental stress are rescaled to their interquartile range. This preserves the continuous form of the predictor but generates a hazard ratio that represents a comparison of hazards across a meaningful distance on the range of the predictor. This scaling distance for each continuous variable is given in column 2. For example, the hazard ratio for age represents the increase in hazard for every 15 year increase in age. Gender was included in the model as a stratification variable.