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## The Mental Stress Ischemia Prognosis Study (MIPS): Objectives, Study Design, and Prevalence of Inducible Ischemia

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### Abstract

**Objective**—Mental stress-induced myocardial ischemia (MSIMI) is a common phenomenon in patients with coronary artery disease (CAD), but contemporary studies of its prognostic significance and its underlying pathophysiology are limited.

**Methods**—We prospectively enrolled patients with confirmed CAD in the Mental Stress Ischemia Prognosis Study (MIPS) between 2011 and 2014. All patients underwent mental stress testing using a standardized public speaking task and ischemia was detected by 99mTc sestamibi myocardial perfusion imaging. Patients also underwent conventional stress testing for myocardial ischemia (CSMI) using exercise or pharmacological stress testing. Furthermore, digital microvascular flow, endothelial function, arterial stiffness and blood sample collections were performed before, during and after mental stress. Two-year adverse clinical outcomes are being assessed.

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**Results**—Six-hundred and ninety-five patients completed baseline enrollment in the MIPS. Their mean (SD) age was 62.9 (9.1) years, 72% were men, 30% were African American, and 32% had a history myocardial infarction. The prevalence of MSIMI and CSIMI are 16.1% and 34.7%, respectively. A total of 151 (22.9%) patients had only CSIMI, 28 (4.2%) had only MSIMI and 78 (11.8%) had both MSIMI and CISIMI. Patients with ischemia had a lower ejection fraction and higher prevalence of previous coronary artery bypass grafting compared to those without inducible ischemia ( $p<0.050$ ). The prevalence of obstructive CAD was not statistically different between patients with and without MSIMI ( $p=0.426$ ); in contrast, it was higher in patients with CSIMI ( $p<0.001$ ).

**Conclusion**—The MIPS data will provide useful information to assess the prognostic significance and underlying mechanisms of MSIMI.

### Keywords

Mental stress; myocardial ischemia; coronary artery disease; prognosis

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### Introduction

The idea that psychological stress can precipitate myocardial ischemia was first described by Deanfield and Selwyn in 1984 when they demonstrated the presence of mental stress-induced reversible perfusion abnormalities using nuclear imaging.<sup>1</sup> It is now well established that emotional stress, anger, depressed mood and other psychological states can trigger acute myocardial infarction and sudden cardiac death in susceptible individuals.<sup>2–9</sup> Mental stress-induced myocardial ischemia (MSIMI) has been shown to occur in a substantial proportion of patients with stable coronary artery disease (CAD) and evidence of exercise-induced ischemia (18% to 67% or more).<sup>10</sup> Limited study data suggest that MSIMI is associated with a doubling of the risk for subsequent death or adverse cardiovascular events,<sup>11</sup> and promising treatments are being tested.<sup>10</sup> Therefore, mental stress testing represents a useful technique for assessing individual patients susceptibility to the effects of psychological stress and emotion on cardiac function. However, MSIMI has not gained broad awareness and is not yet being assessed clinically. Only five previous studies have assessed and published the impact of MSIMI on the incidence of adverse cardiovascular events.<sup>12–16</sup> These studies were generally small (the largest study enrolled <200 patients) and they included largely white male patients, were performed in cohorts enrolled decades ago, and none used myocardial perfusion imaging (the current gold standard for ischemia detection).<sup>17</sup> A larger investigation to study a diverse contemporary population was therefore needed to assess the prognosis of MSIMI and investigate its underlying mechanisms.

The specific aims of the Mental Stress Ischemia Prognosis Study (MIPS) are to study the impact of MSIMI on long-term cardiovascular outcomes in a contemporary cohort of patients with CAD and to identify potential vascular, neurobiological and genetic determinants of this phenomenon.

## Methods

### Study Sample and Patient Enrollment

MIPS is a prospective study of stable CAD patients enrolled between June 2011 and August 2014 from Emory University affiliated hospitals and clinics, including Emory University Hospital, Grady Memorial Hospital, Emory Midtown Hospital and the Atlanta VA Medical Center. Patients were enrolled if they were 30 to 79 years of age and had documented CAD defined as any of the following: an abnormal coronary angiogram demonstrating evidence of atherosclerosis with at least luminal irregularities, previous percutaneous or surgical coronary revascularization, a history of myocardial infarction (MI), or a positive nuclear stress test. Patients were excluded if they had an acute coronary syndrome or decompensated heart failure in the prior week, severe psychiatric conditions other than major depression, pregnancy (women of childbearing age were screened by pregnancy test), uncontrolled high blood pressure (180/110 mmHg), or with contraindications for regadenoson administration. Beta-adrenergic antagonists were held for 24 hours and calcium channel blockers and nitrates for at least 12 hours prior to the stress test. Patients for whom withholding medications was considered unsafe were excluded. The diagnosis of heart failure was made using the following criteria: a) self-reported history of heart failure that was confirmed by chart review; b) medical chart review for previous diagnosis of heart failure (all patients were seen by a cardiologist at Emory affiliated hospitals before enrollment); c) ICD codes and adjudication by research personnel. Coronary angiographic data were collected by chart review with a median time between the angiogram and enrollment of 2.1 (1.0 – 4.4) years. The Emory University Institutional Review Board approved the research protocol, and all participants provided written informed consent.

### Study Protocol

Baseline studies were performed during two visits within a week (Figure 1). At the initial visit (Visit 1), patients were consented and underwent a medical history and psychosocial/psychiatric assessments, blood draw, baseline vascular function testing and a resting SPECT study. This was followed by a stress SPECT study after either a conventional (exercise or chemical) stress test or a mental stress test. During Visit 2, they had the other stress test performed. The sequence of the two stressors was randomly assigned.

### SPECT Imaging Protocol

For resting myocardial blood flow assessment, patients were injected with a low dose 99mTc-sestamibi (10–14 mCi based on weight). Thirty to 45 minutes after injection, resting SPECT images were acquired.

### Conventional (Exercise or Pharmacological) Stress Test

Patients underwent treadmill exercise testing using the standard Bruce protocol. The ECG, blood pressure and heart rate were continuously monitored. Once the subject attained 85% of their target heart rate, they were injected with a regular dose of 99mTc-sestamibi (30–40 mCi based on weight) intravenously. Patients who were unable to exercise<sup>18</sup> underwent pharmacological stress testing with regadenoson (Astellas, Northbrook, IL). Forty to 60

minutes after isotope injection, stress SPECT imaging was performed. A physician was present during the study and the electrocardiogram and vital signs were continuously monitored.

### **Mental Stress Testing**

After a 30-minute rest period in a quiet room, mental stress testing was performed by trained staff. Patients were required to listen to a scripted message that provided instructions for the mental stress task. They were asked to imagine a stressful situation, using a scenario in which a close relative had been mistreated in a nursing home. They then were asked to prepare a statement for 2 minutes and then present it over a 3-minute period in front of a video camera and an audience wearing white coats. Patients were told that their speech would be evaluated for content and duration. Blood pressure and heart rate were recorded at 5-minute intervals during the resting phase and at 1-minute intervals during the mental stress period using an automatic oscillometric device. At 60 seconds into the mental stress task, a regular dose of  $^{99m}\text{Tc}$ -sestamibi (30–40 mCi based on weight) was injected intravenously and images were acquired 40 minutes to 1 hour later.

### **SPECT Image Interpretation**

Myocardial perfusion images were interpreted by two experienced readers blinded to the stressor (mental or conventional) and without prior knowledge of the medical history or angiographic data. Discrepancies in interpretation of SPECT images were resolved by consensus. Rest and stress images were visually compared for the number and severity of perfusion defects using a 17-segment model.<sup>19</sup> Each segment was scored from 0 to 4, with 0 being normal uptake, 1 possibly normal perfusion, 2 definitely abnormal perfusion, 3 severe perfusion defect and 4 no uptake. A sum rest score was calculated by adding up the perfusion scores across the 17 myocardial segments. Ischemia was defined as a new myocardial perfusion defect with a score of  $\geq 2$  in any segment, or worsening of a pre-existing impairment of at least 2 points in a single segment, or worsening of at least 1 point in 2 or more contiguous segments.<sup>19</sup> We also assessed ischemia using The Emory Cardiac Tool Box (Emory University, Atlanta, GA) software, which is a quantitative, operator independent assessment of myocardial perfusion as previously described.<sup>20</sup>

### **Long-Term Follow-Up**

Patients are being followed periodically by phone calls and clinic visits for a mean follow up period of 2 years (Figure 1). At 1 year and at 2 years, patients have a clinic visit where medical history, psychosocial and vascular assessments that were collected at baseline are repeated. At 6-month and 3-year intervals, patients are contacted by phone to assess health status, evaluate selected psychosocial factors, and study outcomes. If patients state that they have been hospitalized or have had a procedure since the last visit, their physicians are contacted and discharge summaries obtained.

### **Primary End-Points**

The primary end points are: 1) death or nonfatal MI and 2) a composite of death, nonfatal MI, hospitalization for unstable angina, and coronary revascularization.

## Other Outcome Measures

**i) Vascular function assessment**—All patients underwent peripheral vascular function assessments including digital blood flow, endothelial function and arterial stiffness measurements. Microvascular blood flow was continuously measured using pulsatile arterial tonometry throughout the mental stress test.<sup>18, 21–24</sup> As previously described, endothelium-dependent function was assessed using brachial artery flow-mediated vasodilation (Acuson Aspen ultrasound system), the reactive hyperemia index using pulsatile arterial tonometry (Itamar Inc.), and arterial stiffness using the SphygmoCor device (Atcor Medical, Australia), before and 30 minutes after mental stress testing.<sup>25–29</sup>

**ii) Blood testing**—Blood samples were obtained for biomarkers, genomic testing, catecholamine levels, oxidative and inflammatory markers and circulating progenitor cells. On the day of the mental stress study, samples were collected at rest, 5 min, 45 min and 90 min after completion of the mental stress test. On the day of the conventional stress test, samples were drawn 45 minutes after the test. Blood samples are being collected at 1- and 2-year visits. Catecholamines were measured at rest and 5 min post mental stress test in heparinized plasma using a commercial high-sensitivity EIA Kit (2-CAT ELISA, Labor Diagnostika Nord as supplied by Rocky Mountain Scientific, Centennial, CO).

**iii) Psychological assessments**—At baseline and at each follow-up visit, patients underwent a comprehensive psychological assessment including the Cook-Medley Hostility Scale,<sup>30</sup> the State-Trait Anger expression scale,<sup>31, 32</sup> the Beck Depression Inventory,<sup>33–35</sup> the State-Trait Anxiety Inventory,<sup>36, 37</sup> the Multidimensional Scale Of Perceived Social Support,<sup>38, 39</sup> the Life Experiences Survey,<sup>40, 41</sup> the Perceived Stress Scale,<sup>42</sup> the Early Trauma Inventory,<sup>43</sup> the Post-Traumatic Stress Disorder checklist (civilian version)<sup>44, 45</sup> and the Wechsler Memory Scale.<sup>46</sup> In addition, we administered the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders for the assessment of psychiatric diagnoses (SCID).<sup>47</sup> Before and after mental stress testing, patients completed the Subjective Units of Distress Scale,<sup>48</sup> an analog scale of subjective distress.

## Data Management

Data are being entered and managed using Clinical DataFAX Systems Incorporated client-server data management software (iDataFAX, Ontario, Canada). The validity and quality of data are checked through regular data queries for out-of-range values and missing values. Omissions and errors are conveyed to the study staff for corrections on an ongoing basis.

## Statistical analysis

For this manuscript, we used Student's t-tests and chi square tests to examine the differences between groups. We used mixed linear models to test the change in hemodynamic parameters and catecholamines during mental stress. All statistical analysis was conducted using SPSS (v 23.0, IBM Corp., Armonk, NY, USA).

## Results

Between June 2011 and August 2014 we enrolled 695 patients in the MIPS. Mean age was  $62.9 \pm 9.1$  years (range of 34 to 79 years), 72% male and 30% African American. As expected, CAD risk factors were prevalent (Table 1); approximately a third (38%) had a previous myocardial infarction, 34.7% had previous coronary artery bypass procedure and 53.4% previous percutaneous intervention. About 14% of our population had a current diagnosis of heart failure. Mean ejection fraction (EF) was lower in patients with heart failure in comparison to patients without history of heart failure (SPECT assessed resting EF of  $71 \pm 11$  vs.  $55 \pm 19\%$ , and echocardiogram assessed EF of  $55 \pm 9$  vs  $39 \pm 16\%$ ,  $p < 0.001$  for both). In a subgroup of patients with available coronary angiogram data ( $n=575$ ), the median time between coronary angiography and enrollment was 2.1 (1.0 – 4.4) years. Most patients had a history of obstructive CAD by angiography (83.8% with at least one coronary artery with 70% stenosis).

More than one quarter of patients met criteria for diagnosis of major depression (26.4%) with the SCID and 6.5% for post-traumatic stress disorder (Table 2).

### Hemodynamic and catecholamine response to mental stress

Significant increases in systolic blood pressure, diastolic blood pressure and heart rate were observed during the mental stress test ( $p < 0.001$  for interaction with time for all, Figure 2). Mean percent increases from rest to stress were  $20 \pm 12\%$ ,  $17 \pm 11\%$  and  $18 \pm 15\%$  for systolic blood pressure, diastolic blood pressure and heart rate, respectively.

Overall, 501 patients had catecholamine levels measured at baseline and 5 minutes after the mental stress test. Significant increases in epinephrine levels were observed with a median (interquartile) change of 77 (13 – 160) %, (Figure 2). In contrast, norepinephrine levels decreased slightly after mental stress with a median (interquartile) change of  $-0.02$  ( $-0.17$  –  $0.16$ ) %.

### MSIMI and CSIMI

Few patients had missing or poor quality SPECT scans. Of the 695 patients enrolled, 680 patients completed scans at rest and after mental stress, 666 patients completed scans at rest and after conventional stress testing, and 660 patients had all scans completed with good imaging quality. For conventional stress testing, most patients underwent a treadmill stress test (68.3%), while the remaining patients had pharmacological stress testing.

Among 660 patients with data during both stress tests, the incidence of MSIMI and CSIMI was 16.1% ( $n=106$ ) and 34.7% ( $n=229$ ), respectively. Table 1 shows the basic demographics, CAD risk factors and medication history in the 660 patients who have available data for all scans. There were no statistical differences between patients with and without ischemia during either stress test, except for a slightly lower ejection fraction and higher prevalence of previous coronary artery bypass grafting in those with ischemia. The prevalence of obstructive CAD was not different between patients with and without MSIMI; in contrast, it was higher in patients with CSIMI (Table 1).

A total of 151 (22.9%) patients had only CSIMI, 28 (4.2%) had only MSIMI and 78 (11.8%) had both MSIMI and CISIMI. The incidence of MSIMI was higher in those who developed CSIMI (34.1%) compared to those without CSIMI (6.5%).

## Discussion

The MIPS will provide important information about the pathophysiology of MSIMI and its impact on long-term outcomes in patients with CAD. The large sample size and ethnic diversity of our cohort, as well as the comprehensive vascular, genetic, molecular and psychosocial assessments are unique features and major strengths of the study that will likely generate useful study data regarding MSIMI.

In this large and diverse sample, we found an overall incidence of MSIMI of 16.1% by means of SPECT myocardial perfusion imaging. MSIMI was more common among patients who had ischemia during conventional stress testing. There were only few correlates of either MSIMI or CSIMI. Patients with either MSIMI or CSIMI had a lower ejection fraction and higher prevalence of previous coronary artery bypass grafting compared to those without inducible ischemia. The prevalence of obstructive CAD was not statistically different between patients with and without MSIMI; in contrast, it was higher in patients with CSIMI. Previous studies have reported an incidence of MSIMI between 18% and 67%, measured with a variety of methods.<sup>13, 15, 16</sup> Although the incidence of MSIMI is lower in our study, these studies are not comparable because of differences in the methodologies for ischemia assessment, mental stress protocols, the definition of ischemia, and characteristics of the study population. For example, only few previous studies have used SPECT myocardial perfusion imaging to assess MSIMI.<sup>49–53</sup> In addition, most previous investigations studied MSIMI only in patients with a documented positive exercise stress test, a subgroup that is at higher risk of MSIMI as also shown in our study. Although investigators have employed different mental stress protocols, the hemodynamic responses achieved in our study were comparable to previously reported changes in heart rate and blood pressure, suggesting that the mental stress challenge was adequate.<sup>54–59</sup> However, the epinephrine response was lower than previously reported, likely because we measured epinephrine levels 5 minutes after the mental stress rather than during the peak mental stress period.<sup>54</sup> Interestingly, we observed a slight decrease in norepinephrine levels 5 minutes after the mental stress.<sup>54</sup>

It is still unclear why some patients develop ischemia during mental stress while others do not. MSIMI is known to be a distinct phenomenon from ischemia induced by a conventional stress test. It is typically painless, occurs at lower levels of oxygen demand than ischemia due to physical exertion, and it is not related to CAD severity.<sup>60</sup> Consistent with previous investigations, we show that some patients develop ischemia with mental stress but not with exercise or pharmacological stress.<sup>51, 61</sup> Thus, other factors besides increases in heart rate and blood pressure due to stress lie behind the MSIMI phenomenon. A promising area of investigation is endothelial and microvascular dysfunction. MSIMI is associated with peripheral vasoconstriction,<sup>54, 62–66</sup> which can be measured as a change in digital arterial pulse volume using digital tonometry.<sup>18, 67, 68</sup> Since changes in peripheral vascular tone may reflect changes in coronary vascular resistance, peripheral microvascular vasomotor



response to mental stress may serve as a surrogate for similar changes in the coronary vasculature.<sup>69</sup>

Although MSIMI has been studied before, there are several important gaps in our knowledge. Most studies have included small, selected samples of CAD patients enrolled decades ago, mostly with a history of exercise-induced myocardial ischemia, a group that represents a minority of CAD patients in the current era of aggressive therapeutic interventions.<sup>12, 13, 15, 16, 70</sup> In contrast, our study is the first to assess prevalence and outcomes of MSIMI in a large and contemporary sample of patients with stable and broadly defined CAD (we only excluded patients who had an acute coronary syndrome within a week prior to enrollment).

Women and minority patients were severely underrepresented in previous studies. A strength of our study is the very good representation of women and African Americans, which makes our study population more representative of stable CAD patients in today's clinical practice. Importantly, many previous studies used the presence of wall motion abnormality or an arbitrary drop in EF (between 5–8%) during mental stress as criteria for MSIMI.<sup>11, 71</sup> Since mental stress is associated with a significant increase in peripheral vascular resistance, a change in left ventricular function may reflect an increase in afterload rather than true myocardial ischemia.<sup>11</sup> An advantage of our protocol is the use of SPECT myocardial perfusion imaging with ischemia definition based on the American Society of Nuclear Cardiology guidelines.<sup>19</sup> A specific advantage of SPECT imaging for MSIMI assessment is that the radioisotope, injected at peak stress, is trapped in the myocytes and thus provides a snapshot of perfusion at the time of stress, even though scanning occurs later.

Additional strengths of our study include the use of conventional stress testing as a control condition, the comprehensive assessment of vascular changes during mental stress to examine vascular dynamics, the collection of blood samples at different time points for the assessment of immune/inflammatory responses and genomic profiling. Finally, the prospective follow-up for a mean of 2 years with independent adjudication of cardiovascular endpoints will provide data on the long term consequences of MSIMI.

## Conclusion

Exposure to psychological stress is pervasive during life, yet its effects in subjects with CAD are poorly understood. The MIPS is the largest prospective study of MSIMI that has been designed to promote a better understanding of this phenomenon, and to help provide robust data on the prognostic significance of MSIMI in individuals with CAD. The study will identify psychosocial and genetic susceptibilities and novel causal mechanisms underlying the effects of acute psychological stress in patients with CAD, and will provide an impetus for the development of effective interventions in this area of critical public health importance.

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## Abbreviations

<b>MSIMI</b>	Mental stress induced myocardial ischemia
<b>CSIMI</b>	Conventional stress induced myocardial ischemia
<b>CAD</b>	Coronary artery disease
<b>SPECT</b>	Single photon emission computed tomography
<b>MI</b>	Myocardial infarction

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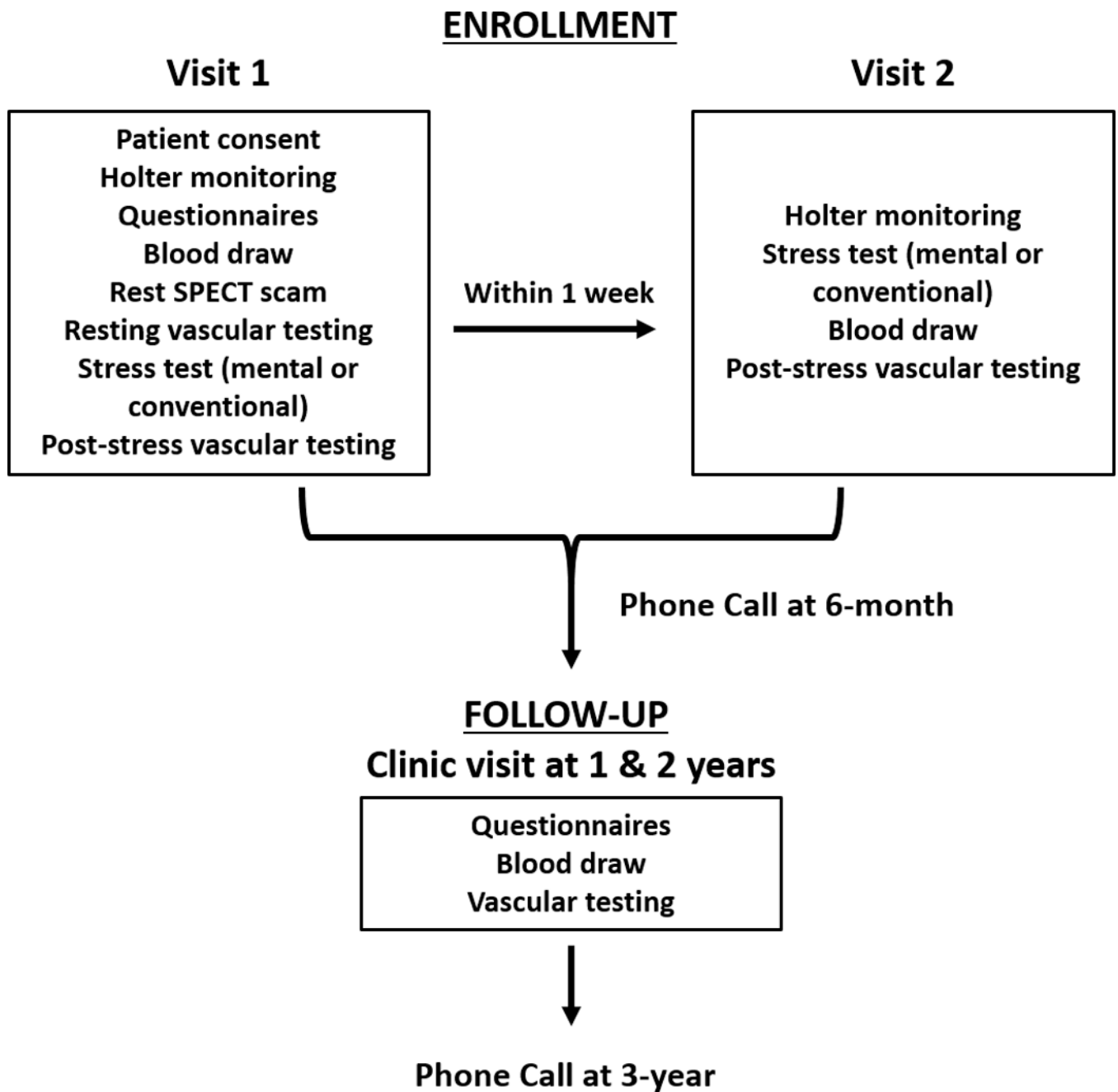
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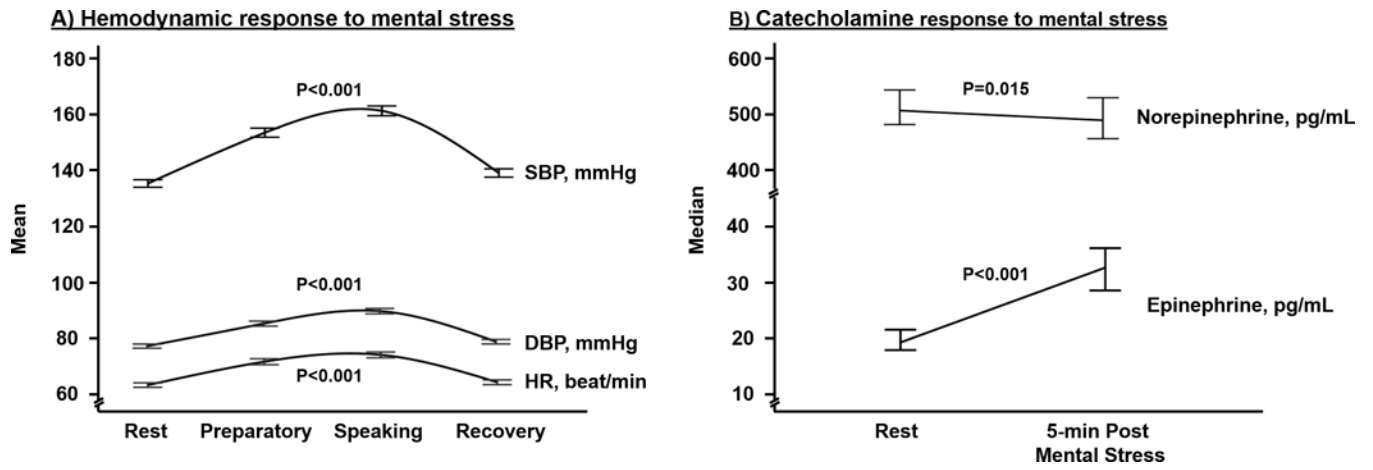
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**Figure 1.**  
Study visits and follow up.



**Figure 2.** A) Hemodynamic and B) catecholamine response to mental stress. SBP: Systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate. Error bars represent 95% CI.



**Table 1**

Baseline characteristics

	MSIMI			CSIMI		
	Negative	Positive	P value	Negative	Positive	P value
Number	554	106		431	229	
Age, years, mean ± SD	63 ± 9	63 ± 9	0.665	63 ± 9	63 ± 9	0.565
Men, %	72	76	0.352	71	76	0.236
African American, %	29	36	0.175	29	32	0.521
Body mass index, kg/m <sup>2</sup> , mean ± SD	30 ± 5	30 ± 5	0.187	30 ± 5	30 ± 5	0.599
Current/former Smoking, %	58	63	0.325	58	60	0.726
Systemic Hypertension, %	75	78	0.505	75	77	0.631
Hyperlipidemia, %	81	82	0.837	80	84	0.233
Diabetes Mellitus, %	31	39	0.133	30	37	0.060
Myocardial infarction, %	36	42	0.202	37	36	0.778
Coronary artery bypass grafting, %	31	52	<0.001	27	49	<0.001
Percutaneous transluminal coronary angioplasty, %	55	50	0.339	53	57	0.342
Congestive heart failure, %	14	15	0.784	13	17	0.208
SPECT LVEF, %, mean ± SD	69 ± 14	65 ± 14	0.010	70 ± 13	66 ± 14	<0.001
Echocardiogram LVEF, %, mean ± SD	53 ± 12	52 ± 11	0.538	53 ± 12	52 ± 11	0.584
At least 1 coronary vessel with 50% stenosis, %	90	93	0.335	89	94	0.037
At least 1 coronary vessel with 70% stenosis, %	83	87	0.426	80	92	<0.001
Aspirin, %	87	86	0.832	86	87	0.849
Clopidogrel, %	34	39	0.317	32	38	0.145
ACEi, %	44	53	0.092	44	48	0.361
ARBs, %	17	14	0.525	16	16	0.821
Beta blocker, %	74	75	0.745	74	75	0.734
Statins, %	85	86	0.857	84	87	0.411
Antidepressant, %	23	19	0.334	23	21	0.409

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MSIMI: Mental stress induced myocardial ischemia. CSIMI: conventional stress induced myocardial ischemia. SPECT: Single-photon emission computed tomography. LVEF: left ventricular ejection fraction. ACEi: Angiotensin converting enzyme inhibitor. ARB: Angiotensin receptor blocker.

\* Coronary angiogram data was available for only 575 patients with a median time between angiogram and enrollment of 2.1 (1.0–4.4) years.

**Table 2**

## Baseline Psychological Characteristics

Lifetime history of major depression, %	26.4
Lifetime history of post-traumatic stress disorder, %	6.5
Beck depression inventory score	8.4 ± 8.4
Post-traumatic stress disorder score	26.7 ± 11.1
Multidimensional scale of perceived social support	67.2 ± 14.8
Cook-Medley hostility scale	16 ± 8
Early trauma inventory self-report	6.5 ± 4.8

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