Journal of Nuclear Medicine, published on July 23, 2015 as doi:10.2967/jnumed.115.157990

High Concordance Between Mental Stress-Induced and Adenosine-Induced Myocardial Ischemia Assessed Using SPECT in Heart Failure Patients: Hemodynamic and Biomarker Correlates

Andrew J. Wawrzyniak,[1] Vasken Dilsizian,[2] David S. Krantz,[1]* Kristie M. Harris,[1,2] Mark F. Smith,[2] Anthony Shankovich,[2] Kerry S. Whittaker,[1] Gabriel A. Rodriguez,[1] John Gottdiener,[3] Shuying Li,[3] Willem Kop,[4] Stephen S. Gottlieb[3]*

[1]Uniformed Services University of the Health Sciences, Bethesda, MD, [2]University of Maryland School of Medicine. Department of Radiology and Nuclear Medicine, Baltimore, MD, [3]University of Maryland School of Medicine. Department of Medicine, Division of Cardiology, Baltimore, MD [4.] Tilburg University, Tilburg, Netherlands

Supported by NHLBI grant 1R01 HL085730.

The opinions and assertions expressed herein are those of the authors and do not necessarily express the views of USUHS or the US Department of Defense. Drs. Gottlieb and Krantz share senior authorship of this study.

Running title: Mental Stress & Adenosine Heart Ischemia

Word count: 4962

Abstract

Background: Mental stress can trigger myocardial ischemia, but the prevalence of mental stress-induced ischemia in CHF patients is unknown. We characterized mental stress-induced and adenosine-induced changes in myocardial perfusion and neurohormonal activation in CHF patients with reduced LV function using single-photon emission computed tomography (SPECT) to precisely quantify segment-level myocardial perfusion.

Materials and Methods:

34 coronary artery disease (CAD) patients (age 62±10 years) with CHF>3 months, ejection fraction<40% underwent both adenosine and mental stress myocardial perfusion SPECT on consecutive days. Mental stress consisted of anger recall (anger-provoking speech) followed by subtracting serial 7s). Presence and extent of myocardial ischemia was quantified using the conventional 17 segment model.

Results: 68% of patients had ⩾1 ischemic segment during mental stress; 81% during adenosine. On segment-by-segment analysis, perfusion to mental stress and adenosine were highly correlated. No significant differences were found between any two time points for BNP, TNF-alpha, IL-1b, troponin, VEGF, IL-17a, MMP-9, or CRP. However, ET-1 and IL-6 increased, and IL-10 decreased, between the stressor and 30 minutes post-stress. Left ventricular end diastolic dimension was 179±65 ml at rest and increased to 217±71 after mental stress and 229±86 after adenosine ($p<0.01$ for both). Resting end systolic volume was 129±60 ml at rest and increased to 158±66 after mental stress ($p<0.05$) and 171±87 after adenosine ($p<0.07$), with no significant differences between adenosine and mental stress. Ejection fraction was 30±12 at baseline, 29±11 with mental stress, and 28±10 with adenosine (p = NS).

Conclusions: There was high concordance between ischemic perfusion defects induced by

adenosine and mental stress, suggesting that mental stress is equivalent to pharmacologic stress in eliciting clinically significant \myocardial perfusion defects in CHF patients. Cardiac dilatation suggests clinically important changes with both conditions. Psychosocial stressors during daily life may contribute to the ischemic burden of CHF patients with CAD.

Key words: heart failure; mental stress; ischemia; myocardial perfusion; adenosine; single-photon emission computed tomography

INTRODUCTION

Mental stress can trigger myocardial perfusion defects and ischemia in a substantial percentage of patients with coronary artery disease (CAD).(*1-4*) Mental stress ischemia is predictive of increased incidence of subsequent cardiac events and all-cause mortality.(*5-7*) However, in stable CAD patients, mental stress ischemia is usually less prevalent, occurs at lower heart rates, often elicits smaller ischemic responses and decreases in myocardial perfusion, compared to both exercise- and adenosine-induced ischemia, (*1,4,8,-11*) Mechanistically, mental stress-induced ischemia has been attributed to increased hemodynamic responses, (*4,9,12,13*) abnormal endothelial function,(*14-16*) increased central nervous system and neuroendocrine activation, (*4,12,17,18*) and/or increased inflammatory responses.(*19*)

Most of these studies have been performed in patients with normal left ventricular (LV) function, with the exception of two studies of patients with reduced LV function, many without heart failure.(*20,21*) In contrast, the prevalence of mental stress induced ischemia is unknown in patients with heart failure and CAD. Increased neuroendocrine activation in these patients could significantly impact the effects of mental stress on coronary blood flow and myocardial perfusion. These and other characteristics of heart failure pathophysiology might cause differences in cardiac responses to mental stress compared to the well-characterized effects of adenosine in heart failure patients.

Therefore, one goal of the current study was to characterize mental stress-induced myocardial ischemia in heart failure patients with reduced LV function using single-photon emission computed tomography (SPECT) to objectively and precisely quantify segment-level myocardial perfusion. Second, we compared the provocative effects of mental stress to adenosine, a well-characterized pharmacologic stressor whose clinical predictive value is

well-established. Third, we examined potential hemodynamic and endocrine mechanisms of mental stress induced decreases in myocardial perfusion.

MATERIALS AND METHODS

Design

As a substudy of the Behavioral Triggers of Heart Failure (BETRHEART) study of biobehavioral aspects of heart failure exacerbation, subjects were recruited from the Heart Failure Clinic at the University of Maryland Medical Center, Baltimore, Maryland. Patients with a history of congestive heart failure $\geq$3 months, ejection fraction <40% in the previous year, and proven coronary artery disease (by history of a myocardial infarction or angiography) were included in this study. After informed consent was obtained, participants were scheduled to undergo both mental stress and adenosine stress tests on consecutive days, in counterbalanced order. This study was approved by IRB's at the University of Maryland Medical Center IRB and Uniformed Services University of the Health Sciences, and all subjects provided written informed consent.

Procedure

On both testing days, patients were asked to fast from midnight the evening before the study and to delay taking their morning beta-blocker and calcium channel blocker medications prior to the lab testing phase. An intravenous cannula was inserted in the antecubital vein upon arrival to permit blood draws during the testing procedure. Blood pressure was continually recorded every 2.5 minutes from the start of the rest period in both stress conditions (DynaPulse; Vista, California).

Adenosine and Mental Stress Testing

Patients rested for 30 minutes prior to mental stress or adenosine administration. For

adenosine testing, patients were administered a standard gated 6-minute adenosine stress test (Adenoscan; Astellas Pharma US; Northbrook, Illinois). For mental stress testing, patients rested for 30 minutes prior to the mental stress which consisted of an anger recall task followed by a mental arithmetic task, both of which reliably elicit increased catecholamines, hemodynamic responses, and myocardial ischemia.(*1,4,9*) For the anger recall stressor, patients gave a 4-minute speech about an anger-provoking incident, and for mental arithmetic, patients verbally subtracted serial 7s from a 4-digit number for 4 minutes while being urged to improve performance. Participants then rested through a 30-minute recovery period (*20*).

Echocardiography

To evaluate cardiac output and systemic vascular resistance, transthoracic Doppler echocardiography (Vivid Seven: GE-Vingmed Ultrasound AS, Horten, Norway) was performed at baseline and during both stressors. Stroke volume was assessed by placement of a pulsed wave Doppler sample volume in the LV outflow tract proximate to the aortic valve; recorded systolic velocity integral was multiplied by the LV outflow tract area, and calculated using measured LV outflow tract radius (r)' as $2\pi r^2$, to obtain stroke volume. Cardiac output (CO) and systemic vascular resistance were determined at the time of recording.

SPECT Acquisition Protocol

Subjects underwent both adenosine and mental stress myocardial perfusion SPECT on consecutive days in randomized order. After a30-minute rest, thallium-201 was injected and rest SPECT images acquired approximately 15 minutes later. After rest image acquisition was completed, patients were given either adenosine or mental stress. For adenosine testing, Tc99m tetrofosmin was injected 3 minutes into the infusion protocol. For mental stress, Tc99m tetrofosmin was injected 3 minutes into the mental stress task. Upon completing the

adenosine infusion or the mental stress task SPECT images were acquired approximately 30-minute after injection of the radiotracer.

Analysis of Myocardial Perfusion Images

Prior to analysis, all images were reviewed for technical quality by a technician blind to study condition. Each scan provided color images of regional perfusion using a 17-segment model (*20,22*) whereby the segment with maximal mean counts per pixel was identified and designated as the normal reference segment(100% or peak activity). The remaining 16 segments were represented as a percentage of activity measured in the reference segment.

Myocardial ischemia: individual segment classification

To classify heart segments as being normal, ischemic, or scar tissue, a previously published scoring system was utilized. (*23-25*) Namely, segments at baseline with $\geqslant$85% perfusion were classified as normal. Segments $\leqslant$85% of peak activity were classified as abnormal. Segments that had both 1) less than a 10% difference between rest and stress, and 2) less than 50% uptake at rest, were classified as scar tissue. Segments with $\geqslant$10% change in uptake between rest and stress and displaying $\geqslant$50% uptake at baseline were classified as ischemic. Using this scheme, the number of normal, ischemic, and scar segments was calculated for each person.

Myocardial ischemia: whole-heart metrics

Whole heart metrics were calculated to draw more general conclusions about overall cardiac function. During stress, each segment was scored on a 5-point scale: 0=normal, indicated by greater than 85% uptake during stress; 1=slight reduction of tracer uptake (equivocal), indicated by >50% uptake at baseline and between 71% and 85% uptake during stress; 2=moderate reduction of uptake (implying significant abnormality), indicated by >50%

uptake at baseline and between 50% and 70% uptake during stress; 3=severe reduction of uptake, indicated by >50% uptake at baseline and <50% uptake during stress; and 4 =absence of uptake, indicated <50% uptake at baseline and <50% uptake during stress, or the difference between baseline and stress uptake being less than 10%.(*23-25)* Totaling scores for each segment generated a summed stress score which was then used to classify patients as being normal or having mild, moderate, or severe reduction in radiotracer uptake; summed stress scores >8 have been found to distinguish ischemic from nonischemic cardiomyopathy.(*26*)

Markers of vascular dysfunction & inflammation

A blood draw was performed prior to stress at the end of the 30-minute rest period. Blood was also drawn 2-3 minutes after starting mental stress and at the end of the recovery period. Samples were analyzed for plasma B-type natriuretic peptide (BNP), a marker of left ventricular wall stretch associated with heart failure severity;(*27*) and serum CRP. Plasma levels of inflammatory markers (IL-6, TNF-alpha, IL-10, IL-1b, IL-17a, CRP), along with biomarkers of cardiac muscle damage (troponin cTn1), angiogenesis (vascular endothelin growth factor: VEGF), vascular matrix protein degeneration (matrix metallopeptidase-9: MMP-9), and endothelial dysfunction (endothelin-1: ET-1), were also assayed.

Data analysis

Data were analyzed using analysis of variance, t-tests, or chi-square as appropriate. Data are presented as mean ± standard error of the mean or as percentages, unless otherwise noted. A two-tailed alpha level of $p<0.05$ was used.

RESULTS

Patient characteristics

Thirty-five patients were recruited for the study; 34 (31 males; mean age=62±10 years, range: 45–85) were included in analyses. One patient who remained hypertensive after the rest period prior to baseline readings was withdrawn from the study. Patient demographic and clinical characteristics at baseline are presented in Table 1. Although all patients had known coronary disease based on prior MI or angiography, only one patient reported ongoing angina.

Hemodynamic responses

Baseline (resting) hemodynamics did not significantly differ between adenosine and mental stress (adenosine condition: systolic blood pressure (SBP)=118±19 mmHg, diastolic blood pressure (DBP)=70±11 mmHg, heart rate (HR)=68±12 bpm; Mental stress condition: SBP=119±22 mmHg, DBP =71±14 mmHg, HR= 66±14 bpm). Hemodynamics during the mental stress testing are presented in Figure 1; repeated measures ANOVA revealed significant changes in SBP (p<0.001), DBP (p<0.001), and HR (p<0.001).

Systemic vascular resistance (SVR) did not significantly change between baseline (29.8 mmHg/ L min^{-1}) and mental stress (31.0 mmHg/ L min^{-1}, p=0.569). Cardiac output significantly increased between baseline (3.30 L/min) and mental stress (3.66 L/min, p=0.048; Figure 2).

Self-reported stress

Participants were asked at baseline, during both mental stress tasks, and during recovery to rate their perceived stress on a 5-point Likert-type scale. Perceived stress was significantly higher during both mental stressors compared to baseline and recovery periods, p<0.001).

Quantifying myocardial ischemia: whole heart metrics

Using the whole-heart metrics classification for each of the 17 segments to generate a

summed stress score to index flow, 32 out of 34 (94.1%) of patients who completed the mental stress protocol and 29 out of 31 (93.5%) patients who completed the adenosine protocol were classified as ischemic using a summed stress score cutoff as ≤8, indicating no difference in the proportion of ischemic patients between conditions (p=0.51). By strict criteria evaluating each segment, of 34 patients completing the mental stress protocol, 23 had at least one ischemic segment (68%); 25 of 31 patients (81%) had at least one ischemic segment during adenosine (p=0.06).

Cardiac function

Ejection fraction at baseline was 30±12 at baseline, 29±11 with mental stress, and 28±10 with adenosine (p=NS). Resting end diastolic volume (EDV) was 179±65 ml, and EDV was 217±71 after mental stress and 229±86 after adenosine. Resting end systolic volume (ESV) was 129±60 ml. ESV was 158±66 after mental stress and 171±87 after adenosine. There were no statistically significant differences between adenosine and mental stress with regard to ESV or EDV. The differences between resting and mental stress were significant for both EDV and ESV, $p<0.01$. The difference between resting and adenosine was significant for ESV, $p<0.05$, and $p=0.07$ for EDV.

Quantifying myocardial ischemia: individual segment classification

Each segment was classified as having normal flow, ischemic, or fixed defect. The total number of each classification was then determined for all patients, and adenosine stress compared to mental stress. The number of segments in each of the three segment groups is shown in Figure 3. Paired t-tests revealed no significant differences in the number of normal, ischemic, or scarred segments between the two types of stressors (normal: $p=.773$; ischemic: $p=0.178$; scar: $p=0.167$). There was a strong correlation between adenosine and mental stress for the number of normal segments (Spearman's rho=0.716, $p<0.001$), ischemic

segments (rho=0.743, $p<0.001$), and scarred segments (rho=0.786, $p<0.001$), indicating that segments that were ischemic during adenosine tended to be ischemic during mental stress.

Segment-by-segment comparison between mental stress and adenosine indicated that perfusion was highly correlated for the two stress types (rho range: 0.436–0.915, *p's*<0.013). Figure 4 presents perfusion concordance for each segment for all participants. Polar maps of rest, mental stress and adenosine perfusion are shown for two patients in Figure 5.

Biomarkers during rest, stress, and post-stress portions of the mental stress procedure

Mean values for each biomarker at each time point are presented in Table 2. No significant differences were found between any two time points for BNP, TNF-alpha, IL-1b, troponin, VEGF, IL-17a, MMP-9, or CRP. However, ET-1 and IL-6 significantly increased between the stressor and 30 minutes post-stress, $p=0.028$, and $p=0.046$, respectively; IL-10 significantly decreased between the same time points, $p=0.035$.

DISCUSSION

Using SPECT perfusion imaging, the present study found a high concordance between ischemic perfusion defects induced by adenosine compared to those induced by mental stress in patients with stable heart failure and coronary artery disease. This was true both in number of segments classified as normal or ischemic, and in segment by segment analyses. Thus, in this sample, mental stress was equivalent to pharmacologic stress testing in eliciting clinically significant defects in myocardial perfusion. These findings suggest that psychosocial stressors during daily life may significantly contribute to the ischemic burden of heart failure patients with coronary artery disease.

Previous research has indicated that mental stress ischemia is of lesser severity

compared to exercise- and/or pharmacologically-induced ischemia. *(1,2,4,9)*. However, none of these studies had compared myocardial perfusion between these two types of stress in patients with heart failure and impaired LV function. Moreover, prior studies did not quantitatively examine direct segment by segment perfusion; this adds precision and allows a more fine-grained analysis of the effects of mental stress.

The perfusion similarities between these two methods for inducing ischemia is particularly notable given the differences in hemodynamic effects of mental stress and adenosine, and the different mechanisms by which they produce ischemia. Mental stress increases blood pressure and heart rate, whereas adenosine, a potent vasodilator, is known to produce either few systemic effects or decreases in blood pressure.(*28,29*) It has been suggested that mental stress reduces perfusion in CAD patients via decreases in myocardial blood flow due to endothelial dysfunction.(*16,30,31*) However, the present study and others indicate that mental stress ischemia is also associated with substantial increases in blood pressure.(*4,9,32,33*) One study (*4*) demonstrated that mental stress-induced wall motion abnormalities were associated with increases in systemic vascular resistance. However, in the present study of heart failure patients, only cardiac output significantly increased due to mental stress, potentially due to an increase in heart rate.

Differences between results of the present study and prior studies may be explained by physiologic characteristics associated with heart failure. Heart failure patients have different hemodynamics, reduced contractile function and reserve capacity, increased neurohormonal activity, and increased peripheral resistance. Medications taken by patients (e.g., diuretics, vasodilators, etc.) may also have reduced the effects of mental stress on cardiac output and systemic vascular resistance.

End systolic and diastolic dimensions were increased during the stress conditions,

most markedly for mental stress. Cardiac dilatation with stress can reflect ischemia, as the dilatation is reduced after bypass surgery.(*34*) Other possible causes include changes in preload or afterload. Vagal effects, such as following adenosine administration, may also occur and affect cardiac function.(*35*)

Biomarkers

Overall, there were only two significant changes in inflammatory markers in response to the acute stress; IL-6 increased and IL-10 decreased between the stress and recovery periods. In a study of healthy young subjects, an increase in IL-6 production was seen with examination stress, and a high anxiety response to stress was associated with lower IL-10 production.(*36*) The time course seen in the present study was the same as the delayed response of IL-6 to mental stress in healthy men.(*37*) Therefore, the present study findings are in line with the extant literature and extends them to a heart failure patient population.

It is noteworthy that endothelin-1 also increased with mental stress. This is consistent with previous studies showing increased systemic vascular resistance and blood pressure associated with mental stress ischemia. However, the present study did not observe a significant increase in total peripheral resistance with stress, and there was no demonstrable association between the change in ET-1 and changes in blood pressure. The lack of association between endothelin-1 and hemodynamics may reflect timing of biomarker measurement and the kinetics of the biomarkers in blood. In addition, actions of the biomarkers at the vascular level may not be adequately reflected in a single measurement at 30 minutes.

Although there was no overall change in BNP concentrations between baseline, peak stress, and recovery, the difference between baseline and recovery levels of BNP was negatively correlated with the number of normally perfused segments and positively

correlated with number of scarred segments during adenosine and mental stress. There was no correlation with the number of ischemic segments. This suggests that mental stress in HF patients with LV scar may be capable of further increasing LV filling pressure, and potentiating HF exacerbation.

Several limitations of the study should be noted. The small sample size may limit the statistical power to observe changes in endocrine markers or hemodynamic variables. In addition, 31 of 34 subjects were male, and extrapolation to females therefore cannot be made. Furthermore, 68% of subjects had diabetes mellitus (see Appendix) and this may impact the results. Regarding biomarkers, the protocol time course for measuring endocrine parameters may not have permitted sufficient time to elapse for changes in biomarker concentration to be assessed in blood. Previous studies have reported significant increases in IL-6 and IL-1Ra only at 2 hours after the stressor, but not at 45 minutes post-task.(*38*)

CONCLUSION

The present study demonstrates that in patients with heart failure and CAD, mental-stress-induced perfusion defects are remarkably similar, both in severity and location, to changes induced by adenosine. This is the case despite differences in the hemodynamic profile associated with adenosine and mental stress. Changes in blood pressure due to mental stress were substantial, and heart rate increases were moderate, but significant. Although some neurohormonal changes did occur, particularly in ET-1 and inflammatory markers, we did not observe associations between these biomarkers and hemodynamic or perfusion changes. These findings suggest that heart failure patients may be particularly vulnerable to ischemic episodes in the presence of mental stress, and that stress induced perfusion defects can be potent and clinically significant. Further studies are needed to

determine the mechanisms associated with mental stress perfusion defects in heart failure patients and determine interventions to reduce the adverse effects of mental stress in these patients.

Acknowledgments

We thank Singulex Inc, Alameda, CA for biomarker analysis.

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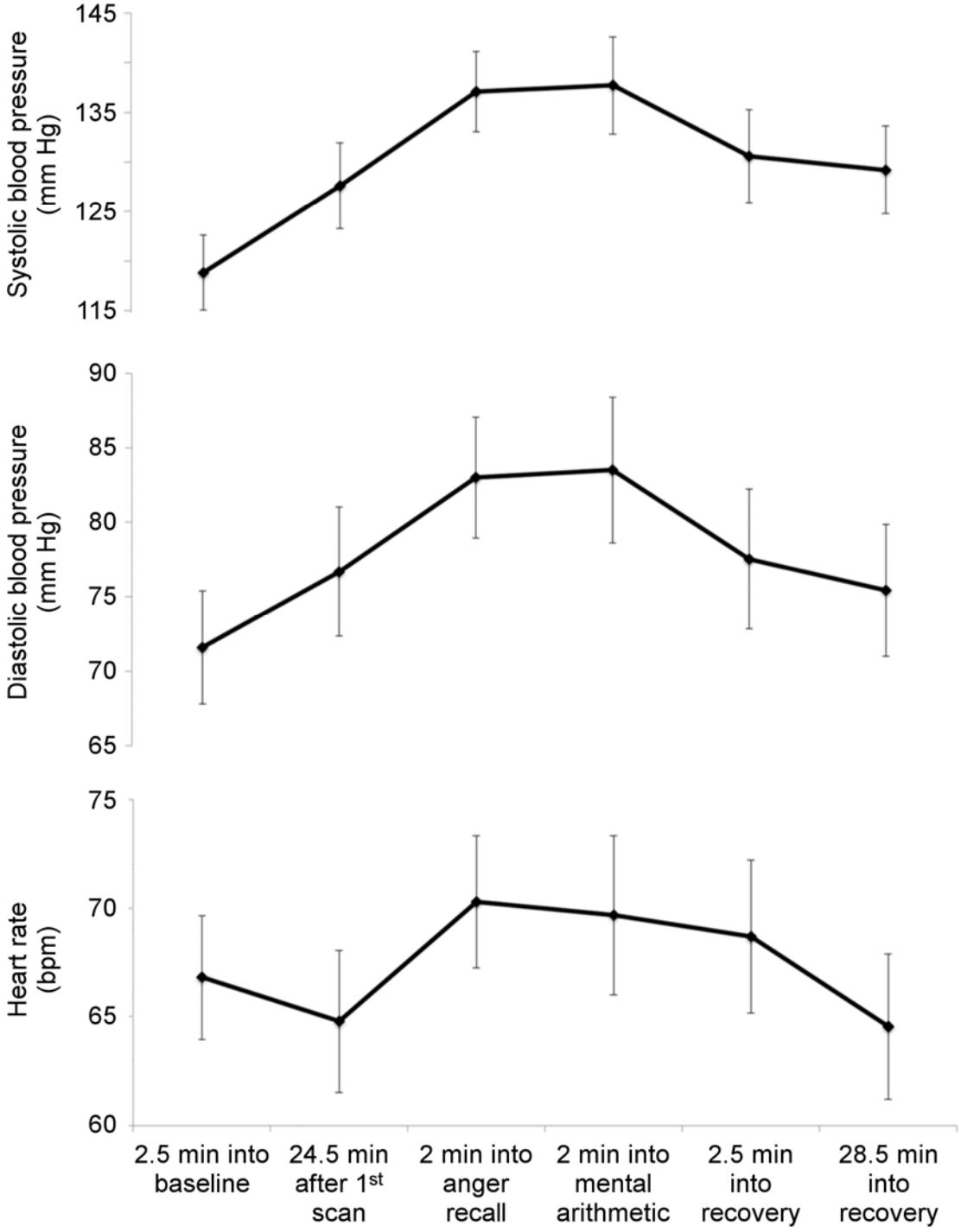
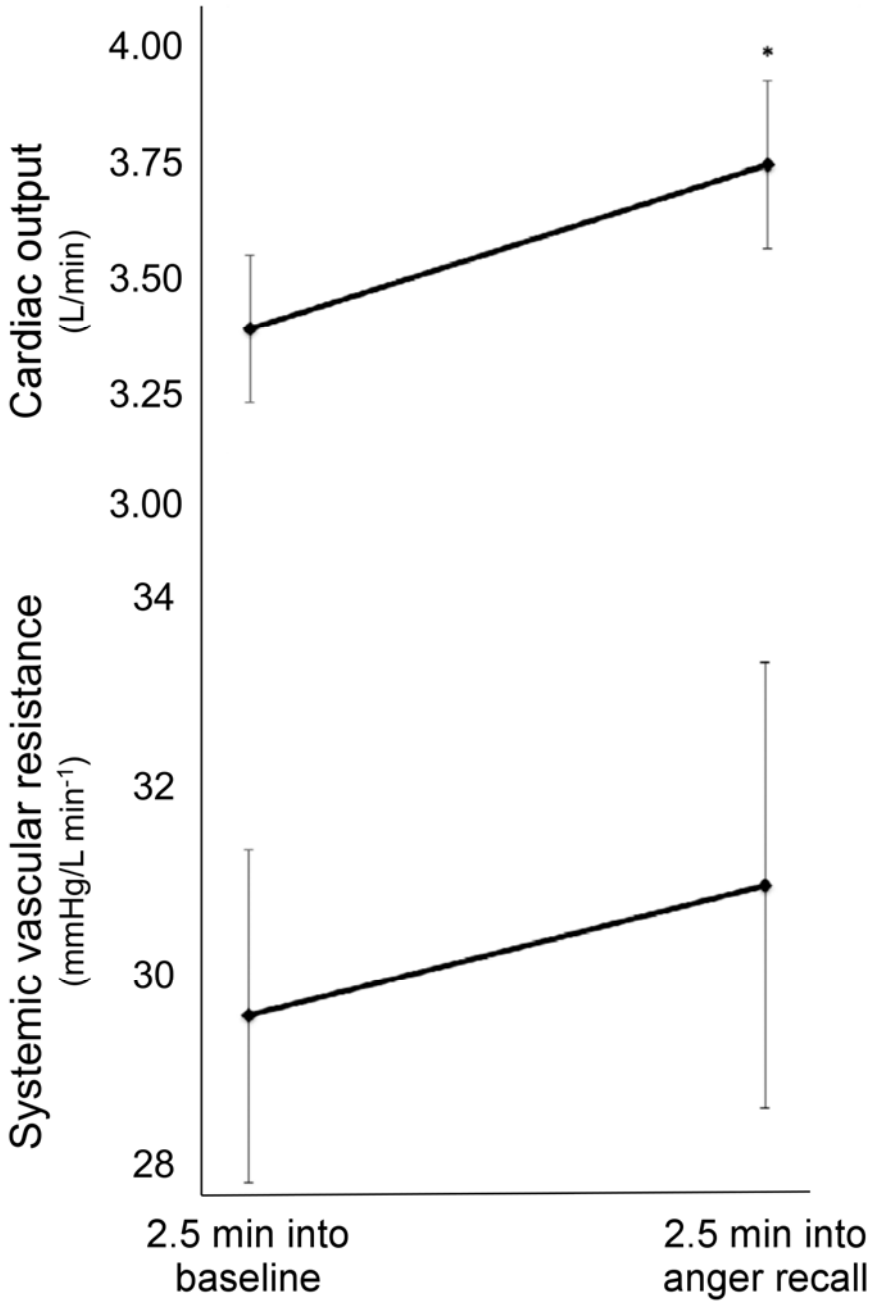
Figure 1



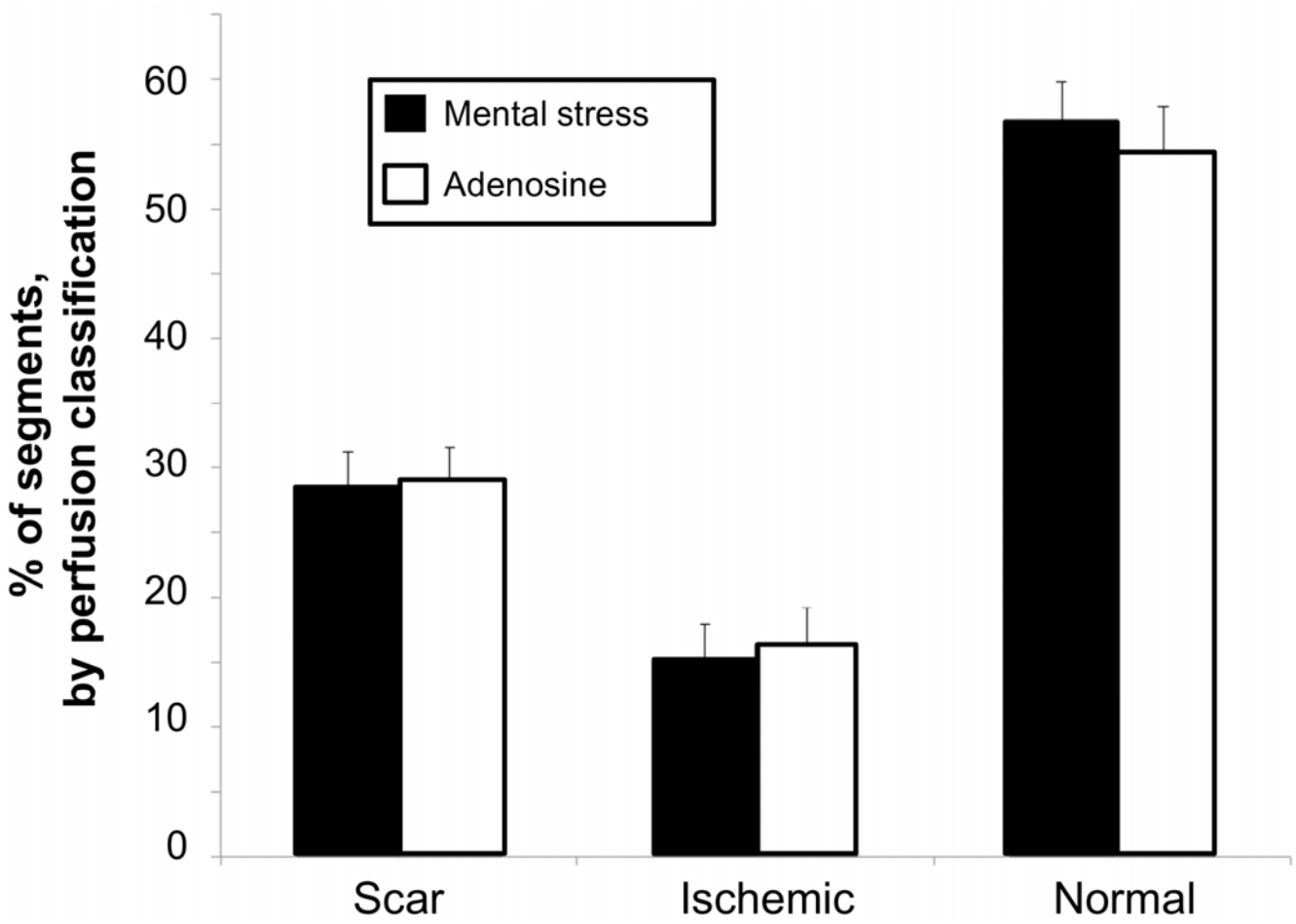
Blood pressure and heart rate during various points in the study protocol, including minutes (min) into rest, mental stress and recovery. Both heart rate and blood pressure increased with stress, $p<0.001$.

Figure 2



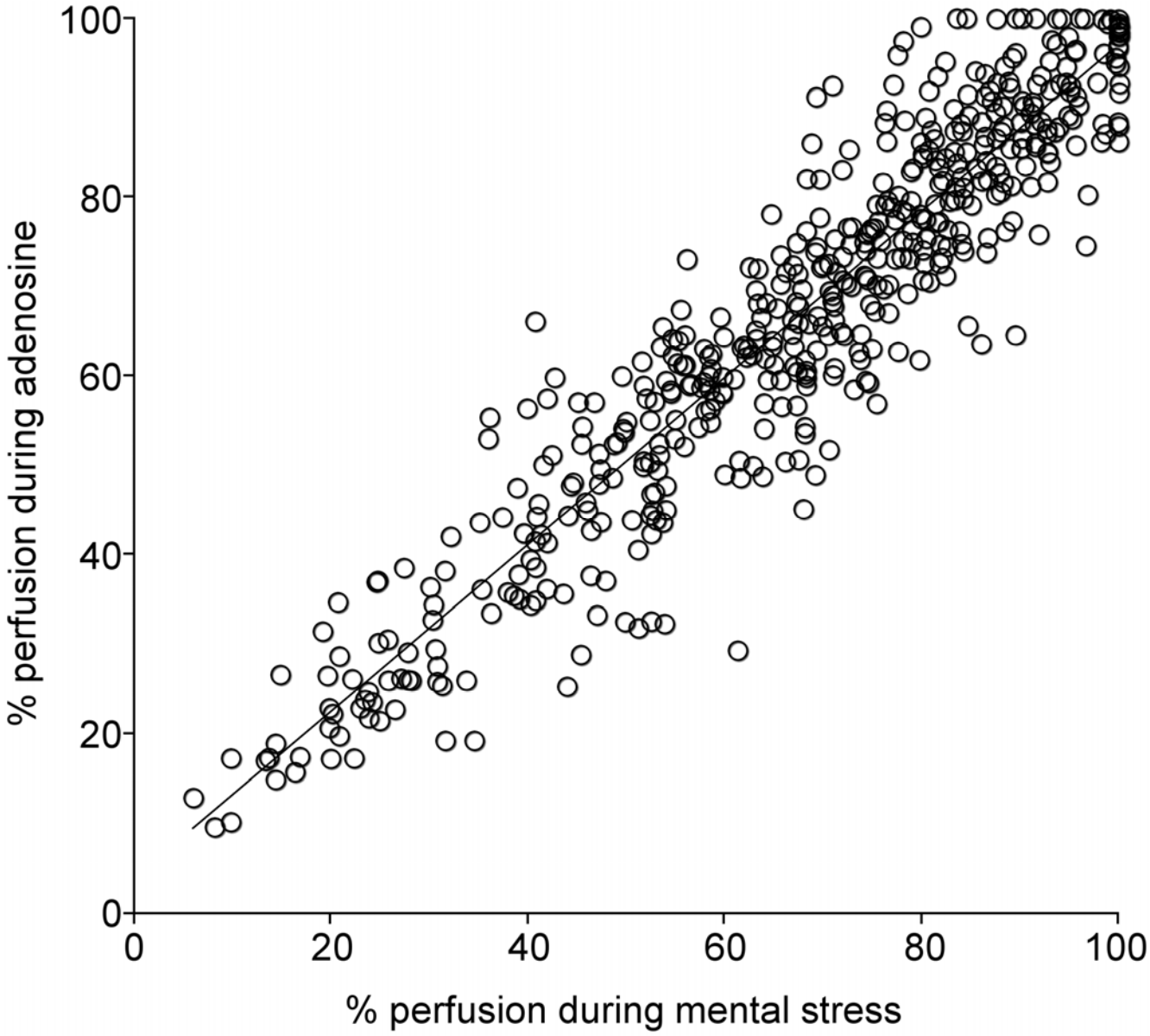
Cardiac output and systemic vascular resistance at baseline and 2 minutes into mental stress procedure. The increase in cardiac output, but not systemic vascular resistance, was statistically significant. (* = $p<0.05$ as compared to baseline)

Figure 3



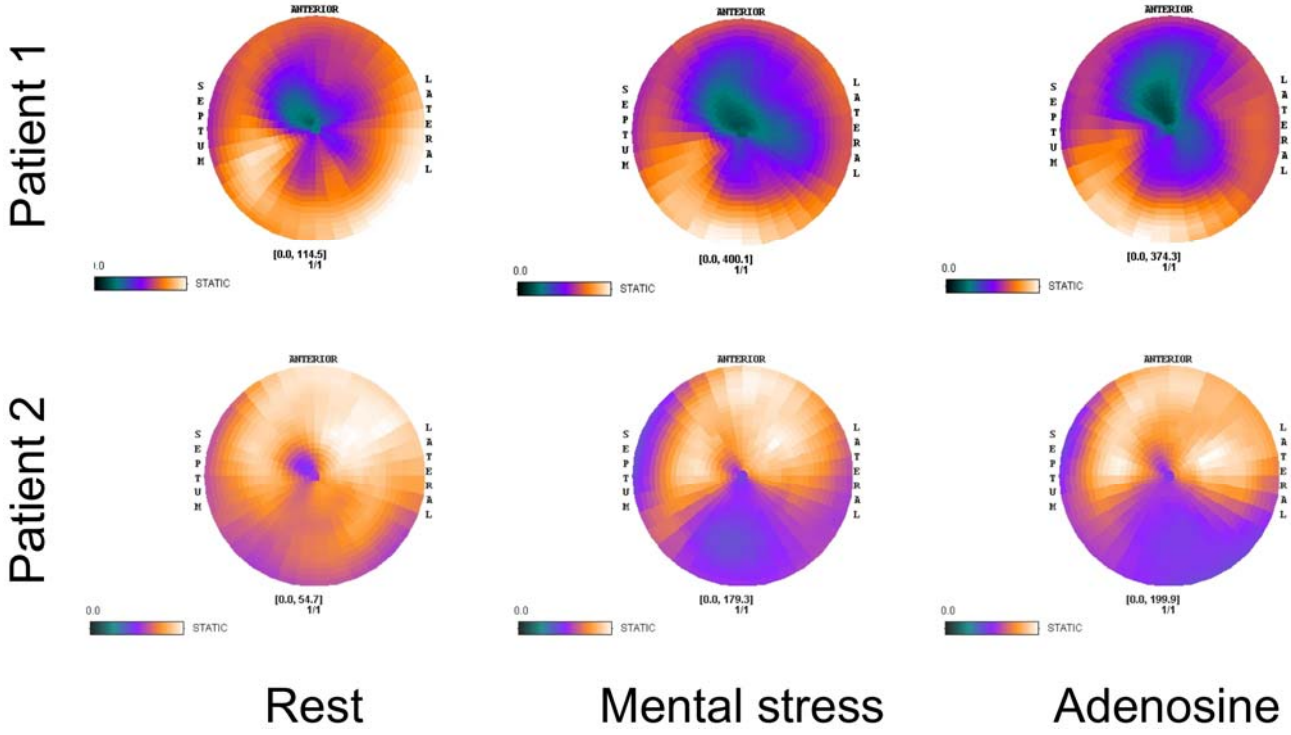
Mean percentage of segments classified as scar, ischemic, or normal during mental stress and after adenosine infusion. There were no differences between mental stress and adenosine interventions.

Figure 4



Scatterplot of percent perfusion for mental stress and adenosine in the same segments for each patient (N=34 patients). There was an excellent correlation between percent perfusion during mental stress and percent perfusion after adenosine infusion, r^2=0.88.

Figure 5



Polar maps of perfusion during rest, mental stress and adenosine are shown for 2 patients. Darker colors indicate decreased perfusion.

Table 1 Patient Demographic and Clinical Characteristics

N	Male	31
	Female	3
Race	African American	15
	Caucasian	19
Age (years)		62 ± 10
NYHA Class	2	19 (56%)
	3	15 (44%)
History of Smoking		28 (82%)
Diabetic		23 (68%)
History of Angina		14 (41%)
History of Atrial Fibrillation		7 (21%)
History of COPD		5 (15%)
History of Hypercholesterolemia		29 (85%)
History of Hypertension		28 (82%)
History of Inducible Ventricular Tachycardia		3 (9%)
History of Valvular Disease		4 (12%)
Prior Myocardial Infarction		27 (79%)
BMI		29.8 ± 6.6)
Baseline Ejection Fraction (%)		27 ± 9
Baseline Cardiac Output		3.30 ± 0.96
N (%)	ACE Inhibitors	27 (79%)
	Angiotension II Receptor Blocker	5 (15%)
	β Blockers	32 (94%)
	Calcium Channel Blocker	2 (6%)
	Vasodilator	7 (21%)
Baseline Systolic Blood Pressure (mmHg)		118 ± 19
Baseline Diastolic Blood Pressure (mmHg)		70 ± 11
Baseline Heart Rate (bpm)		68 ± 12

Table 2 Neurohormonal Values at Rest, During Mental Stress, and Post-Stress

	Rest	Stress	Post-stress
BNP (pg/mL)	410 ±495	390 ± 516	412 ± 520
IL-6 (pg/mL)	5.96 ± 6.12	5.75 ± 5.91	6.27 ± 5.85 *
TNF-alpha (pg/mL)	6.45 ± 3.57	6.38 ± 3.69	5.85 ± 3.17
IL-10 (pg/mL)	1.69 ± 0.94	1.81 ± 0.96	1.71 ± 1.04 *
IL-1b (pg/mL)	0.18 ± 0.15	0.22 ± 0.21	0.24 ± 0.25
hs-troponin (pg/mL)	17.9 ± 28.4	16.8 ± 23.7	18.2 ± 28.5
VEGF (pg/mL)	55.5 ± 62.8	59.1 ± 50.8	58.3 ± 53.4
IL-17a (pg/mL)	0.31 ± 0.26	0.33 ± 0.27	0.33 ± 0.28
MMP-9 (ng/mL)	1281 ± 1094	1326 ± 1124	1238 ± 1058
hsCRP (mg/L)	5.9 ± 7.3	5.7 ± 7.6	5.8 ± 7.8
ET-1 (pg/mL)	6.4 ± 2.6	6.1 ± 2.7	6.8± 2.8 *

* =p<0.05 compared to stress value