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Variability of Myocardial Ischemic Responses to Mental versus Exercise or Adenosine Stress in Patients with Coronary Artery Disease

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Abstract

Background—Mental stress precipitates myocardial ischemia in a significant percentage of Coronary Artery Disease (CAD) patients. Exercise or adenosine stresses produce different physiologic responses and cause myocardial ischemia via different mechanisms. Little is known about the comparative severity and location of myocardial ischemia provoked by these different stressors. In this study we sought to compare the within-individual ischemic responses to mental versus exercise or adenosine stress in a cohort of CAD patients.

Methods—All patients underwent mental stress and either exercise or adenosine testing within a one week period. Mental stress was induced via a public speaking task. Rest-stress myocardial perfusion imaging was used with all testing protocols.

Results—Participants were 187 patients [65 (35%) females] with a documented history of CAD and a mean age of 64±9 years. Mental Stress-induced Myocardial Ischemia (MSIMI) was less prevalent and frequently of less magnitude than exercise or adenosine-induced ischemia. Ischemia induced by exercise or adenosine testing did not accurately predict the development or the location of MSIMI. The overall concordance between these stressors for provoking ischemia was weak (percent agreement=71%;kappa±SE= 0.26±0.07). In a minority of patients (11%) mental stress provoked ischemia in the absence of exercise or adenosine-induced ischemia. Moreover, in patients who had myocardial ischemia during both stressors; there were significant within-individual differences in the coronary artery distribution of the ischemic regions. MSIMI was more likely to occur in a single vessel distribution (86%) compared to exercise or adenosine-induced ischemia (54%). The stressors had moderate agreement if the ischemic region was in the right coronary artery territory (percent agreement and kappa±SE were 76% and 0.52±0.19), or the left anterior descending

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coronary artery (percent agreement=76%; $\kappa \pm \text{SE} = 0.51 \pm 0.19$), and significantly lower agreement in the left circumflex territory (percent agreement=62%; $\kappa \pm \text{SE} = 0.22 \pm 0.18$)

Conclusions—Our findings indicate that mental and exercise or adenosine stresses provoke different myocardial ischemic responses. These observations suggest that exercise or adenosine testing may not adequately assess the likelihood of occurrence or severity of MSIMI and that different mechanisms are operative in each condition.

Keywords

Psychological Stress; Exercise Test; Adenosine; Myocardial Ischemia

Mentally stressful tasks can provoke transient myocardial ischemia in a significant proportion of patients with Coronary Artery Disease (CAD).^{1–4} Mental stress testing in the laboratory is a simulation of daily life stress.^{2, 3} Several studies have shown that the development of myocardial ischemia in this setting, predicts ischemia during daily life, is a poor prognostic factor and is linked to fatal and nonfatal cardiac events in patients with CAD.^{2–8}

Exercise or adenosine stress testing is commonly used in clinical settings as a risk stratification tool in patients with CAD. However there is evidence that these testing modalities may not adequately assess the likelihood of risk related to mental stress.^{9–11} One study reported that the addition of mental stress to exercise testing improved the detection of myocardial ischemia.¹⁰ We recently reported that mental stress could provoke ischemia in CAD patients with negative exercise or adenosine testing.⁹ If it is eventually proven that this category of patients have increased risk for adverse events, this will have significant implications for our current methods of risk stratification. Studying the variability of responses to mental and exercise or adenosine stress may improve our understanding of the pathophysiologic mechanisms operative in these settings and may consequently help in improving our risk prediction strategies.

In this study we compared the variability of myocardial ischemic responses to mental versus exercise or adenosine stress in a cohort of CAD patients. We studied the within-individual concordance between these stress modalities in provoking myocardial ischemia. We also examined the variability in the regional distribution and magnitude of ischemia in individuals who developed it during both stress modalities.

Methods

Study Design

The study protocol was approved by the University of Florida Institutional Review Board. Informed consent was obtained from all participants. In a random order, all patients underwent mental stress and exercise or adenosine stress testing on separate mornings within a one week period. None of the participants had any changes in their medications or clinical status between the testing sessions. The tests were conducted after an overnight fast. Beta-blockers, calcium-channel blockers and long acting nitrates were withheld the nights before testing.

Subjects

Participants were recruited from outpatient clinics affiliated with a university based medical center. Eligibility criteria included age >18 years with a documented clinical diagnosis of CAD supported by 1) angiographic evidence of >50% stenosis in one or more coronary arteries or previous percutaneous intervention or Coronary Artery Bypass Graft surgery (CABG), 2) previous Myocardial Infarction (MI) documented with elevated troponin levels, Q-wave abnormalities on Electrocardiogram (ECG), or non-artifactual fixed perfusion abnormalities

on nuclear scan, or 3) a positive radionuclide pharmacologic or exercise stress test. Patients were excluded if they had unstable angina or acute MI within the two months prior to enrollment, were pregnant or weighed over 400 lbs.

Mental stress procedure

Patients were initially rested in a dark and quiet room for 30 minutes while their Heart Rate (HR) and blood pressure were measured every 5 minutes using an ECG monitor and automatic oscillometric device (Dynamap Critikon Inc.), respectively. Mental stress was then induced via a public speaking task performed in front of a small audience, as in prior research.¹² Participants were asked to speak on an assigned topic describing a stressful real life event. They were given two minutes to prepare their speech and three minutes to speak. They were told that their speech would be video-taped and later rated by the research staff for content, quality and duration. Hemodynamic measurements were obtained every minute during the preparation and the speech periods and at 1, 3, 5 and 10 minutes into the recovery period. Systolic blood pressure (SBP) and HR were used to calculate the Double Product (DP) value ($DP=SBP \times HR$).

Exercise or adenosine testing

After a 30 minute rest period, a symptom-limited exercise stress test was performed in a standard fashion according to the Bruce protocol.¹³ Patients were exercised to achieve $\geq 85\%$ of their age-predicted target HR.¹³ Twelve-lead ECGs were acquired in the sitting and standing positions before exercise, at each minute during exercise, at peak exertion and at each minute into recovery for 10 minutes or until exercise-induced ST segment changes resolved. Blood pressure and HR were recorded at minute two of each exercise stage and at minutes 1, 3, 5 and 10 of recovery. If the patient could not exercise, a standard 6 minute adenosine stress test was performed instead.¹⁴ Xanthine derivatives and caffeine-containing products were discontinued 48 and 12 hrs before testing, respectively. Whenever possible, adjunctive low-level treadmill exercise was used.¹⁵

Myocardial perfusion imaging

Myocardial perfusion imaging with 99m-Tc-sestamibi was used. A standard two-day imaging protocol was conducted for all stress modalities. During the mental stress procedure, the radioisotope injection was given at one minute into the speech (a total dose of 20–30 mCi, based on patient's body weight). This timing is based on previous reports that maximal heart rate, blood pressure and neurohormonal responses to mental stress usually occur at the near onset of the stressful task, and ischemic abnormalities are induced relatively rapidly during this process.^{1, 16, 17} The radioisotope injection was given at peak exertion during the exercise test and at 3 minutes during the adenosine protocol. Exercise was continued for at least one minute after the injection. Stress images were acquired 30–60 minutes later using conventional methodology¹⁸ with Single Photon Emission Computed Tomography (SPECT) (64 projections over a circular 180 degree orbit, with the gamma camera set at a 140 keV energy peak with a 20 percent window). A high resolution collimator and two dimensional Butterworth filter were used and trans-axial tomograms were reconstructed using back projections with a ramp filter. Resting images were obtained within one week of the stress test. We did not use an attenuation correction algorithm in this study. However, we routinely used other well accepted techniques to reduce the impact of attenuation artifacts such as prone imaging and walking instead of resting adenosine, whenever appropriate.¹⁸ The studies were interpreted by an experienced nuclear cardiologist (DSS) blinded to the condition (mental versus exercise or adenosine). Another nuclear cardiologist performed a second read of some randomly selected studies (n=59). The agreement rate between the two readers was 90%. Disagreements were resolved by consensus. Rest and stress images were visually compared for number and

severity of perfusion defects using a 20 segment model. A scoring method from zero to four was used; with zero being normal uptake and four no uptake.¹⁶ A summed difference score (SDS) was calculated as the difference between summed stress and rest scores. Ischemia was defined as new or worsening perfusion defects during mental, exercise or adenosine stress as compared to the resting baseline images with an SDS of ≥ 4 . For the purpose of comparison in this study the same ischemia definition was used for all testing protocols.

Standard criteria were used for assignment of vessel territories.^{18, 19} Each myocardial segment was assigned to one of the coronary territories according to published guidelines.¹⁹ Specifically, segments # 1, 2, 7, 8, 13 and 14 were assigned to the LAD, segments 3, 4, 9, 10, 15, and 16 to the RCA and segments # 5, 6, 11, 12, 17, and 18 to the LCX artery. Segments in the apical cap (# 19 and 20) were considered watershed areas and no vessel territory was assigned to them.¹⁹ Involvement of a coronary territory was concluded when at least two adjacent segments within the distribution of that artery show reversible perfusion defects. This criterion is intended to account for potential overlap in the distribution of the three coronary territories.

Statistical Analysis

Results were expressed as means $\pm$ standard deviations for continuous variables and frequencies and percentages for categorical variables. Stress hemodynamic responses were calculated as the difference between the peak stress and baseline resting measurements. For continuous variables, statistical differences between groups were determined using Student's *t* test for normally distributed and Mann-Whitney U test for non-normal distribution data. Differences between categorical variables were determined using chi-square analyses. Statistical significance was considered as $p < 0.05$. Based on the published evidence that exercise and adenosine stress testing are highly concordant in provoking myocardial ischemia,^{20–22} these modalities were grouped together and compared to mental stress. Within individuals, the variability of myocardial ischemic responses to mental versus exercise or adenosine stress (ischemia defined as $\text{SDS} \geq 4$ on perfusion imaging) was examined using kappa statistics.²³ This procedure is preferred to the simple percent agreement because it measures the extent to which the agreement between the two testing modalities exceeds the level to be expected based on chance alone. We report it here as kappa $\pm$ its standard error. A value of 1 denotes perfect agreement and 0 no agreement beyond chance.

Results

Patient characteristics and baseline data

A total of 187 patients were studied, 65 of them (35%) were females. Mean age was 64 ± 9 years. The majority (88%) were Caucasians, 7% were African Americans. All participants had CAD. Sixty five percent of patients satisfied entry criteria based on abnormal coronary angiograms, 35% percent had history of CABG, 19% had prior MI and 63% had history of anginal symptoms. Other co-morbid medical conditions included diabetes (32%), hypertension (78%), hyperlipidemia (89%) and past or current smoking (72%). Demographic and clinical characteristics of the study population are described in table 1. All patients underwent mental stress testing. Ninety patients (48%) underwent exercise stress and 97 (52%) patients received an adenosine infusion protocol.

Hemodynamic responses

Mental stress induced significant changes in SBP, diastolic blood pressure (DBP), HR and DP compared to the resting condition. The mean increase in these values from rest to stress was 43 ± 19 mm/Hg for SBP, 28 ± 11 mm/Hg for DBP, 19 ± 12 beats/minute for HR and 5762 ± 2976 for DP ($p < 0.001$). Within individuals, exercise induced higher increases in HR and DP and

lesser increases in SBP and DBP compared to the mental stress (all p values <0.001). The mean exercise-induced increases in these variables were 68 ± 15 beats/min, 13281 ± 3641 , 30 ± 20 mm/Hg and 11 ± 10 mm/Hg, respectively. Adenosine induced smaller increases in SBP (8 ± 15 mm/Hg); DBP (5 ± 10 mm/Hg), HR (24 ± 15 beats/min) and DP (4006 ± 2584) compared to the exercise or mental tests (all p values <0.001). ECG changes of ischemia (>1 mm ST depression) occurred in 23 (12%) patients during exercise or adenosine testing. Such changes were very rare during mental stress (3 patients, 2%). Hemodynamic responses to the three stress testing modalities are shown in table 2.

Myocardial ischemia

MSIMI was less prevalent (35 patients; 19%) than exercise or adenosine-induced ischemia (62 patients; 33%). MSIMI occurred at a lower DP value (6100 ± 2561) compared to exercise or adenosine-induced ischemia (8109 ± 5306). Twenty one patients developed ischemia during both mental and exercise or adenosine stress (exercise testing was used in 8 of the 21 patients). Among those 21 patients, there was a trend for increased severity of ischemia (measured by SDS) with exercise or adenosine compared to mental stress [mean SDS for exercise or adenosine was 7.5 ± 2.5 compared to 6.2 ± 2.0 for mental stress; ($p=0.11$)]. MSIMI occurred in 14 patients (11%) with negative exercise or adenosine ischemia. The overall concordance between the two testing modalities was weak (percent agreement = 71%; $\kappa \pm SE = 0.26 \pm 0.07$). A 2×2 table for the binary ischemia outcome by the stress modalities is shown in table 3. When adenosine and exercise were separately compared to mental stress, similar concordance rates were observed (percent agreement and $\kappa \pm SE$ values were 71% and 0.31 ± 0.09 for adenosine and 70% and 0.20 ± 0.11 for exercise, respectively). Figure 1 shows perfusion images for three patients in the study. Patient A developed ischemia during both mental and adenosine stress, patient B developed ischemia during exercise but not mental stress and patient C developed ischemia during mental but not exercise stress.

We further compared the coronary artery distribution of the ischemic segments in the 21 patients who developed ischemia during both stress procedures (mental versus exercise or adenosine). MSIMI was more likely to occur in a single vessel distribution (18 of 21 patients, 86%) compared to exercise or adenosine-induced ischemia (11 of 21 patients, 54%). When individual vessels were compared, the concordance rate was moderate for segments in the RCA territory (percent agreement and $\kappa \pm SE$ were 76% and 0.52 ± 0.19), and the LAD (percent agreement = 76%; $\kappa \pm SE = 0.51 \pm 0.19$) and significantly lower for segments within the LCX territory (percent agreement = 62%; $\kappa \pm SE = 0.22 \pm 0.18$). This information is detailed in table 4.

Discussion

Our findings in this study indicate that there is a significant variability in ischemic responses to mental versus exercise or adenosine stress. The overall concordance for provoking ischemia between these testing modalities was weak (percent agreement = 71%; $\kappa = 0.26$). In a minority of patients (11%) mental stress provoked ischemia in the absence of exercise or adenosine-induced ischemia. Moreover, among the patients who had myocardial ischemia during both stressors; there were significant differences in the coronary artery distribution of the ischemic regions. MSIMI was more likely to occur in a single vessel distribution. The stressors had moderate agreement if the ischemic segments were in the RCA or LAD territories and significantly lower agreement in the LCX territory. Collectively, these findings suggest that exercise or adenosine stress testing does not accurately predict the development or the location of MSIMI.

Several mechanisms are operative in the development of myocardial ischemia during each of these stressors. Sympathetic stimulation and parasympathetic withdrawal seem to be involved

with both exercise and mental stress.^{17, 24} Rozanski et al and others suggested that the mechanisms underlying MSIMI seem to be related to the acute presentation of the stressor, while, for example, response to exercise is usually gradual; a mentally challenging task provides a sudden stressor without a warm-up period.^{1,17, 24} Adenosine, on the other hand, induces coronary vasodilatation via its effect on adenosine A2A receptors, creating flow disparities with increased blood flow to normal areas and reduced flow to areas distal to a significant coronary stenosis.^{14,18} The observed high disagreement rate between these tests for inducing ischemia is most likely related to differences in the types and intensity of the physiologic responses provoked. Both epicardial coronary vasoconstriction and microvascular dysfunction of the coronary arterial bed have been suggested as underlying mechanisms for MSIMI.^{25–27} These mechanisms may explain the disagreement in the regional distribution of the ischemic segments between mental and exercise or adenosine stress. Collectively, these observations suggest that MSIMI is a distinct clinical phenotype, different from exercise or adenosine-induced ischemia. If proven, this could have significant implications for our current risk stratification strategies.

Several studies have established the accuracy of SPECT imaging with 99m-Tc-sestamibi in the regional diagnosis and coronary localization of CAD.^{28–30} It is possible that the observed disagreements between these tests could partially be explained by variability in interpretation of the imaging studies. However this is unlikely to fully explain the observed differences. In our study, standardized image acquisition and interpretation protocols were used for all testing modalities. The studies were interpreted by an experienced reader who was blinded to the stress condition (DSS).

The prevalence of MSIMI in this study was 19%; this is similar to the prevalence reported in the PIMI study,⁵ but somewhat lower than the rates reported in other studies.^{2, 6,7} The ischemia detection methods used in those studies were different. While we used perfusion SPECT imaging, most previous studies used radionuclide ventriculography. We have shown that the detection of MSIMI using SPECT imaging has good sensitivity, specificity and reproducibility.³¹ It is also possible that the lower rate of ischemia observed in this study is due to differences in patients' inclusion criteria. Specifically, our study did not require a positive exercise stress test or a coronary stenosis beyond a certain severity for inclusion, while most of the previous studies did. The definition of MSIMI used in our protocol is new or worsening perfusion defects with a summed difference score of ≥ 4 . To serve the comparative design of our study, we applied the same ischemia definition used for exercise or adenosine stress testing. This may have also influenced the percentage of patients with ischemia. However, knowing that MSIMI is usually of less magnitude than exercise-induced ischemia, a lower definition threshold should probably be used for the detection of MSIMI.

In a small pilot study, Ramachandruni et al recently showed that mental stress can provoke ischemia in CAD patients with negative exercise or adenosine tests.⁹ In that study six of 21 (29%) subjects with negative exercise or adenosine ischemia demonstrated reversible ischemia with mental stress. This percentage is higher than our current finding which is most likely due to the more conservative ischemia definition used in the present study. The design of our current protocol eliminates confounding factors, as an intra-individual comparison approach was used. The time proximity of the two tests was one week, which further strengthens the protocol.

Limitations

Arguably many factors may be involved in the observed variability reported in this study. Variability in image acquisition techniques, image interpretation, image quality and attenuation artifacts may all account for some of the observed differences. Differences in the potency of stressors used, is another factor. There are established criteria for ensuring adequacy of exercise stress testing i.e. patients to achieve at least 85% of their age-predicted heart rate.¹³ No such

criterion has yet been developed for mental stress testing. However it is well documented that mental stress induced by a public speaking task has good reliability and reproducibility.^{31,32}

The discordance in the ischemic response between the two stress testing modalities could be due to the fact that MSIMI is usually of less magnitude than exercise or adenosine-induced ischemia; however this does not explain the finding that MSIMI occurred in patients with negative exercise or adenosine tests.

One possible limitation pertains to the fact that exercise and adenosine results were grouped together and compared to mental stress. This approach is supported by a large body of literature suggesting that ischemia induction by exercise and adenosine is highly reproducible.^{20–22}

Conclusion

Our findings in this study indicate that there is marked variability in ischemic responses to exercise or adenosine versus mental stress testing. Whatever the underlying mechanisms, it will be important to determine whether mental stress testing provides additional risk prediction above and beyond the other traditional risk stratification tools in different categories of patients.

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Abbreviations list

MSIMI, Mental Stress- induced Myocardial Ischemia
 CAD, Coronary Artery Disease
 HR, Heart Rate
 SBP, Systolic Blood Pressure
 DBP, Diastolic Blood Pressure
 DP, Double Product
 MI, Myocardial Infarction
 CABG, Coronary Artery Bypass Graft surgery
 ECG, Electrocardiogram
 SPECT, Single Photon Emission Computed Tomography
 SDS, Summed Difference Score
 LAD, Left Anterior Descending Coronary Artery
 LCX, Left Circumflex Coronary Artery
 RCA, Right Coronary Artery

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A. Patient A.

B. Patient B

C. Patient C

Figure 1.

Representative perfusion images from three participants in the study. Patient A developed ischemia during both mental and adenosine stress. Patient B developed ischemia with exercise testing, but had no evidence of mental stress-induced ischemia. Patient C is an example of a positive mental stress ischemia and negative exercise-induced ischemia.

Table 1

Clinical and demographic characteristics of the study sample.

Mean age (years)	64±9
Gender (Females)	65 (35%)
Ethnicity (Caucasian)	162 (88%)
(African American)	12 (7%)
Previous MI	35 (19%)
Previous CABG	65 (35%)
Previous PCI	81 (43%)
Smoking past or current	134 (72%)
Hypertension	146 (78%)
Diabetes	59 (32%)
History of angina	117 (63%)
Hyperlipidemia	167 (89%)
Beta Blockers	146 (78%)
ACEI	102 (55%)
Calcium Channel Blockers	40 (21%)
Mean LVEF (%)	55±13
Body Mass Index	30±6

Values are expressed as mean ± standard deviation or number (%)

Abbreviations: MI=Myocardial Infarction; CABG=Coronary Artery Bypass Graft surgery; PCI= Percutaneous Coronary Intervention; ACEI=Angiotensin Converting Enzyme Inhibitor; LVEF= Left Ventricular Ejection Fraction

Table 2
Hemodynamic and ischemic variables by stress testing modality

Variables	Mental stress n=187	Exercise stress n=90	Adenosine stress n=97
Mean rest SBP mm/Hg	120±18	137±19	142±22
Mean stress SBP mm/Hg	163±26	167±21	150±23
Mean SBP difference mm/Hg	43±19	30±20	8±15
Mean rest DBP mm/Hg	65±9	75±9	78±11
Mean stress DBP mm/Hg	93±13	86±11	83±12
Mean DBP difference mm/Hg	28±11	11±10	5±10
Mean rest HR beat/min	60±10	63±12	64±11
Mean stress HR beat/min	79±16	131±14	88±16
Mean HR difference beat/min	19±12	68±15	24±15
Mean rest DP	7219±1604	8608±1812	9100±2117
Mean stress DP	12982±3629	21901±3677	13107±3064
Mean DP difference	5762±2976	13281±3641	4006±2584
N(%) with Myocardial Ischemia*	35 (19%)	26 (29%)	36 (37%)
Mean Summed difference score [†]	1.5±2.4	2.3±2.8	2.9±3.4

* Myocardial ischemia was defined as a summed difference score of ≥ 4 on radionuclide perfusion imaging.

[†] This analysis included all patients with and without stress-induced ischemia.

Abbreviations: SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure; HR=Heart Rate; DP=Double Product.

Table 3

A 2×2 table showing the agreement between mental and exercise or adenosine stress testing in provoking myocardial ischemia. Twenty one patients developed ischemia during both stressors. The overall concordance between the two testing modalities was weak (percent agreement=71%; kappa±SE=0.26±0.07).

Exercise or adenosine stress			
Mental stress		Ischemia (SDS>3) n=62	No Ischemia n=125
	Ischemia (SDS>3) n=35	21	14
	No Ischemia n=152	41	111

Abbreviations: SDS=Summed Difference Score.

Table 4

Concordance in the coronary distribution of the ischemic segments between mental and exercise or adenosine tests. Included in this analysis are the 21 patients who developed ischemia during both stress procedures.

Coronary Territories	Exercise or adenosine	Mental stress	
		Absent	Present
LAD	Absent	6	2
	Present	3	10
	Percent agreement=76%;	Kappa±SE=0.51±0.19; p=0.020	
LCX	Absent	10	1
	Present	7	3
	Percent agreement=62%;	Kappa±SE=0.22±0.18, p=0.223	
RCA	Absent	9	2
	Present	3	7
	Percent agreement=76%;	Kappa±SE=0.52±0.19, p=0.017	

Abbreviations: LAD=Left Anterior Descending Coronary Artery; LCX=Left Circumflex Coronary Artery; RCA=Right Coronary Artery.