Association between anger and mental stress–induced myocardial ischemia

Pratik Pimple, MBBS, MPH,[a] Amit Shah, MD, MSCR,[a,b] Cherie Rooks, PhD,[a] J. Douglas Bremner, MD,[c] Jonathon Nye, PhD,[d] Ijeoma Ibeanu, MPH,[a] Nancy Murrah, RN,[a] Lucy Shallenberger, MPH,[a] Mary Kelley, PhD,[e] Paolo Raggi, MD, FACC,[a,b,f] and Viola Vaccarino, MD, PhD[a,b] *Atlanta, GA and Alberta, Canada*

Background Mental stress–induced myocardial ischemia is associated with adverse prognosis in coronary artery disease patients. Anger is thought to be a trigger of acute coronary syndromes and is associated with increased cardiovascular risk; however, little direct evidence exists for a link between anger and myocardial ischemia.

Methods [^{99m}Tc]-sestamibi single-photon emission tomography was performed at rest, after mental stress (a social stressor with a speech task) and after exercise/pharmacologic stress. Summed scores of perfusion abnormalities were obtained by observer-independent software. A summed-difference score, the difference between stress and rest scores, was used to quantify myocardial ischemia under both stress conditions. The Spielberger's State-Trait Anger Expression Inventory was used to assess different anger dimensions.

Results The mean age was 50 years, 50% were female, and 60% were non-white. After adjusting for demographic factors, smoking, coronary artery disease severity, depressive, and anxiety symptoms, each IQR increment in state-anger score was associated with 0.36 U–adjusted increase in ischemia as measured by the summed-difference score (95% CI 0.14-0.59); the corresponding association for trait anger was 0.95 (95% CI 0.21-1.69). Anger expression scales were not associated with ischemia. None of the anger dimensions was related to ischemia during exercise/pharmacologic stress.

Conclusion Anger, both as an emotional state and as a personality trait, is significantly associated with propensity to develop myocardial ischemia during mental stress but not during exercise/pharmacologic stress. Patients with this psychologic profile may be at increased risk for silent ischemia induced by emotional stress, and this may translate into worse prognosis. (Am Heart J 2015;169:115-121.e2.)

Psychologic stress has long been suspected to be a risk factor for coronary heart disease (CHD), but its exact role as a trigger of acute ischemia is unclear.[1] Mental stress–induced myocardial ischemia is a transient myocardial ischemic response to a standardized mental stress challenge,[2] which can be induced in approximately one-third to one-half of patients with CHD.[2] Mental stress ischemia is analogous to exercise or pharmacologically induced myocardial ischemia during standard cardiac testing (here referred together as *physical stress–induced myocardial ischemia*), except that the stressor used is psychologic instead of physical.[2] Mental stress ischemia has similar prognostic value to physical stress ischemia but is typically painless, occurs at lower levels of oxygen demand, and is not related to severity of coronary artery disease (CAD)[2,3] or previous revascularization.[2,3] Mental stress, but not physical stress–induced myocardial ischemia, correlates with myocardial ischemia measured in daily life ambulatory monitoring[4] and is associated with worse prognosis in subjects with stable CHD, with a 2-fold increased risk of future cardiac events independent of physical stress–induced ischemia.[5]

Anger has long been considered a potential precipitant of acute myocardial infarction (MI) and a significant risk factor for CHD. A recent meta-analysis of 44 prospective studies found that anger and hostility were significantly associated with increased CHD risk in both healthy (19% increase) and preexisting CHD populations (24% increase).[6] Substantial research also suggests that acute anger is a potential trigger of acute coronary syndromes.[1,7] These previous data suggest that anger could

From the [a]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, [b]Department of Medicine, Division of Cardiology, Emory University School of Medicine, Atlanta, GA, [c]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, [d]Department of Radiology, Emory University School of Medicine, Atlanta, GA, [e]Department of Biostatistics and Bioinformatics, Rollins School of Public Health, Emory University, Atlanta, GA, and [f]Mazankowski Alberta Heart Institute, University of Alberta School of Medicine, Edmonton, Alberta, Canada.

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Reprint requests: Viola Vaccarino, MD, PhD, Emory University, Department of Epidemiology, Rollins School of Public Health, 1518 Clifton Rd NE, Room 3011, Atlanta, GA 30322.
E-mail: viola.vaccarino@emory.edu

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play a role in the development of acute myocardial ischemia. However, direct evidence of a link between anger and myocardial ischemia is scarce.[8]

To clarify this issue, we examine whether anger as an acute state or as a personality trait or specific anger expression patterns is positively associated with the occurrence of mental stress but not physical stress–induced ischemia. Given that emotional distress appears to play a larger role in early-onset CHD than in older age groups,[9] we elected to study young and middle-aged (≤60 years) men and women who survived a recent MI.

Methods

Subjects

Between July 2009 and April 2012, the Myocardial Infarction and Mental Stress (MIMS) study enrolled 98 patients between the age of 38 and 60 years with a documented history of MI within the previous 6 months (range 1.3-6 months). Men and women were matched for age (±2 years), type of MI (ST-elevation MI or non–ST-elevation MI), and time since the MI (±2 months). Other inclusion and exclusion criteria and details of sample construction have been described elsewhere.[10]

Study design

Subjects underwent 3 single-photon emission computed tomography (SPECT) imaging studies; 1 at rest, 1 with mental stress, and 1 with exercise or pharmacologic stress. The 2 stress scans were obtained in separate days within 1 week of each other (the order was balanced), and the rest scan was obtained during the first session. All testing was done after an overnight fast, and antiischemic medications were held for 24 hours before testing. Sociodemographic and psychosocial data were collected at the first visit before stress testing. At the end of the study protocol, medical records were abstracted for clinical information. The study protocol was approved by the Emory University Institutional Review Board, and informed consent was obtained from all participants.

Mental and physical stress procedures

Mental stress was induced by a standardized social stressor using a public speaking task as previously described.[11] Briefly, subjects were asked to imagine a real-life stressful situation and to make up a realistic story around this scenario. They were given 2 minutes to plan the story and 3 minutes to present it in front of a video camera and a small audience wearing white coats. Subjects were told that their speech would be evaluated by the laboratory staff for content, quality, and duration. For physical stress, subjects underwent a Bruce protocol by walking on a treadmill, with exercise target set at 85% of maximum predicted heart rate based on the patient's sex and age. For 16 subjects who were unable to reach the heart rate target, we performed a pharmacologic stress test with regadenoson (Astellas, Northbrook, IL), an adenosine receptor agonist. Blood pressure and heart rate were monitored during each stress test. Subjective ratings of distress were obtained at baseline and after mental stress with the Subjective Units of Distress Scale[12] on a linear scale of 0 to 100 (100 = highest level of distress). We also obtained visual analog ratings of nervousness, anxiety, fear, and anger with a scale of 0 to 4, with 4 being extreme.

Myocardial perfusion imaging

Subjects underwent [^{99m}Tc]-sestamibi SPECT myocardial perfusion imaging at rest, during mental stress, and during physical stress on a dedicated ultrafast solid-state camera (Discovery NM 530c; GE, Milwaukee, WI) without attenuation correction. We used [^{99m}Tc]-sestamibi dosages of 10 to 15 mCi for the rest scan and of 30 to 45 mCi for the stress scans, according to body weight and with a dose ratio of rest to stress of 1:3. For mental stress, the radioisotope was injected 1 minute after the onset of the speech; whereas for exercise stress, it was injected at peak exertion after the Bruce protocol. Following standard procedures, stress images were acquired 45 to 60 minutes after [^{99m}Tc]-sestamibi injection.

Myocardial perfusion was quantified by means of the Emory Cardiac Toolbox software, which provides objective (operator-independent) quantitative assessment of perfusion with established validity and reproducibility.[13] Briefly, the 3-dimensional tracer uptake distribution in the left ventricle was oriented along the short axis and sampled onto a 2-dimensional polar map. A summed score, quantifying the extent and severity of perfusion defects across 17 myocardial segments, was computed.[13] In each region, defect severity was quantified using a 4-point scale from normal (score 0) to absent perfusion (score 4). The regional severity scoring was then summed up across the 17 myocardial segments. Separate scores were obtained for the rest images (summed-rest score [SRS]) and the stress images (summed-stress score [SSS]). For each stress, a summed-difference score (SDS), quantifying the number and severity of reversible (ischemic) myocardial perfusion defects, was obtained by subtracting the rest score from the stress score; a positive SDS would indicate presence of ischemia. We also calculated the percentage of myocardial involvement by dividing the number of myocardial segments with perfusion defects (score >0) by the total number of segments (17). The use of automated image analysis has specific advantages for our study. Quantitative SPECT image analysis is equivalent to visual analysis from expert readers[14,15] but is more reproducible[16,17] because it eliminates interpreter variability. Thus, it is better suited for protocols with serial SPECT scans such as in our study.

Measurement of anger and other covariates

Anger was assessed using the Spielberger's State-Trait Anger Expression Inventory, a 57-item questionnaire,

which measures the following anger dimensions: (1) state anger (intensity of anger at a particular time); (2) trait anger (disposition to experience angry feelings as a trait); and (3) anger expression, including anger out (anger expressed toward others or the environment), anger in (suppression of anger), and anger control; the latter consisting of 2 subscales: anger control (out), the ability to limit expression of anger and anger control (in), the ability to calm down.[18,19] Larger scores for each dimension indicate more severity of anger, except for the anger-control subscales (higher score indicating better anger control). All scales have good internal consistency (α ranging from 0.70 to 0.87) and validity.[19]

Sociodemographic factors and medical history were assessed using standardized questionnaires. Angiographic data were obtained from the coronary angiogram performed in conjunction with the index MI. Coronary artery disease severity was quantified using the Gensini semiquantitative angiographic scoring system,[20] which takes into account the degree of luminal narrowing along with a multiplier for specific coronary tree locations. If a patient underwent revascularization, the percentage of coronary obstruction used in the scoring reflected the postrevascularization results. Depressive symptoms were assessed with the Beck Depression Inventory II (BDI-II).[21] We also administered the State-Trait Anxiety Inventory to measure state and trait anxiety[22] and the Seattle Angina Questionnaire to assess angina symptoms.[23]

Statistical analysis

Multiple linear regression models were used to assess the association between summed scores of myocardial perfusion with mental/physical stress and the 6 anger subscales, adjusting for possible confounding factors. The SDS for ischemia quantification was our main outcome variable of interest. Because the SDS for both mental and physical stress was skewed, whereas the SSS for both conditions was normally distributed, we used the SSS scores as dependent variables while adjusting for the rest score (SRS). Because of the mathematical relationship between these scores, the coefficient from a model with SSS as dependent variable, adjusted for SRS, is identical to that from a model, where the dependent variable is the SDS. This strategy allowed us to obtain nonbiased standard errors and *P* values.

In cumulative hierarchical models, we adjusted for a set of factors that were considered a priori either possible confounding factors or mediators of the relationships under study. Because of the relatively small sample size, we were careful to develop parsimonious models. Adjustment factors included sociodemographic and lifestyle characteristics (age, sex, race, and current cigarette smoking), CAD severity (Gensini score), depressive symptoms (BDI-II score), and trait anxiety. To allow comparison of effects across different anger subscales with unequal score range, we used the interquartile range (IQR) as scaling factor, that is, the distance between the 25th and 75th percentiles. We also assessed the interaction of sex and age (≤50 and >50 years) for each anger subscale in the final models. We performed thorough regression diagnostics to rule out collinearity and outliers[24]; these analyses showed that our models were appropriate, and no influential data points were present. In additionally, we repeated the analysis using nonparametric generalized additive modeling,[25] which yielded similar results.

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Results

Study sample

The mean and median age was 50 years, half of patients were women, and 60% were non-white (Table I). Almost half of the patients had an ST-elevation MI (45%); and after the index MI, 75% underwent percutaneous coronary interventions and 11% coronary artery bypass surgery. Psychosocial factors were common, with almost one-third of patients (32%) reporting income below poverty and 37% having significant depressive symptoms (BDI-II score >13).

Myocardial perfusion could not be quantified in 5 subjects due to poor image quality. For mental stress, the mean and SD for the SDS for ischemia quantification was 2.31 ± 2.69 (range 0-13). For physical stress, the mean SDS was 2.74 ± 3.24 (range 0-13). Based on a predefined cut-off point of SDS ≥3 for mental stress and ≥4 for exercise/pharmacologic stress,[26] 36 patients (39%) had mental stress ischemia, 32 (34%) had physical stress ischemia, and 18 (20%) had both mental and physical stress ischemia. Seven (9%) subjects had angina during exercise, and 18 (22%) had ST-segment depression with exercise stress. Descriptive characteristics of anger subscales are shown in Table II.

Correlates of anger subscales

Age was inversely associated with state and trait anger, indicating that the older the age, the less severe the anger scores (online Appendix Supplementary Table I). There were no significant differences based on other demographic factors. Current smokers, hypertensive subjects, and subjects reporting ≥1 angina episode per month tended to have higher anger-out scores, but the levels of other anger dimensions were similar. All anger subscales were positively associated with higher depressive and anxiety symptoms.

Changes in hemodynamic measures and subjective distress with mental stress

Heart rate, systolic and diastolic blood pressure, and rate-pressure product (heart rate times systolic blood

Table I. Characteristics of the study population

Variables	Characteristics (n = 98)
Demographics	
Age in years, mean (SD)	50 (6)
Age≤50 y (%)	49 (50%)
Female (%)	49 (50%)
Non-white (%)	59 (60%)
Income below poverty line (%)*	31 (32%)
Current smokers (%)	28 (29%)
Medical history and CHD risk factors	
ST-elevation MI (%)	44 (45%)
Time since MI (m), mean (SD)	4.8 (1.3)
Hypertension (%)†	67 (69%)
Hyperlipidemia (%)†	71 (73%)
Diabetes (%)†	20 (21%)
BMI (kilograms per square meter), mean (SD)†	31 (6)
Obese (BMI ≥30 kg/m^2) (%)†	45 (46%)
Gensini score, mean (SD)	17 (32)
> 0 (%)	65 (66%)
≥1 angina episode in past month (%)	41 (42%)
Treatment history and current medications	
Percutaneous coronary intervention (%)	73 (75%)
Coronary artery bypass graft (%)	11 (11%)
Aspirin (%)†	85 (88%)
β-blockers (%)†	85 (88%)
ACE inhibitors (%)†	53 (55%)
Statins (%)†	85 (88%)
Antidepressants (%)†	13 (13%)
Psychologic factors	
BDI-II score, mean (SD)	11 (9)
>13	36 (37%)
Anxiety state, mean (SD)†	38 (11)
Anxiety trait, mean (SD)†	39 (11)

Abbreviations: *BMI*, Body mass index; *ACE*, angiotensin-converting enzyme.
*Two observations missing.
†One observation missing.

Table II. Characteristics of anger subscales

Anger subscales	No of items	Scale score mean (SD)	Scale score range	Scale item mean (SD)*
Anger state	15	18.0 (7.5)	15-60	1.20 (0.50)
Anger trait	10	15.8 (4.9)	10-36	1.58 (0.49)
Anger expression				
Anger out	8	13.9 (3.5)	8-27	1.73 (0.44)
Anger in	8	15.8 (4.3)	8-28	1.98 (0.54)
Anger control (out)	8	24.1 (5.3)	14-32	3.01 (0.66)
Anger control (in)	8	23.1 (5.2)	10-32	2.89 (0.65)

*Scale items ranged between 1 and 4 on a Likert scale from 1, almost never, to 4, almost always.

pressure) significantly increased with mental stress (online Appendix Supplementary Table II) and with exercise/pharmacologic stress. None of these changes was significantly associated with anger dimensions (data not shown). Changes in subjective ratings of distress, nervousness, fearfulness, and anxiety with mental stress were also not related to anger, but the change in subjective ratings of anger was weakly but significantly associated with trait anger (regression coefficient 0.05; 95% CI 0.01-0.09). None of the above subjective ratings was found to be associated with ischemia during mental stress.

Mental stress–induced myocardial ischemia and anger

State anger, trait anger, and anger expression out were all significantly associated with the SDS with mental stress in unadjusted analysis, denoting more ischemia (Table III). After adjustment for age, sex, race, smoking status, Gensini score, and depression and anxiety symptoms, both state and trait anger remained significantly associated with the SDS with mental stress. Each incremental IQR increase in state-anger score (corresponding to 3 score points) was associated with 0.36 U–adjusted increase in SDS (95% CI 0.14-0.59); the corresponding association for trait anger was 0.95 (95% CI 0.21-1.69) per IQR increase (corresponding to 6 points). These associations translated into 2.1% increased myocardium ischemic involvement with each IQR progressively higher state-anger score (95% CI 1.0%-3.2%) and 5.4% increased myocardial ischemic involvement with each IQR higher trait-anger score (95% CI 1.8%-8.9%). For both state and trait anger, the SDS was higher for higher levels of scale item means (Figure). For state anger, being on average moderately angry or very angry was associated with approximately 4 times higher SDS compared with the 2 lower categories. For trait anger, there was a gradual increase in SDS going from 1 (almost never angry), to 4 (almost always angry). Anger out was no longer significantly associated with the SDS after adjustment for depression and anxiety symptoms. No association was found for the other anger dimensions. No significant sex or age interactions were found.

Using a similar analytic strategy, we found that none of the anger dimensions was significantly associated with the SDS during exercise or pharmacologic stress (online Appendix Supplementary Table III).

To rule out the possibility that SPECT imaging artifacts may have influenced our results, we performed a sensitivity analysis after excluding 9 subjects with significant artifacts identified through a systematic review of all SPECT scans by an experienced cardiologist. Such exclusion did not change the association between anger subscales and both mental and physical stress SDS (online Appendix Supplementary Table IV).

Discussion

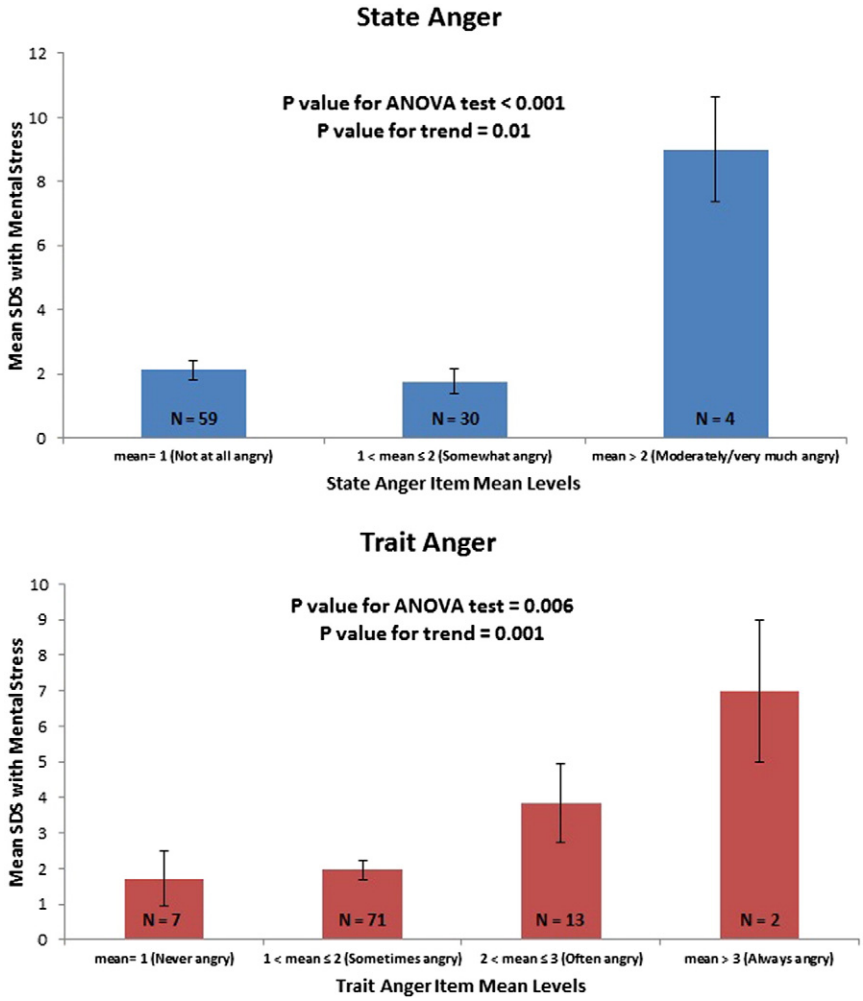
In a sample of young and middle-aged survivors of acute MI, we found that patients scoring higher in either state or trait anger were more likely to develop myocardial ischemia due to emotional stress than those with lower anger scores. The association was robust and clinically significant; each incremental IQR for both state and trait

Table III. Association between anger subscale scores and myocardial ischemia severity, as quantified by the SDS, during mental stress

Anger subscales	Model 1		Model 2		Model 3	
	Δ (95% CI)	*P*	Δ (95% CI)	*P*	Δ (95% CI)	*P*
Anger state	0.40 (0.20-0.60)	<.001	0.41 (0.20-0.62)	<.001	0.36 (0.14-0.59)	.002
Anger trait	1.02 (0.39-1.65)	.002	1.12 (0.46-1.78)	.001	0.95 (0.21-1.69)	.01
Anger expression						
Anger out	0.68 (0.08-1.29)	.03	0.68 (0.06-1.31)	.03	0.52 (–0.15 to 1.18)	.13
Anger in	0.67 (–0.09 to 1.42)	.08	0.68 (–0.10 to 1.46)	.09	0.31 (–0.62 to 1.23)	.52
Anger control (out)	–0.69 (–1.51 to 0.13)	.10	–0.72 (–1.54 to 0.10)	.08	–0.52 (–1.39 to 0.35)	.24
Anger control (in)	–0.27 (–1.22 to 0.67)	.57	–0.33 (–1.27 to 0.61)	.49	0.01 (–0.99 to 1.02)	.98

Abbreviation: Δ, Unit change in SDS per increase in IQR of corresponding anger subscale.
Model 1: unadjusted model.
Model 2: adjusted for age, gender, race, smoking status, and Gensini score.
Model 3: adjusted for all the covariates in model 2 + BDI-II score and trait anxiety.

Figure



Mental stress SDSs according to state and trait anger levels. Shown are mental-stress mean SDS and SEs according to state and trait anger score item mean levels. Numbers on bars indicate number of patients. For state anger, categories 3 and 4 were collapsed due to limited sample size.

anger led to approximately 2% and 5% increase in ischemic myocardium, respectively. In addition, the association was specific to mental stress because it was not seen for exercise or pharmacologically induced ischemia. Furthermore, it was independent of traditional coronary risk factors and CAD severity and held true even after adjustment for other indicators of psychosocial distress (depression and anxiety symptoms). These results suggest that patients with higher levels of anger, either as a transitory emotional response or as a personality trait, are at increased risk for silent ischemia induced by emotional stress. This psychologic profile may help identify patients at risk for mental stress–induced adverse outcomes.

To the best of our knowledge, ours is the first study to systematically examine the association between various anger dimensions and mental stress–induced ischemia measured by myocardial perfusion imaging. A previous study of 180 patients with stable CHD and a positive exercise stress test[27] reported no association between anger expression and mental stress–induced ischemia assessed by radionuclide ventriculography and electrocardiography, but state and trait anger were not measured. This study did find a relationship between anger/irritability ratings in response to the speech stressor and myocardial ischemia. On the other hand, in a study of 30 CHD patients with a positive exercise or pharmacologic stress test, Burg et al[28] found that higher trait anger and lower anger control predicted the development of mental stress ischemia measured by radionuclide ventriculography. Anger in and anger out were not associated with mental stress ischemia, whereas state anger was not measured. Additional studies have provided evidence that anger experimentally induced in the laboratory can provoke myocardial ischemia, both in patients and in animal models.[29,30] Thus, our results extend these important previous findings by examining a comprehensive set of anger dimensions, by using myocardial perfusion imaging, which is currently the criterion standard for myocardial ischemia assessment, and by including a well-characterized sample of MI patients enriched with younger individuals, women and minorities, a diverse group with a substantial level of psychosocial burden.

Acute anger has been consistently implicated as an important precipitant for angina and/or MI.[1,7] A recent meta-analysis found that both anger and hostility were significantly associated with increased risk of CHD events. Higher trait anger was associated with 98% increased risk of CHD events in subjects with preexisting CHD.[6] However, whether anger is an independent risk factor for CHD or rather an epiphenomenon of unmeasured risk factors or even a prodrome of CHD itself is still debated.[8] Our findings of a relationship between anger, both as a state and as a trait, and mental stress–induced ischemia are consistent with the notion that anger is indeed linked to the risk of CHD. Our data also provide a novel mechanistic pathway through which young and middle-aged survivors of MI might be at risk for recurrent CHD events.

Our study has several strengths. We included a well-defined population of young and middle-aged post-MI patients, who are likely to have enhanced vulnerability to psychologic stressors, with balanced representation of women and minorities. In addition, we assessed ischemia using state-of-the-art myocardial perfusion imaging and a quantitative, reader-independent ischemia scoring system.[2,31]

The main limitation of our study is the relatively small sample size that may have caused wide CIs. Small sample size may also have precluded conclusively proving the association (or lack thereof) between anger expression subscales and mental stress–induced ischemia. Nonetheless, the directionality of the associations consistently holds true with the underlying assumption, with anger out and anger in being directly related and anger control indirectly related, with mental stress–induced myocardial ischemia. Most of our MI patients received revascularization procedures, reflecting current treatment standards, which may have affected the detection of ischemia. However, mental stress–induced myocardial ischemia is known to be unrelated to severity of coronary obstruction or previous revascularization and can occur in the setting of a negative exercise or adenosine stress test.[3] We are unable to explain why mental stress–induced myocardial ischemia shows a robust relationship only with state/trait anger and not with anger expression, but our results are consistent with a recent meta-analysis,[6] where an association with CHD was found for trait anger but not for anger expression. Another limitation is the lack of CHD outcome data. Therefore, our results need to be replicated in larger studies with prospective follow-up to assess if mental stress–induced ischemia explains the relationship between anger and increased risk of cardiac events.

Conclusion

Among young and middle-aged survivors of an MI, anger, both as a psychologic state and as a personality trait, is associated with a greater propensity to develop myocardial ischemia with emotional stress. Our results suggest that MI patients with this psychologic profile are at increased risk for silent ischemia induced by emotional stress, which in turn may increase their risk for adverse outcomes. Incorporation of psychologic evaluations for anger assessment, especially among young post-MI patients, may help identify patients at risk for mental stress–induced adverse outcomes. New treatments should be evaluated that specifically target anger to reduce the risk of future cardiac events.

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Appendix

Supplementary Table I. Association between anger subscale scores and other study factors

					Anger expression							
Covariates	**Anger-state, mean (SD) or r**	***P***	**Anger-trait, mean (SD) or r**	***P***	**Anger-out, mean (SD) or r**	***P***	**Anger-in, mean (SD) or r**	***P***	**Anger-control (out), mean (SD) or r**	***P***	**Anger-control (in), mean (SD) or r**	***P***
Demographic and lifestyle covariates												
Age	–0.13	.05	–0.26	.01	–0.18	.08	0.007	.95	0.05	.60	–0.04	.73
Gender												
Female	19.5 (9.8)	.36	15.8 (5.2)	.94	14.1 (3.8)	.51	16.3 (4.5)	.33	24.1 (4.8)	.94	23.4 (5.2)	.63
Male	16.6 (3.5)		15.9 (4.7)		13.6 (3.2)		15.4 (4.1)		24.1 (5.8)		22.9 (5.4)	
Race												
White	17.9 (7.6)	.61	16.2 (3.9)	.57	13.9 (3.1)	.87	16.4 (3.8)	.29	23.6 (5.0)	.47	22.4 (5.1)	.24
Non-white	18.1 (7.5)		15.6 (5.6)		13.8 (3.8)		15.5 (4.6)		24.4 (5.5)		23.6 (5.3)	
Income status												
Above poverty	17.0 (6.1)	.15	15.5 (4.0)	.53	13.3 (3.0)	.06	15.5 (3.8)	.47	24.5 (5.1)	.37	23.2 (5.2)	.82
Below poverty	20.0 (9.8)		16.3 (6.5)		15.0 (4.1)		16.3 (5.2)		23.4 (5.7)		22.9 (5.4)	
Smoking status												
Non-smokers	17.1 (6.0)	.07	15.3 (4.3)	.18	13.4 (3.3)	.04	15.1 (3.9)	.02	24.4 (5.4)	.32	23.2 (5.7)	.67
Current smokers	20.5 (10.1)		17.1 (6.2)		15.1 (3.8)		17.6 (4.9)		23.3 (5.0)		22.8 (3.9)	
Medical history and coronary angiographic data												
Hypertension												
Absent	17.1 (3.0)	.54	14.8 (3.7)	.09	12.9 (2.5)	.02	15.4 (4.5)	.47	24.5 (5.5)	.60	22.5 (4.6)	.48
Present	18.5 (8.8)		16.4 (5.4)		14.4 (3.8)		16.1 (4.3)		23.9 (5.3)		23.3 (5.5)	
Gensini score	–0.03	.76	–0.09	.37	0.05	.62	0.04	.69	–0.07	.50	–0.07	.52
Angina frequency												
None	17.6 (6.5)	.57	15.4 (4.3)	.37	13.0 (3.0)	.01	15.7 (4.3)	.66	24.3 (5.2)	.62	23.6 (5.2)	.27
At least 1/month	18.7 (8.8)		16.4 (5.8)		15.1 (3.8)		16.1 (4.5)		23.8 (5.5)		22.4 (5.2)	
Psychosocial factors												
BDI-II score	0.48	<.001	0.45	<.001	0.40	<.001	0.57	<.001	–0.28	.005	–0.29	.004
Anxiety-state	0.47	.005	0.31	.002	0.23	.02	0.43	<.001	–0.26	.01	–0.29	.003
Anxiety-trait	0.39	.03	0.35	<.001	0.23	.02	0.54	<.001	–0.30	.002	–0.37	<.001

SD: standard deviation; r: Pearson/Spearman correlation coefficients; BDI: Beck Depression Inventory.
The table shows means and standard deviation of anger subscales according to levels of categorical variables, or regression coefficient for continuous variables.

Supplementary Table II. Hemodynamic and subjective distress rating changes with mental stress

Variables	**Change, post test vs. pre test**	***P* value***
Hemodynamic measures		
Systolic blood pressure (mmHg), mean change (SD)	48 (23)	<.001
Diastolic blood pressure (mmHg), mean change (SD)	30 (13)	<.001
Heart rate (beats/min), mean change (SD)	28 (18)	<.001
Rate-pressure product, mean change (SD)	7850 (4519)	<.001
Subjective ratings of distress		
Subjective Units of Distress Scale, mean change (SD)	15 (34)	<.001
Visual analog scale of nervousness, mean change (SD)	0.5 (1.4)	.001
Visual analog scale of anxiety, mean change (SD)	0.3 (1.6)	.08
Visual analog scale of fear, mean change (SD)	0.4 (1.1)	.002
Visual analog scale of anger, mean change (SD)	0.4 (1.1)	.002

* P value for one sample t-test with null hypothesis being mean = 0.

Supplementary Table III. Association between anger subscale scores and myocardial ischemia severity, as quantified by the SDS, during physical stress

	Model 1		Model 2		Model 3	
Anger subscales	**Δ (95% CI)**	***P***	**Δ (95% CI)**	***P***	**Δ (95% CI)**	***P***
Anger-state	–0.06 (–0.32-0.20)	.63	–0.07 (–0.34-0.20)	.61	–0.10 (–0.39-0.19)	.51
Anger-trait	–0.32 (–1.16-0.47)	.42	–0.34 (–1.17-0.48)	.41	–0.37 (–1.29-0.55)	.43
Anger expression						
Anger-out	–0.22 (–0.98-0.53)	.56	–0.28 (–1.05-0.49)	.47	–0.29 (–1.10-0.52)	.48
Anger-in	0.41 (–0.48-1.32)	.36	0.36 (–0.57-1.29)	.45	0.85 (–0.24-1.96)	.13
Anger-control (out)	0.64 (–0.33-1.61)	.20	0.61 (–0.36-1.59)	.21	0.45 (–0.57-1.47)	.39
Anger-control (in)	0.39 (–0.73-1.50)	.50	0.36 (–0.74-1.47)	.52	0.09 (–1.09-1.26)	.88

Δ: unit change in SDS per increase in IQR of corresponding anger subscale.
Model 1: unadjusted model.
Model 2: adjusted for age, gender, race, smoking status, and Gensini score.
Model 3: adjusted for all the covariates in model 2 + BDI-II score and anxiety-trait.

Supplementary Table IV. Sensitivity analysis for the association between anger subscale scores and myocardial ischemia severity (quantified by the SDS), during both mental and physical stress, after excluding 9 subjects with SPECT imaging artifacts

	SDS during mental stress (unadjusted)*		SDS during physical stress (unadjusted)*	
Anger subscales	**Δ (95% CI)**	***P***	**Δ (95% CI)**	***P***
Anger-state	0.24 (0.12 - 0.36)	.0001	–0.02 (–0.18 - 0.15)	.86
Anger-trait	0.83 (0.23 - 1.42)	.006	–0.43 (–1.19 – 0.33)	.27
Anger expression				
Anger-out	0.75 (0.05 - 1.45)	.04	–0.28 (–1.18 – 0.62)	.54
Anger-in	0.41 (–0.34 - 1.17)	.28	0.62 (–0.30 - 1.54)	.19
Anger-control (out)	–0.30 (–1.07 - 0.49)	.46	0.88 (–0.05 – 1.82)	.07
Anger-control (in)	–0.03 (–0.90 - 0.85)	.95	0.63 (–0.43 – 1.69)	.25

*: N = 84, 9 subjects with significant SPECT scan artifacts excluded.
Δ: unit change in SDS per increase in IQR of corresponding anger subscale.