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ORIGINAL RESEARCH

Association Between Symptoms of Chronic Psychological Distress and Myocardial Ischemia Induced by Mental Stress in Patients With Coronary Artery Disease

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BACKGROUND: Mental stress–induced myocardial ischemia is a frequent phenomenon in patients with coronary artery disease and is associated with a greater risk of future cardiovascular events. The association between chronic symptoms of psychological distress and mental stress–induced ischemia is not clear.

METHODS AND RESULTS: We used a composite score of psychological distress derived from symptoms of depression, posttraumatic stress disorder, anxiety, anger, and perceived general stress. Participants underwent myocardial perfusion imaging with both mental (public speaking task) and conventional (exercise or pharmacological) stress testing. Overall, 142 (15.9%) patients experienced mental stress–induced myocardial ischemia. After adjusting for demographic factors, medical history, and medication use, patients in the highest tertile of psychological distress score had 35% higher odds of having mental stress–induced ischemia compared to those in the lowest tertile (odds ratio [OR], 1.35 [95% CI, 1.06–2.22]). Stratified analyses showed that the association between psychological distress score and mental stress–induced myocardial ischemia was significantly associated only within the subgroup of patients with a prior myocardial infraction, with patients with a prior myocardial infarction in the highest tertile having a 93% higher odds of developing myocardial ischemia with mental stress (95% CI, 1.07–3.60). There was no significant association between psychological distress and conventional stress–induced ischemia (OR, 1.19 [95% CI, 0.87–1.63]).

CONCLUSIONS: Among patients with a history of myocardial infarction, a higher level of psychosocial distress is associated with mental stress–induced myocardial ischemia but not with ischemia induced by a conventional stress test.

Key Words: coronary artery disease ■ mental stress–induced myocardial ischemia ■ myocardial infraction ■ psychological distress

Psychological distress has emerged as an important risk factor for the development and progression of coronary artery disease (CAD).[1] In approximately one-fifth of individuals with stable CAD, an acute mental stress challenge in the laboratory can trigger myocardial ischemia detected with myocardial perfusion imaging.[2–6] Mental stress–induced myocardial ischemia is associated with a 2-fold increase in the risk of future cardiovascular events in the CAD population.[2,7] In contrast to myocardial ischemia provoked by exercise stress testing, mental stress–induced myocardial ischemia is usually asymptomatic, occurs at lower levels of oxygen demand, and can occur in individuals who do not have a positive exercise stress test result.[3–6]

Various mechanisms have been implicated in the pathophysiology of myocardial ischemia with mental

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CLINICAL PERSPECTIVE

What Is New?

- A composite measure of psychosocial distress is associated with both presence and severity of ischemia induced by mental stress in patients with prior myocardial infarction.
- Psychological distress is not associated with myocardial ischemia induced by a conventional stress test (exercise or pharmacological stress).

What Are the Clinical Implications?

- Assessment of a patient's psychological status using a composite distress score could be valuable for patients with a history of myocardial infarction.

Nonstandard Abbreviations and Acronyms

SPECT	Sestamibi single-photon emission computed tomography

stress, including abnormal coronary or peripheral vasomotion, endothelial dysfunction, coronary microvascular disease, and platelet reactivity.[8–10] However, the ultimate reasons why some individuals develop ischemia with mental stress and others do not are unclear. It has been suspected that patients with CAD and adverse psychological profiles may be more susceptible to developing mental stress ischemia, but studies have provided conflicting results.[11–17] Most of these studies have largely enrolled older, male, and White patients and have treated each psychosocial phenotype as an independent exposure. A combined measure of chronic psychological distress may provide a more comprehensive assessment of maladaptive psychological functioning and thus may be more valid and have greater potential for clinical utility.

In a diverse sample of individuals with CAD, we investigated the association between a composite measure of chronic psychosocial distress and myocardial perfusion abnormalities with mental stress. To understand if the relationship is specific for ischemia provoked by mental stress, we contrasted the results with those obtained with a conventional (exercise or pharmacological) stress test. Given the established relationship between chronic stress and inflammation,[18] as well as between inflammation and myocardial perfusion,[19] we also examined the role of baseline inflammation in the association.

METHODS

Study Sample

The data that support the findings of this study are available from the corresponding author upon reasonable request. The research protocol for both study cohorts was approved by the institutional review board of Emory University, and all participants provided written informed consent. Between 2011 and 2016, we enrolled individuals with stable CAD in 2 parallel studies with similar protocols, the MIPS (Mental Stress Ischemia Prognosis Study)[20] and the MIMS2 (Myocardial Infarction and Mental Stress Study 2).[3] Both studies recruited patients with stable CAD from hospitals and clinics affiliated with Emory University and shared protocols, staff, facilities, and equipment. The inclusion and exclusion criteria for each cohort are presented in Supplemental Material. Given the similarity of protocols, the 2 cohorts were combined in this study, as we have previously done.[2]

Mental Stress Procedure

All patients underwent mental stress testing in the morning after a 12-hour fast. Following a 30-minute rest in a quiet, dimly lit, temperature-controlled room, mental stress was induced by a standardized public speaking task as previously described.[20] Participants were asked to imagine a real-life stressful situation in which a close relative had been mistreated in a nursing home and were asked to make up a realistic story around this scenario. Each participant was given 2 minutes to prepare a statement and then 3 minutes to present it in front of a video camera and an audience wearing white coats who would evaluate their speech for content, quality, and duration.

Myocardial Perfusion Imaging

All patients underwent 3 technetium Tc 99m (^{99m}TC) Sestamibi single-photon emission computed tomography (SPECT) scans at rest, during mental stress, and during conventional stress, following standard protocols.[4] Testing was performed on 2 separate days up to 1 week apart on a dedicated SPECT camera (Philips Cardio MD). All antianginal medications were withheld for 24 hours before stress testing. On the mental stress day, ^{99m}TC sestamibi was injected 1 minute into the speech task. On the conventional stress day, participants underwent a standard Bruce protocol, or, if unable to exercise, a pharmacological stress test with regadenoson (Astellas).

SPECT scans were interpreted by 2 experienced readers blinded to stress test type (mental or exercise or pharmacological stress) and other clinical data. Discrepancies were resolved by consensus or, if needed, a third reader. Each reader would

visually compare the rest and stress images using a 17-segment model. Each segment was scored from 0 to 4, with 0 being normal uptake and 4 no uptake. Ischemia was defined as at least 1 reversible defect with 2 or more points of improvement at rest or improvement to a score of 1 according to current guidelines.[21] In addition, we calculated a summed difference score through the entire myocardium to assess the severity of ischemia and to evaluate the robustness of the results. The interrater reliability and reproducibility for the interpretation of SPECT images were previously published.[22] For mental stress–induced ischemia we have demonstrated 90% agreement for repeated testing 2 weeks apart and 94% agreement between readers using Bland–Altman plots.[2]

Psychosocial Distress

We assessed chronic psychosocial distress by constructing a global distress measure that integrates scales of psychological characteristics with recognized validity and reliability and known association with cardiovascular disease, with similar methodology previously followed by ourselves and others.[17,23,24] These included symptoms of depression, posttraumatic stress disorder, anxiety, anger, and perceived general stress. Depressive symptoms were assessed with the Beck Depression Inventory-II, a 21-item self-administered scale.[25] Posttraumatic stress disorder symptoms were assessed using the civilian version of the PTSD Symptom Checklist, a 17-item scale.[26] State anxiety was measured with a 20-item subscale of the State–Trait Anxiety Inventory.[27] State anger was assessed with a 15-item subscale of the Spielberger's State–Trait Anger Expression Inventory,[28] and general perceived stress was assessed with the 10-item Perceived Stress Scale.[29] Patients were ranked on each of the 5 psychological measures; then all ranks were averaged for each individual to obtain a composite psychological distress score.[23] Because ranking values depends on sample size, and we used 2 different pooled cohorts of unequal sample size to obtain unbiased categorization of patients in the pooled sample, tertiles were first calculated within cohort and then merged in the pooled sample. We used these tertiles (indexing "low," "moderate," and "severe" psychological distress) as our main exposure variable.

Covariables

Information on sociodemographic and lifetime clinical factors was obtained using standardized questionnaires and chart reviews. Height and weight were measured to calculate body mass index. Race and ethnicity were reported by participants according to investigator-defined categories. Because few participants were of race other than non-Hispanic Black or non-Hispanic White, we included only 2 categories in the models, non-Hispanic Black versus all others. We monitored blood pressure and heart rate during the resting stage (every 5 minutes) and during mental and conventional stress test (every 1 minute). We calculated the rate-pressure product as the mean systolic blood pressure × the mean heart rate. Quantitative angiographic scoring was performed using the Gensini score, which quantifies CAD severity by a nonlinear point system for degree of luminal narrowing, along with a multiplier for specific coronary tree locations.[30] Inflammation at baseline was assessed by measuring plasma interleukin-6 (IL-6) levels, which were assessed with the MesoScale system (Meso Scale Diagnostics Rockville, MD) using the SECTOR Imager 2400.

Statistical Analysis

Continuous variables are presented as mean and SD, and categorical variables are presented as proportions. For our main analyses, we performed 2 separate multivariable logistic regression analyses with ischemia with mental or conventional stress as outcomes and tertiles of the composite psychological distress score as the main predictor variable. Multivariable linear regression analyses were repeated, with the summed difference score as a continuous measure of ischemic burden for either mental or conventional stress as outcome variables. Assumptions for linearity, normality, and multicollinearity were tested and found to be met, using residual plots, Q-Q plot of the residuals, and variance inflation factors. Sequential models were constructed after including prespecified variables to the unadjusted model (Model 1). In Model 2, we added demographic factors, including age, sex, and race. In Model 3, we added cardiovascular risk factors and other relevant medical factors, including ever smoking, body mass index, history of hypertension, hyperlipidemia, diabetes, heart failure, and history of revascularization. In Model 4, we added current medications (β-blockers, statins, angiotensin-converting enzyme inhibitors, and aspirin). We also examined whether the association of mental stress–induced ischemia with psychological distress varied according to a priori selected strata, including age (≤50 versus >50 years), sex, race (Black versus non-Black), history of diabetes, history of heart failure, and history of smoking. We also examined the association of the different psychological scale components of the distress score with mental stress–induced ischemia. In order to account for differences in units across scales, *Z* scores were calculated for each scale by subtracting the mean from the individual values and dividing it by the SD.

We performed a mediation analysis with bootstrapping (1000 bootstrap samples and a 95% CI) to test the hypothesis that IL-6 levels mediate the relationship

between psychological distress and severity of mental stress–induced ischemia using the method by Preacher and Hayes.[31] Significance testing was 2 sided with a significance threshold of $P<0.05$, and all statistical analyses were performed using Stata software, version 14.0 (StataCorp).

RESULTS

Study Population

Of the 951 total study participants, 60 individuals had missing information on either exposure or outcome, leaving an analytical sample size of 891. Demographic and clinical characteristics of the sample are shown in Table 1. Individuals with higher psychological distress score tertile were more likely to be female and Black, live in poverty, and have lower education, a history of hypertension, diabetes, smoking, heart failure, and revascularization, but less severe burden of CAD (Table 1). However, there were no substantial differences in blood pressure and heart rate responses with stress among the 3 groups.

Association of Mental Stress–Induced Ischemia With Psychological Distress

A total of 142 (15.9%) individuals experienced myocardial ischemia with the laboratory mental stress challenge. Patients with mental stress–induced myocardial ischemia had a higher Gensini score (57.6 versus 43.1, $P=0.003$), indicative of a higher burden of CAD. The frequency of mental stress–induced ischemia was 14.1% among patients in the lowest tertile of distress score and 21.0% among those in the highest distress score tertile.

As shown in Table 2, tertiles of the psychological distress score were associated with presence of mental stress–induced myocardial ischemia (odds ratio [OR] for the highest tertile compared with the lowest tertile, 1.38 [95% CI, 1.11–2.25]). Further adjustment for demographic, clinical factors, and medication use did not significantly affect the association (Table 2). When using the summed difference score as a continuous measure of the severity of mental stress ischemia, the results remained consistent (Table 2). Stratified analyses showed that the association between psychological distress score and mental stress–induced myocardial ischemia was significantly associated only within the subgroup of patients with a prior myocardial infarction (MI) (Table 3). After adjusting for demographic, clinical factors, and medications use, patients with a prior MI who were in the highest tertile had 93% higher odds of experiencing myocardial ischemia with mental stress compared with the lowest tertile (95% CI, 1.07–3.60, Table 3). Similar results were found when examining the summed difference score as a continuous measure of the severity of mental stress ischemia. Also, as shown in Figure 1, subgroup analyses showed that the association between psychological distress score and mental stress–induced myocardial ischemia tended to be stronger in patients older than 50 years of age, men, non-Black patients, and those with no history of heart failure and no smoking history. Although the P value for interaction did not reach statistical significance for any of these subgroups, the results should be interpreted cautiously in the presence of differences in power and imbalances. When examining the individual component scales, all were positively associated with presence and severity of mental stress–induced myocardial ischemia in the fully adjusted model, and the associations were significant for all scales except for perceived stress and state anger (Table 4).

Association of Conventional Stress–Induced Ischemia With Psychological Distress

Within a week of mental stress testing, patients underwent a conventional stress test, with 612 (68.7%) individuals receiving exercise stress testing and the remaining patients receiving pharmacologic stress testing. Among these patients, myocardial ischemia provoked by conventional stress test was detected in 275 (30.9%) patients. There was a significant relationship between the severity of myocardial ischemia induced by mental and conventional stress tests (β, 0.19 [95% CI, 0.15–0.23]). Overall, 92 patients (10.5%) had both mental and conventional stress–induced ischemia. As shown in Table 5, there was no significant association between either the presence or the severity (summed difference score) of conventional stress–induced myocardial ischemia with psychological distress. Also, those with both mental and conventional stress–induced ischemia did not have a higher burden of psychological distress compared with those with only mental stress–induced ischemia ($\beta=0.01$ [95% CI, −0.07 to 0.08], $P=0.65$).

Mediating Role of Il-6

Among patients with a prior MI, mean geometric IL-6 levels were higher among those in the highest tertile of psychological distress compared with individuals in the lowest tertile (0.49±0.65 versus 0.33±0.60, $P=0.009$). As shown in Figure 2, higher baseline IL-6 levels were significantly associated with both higher psychological distress and severity of mental stress–induced ischemia. After adjusting for the full model, IL-6 levels partially mediated the relationship between psychological distress and mental stress–induced ischemia on average by 22.2% (95% CI, 14–35).

Table 1. Baseline Characteristics of the Cohort Stratified Based on Tertiles of Composite Distress Score

	Tertile 1 (Low psychological distress) N=298	Tertile 2 (Moderate psychological distress) N=297	Tertile 3 (Severe psychological distress) N=296
Demographics			
Age, y, mean (SD)	61 (10)	60 (10)	57 (9)
Female sex, n (%)	79 (26.5)	102 (34.3)	119 (40.2)
Black race, n (%)	92 (30.9)	112 (37.7)	145 (49.0)
Income <$35 000, n (%)	23 (7.7)	55 (18.5)	98 (33.1)
Education >12 y, n (%)	225 (75.5)	200 (67.3)	184 (62.2)
Clinical risk factors			
Hyperlipidemia, n (%)	247 (82.9)	238 (80.1)	241 (81.4)
Hypertension, n (%)	223 (74.8)	222 (74.7)	239 (80.7)
Diabetes, n (%)	85 (28.5)	96 (32.3)	105 (35.5)
Ever smoker, n (%)	158 (53.0)	173 (58.2)	187 (63.2)
Body mass index, mean (SD)	29.2 (4.8)	30.1 (6.1)	30.8 (6.7)
History of heart failure	26 (8.7)	37 (12.5)	52 (17.6)
Left ventricular ejection fraction, mean (SD)	63.3 (14.7)	60.1 (16.1)	61.1 (15.1)
History of revascularization, n (%)	178 (59.7)	181 (60.9)	183 (61.8)
History of myocardial infarction, n (%)	157 (52.7)	156 (52.5)	162 (54.7)
Clinical characteristics			
≥1 Coronary vessel with 70% stenosis, n (%)	238 (79.9)	224 (75.4)	200 (67.6)
Gensini score, median (interquartile range)	26 (10–65)	27 (10–54)	25 (7–57)
Myocardial infarction with nonobstructive coronary arteries, n (%)	11 (7)	14 (9)	19 (11.7)
Medications, n (%)			
Statin	258 (86.6)	247 (83.2)	256 (86.5)
Aspirin	257 (86.2)	255 (85.9)	242 (81.8)
Beta blocker	214 (71.8)	232 (78.1)	242 (81.8)
Angiotensin-converting enzyme inhibitor	139 (46.6)	132 (44.4)	133 (44.9)
Antidepressants	28 (9.4)	66 (22.2)	106 (35.8)
Mental stress testing, mean (SD)			
Resting blood pressure, mm Hg			
Systolic	132.2 (17.4)	135.1 (19.4)	136.0 (19.7)
Diastolic	77.6 (10.1)	79.9 (10.9)	81.4 (11.7)
Maximum blood pressure, mm Hg			
Systolic	172.4 (17.0)	176.2 (17.9)	176.0 (17.1)
Diastolic	92.1 (10.8)	101.5 (11.3)	100.3 (10.7)
Baseline heart rate, beats/min	62.3 (10.3)	63.3 (11.0)	65.3 (10.9)
Maximum heart rate, beats/min	83.4 (13.0)	81.8 (12.5)	81.2 (11.3)
RPP, change, per 1000	6.2 (2.9)	5.6 (2.9)	5.1 (2.4)
Summed rest score	5.1 (5.9)	6.0 (6.3)	5.5 (5.8)
Summed difference score	1.2 (1.8)	1.8 (2.2)	2.6 (2.2)
Number of ischemic segments with stress, n (%)	0.42 (1.1)	0.73 (1.7)	0.98 (1.2)
Conventional stress testing, mean (SD)			
Resting blood pressure, mm Hg			
Systolic	132.8 (15.1)	133.4 (14.2)	131.3 (12.1)
Diastolic	76.2 (9.2)	79.1 (10.1)	80.2 (11.3)
Maximum blood pressure, mm Hg			
Systolic	168.4 (14.3)	167.2 (21.1)	167.8 (18.9)
Diastolic	81.2 (12.4)	83.5 (11.0)	84.5 (8.8)

(*Continued*)

Table 1. Continued

	Tertile 1 (Low psychological distress) N=298	Tertile 2 (Moderate psychological distress) N=297	Tertile 3 (Severe psychological distress) N=296
Baseline heart rate, beats/min	61.4 (10.9)	60.3 (10.2)	62.1 (10.1)
Maximum heart rate, beats/min	127.4 (17.3)	131.0 (16.5)	132.5 (18.2)
RPP, change, per 1000	9.1 (4.2)	9.2 (4.0)	9.2 (4.2)
Perfusion defect severity at rest	6.0 (5.8)	5.9 (6.1)	5.6 (6.2)
Perfusion defect severity during ischemia	2.6 (3.4)	2.7 (3.3)	2.6 (3.1)
Number of ischemic segments with stress, n (%)	1.4 (2.6)	1.6 (2.7)	1.3 (2.3)
Psychological factors, mean (SD)			
Beck Depression Inventory II	2.9 (2.6)	7.3 (4.6)	18.2 (10.1)
Posttraumatic stress disorder symptom checklist	19.6 (2.9)	25.4 (7.2)	39.6 (13.8)
Cohen perceived stress scale	6.5 (3.9)	12.9 (5.2)	21.1 (6.7)
State anxiety	23.0 (3.8)	30.1 (7.3)	44.3 (10.8)
State anger	15.1 (0.63)	15.9 (3.2)	20.7 (8.2)

RPP indicates rate-pressure product.

DISCUSSION

Among individuals with stable CAD, we observed that chronic psychosocial distress, defined as a composite measure of psychosocial scales (depression, posttraumatic stress disorder, anxiety, anger, and perceived stress) was significantly associated with both presence and severity of ischemia induced by mental stress. These associations were independent of demographic factors, medical conditions, and medication use. In contrast, chronic psychological distress was not associated with corresponding indices of ischemia induced by a conventional stress test (exercise or pharmacological stress). Subgroup analyses revealed that the

Table 2. Association of the Composite Score of Psychosocial Distress With Presence of Mental Stress–Induced Myocardial Ischemia and Severity of Mental Stress–Induced Myocardial Ischemia (Summed Difference Score)

	OR* (95% CI)			*P* value for trend
Presence of mental stress–induced ischemia	**Tertile 1 (Low psychological distress)**	**Tertile 2 (Moderate psychological distress)**	**Tertile 3 (Severe psychological distress)**	
Unadjusted	Ref	1.12 (1.08–2.18) *P*=0.002	1.38 (1.11–2.25) *P*<0.001	0.009
Adjusted for demographic factors‡	Ref	1.10 (1.07–2.16) *P*=0.003	1.37 (1.09–2.23) *P*=0.001	0.005
Preceding variables+clinical risk factors§ and medications‖	Ref	1.08 (1.06–2.14) *P*=0.01	1.35 (1.07–2.20) *P*=0.01	0.007
Preceding variables+Gensini score	Ref	1.07 (1.05–2.11) *P*=0.01	1.33 (1.05–2.18) *P*=0.01	0.007
	B† (95% CI)			
Severity of ischemia (summed difference score)	**Tertile 1 (Low psychological distress)**	**Tertile 2 (Moderate psychological distress)**	**Tertile 3 (Severe psychological distress)**	
Unadjusted	Ref	0.43 (0.09–0.77) *P*=0.008	0.58 (0.24–0.92) *P*<0.001	<0.001
Adjusted for demographic factors‡	Ref	0.41 (0.06–0.75) *P*=0.01	0.55 (0.21–0.88) *P*<0.001	<0.001
Preceding variables+clinical risk factors§ and medications‖	Ref	0.40 (0.05–0.74) *P*=0.02	0.53 (0.18–0.85) *P*=0.003	
Preceding variables+Gensini score	Ref	0.38 (0.03–0.71) *P*=0.03	0.52 (0.17–0.82) *P*=0.007	<0.001

OR indicates odds ratio.

*Odds ratio calculated for every SD higher psychological distress score.

†B represents estimated point increase in perfusion defect score (summed difference score) during mental stress for every SD higher psychological distress score.

‡Age, sex, and race (Black vs non-Black participants).

§Ever smoking, body mass index, history of hypertension, history of diabetes, history of dyslipidemia, history of heart failure, history of revascularization, and summed rest score.

‖β-blockers, statins, angiotensin-converting enzyme inhibitors, and aspirin.

Table 3. Association of the Composite Score of Psychosocial Distress With Presence of Mental Stress–Induced Myocardial Ischemia Among Patients With and Without a History of Myocardial Infarction

Patients with a history of myocardial infarction (N=475)				
Presence of mental stress–induced ischemia	**OR (95% CI)**			***P* value for trend**
	Tertile 1 (Low psychological distress)	Tertile 2 (Moderate psychological distress)	Tertile 3 (Severe psychological distress)	
Unadjusted	Ref	1.57 (1.08–2.91) *P*=0.006	1.96 (1.10–3.65) *P*<0.001	<0.001
Adjusted for demographic factors*	Ref	1.55 (1.07–2.83) *P*=0.009	1.95 (1.09–3.64) *P*<0.001	0.002
Preceding variables+clinical risk factors† and medications‡	Ref	1.53 (1.06–2.81) *P*=0.01	1.93 (1.07–3.60) *P*=0.005	<0.001
Preceding variables+Gensini score	Ref	1.52 (1.04–2.78) *P*=0.02	1.91 (1.06–3.55) *P*=0.01	<0.001
Patients without a history of myocardial infarction (N=416)				
Presence of mental stress–induced ischemia	**OR (95% CI)**			
	Tertile 1 (Low psychological distress)	**Tertile 2 (Moderate psychological distress)**	**Tertile 3 (Severe psychological distress)**	
Unadjusted	Ref	1.22 (0.62–1.99) *P*=0.23	1.08 (0.53–1.65) *P*=0.41	0.35
Adjusted for demographic factors*	Ref	1.18 (0.61–1.96) *P*=0.31	1.05 (0.52–1.55) *P*=0.51	0.55
Preceding variables+clinical risk factors† and medications‡	Ref	1.16 (0.58–1.90) *P*=0.35	1.04 (0.50–1.55) *P*=0.68	0.48
Preceding variables+Gensini score	Ref	1.15 (0.55–1.92) *P*=0.41	1.03 (0.48–1.53) *P*=0.58	0.48

OR indicates odds ratio. Significance for all is *P*<0.05.
*Age, sex, and race (Black vs non-Black participants).
†Ever smoking, body mass index, history of hypertension, history of diabetes, history of dyslipidemia, history of heart failure, history of revascularization, and summed rest score.
‡β-blockers, statins, angiotensin-converting enzyme inhibitors, and aspirin.

association between chronic psychological distress and mental stress–induced ischemia was present only among those with a prior MI. We also found that baseline IL-6 levels partly mediated the association between higher psychological distress and mental stress–induced ischemia.

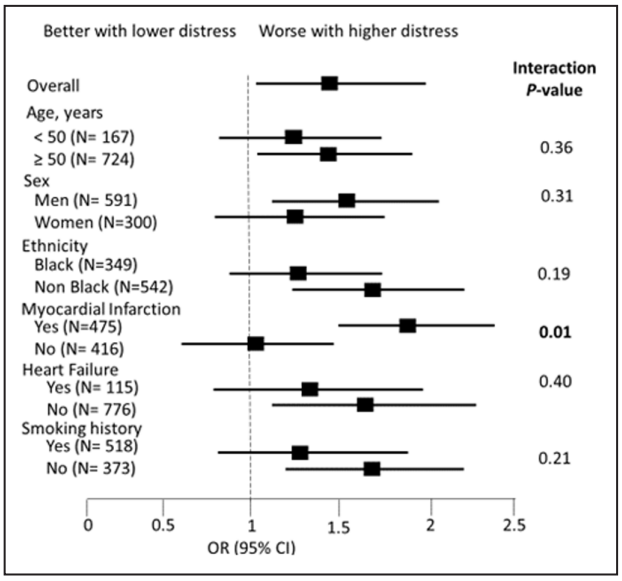

Figure 1. Association between composite distress score with mental stress–induced myocardial ischemia according to subgroups comparing high (third tertile) and low (first tertile) psychological distress.

In our study, when individual psychological scales were examined separately, all were positively associated with the presence of mental stress–induced ischemia, an association that was statistically significant for depression and anxiety. This suggests that a composite measure of distress may have a higher sensitivity for detecting vulnerability to cardiovascular consequences of stress, such as myocardial ischemia, than individual scales assessed separately. Our findings highlight the potential advantage of measuring an individual's psychological status more globally in uncovering its impact on cardiovascular health.

Few previous studies have investigated the relationship of patients' psychological profile with mental stress–induced myocardial ischemia, and those that examined this question had small samples and their results conflicted.[11–17,32] For instance, whereas earlier studies did not show significant associations between depressive symptoms and myocardial ischemia or left ventricular dysfunction provoked by mental stress,[12,14] more recent studies have shown a positive association between the severity of depressive symptoms and the likelihood of new or worsening impairment in myocardial perfusion with mental stress.[13,16,32] Our results are in line with the latter group showing independent

Table 4. Association Between Mental Stress–Induced Myocardial Ischemia (Outcome Variable) and Individual Psychological Scales

	Presence of mental stress–induced ischemia	Severity of ischemia (summed difference score)
Psychological scale	OR (95% CI)*	B (95% CI)†
Beck Depression Inventory II	1.11 (1.01 to 1.35), *P*=0.01‡	0.14 (0.02 to 0.31), *P*=0.01‡
PTSD Symptom Checklist	1.08 (0.88 to 1.43), *P*=0.13	0.12 (0.02 to 0.28), *P*=0.02‡
Cohen Perceived Stress Scale	1.07 (0.89 to 1.32), *P*=0.11	0.16 (–0.03 to 0.40), *P*=0.14
State anxiety	1.10 (1.01 to 1.22), *P*=0.02‡	0.20 (0.02 to 0.41), *P*=0.02‡
State anger	1.01 (0.82 to 1.18), *P*=0.21	0.08 (–0.19 to 0.31), *P*=0.24

Model adjusted for demographic factors (age, sex, and race), clinical risk factors (ever smoking, body mass index, history of hypertension, history of diabetes, history of dyslipidemia, history of heart failure, and history of revascularization), and medication use (β-blockers, statins, angiotensin-converting enzyme inhibitors, and aspirin).

OR indicates odds ratio.

*Odds ratio calculated for every SD higher psychological scale score.

†B represents estimated point increase in perfusion defect score (summed difference score) during mental stress for every SD higher psychological distress score.

‡Significant at *P*<0.05.

associations between depressive symptoms and presence of mental stress–induced myocardial ischemia. In addition to small sample sizes, a reason for these discrepancies may be variations in research protocols where ischemia was measured with different modalities, with only few studies using myocardial perfusion imaging. In our study, we used [^{99m}Tc] sestamibi SPECT myocardial perfusion imaging, which is a customary method for the detection of ischemia in contemporary clinical care.

In our study, baseline inflammation measured by IL-6 partially explained the relationship between psychological distress and mental stress–induced ischemia. Previous studies have shown that both acute and chronic psychological stressors increase inflammatory markers in both populations with and without CAD.[18] Our group has also shown previously that a decrease in coronary microvascular function is accompanied by a systemic inflammatory response, independent of CAD risk factors.[19] These findings collectively indicate that inflammation plays a role in the connection between psychological distress and mental stress–induced ischemia. Future studies are needed to clarify whether inflammatory responses to repetitive or prolonged stress exposure result in chronic low-grade inflammation and whether both these processes are indeed excessive in patients with CAD compared with controls without CAD.

Table 5. Association of the Composite Score of Psychosocial Distress With Presence of Conventional Stress–Induced Myocardial Ischemia and Severity of Conventional Stress–Induced Myocardial Ischemia (Summed Difference Score)

	OR (95% CI)		
Presence of conventional stress–induced ischemia	**Tertile 1 (Low psychological distress)**	**Tertile 2 (Moderate psychological distress)**	**Tertile 3 (Severe psychological distress)**
Unadjusted	Ref	1.12 (0.79 to 1.58) *P*=0.34	0.95 (0.67 to 1.36) *P*=0.31
Adjusted for demographic factors†	Ref	1.14 (0.80 to 1.61) *P*=0.44	1.01 (0.70 to 1.46) *P*=0.34
Preceding variables+clinical risk factors‡ and medications§	Ref	1.08 (0.77 to 1.58) *P*=0.46	1.01 (0.69 to 1.47) *P*=0.39
	B (95% CI)*		
Severity of conventional stress–induced ischemia (summed difference score)	**Tertile 1 (Low psychological distress)**	**Tertile 2 (Moderate psychological distress)**	**Tertile 3 (Severe psychological distress)**
Unadjusted	Ref	0.15 (–0.37 to 0.68) *P*=0.41	0.09 (–0.44 to 0.63) *P*=0.51
Adjusted for demographic factors†	Ref	0.11 (–0.40 to 0.64) *P*=0.49	0.11 (–0.42 to 0.64) *P*=0.61
Preceding variables+clinical risk factors‡ and medications§	Ref	0.10 (–0.42 to 0.62) *P*=0.51	0.05 (–0.49 to 0.59) *P*=0.58

Odds ratio calculated for every SD higher psychological scale score. Significance for all is *P*<0.05.

OR indicates odds ratio.

*B represents estimated point increase in perfusion defect score (summed difference score) during conventional stress for every SD higher psychological distress score.

†Age, sex, and race (Black vs non-Black participants).

‡Ever smoking, body mass index, history of hypertension, history of diabetes, history of dyslipidemia, history of heart failure, history of revascularization, and summed rest score.

§β-blockers, statins, angiotensin-converting enzyme inhibitors, and aspirin.

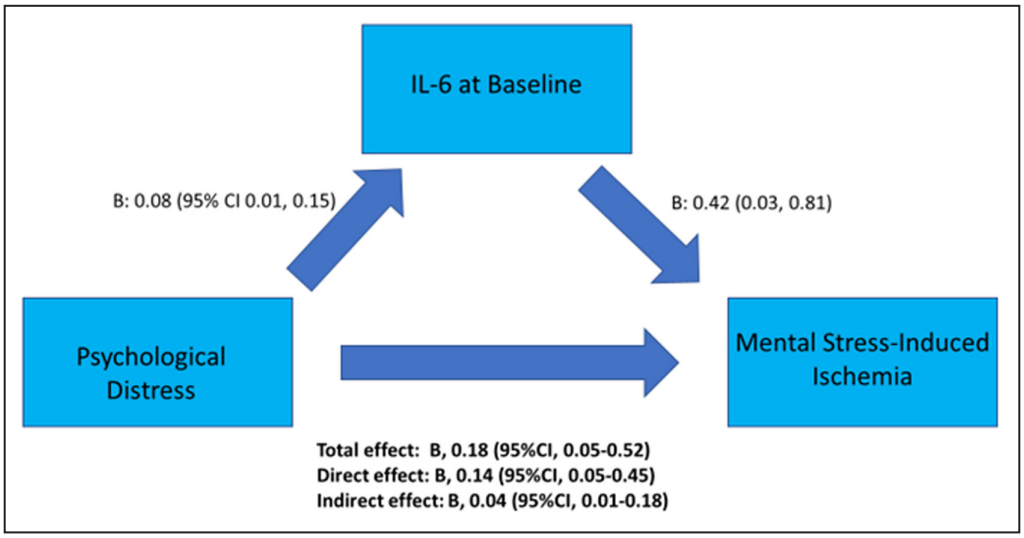

Figure 2. Mediation analysis for IL-6 levels as mediator of the relationship between composite distress score and mental stress–induced myocardial ischemia in patients with myocardial infarction.

Total effect: effect of psychological distress on mental stress–induced ischemia; Direct effect: effect of psychological distress on mental stress–induced ischemia after controlling for IL-6 levels. Indirect effect: effect of psychological distress on mental stress–induced ischemia through the IL-6 pathway, corresponding to the total effect minus the direct effect. The model included age, sex, and race (Black vs non-Black participants), ever smoking, body mass index, history of hypertension, history of diabetes, history of dyslipidemia, history of heart failure, history of revascularization, and current use of medications (β-blockers, statins, angiotensin-converting enzyme inhibitors, and aspirin) as potential confounders. IL-6 indicates interleukin-6.

The only previous study that used a composite distress score to examine the association between psychological factors and mental stress–induced ischemia in the population with CAD used data from MIPS only.[17] This study reported no significant association between a higher level of psychosocial distress and ischemia with mental stress.[17] In the current study, we included the MIPS2 sample of patients with a previous MI, which had a similar protocol, yielding a larger and more diverse sample of patients with CAD and allowing us to conduct subgroup analyses. Our findings show that the association between higher levels of psychological stress and mental stress–induced ischemia is significant only among those with a prior history of MI.

Our findings that a higher burden of chronic psychological distress was associated not only with the presence of mental stress–induced ischemia but also with the severity of perfusion defects during mental stress add validity to our findings and support the notion that psychological factors play an important role in the pathogenesis of mental stress–induced ischemia in this patient population. These findings suggest that individuals who have experienced a previous MI may be more vulnerable to the impacts of psychological distress compared with other subsets of people with CAD.

In our study, a higher burden of psychological distress was associated only with mental stress–induced myocardial ischemia and not with ischemia induced by a conventional (exercise or pharmacological) stress test. These findings underline the notion that mental stress– and conventional stress–induced ischemia are distinct phenomena with different pathophysiological substrates. Mental stress–induced ischemia develops at a lower hemodynamic workload than exercise-induced ischemia and is less strongly related to severity of coronary atherosclerosis than exercise or pharmacological stress–induced ischemia.[5,10] Also, the systemic vascular resistance falls in response to exercise,[8] whereas it rises with mental stress, due to peripheral vasoconstriction, which could ultimately contribute to mental stress–induced ischemia by increasing systemic vascular resistance.[4] Furthermore, inflammation, which tends to be elevated in the setting of higher chronic psychological burden,[33] is also increased with acute mental stress,[34] although its relationship with mental stress–induced ischemia has not been established.[34]

The clinical implications of our findings are significant as they suggest that regular assessments of a patient's psychological status using a composite distress score could be valuable in clinical practice and especially for people with a history of MI. For patients who exhibit high levels of distress, treatment modalities aimed at alleviating psychological distress, including

traditional medical therapies and holistic approaches such as meditation or relaxation techniques, are reasonable approaches, although their value in decreasing susceptibility to mental stress–induced ischemia needs further evaluation.[35]

Our study is strengthened by examining a well-characterized population of individuals with CAD, with data on psychosocial exposures across multiple domains and with high representation of women and Black patients. Other strengths of our study include the use of a standardized mental stress protocol and myocardial perfusion imaging with concomitant conventional stress testing, which enabled direct comparisons between these 2 approaches. This study also has a number of limitations. First, psychological distress measurement scales were self-reported and retrospective; therefore, whether this chronic distress measure is related to stress or mental health disturbances in everyday life needs further evaluation using objective and prospective approaches. Second, our study was conducted at a single institution, which may limit generalizability to other populations or clinical settings. On the other hand, our ability to recruit a diverse population reflective of the metro Atlanta area is an advantage of our investigation. Our study also lacks the prospective testing of the composite psychological distress score in a separate cohort of individuals with CAD. Finally, the psychological assessments employed in the present study assessed the recent burden of distress. Future longitudinal studies are needed to investigate the chronic nature of psychological stressors over time and whether chronicity of stress influences the severity of mental stress–induced ischemia.

CONCLUSIONS

Among individuals with CAD, and especially those with a history of MI, a higher level of psychosocial distress was associated with a higher propensity of developing mental stress–induced myocardial ischemia. These findings suggest an important mechanism through which chronic stress may affect subsequent risk in patients with CAD. They also provide new evidence for the potential value of assessing psychological status using a composite distress score. Future studies are needed to identify underlying mechanisms and to explore whether treatment modalities targeted to ameliorate psychological distress could in fact modulate the susceptibility of individuals to mental stress–induced ischemia and ultimately improve cardiovascular outcomes.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Supplemental Material

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