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Depressive Symptoms are Associated with Mental Stress-Induced Myocardial Ischemia after Acute Myocardial Infarction

By

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Degree to be awarded: MSPH

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By

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Bachelor of Medicine
Shanghai Jiao Tong University
2012

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An abstract of
A thesis submitted to the Faculty of the
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Abstract

Depressive Symptoms are Associated with Mental Stress-Induced Myocardial Ischemia after Acute Myocardial Infarction

By Jingkai Wei

Objectives. Depression is an adverse prognostic factor after an acute myocardial infarction (MI), and an increased propensity toward emotionally-driven myocardial ischemia may play a role. We aimed to examine the association between depressive symptoms and mental stress-induced myocardial ischemia in young survivors of an MI.
Methods. We studied 98 patients (49 women and 49 men) age 38-60 years who were hospitalized for acute MI in the previous 6 months. Patients underwent myocardial perfusion imaging at rest, after mental stress (speech task), and after exercise or pharmacological stress. A summed difference score (SDS), obtained through observer-independent software, was used to quantify myocardial ischemia under both stress conditions. The Beck Depression Inventory-II (BDI-II) was used to measure depressive symptoms, which were analyzed as overall score, and as separate somatic and cognitive depressive symptom scores.
Results. There was a significant positive association between depressive symptoms and SDS with mental stress, denoting more ischemia. After adjustment for demographic and lifestyle factors, disease severity and medications, each incremental depressive symptom was associated with 0.14 points higher SDS. When somatic and cognitive depressive symptoms were examined separately, both somatic [β=0.17, 95% CI: (0.04, 0.30), p=0.01] and cognitive symptoms [β=0.31, 95% CI: (0.07, 0.56), p=0.01] were significantly associated with mental stress-induced ischemia. Depressive symptoms were not associated with ischemia induced by exercise or pharmacological stress.
Conclusion. Among young post-MI patients, higher levels of both cognitive and somatic depressive symptoms are associated with a higher propensity to develop myocardial ischemia with mental stress, but not with exercise/pharmacological stress.

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Table of Contents

Chapter I: Background

Depression has become one of the most serious health problems at the global level. Previous literature has predicted that in 2020, major depression will be one of the top health burdens worldwide (1). Depression is found to be positively associated with myocardial infarction (MI). In the United States, about 20% of post-MI patients suffer from depression, and more than 1 million people were affected (2).

In recent studies, depression has been recognized as an important risk factor for cardiac events among post-MI patients. A meta-analysis by Meijer et al. included 29 prospective studies of the prognostic association of depression with mortality and cardiovascular events among post-MI patients (3). The study pooled 6,367 post-MI patients from 16 cohorts. The results indicate that post-MI depression is significantly associated with all-cause mortality (OR=2.38, 95% CI: 1.76-3.22), cardiac mortality (OR=2.59, 95% CI: 1.77-3.77) and new cardiovascular events (OR=1.95, 95% CI: 1.33-2.85). An individual patient data meta-analysis by the same authors included 16 studies and 10,175 post-MI patients (4). The result indicates that there is significant adjusted prognostic association of depression following myocardial infarction with all-cause mortality (HR=1.32, 95% CI: 1.26-1.38) and cardiovascular events (HR=1.19, 95% CI: 1.14-1.24).

Furthermore, studies have also indicated that specific depressive symptom dimensions carry different risks with respect to cardiovascular prognosis. Specifically, somatic symptoms of depression, such as sleep, appetite disturbance and fatigue, have been reported in several studies as being more predictive of cardiac events in patients

with coronary artery disease (CAD) than cognitive symptoms, such as feelings of sadness, pessimism, and failure (5, 6).

The exact mechanism of the association between depression and subsequent adverse cardiac events has not been known yet. Various possible theories have been put forward. Carney et al. reported that autonomic nervous system (ANS) dysfunction, including elevated heart rate, low heart rate variability, exaggerated heart rate responses to physical stressors, high variability in ventricular repolarization and low baroreceptor sensitivity are more common in patients with depression and are associated with increased risks of mortality and cardiac morbidity in patients with coronary heart disease (7). Steptoe et al. found that inflammation during acute coronary syndrome (ACS) contributes to later depression, and high level of inflammation is associated with ACS (8). Duivis et al. suggested that adverse health related behaviors associated with depressive symptoms may be implicated (9). However, the above hypotheses are still debatable.

Recently, studies have suggested that post-MI patients with depression are more likely to develop myocardial ischemia under mental stress, which therefore may be a potential mechanism for the association between depression and subsequent adverse cardiac events (10). Mental stress-induced myocardial ischemia is prevalent among patients with coronary artery disease, and is positively associated with subsequent cardiac events and death (11-16). Jiang et al. investigated 126 documented CAD patients with exercise-induced myocardial ischemia, and induced myocardial ischemia through mental stress in laboratory setting (11). The participants were followed up for up to 5 years. The result indicates that baseline mental stress-induced ischemia was associated with

significantly higher rates of subsequent cardiac events (OR=2.8, 95% CI: 1.0-7.7, $p<0.05$). Jain et al. studied 30 patients with stable angina pectoris, and 15 of the patients received mental arithmetic to induce mental stress-induced myocardial ischemia (14). All the patients were followed for 2 years for adverse cardiac events. Nine of 15 patients (60%) with mental stress-induced left ventricular (LV) dysfunction, and only 3 of 15 (20%) without mental stress-induced LV dysfunction developed cardiac events ($p = 0.025$). Babyak et al. examined 138 patients with stable CAD who underwent mental stress testing and were followed for a median of 5.9 years to assess the occurrence of the combined end point of myocardial infarction or all-cause mortality (15). The results indicate that 11 patients (42%) among the 26 exhibiting myocardial ischemia during mental stress experienced subsequent cardiac events, compared with 21 (19%) of the patients without mental stress-induced ischemia. Sheps et al. evaluated 196 patients with documented CAD and exercise-induced ischemia (13). The participants underwent bicycle exercise and psychological stress testing, and were followed-up for 3.5 to 5.2 years. The result showed that mental stress-induced ischemia predicted all-cause mortality (RR=3.0, 95% CI: 1.04-8.36). Krantz et al. studied 79 patients with stable CAD, who were exposed to mental arithmetic and public speech to induce myocardial ischemia (12). Patients were observed after a median follow-up duration of 3.5 years (range 2.7 to 7.3 years). The results indicate that there was a significantly higher relative risk of subsequent cardiac events for patients with high versus low peak stress-induced diastolic blood pressure responses (RR = 2.4, 95% CI: 1.1 to 5.2). All these studies have shown consistency in the positive association between mental stress-induced ischemia and subsequent cardiac events.

To substantiate that mental stress-induced ischemia could be a mediator in the association between depression and CAD, it is necessary to investigate the association between depression and mental stress-induced ischemia. Only a small number of studies have examined the association between depressive symptoms and mental stress-induced myocardial ischemia, yielding inconsistent results. Jiang et al. found a significant association between depressive symptoms measured by the Center for Epidemiological Studies-Depression scale score and the probability of mental stress-induced ischemia in stable CAD patients (17). Similarly, Boyle et al. found a significant association between BDI-II score and the probability of mental stress-induced ischemia (18). On the other hand, Ketterer et al. and Burg et al. did not detect a significant association between depression and mental stress-induced myocardial ischemia in patients with CAD (10, 19). These discrepancies may be due to differences in study populations and differences in research protocols. No previous studies have used myocardial perfusion imaging, the current gold-standard for ischemia assessment. Furthermore, previous studies included selected patient populations of mainly older, predominantly male and Caucasian patients, while depression is more common among women and younger patients (20).

Chapter II: Manuscript

INTRODUCTION

Depression is a prevalent, debilitating, and underdiagnosed condition that affects over 20% of patients with recent myocardial infarction (MI), and is associated with increased risk of recurrent cardiac events (3, 21). Recent literature suggests that specific depressive symptom dimensions carry different risks with respect to cardiovascular prognosis. Specifically, somatic symptoms of depression, such as sleep, appetite disturbance and fatigue, have been reported in several studies as being more predictive of cardiac events in patients with coronary artery disease (CAD) than cognitive symptoms, such as feelings of sadness, pessimism, and failure (5, 6).

The precise mechanisms through which depression increases the risk for adverse cardiovascular outcomes after an acute MI are not known. Adverse behaviors, increased inflammation and abnormal autonomic function have been linked to both depression and recurrent CAD events, but whether these factors explain the increased risk associated with depression after MI is debatable (7-9). One rarely considered possibility is that depressed post-MI patients are more likely to develop myocardial ischemia during psychological stress, which, in turn, may increase the risk for recurrent cardiac events (22, 23). Myocardial ischemia induced by emotional stress can be studied experimentally in the laboratory by using a standardized mental stress test (10). Mental stress-induced ischemia is common in stable CAD patients, and is associated with increased risk of cardiac events and death (11-16).

We systematically tested a sample of young and middle-aged post-MI patients, a group with high burden of psychosocial distress for inducible ischemia with both mental stress and exercise/pharmacological stress using single-photon emission tomography (SPECT) (24). We addressed the hypothesis that an increased level of depressive symptoms is a risk factor for mental stress-induced ischemia, but not for exercise/pharmacological stress-induced ischemia. Furthermore, we examined whether somatic and cognitive symptoms of depression differed in their association with mental stress-induced ischemia.

METHODS

Subjects

Participants for this study were recruited from the pool of patients <60 years old admitted in the previous 6 months with a confirmed diagnosis of MI at Emory-affiliated hospitals as part of the Myocardial Infarction and Mental Stress Study (MIMS); detailed methods have been described (20). Subjects were excluded if they had unstable angina or acute MI within the past week, or they had a severe comorbid medical or psychiatric disorder that could interfere with study results, such as cancer, renal failure, current alcohol or substance abuse or schizophrenia; if they weighed over 400 pounds, if they were pregnant or breastfeeding, or if they were currently using postmenopausal hormone therapy or psychotropic medications other than antidepressants. Patients were also excluded if they were unable to exercise on a treadmill, based on a score <5 metabolic equivalents (METs) on the Duke Activity Status Index (DASI), which identifies patients who cannot exercise to heart rate targets (25).

Study Design

Study subjects underwent three SPECT imaging scans, one with rest, one with mental stress and one with physical stress. The latter included predominantly exercise stress. However, 16 patients were unable to reach their target heart rate despite scoring ≥ 5 METs on the DASI and therefore underwent a pharmacological stress test. The two stress scans were performed on separate days, within one week of each other, and the rest scan was performed on the first visit. All testing was done after an overnight fast, and anti-ischemic medications were held for 24 hours prior to testing. Sociodemographic and psychosocial data were collected at the first visit prior to cardiac testing. At the end of the study protocol, medical records were abstracted for clinical information, including catheterization data. The study protocol was approved by the Emory University Institutional Review Board, and informed consent was obtained from all participants.

Mental Stress Procedure

Initially, patients rested for 30 minutes in a quiet, dimly lit, temperature-controlled room. At the end of the resting period, mental stress was induced by a standardized public speaking task as previously described (26). Patients were asked to imagine a real-life stressful situation, such as a close relative been mistreated in a nursing home, and asked to make up a realistic story around this scenario. They were given two minutes to prepare a statement and then three minutes to present it in front of a video camera and an audience wearing white coats. Subjects were told that their speech would be evaluated by the laboratory staff for content, quality and duration.

Myocardial Perfusion Imaging

Subjects underwent three SPECT myocardial perfusion imaging scans following injection of sestamibi radiolabelled with Technetium-99m (99mTc sestamibi), at rest, and after mental stress, and “physical stress” (exercise or pharmacological stress). Testing was done on a dedicated ultra-fast solid-state camera (Discovery NM 530c, General Electric, Milwaukee, WI) without attenuation correction (27). Only one resting scan was performed with myocardial perfusion images acquired after the injection of 8-15 mCi of [99mTc] sestamibi according to body weight. The stress scan (either mental or physical) followed at least 2 hours later and 20-30 mCi of [99mTc] sestamibi were used for this phase.

On the mental stress day, [99mTc]sestamibi was injected one minute after the onset of the public speech. On the exercise stress day, subjects were submitted to a standard Bruce protocol with exercise target set at 85% of maximum predicted heart rate based on the patient’s sex and age. [99mTc]sestamibi was injected at peak exertion. Stress images were acquired 45-60 minutes later using previously described methodology (28). The ECG, blood pressure and heart rate were continuously monitored during the procedure. For patients undergoing a pharmacological stress test, 0.4 mg of regadenoson (Abbott, Chicago, IL), an adenosine receptor agonist, were administered intravenously in approximately 10 seconds, and [99mTc] sestamibi was injected right after regadenoson. SPECT images were then obtained as described above.

Myocardial perfusion abnormalities were quantified by means of the Emory Cardiac Toolbox software, which provides objective quantitative assessment of perfusion with established validity and reproducibility (29, 30). Briefly, the three-dimensional tracer uptake distribution in the left ventricle was oriented along the short axis and

sampled onto a two-dimensional polar map. An operator-independent summed score, quantifying the extent and severity of perfusion defects across 17 segments of the myocardium at rest and during stress, was computed by the software according to published methodology (29). The regional severity scoring was then summed up across the 17 myocardial segments yielding a total score. Separate scores were obtained for the rest images (summed rest score, SRS) and the stress images (summed stress score, SSS). A summed difference score (SDS), or ischemia score, was obtained by subtracting the rest score from the stress score; in the presence of a reversible defect (or ischemia), the score is positive. For simplicity, we will refer to ischemia secondary to exercise/pharmacological stress as “physical stress-induced ischemia.”

Measurements of Depressive Symptoms

Depressive symptoms were assessed with the Beck Depression Inventory-II (BDI-II), a reliable and valid self-administered questionnaire which has been widely used in cardiac populations (31). The BDI-II includes 21 items, each containing 4 statements, scoring 0 to 3, with higher scores indicating higher severity of depression. All the depressive symptoms were categorized into somatic symptoms (for example, items on sleep, fatigability, appetite), and cognitive depressive symptoms (for example, items on sadness, guilty feelings, pessimism, sense of failure) according to established criteria (31).

Other Measurements

Information on sociodemographic factors was collected using standard questionnaires from population studies. A detailed medical history including medication

use was obtained by a research nurse. Weight and height were used to calculate body mass index. Venous blood samples were drawn for the measurements of glucose and lipid profile after an overnight fast.

Angiographic data were obtained from the coronary angiogram performed in conjunction with the index MI. CAD severity was quantified using the Gensini semi-quantitative angiographic scoring system, which takes into account degree of luminal narrowing along with a multiplier for specific coronary tree locations (32). From coronary angiograms or echocardiography reports, we also abstracted the left ventricular ejection fraction.

Statistical Analysis

Descriptive statistics were computed by comparing mean BDI-II scores according to levels of other study variables. Next, multivariate linear regression models were used to examine the association between depressive symptoms and stress perfusion scores adjusting for possible confounding factors. The SDS, which quantifies ischemia, was our main outcome of interest. Since the SDS for both mental and physical stress was highly skewed, while the SSS was approximately normally distributed, we used the SSS scores as dependent variables while adjusting for the rest score (SRS), yielding coefficients identical to those from a model where the dependent variable is the difference score (SDS), adjusted for the SRS. In a series of cumulative hierarchical models, we adjusted for a set of factors that were considered a-priori as either possible confounding factors or mediators of the relationships under study. Adjustment factors included sociodemographic and lifestyle characteristics (sex, employment, race, marital status and

cigarette smoking), medications (use of statins, beta-blockers and anti-depressants), CAD severity (Gensini score, left ventricular ejection fraction), traditional CAD risk factors (history of diabetes and hypertension, and BMI), and previous revascularization procedures (coronary artery bypass grafting and percutaneous coronary intervention).

RESULTS

Study Sample

Between 2009 and 2012, 49 male and 49 female MI patients younger than 60 years were included in the study. The mean and median age was 50 years. Overall, 55% of the participants were African-American; 57% had at least high school education and 66% had an income below the poverty level (Table 1).

BDI-II Scores

The BDI-II total scores were approximately normally distributed, with a mean of 11.2 (SD: 8.6, range: 0-37). The mean somatic symptom score was 2.8 (SD: 3.3, range: 0, 13), and the mean cognitive symptom score was 8.4 (SD: 6.1, range: 0-24). BDI-II total scores were higher among women, among patients with income below poverty and among current smokers (Table 1).

Myocardial Perfusion

Three patients, 1 woman and 2 men, had missing myocardial perfusion data for both mental stress and exercise or pharmacological stress, and were excluded from the perfusion imaging analyses. The median SDS with mental stress was 2.0 [interquartile

range (IQR): 0, 3], and the median SDS with physical stress was also 2.0 (IQR: 0, 5). The SDS with mental stress and physical stress were not correlated (Spearman r=0.11, p=0.31).

Association of Depressive Symptoms with SDS (Ischemia Score)

The BDI-II total score was associated with increased propensity for ischemia with mental stress in a graded fashion (Figure 1). After adjustment for demographic and lifestyle factors, CAD severity and medications, each 1-point increase in BDI-II total score was associated with 0.14 points increase in SDS with mental stress (95% CI: 0.03 to 0.24, p=0.01). In contrast, the BDI-II total score was not associated with the SDS with physical stress (Figure 2 and Table 2).

Next, depressive symptoms were analyzed as separate somatic and cognitive components (Table 3). Somatic depressive symptoms were associated with ischemia perfusion defects with mental stress in both unadjusted and adjusted analysis. In the final model there was a 0.17-point increase in SDS for each increment in somatic symptoms (β=0.17, 95% CI, 0.04 to 0.30, p=0.01). For cognitive depressive symptoms, the unadjusted association was marginally significant, but it strengthened in the final adjusted model (β=0.31, 95% CI, 0.07 to 0.56, p=0.01). Neither symptom dimension was associated with physical stress ischemia.

DISCUSSION

In an experimental study of young and middle-aged post-MI patients, we showed a robust association between baseline depressive symptoms and inducible myocardial

ischemia with mental stress, but not with exercise/pharmacological stress. We also show that the association exists for both somatic and cognitive depressive symptoms. Given that mental stress-induced ischemia is a prognostic indicator in CAD patients (11-15), these findings provide a possible explanation for the increased risk for adverse events associated with depression in post-MI patients (3, 33).

Only a small number of studies have examined the association between depressive symptoms and mental stress-induced myocardial ischemia, yielding inconsistent results. Jiang et al. found a significant association between depressive symptoms measured by the Center for Epidemiological Studies-Depression scale score and the probability of mental stress-induced ischemia in stable CAD patients (17). Similarly, Boyle et al. found a significant association between BDI-II score and the probability of mental stress-induced ischemia (18). On the other hand, Ketterer et al. and Burg et al. did not detect a significant association between depression and mental stress-induced myocardial ischemia in patients with CAD (10, 19). Finally, in the study by Boyle et al, somatic depressive symptoms were better predictors of mental stress-induced ischemia than cognitive symptoms, which differs from our study (18). These discrepancies may be due to differences in study populations, as the above investigations included older, predominantly male and Caucasian patients while we examined young and middle-age patients with a large proportion of minority participants and an equal representation of men and women. Additionally, we focused on a well-characterized post-MI population within 6 months of their index MI, while all previous investigators examined patients with different medical histories and disease stages.

Potential mechanisms that might be invoked to explain the association between depressive symptoms and mental stress-induced myocardial ischemia are the downstream physiologic effects of stress-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis, which is dysregulated in depression (34). Furthermore, inflammation, which is enhanced in depression, may be implicated. Patients with CAD display increased inflammatory responses to mental stress, and inflammation is associated with decreased coronary microvascular function, which, in turn, could be a mechanism of mental stress-induced ischemia (35-37). Autonomic nervous system dysfunction is also a common factor in both depression and CAD (7). Previous studies have shown that the autonomic nervous system, especially parasympathetic withdrawal, plays a significant role in the pathophysiology of ambulatory ischemic episodes and may be responsible for triggering ischemia (38).

In our study, depressive symptoms were associated only with mental stress-induced myocardial ischemia and not with physical stress-induced ischemia. This result differs from the study by Boyle et al, where depressive symptoms were associated with both mental stress and exercise-induced myocardial ischemia (18). Again, differences in results may be due to differences in study populations. Our findings imply that, among young post-MI patients, mental stress and physical stress-induced ischemia have different effects on the myocardium. Our results are corroborated by emerging evidence that mental stress- and physical stress-induced ischemia have different pathophysiological substrates. Mental stress-induced ischemia likely involves microvascular dysfunction, resulting in abnormal coronary or peripheral vasomotion due to enhanced vasoconstrictive responses to mental stress. Physical stress-induced ischemia, on the

other hand, is induced primarily by coronary steal, where restricted vasodilation in diseased epicardial vessels causes selective hypoperfusion (35, 39).

Our findings have significant relevance for public health and clinical medicine. Depression affects approximately 20% of post-MI men and 40% of post-MI women below the age of 60, many of whom may experience ischemia due to psychological stress in everyday life (40). Unlike physical stress-induced ischemia, ischemia triggered by mental stress is mostly silent and not associated with electrocardiographic changes, thus it may go unrecognized (39). Recently, the REMIT trial found that a 6-week regimen with escitalopram resulted in a lower rate of mental stress-induced ischemia in stable CAD patients compared with the placebo group. Thus, pharmacological treatment of depression may be promising to reduce mental stress-induced ischemia (41). It is not yet known, however, whether reducing the frequency of mental stress ischemia through pharmacological intervention or other methods translates into better clinical outcomes. It is also unknown if such interventions are equally useful in young post-MI patients who suffer from disproportionately high rates of depression.

The main limitation of our study is its small sample size, which may decrease statistical power. In addition, the study was restricted to young post-MI patients, so our results may not be generalizable to other stable CAD patient populations or older age groups. Finally, we did not have data linking mental stress ischemia to clinical outcomes. Nonetheless, the accuracy of our data is ensured by a standardized mental stress protocol and a well-defined patient population which is known to have a substantial prevalence of depression.

In conclusion, depressive symptoms are associated with mental stress-induced ischemia in young post MI patients. This association is robust even after multivariate adjustments and applies to both somatic and cognitive depressive symptoms. Since patients who experience ischemia with mental stress are at elevated risk for adverse outcomes, mental stress ischemia could explain, in part, the increased CAD risk associated with depression (11-15). Additional studies should be conducted to explore possible treatments for mental stress-induced ischemia and depression, as well as their effects on outcomes, in young post-MI patients.

Chapter III: Summary, Public Health Implications, Possible Future Directions

The finding that depressive symptoms are associated with mental stress-induced ischemia has significant relevance for public health and clinical medicine. Depression affects approximately 20% of post-MI men and 40% of post-MI women below the age of 60, many of whom may experience ischemia due to psychological stress in everyday life (40). Unlike physical stress-induced ischemia, ischemia triggered by mental stress is mostly silent and not associated with electrocardiographic changes, thus it may go unrecognized (39). Our results suggest that, if mental stress-induced ischemia truly mediates adverse cardiovascular risks associated with depression in post-MI patients, treatments should be evaluated that may reduce mental stress-induced ischemia in depressed patients.

Both selective serotonin reuptake inhibitors (SSRIs) and nontricyclic antidepressant have been evaluated for the treatment of depression in clinical trials of CAD patients. The Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) studied 369 patients with major depression after recent MI or unstable angina (42). Patients taking Sertraline had fewer adverse cardiac events, including death, MI, congestive heart failure, stroke, angina [OR=0.77, 95% CI: 0.51-1.16], although it was not statistically significant. The Myocardial INfarction and Depression-Intervention Trial (MIND-IT) evaluated post-MI patients with depression. Two hundred and twenty-nine patients (intervention group) received mirtazapine for treatment, while 122 patients (control group) received usual care (43). The results showed no difference between the two groups of patients in adverse cardiac events (OR=1.07, 95% CI: 0.57-2.00).

Psychotherapeutic interventions have also been conducted to evaluate the prognosis of CAD patients with depression. The Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) randomized trial, which studied 2481 post-MI patients with depression was conducted (44). Participants were randomly assigned to a group of cognitive behavior therapy or a group of usual care. The results showed no significant difference in event-free survival between the two groups (75.9% vs. 75.8%). The Montreal Heart Attack Readjustment Trial (M-HART) in earlier time studied the effect of a home-based psychosocial nursing intervention in post-MI patients (45). The results showed that women in the intervention group have higher cardiac mortality (9.4 vs 5.0%, $p = 0.064$) and all-cause mortality (10.3 vs 5.4%, $p = 0.051$). For men, there were no significant differences between the two groups (cardiac mortality: 2.4 vs 2.5%, $p = 0.94$; all-cause mortality: 3.1 vs 3.1%, $p = 0.93$). Therefore, there is no strong evidence indicating that psychotherapeutic interventions are effective in reducing adverse cardiac events among CAD patients.

Recently, the Responses of Mental Stress Induced Myocardial Ischemia to Escitalopram Treatment (REMIT) trial found that a 6-week regimen with escitalopram resulted in a lower rate of mental stress-induced ischemia in stable CAD patients compared with the placebo group (OR=2.62 for the placebo group, 95% CI: 1.06-6.44) (41). Given the association between depressive symptoms and mental stress-induced ischemia, as well as the association between mental stress-induced ischemia and adverse cardiac events, this trial provides insight for prevention of cardiac events among CAD patients with depression. It is not yet known, however, whether reducing the frequency of mental stress ischemia through pharmacological intervention or other methods translates

into better clinical outcomes. It is also unknown if such interventions are equally useful in young post-MI patients who suffer from disproportionately high rates of depression. Antidepressant treatment of mental stress-induced ischemia may be a potential direction for reducing cardiac events among CAD patients with depression. More studies of the effects of antidepressant treatment on mental stress-induced ischemia should be conducted in the future. It is expected that the phenomenon of mental stress-induced ischemia will be better characterized, and its relationship with depression confirmed in post-MI patients and possibly in other patients with CAD.

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APPENDIX

FIGURE LEDGENDS

Figure 1. Scatterplot of depressive symptoms (BDI-II total score) against myocardial perfusion ischemic defect severity [summed difference score (SDS)] with mental stress. There was a significant correlation between depressive symptoms and ischemia severity with mental stress.

Figure 2. Mean myocardial perfusion ischemic defect severity [summed difference score (SDS)] with mental stress according to five groups of progressively higher depressive symptoms using quintiles of the BDI-II total score. There was a statistically significant progressive increase in mental stress-induced myocardial ischemia with increasing depressive symptom severity.

Figure 3. Scatterplot of depressive symptoms (BDI-II total score) against myocardial perfusion ischemic defect severity [summed difference score (SDS)] with physical stress. There was no significant correlation between depressive symptoms and ischemia severity with physical stress.

Figure 4. Mean myocardial perfusion ischemic defect severity [summed difference score (SDS)] with physical stress according to five groups of progressively higher depressive symptoms using quintiles of the BDI-II total score. There was no statistical difference in physical stress-induced myocardial ischemia with increasing depressive symptom severity.

TABLES

Table 1. Mean depressive symptoms (BDI-II total score) according to patients characteristics.

	N (%)	BDI-II Total Score †	p value
Gender			
Male	49 (50%)	9.4 (6.8)	0.042
Female	49 (50%)	13.0 (9.8)	
Age			
≤50	49 (50%)	10.9 (8.6)	0.718
>50	49 (50%)	11.5 (8.7)	
Race			
Black	54 (55.1%)	10.4 (9.3)	0.285
Non-Black	44 (44.9%)	12.2 (7.7)	
Currently Married			
Yes	40 (40.8%)	10.6 (7.0)	0.551
No	58 (59.2%)	11.6 (9.6)	
Education			
≥high school	56 (57.1%)	10.1 (7.5)	0.130
<high school	42 (42.9%)	12.7 (9.8)	
Employment			
Not laid off	81 (82.7%)	13.2 (10.1)	0.298
Laid off	17 (17.3%)	10.8 (8.3)	
Income below poverty level			
Yes	65 (66.3%)	9.3 (6.9)	0.011
No	31 (31.6%)	14.5 (9.8)	
Current smoking			
Yes	28 (28.6%)	14.9 (10.2)	0.021
No	70 (71.4%)	9.7 (7.4)	
Hypertension			
Yes	67 (68.4%)	12.2 (8.6)	0.106
No	30 (30.6%)	9.2 (8.3)	
Diabetes			
Yes	20 (20.4%)	11.7 (10.9)	0.807
No	77 (78.6%)	11.2 (8.0)	

†.Values given as mean (standard deviation). BDI: Beck Depression Inventory.

Table 1 (Continued)

	N (%)	BDI-II Total Score †	p value
Obesity			
Yes	45 (45.9%)	12.0 (8.9)	0.445
No	52 (53.1%)	10.7 (8.4)	
Statins			
Yes	85 (86.7%)	13.2 (10.2)	0.610
No	12 (12.2%)	9.6 (7.6)	
Beta blockers			
Yes	85 (86.7%)	11.9 (8.7)	0.071
No	12 (12.2%)	7.1 (7.3)	
ACE-Inhibitors‡			
Yes	53 (54.1%)	12.5 (9.2)	0.129
No	44 (44.9%)	9.8 (7.7)	
Aspirin			
Yes	85 (86.7%)	11.2 (8.7)	0.705
No	12 (12.2%)	12.2 (8.0)	
Anti-depressants			
Yes	13 (13.3%)	21.4 (8.8)	<0.001
No	84 (85.7%)	9.7 (7.5)	
CABG§			
Yes	20 (20.4%)	10.1 (10.0)	0.506
No	76 (77.6%)	11.5 (8.2)	
PTCA¶			
Yes	73 (74.5%)	11.6 (8.6)	0.448
No	21 (21.4%)	10.0 (9.2)	
MI type††			
STEMI	44 (44.9%)	10.7 (8.0)	0.614
NSTEMI	54 (55.1%)	11.6 (9.1)	

†.Values given as mean (standard deviation). BDI-II: Beck Depression Inventory-II.

‡. ACE-Inhibitors: angiotensin-converting-enzyme inhibitor.

§. CABG: Coronary artery bypass grafting.

¶. PTCA: Percutaneous transluminal coronary angioplasty.

††. MI: Myocardial Infarction. STEMI: ST segment elevation myocardial infarction. NSTEMI: non-ST segment elevation myocardial infarction.

Table 2. Association between BDI-II total score and myocardial perfusion ischemia severity (SDS) with mental stress and physical stress.

	β (95% CI)†	P value
Mental Stress		
Model 1: Unadjusted	0.07 (0.01, 0.14)	0.02
Model 2: Adjusted for demographic and lifestyle factors‡	0.07 (0.01, 0.14)	0.04
Model 3: Adjusted for the above plus CAD severity, traditional risk factors and medications§	0.14 (0.05, 0.23)	0.01
Physical Stress		
Model 1: Unadjusted	-0.01 (-0.09, 0.07)	0.75
Model 2: Adjusted for demographic and lifestyle factors‡	-0.01 (-0.09, 0.08)	0.73
Model 3: Adjusted for the above plus CAD severity, traditional risk factors and medications§	0.06 (-0.05, 0.17)	0.29

BDI-II: Beck Depression Inventory-II; CAD: coronary artery disease; SDS: summed difference score.

† The β coefficient expresses the difference in SDS score points with a 1-point increase in BDI-II total score. Each model was constructed with SSS as dependent variable adjusting for the rest score (SRS). SE: standard error.

‡ Demographical and lifestyle factors: sex, employment, race, marital status and cigarette smoking.

§ Gensini angiographic CAD severity score, left ventricular ejection fraction, hypertension, diabetes, BMI, previous revascularization procedures , use of statins, beta-blockers, and anti-depressants.

Table 3. Association between BDI-II somatic and cognitive symptom scores and myocardial perfusion ischemia severity (SDS) with mental stress.

	β (95% CI)†	P value
Somatic Depressive Symptoms		
Model 1: Unadjusted	0.10 (0.01, 0.19)	0.03
Model 2: Adjusted for demographic and lifestyle factors‡	0.10 (0.0003, 0.20)	0.05
Model 3: Adjusted for the above plus CAD severity, traditional risk factors and medications§	0.17 (0.04, 0.30)	0.01
Cognitive Depressive Symptoms		
Model 1: Unadjusted	0.16 (-0.01, 0.33)	0.06
Model 2: Adjusted for demographic and lifestyle factors‡	0.16 (-0.01, 0.34)	0.15
Model 3: Adjusted for the above plus CAD severity, traditional risk factors and medications§	0.31 (0.07, 0.56)	0.01

BDI-II: Beck Depression Inventory-II; CAD: coronary artery disease; SDS: summed difference score.

† The β coefficient expresses the difference in SDS score points with a 1-point increase in BDI-II total score. Each model was constructed with SSS as dependent variable adjusting for the rest score (SRS). SE: standard error.

‡ Demographical and lifestyle factors: sex, employment, race, marital status and cigarette smoking.

§ Gensini angiographic CAD severity score, left ventricular ejection fraction, hypertension, diabetes, BMI, previous revascularization procedures, use of statins, beta-blockers, and anti-depressants.

FIGURES

Figure 1

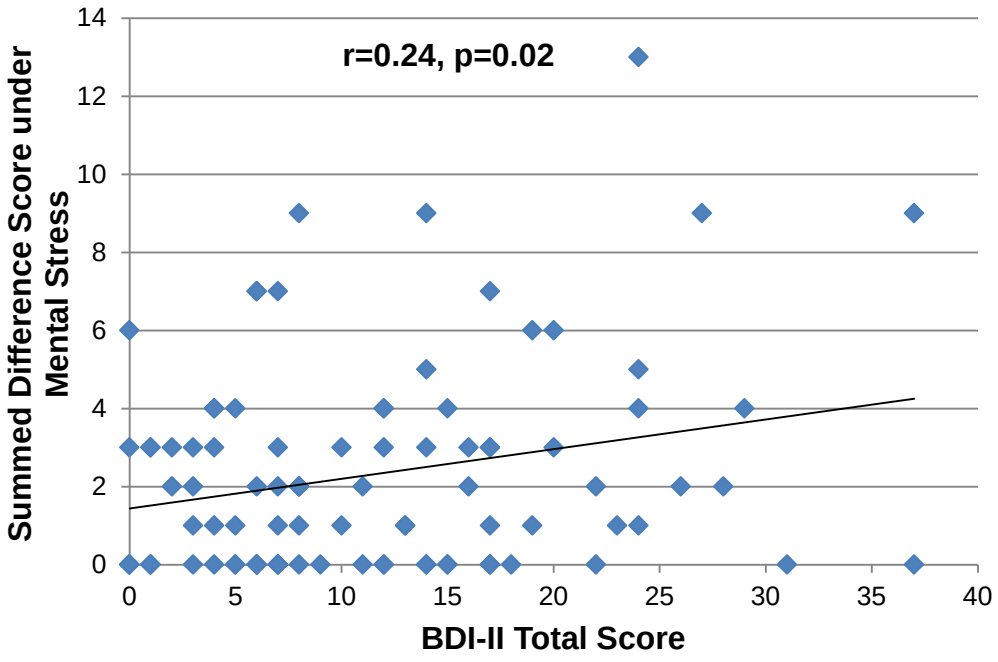


Figure 2

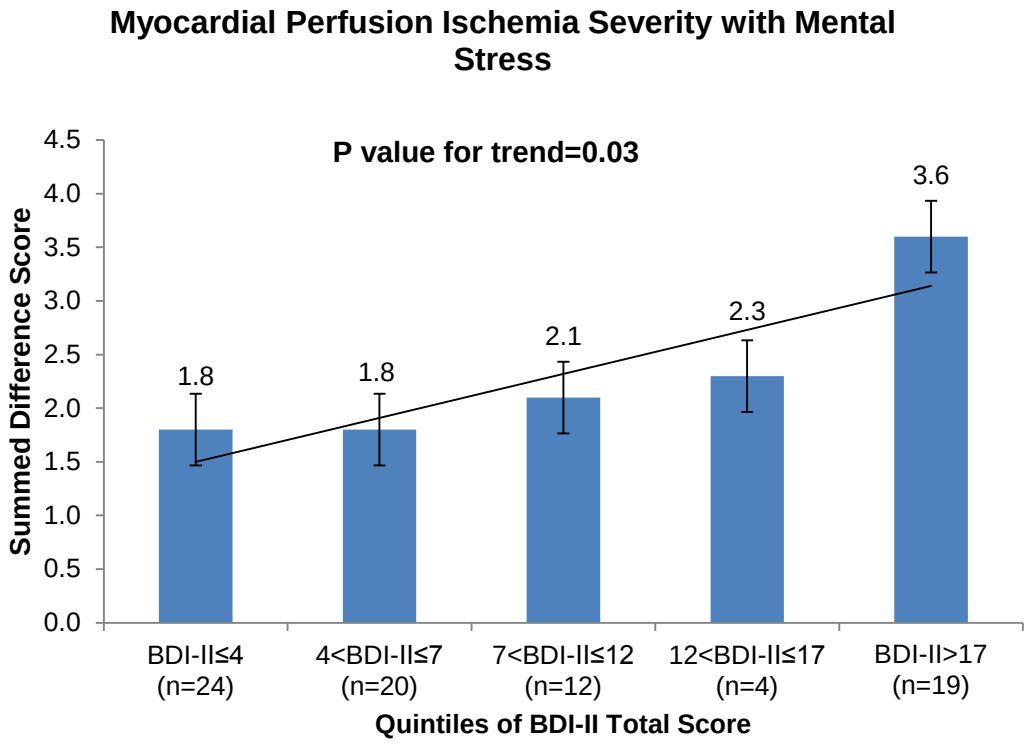

Myocardial Perfusion Ischemia Severity with Mental Stress
P value for trend=0.03
Summed Difference Score
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.8
1.8
2.1
2.3
3.6
BDI-II≤4 (n=24)
4<BDI-II≤7 (n=20)
7<BDI-II≤12 (n=12)
12<BDI-II≤17 (n=4)
BDI-II>17 (n=19)
Quintiles of BDI-II Total Score

Figure 3

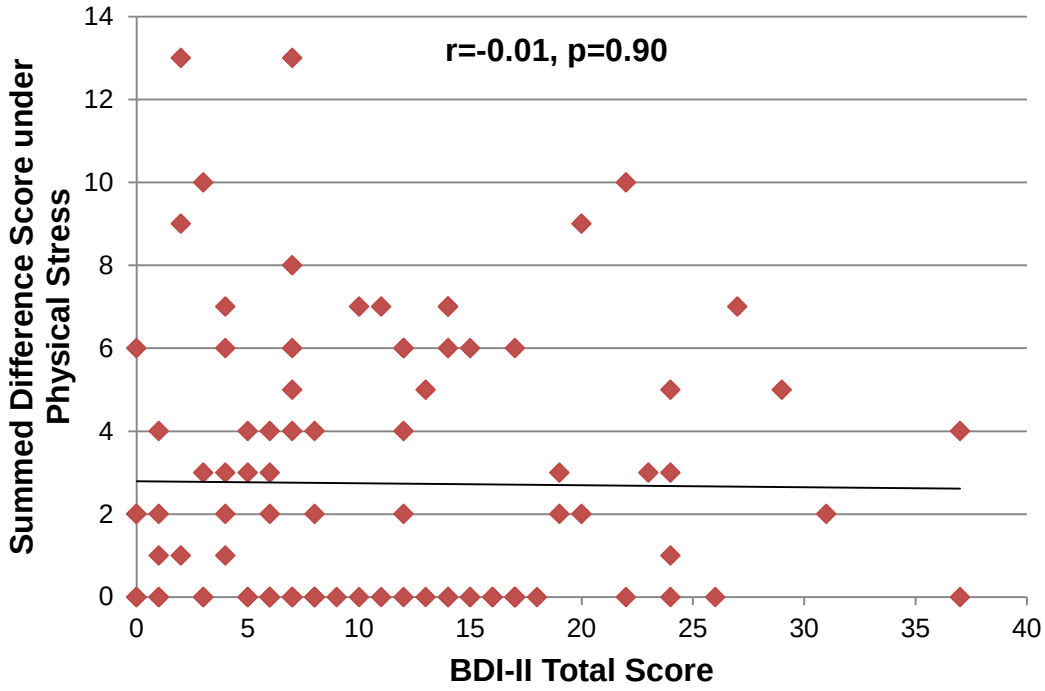
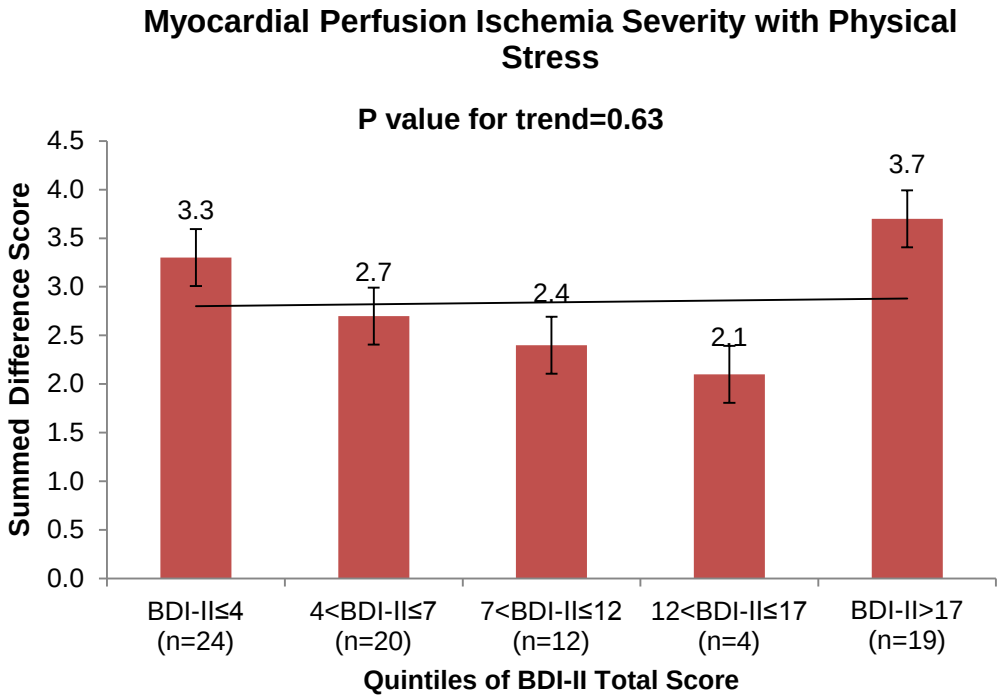

r=-0.01, p=0.90
Summed Difference Score under Physical Stress
BDI-II Total Score
0
2
4
6
8
10
12
14
0
5
10
15
20
25
30
35
40

Figure 4


Myocardial Perfusion Ischemia Severity with Physical Stress
P value for trend=0.63
Summed Difference Score
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
3.3
2.7
2.4
2.1
3.7
BDI-II≤4 (n=24)
4<BDI-II≤7 (n=20)
7<BDI-II≤12 (n=12)
12<BDI-II≤17 (n=4)
BDI-II>17 (n=19)
Quintiles of BDI-II Total Score