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Confluence of Depression and Acute Psychological Stress Among Patients With Stable Coronary Heart Disease: Effects on Myocardial Perfusion

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***Background*—**Depression is prevalent in coronary heart disease (CHD) patients and increases risk for acute coronary syndrome (ACS) recurrence and mortality despite optimal medical care. The pathways underlying this risk remain elusive. Psychological stress (PS) can provoke impairment in myocardial perfusion and trigger ACS. A confluence of acute PS with depression might reveal coronary vascular mechanisms of risk. We tested whether depression increased risk for impaired myocardial perfusion during acute PS among patients with stable CHD.

***Methods and Results*—**Patients (N=146) completed the Beck Depression Inventory-I (BDI-I), a measure of depression linked to recurrent ACS and post-ACS mortality, and underwent single-photon emission computed tomography myocardial perfusion imaging at rest and during acute PS. The likelihood of new/worsening impairment in myocardial perfusion from baseline to PS as a function of depression severity was tested. On the BDI-I, 41 patients scored in the normal range, 48 in the high normal range, and 57 in the depressed range previously linked to CHD prognosis. A BDI-I score in the depressed range was associated with a significantly greater likelihood of new/worsening impairment in myocardial perfusion from baseline to PS (odds ratio =2.89, 95% CI: 1.26 to 6.63, *P*=0.012). This remained significant in models controlling ACS recurrence/mortality risk factors and medications. There was no effect for selective serotonin reuptake inhibitor medications.

***Conclusions*—**Depressed patients with CHD are particularly susceptible to impairment in myocardial perfusion during PS. The confluence of PS with depression may contribute to a better understanding of the depression-associated risk for ACS recurrence and mortality. **(*J Am Heart Assoc*. 2014;3:e000898 doi: 10.1161/JAHA.114.000898)**

Key Words: depression • myocardial perfusion • stress

Prospective observational studies show that among patients with CHD, elevated symptoms of depression significantly increase the risk for recurrence of acute coronary syndrome (ACS) events[1] and early mortality,[2] after adjustment for CHD severity and medical comorbidities, and despite the continued improvement in cardiologic care that has marked the last 2 decades.[2–7] Furthermore, post-ACS depression clinical trials show no reduction in risk (cf. ref 8). Research on the causal pathways or mechanisms through which depression confers risk has included autonomic dysregulation, inflammation, platelet function, and behavioral mechanisms, yet the findings of this research have been equivocal and thus the key pathway or pathways remain elusive.[9,10]

In a recent review[11] the multifactorial nature of ACS was discussed, with the authors describing that ACS does not result from a single factor, but rather from a confluence of multiple factors that can give rise to coronary vascular dysfunction, atherosclerotic plaque rupture, and thrombotic cascade. Thus, investigation of only 1 variable in isolation, such as depression, can provide merely an incomplete picture that does not lead to a greater understanding of the mechanistic underpinning between that variable and poor prognosis in CHD patients. From this we proposed a model informed by the confluence of depression with acute stress as a triggering event that might better reveal key mechanisms of risk linking depression to post-ACS outcomes.[12]

Research has shown that psychological stress can trigger ACS and sudden cardiac death (cf. refs 13–16). The pathophysiology of this stress-triggered ACS has been modeled

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under controlled laboratory conditions in studies that have demonstrated coronary vascular dysfunction—impairment in myocardial perfusion—provoked by acute psychological stress (cf. refs 17–20). Of note, prior research has shown that among patients with stable coronary disease, those with elevated depression symptoms are more likely to evidence left ventricular dysfunction during psychological stress administered under controlled laboratory conditions.[21,22] The purpose of this study was to test whether depression increases the likelihood of coronary vascular dysfunction—indexed by new impairment in myocardial perfusion during acute psychological stress—among patients with stable CHD.

Methods

Subjects

Patients with chronic stable CHD (n=146), documented by history of ACS, surgical or percutaneous revascularization, and/or a myocardial perfusion defect with exercise or pharmacologic stress, were recruited from the cardiology outpatient clinics at Yale University Medical Center and VA Connecticut Healthcare System from January 2007 to December 2012. Patients with a diagnosis of ACS within 3 months of the study, surgical or percutaneous revascularization within 6 months of the study, major cardiac arrhythmia or use of a pacemaker or implantable cardioverter defibrillator, decompensated heart failure, incapacitating or life-threatening illness, major psychiatric disorder, cognitive impairment, pregnancy, and/or inability to speak or read English were excluded. The study complies with the Declaration of Helsinki, was approved by the Institutional Review Board at both hospitals, and informed consent was obtained from all patients.

Medical chart review and patient interview were used to obtain demographic information and determine cardiovascular risk profile, including history of ACS and/or revascularization. Patients with a recent history of systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or currently taking antihypertensive medication were classified as having hypertension; those with total cholesterol of >200 mg/dL, low-density lipoprotein of >130 mg/dL, or taking cholesterol-lowering medications were classified as having hypercholesterolemia. Use of β-blockers, aspirin, statins, angiotensin-converting enzyme inhibitors, calcium-channel blockers, and antidepressant medication was documented. Tobacco use was also determined. Patient characteristics are described in Table 1.

Stress Procedure

As part of a larger investigation concerning the effects of emotional stress on coronary vascular performance, patients reported to the Yale University Cardiovascular Behavioral Medicine Research Laboratory at 9 AM on the day of study. Patients were asked to eat a light breakfast and take their normal medications, and adherence to this was confirmed on their arrival. Patients completed a questionnaire battery that included the Beck Depression Inventory-I (BDI-I), a 21-item self-report questionnaire designed to assess depression symptom severity.[23] Each of the items in this questionnaire describes a symptom or characteristic of the depression constellation, and respondents indicate on a 0 to 3 scale the intensity with which they have experienced the symptom in the past 2 weeks. This questionnaire has been used in studies of patients with stable CHD and after ACS, and in particular, scores of ≥10 have been linked to increased risk for major adverse cardiac events and mortality in these populations.[24] The Cronbach's α for total BDI-I scale for the current sample was 0.92.

After completing the questionnaire, an indwelling intravenous catheter was inserted in the patient's nondominant arm. Both resting and psychological stress single-photon emission computed tomography (SPECT) myocardial perfusion imaging scans were performed on the same day. Under resting conditions, the patient received intravenous injection of 10 to 12 mCi ^{99m}Tc tetrofosmin (Myoview, GE Healthcare, Buckinghamshire, England). Resting SPECT imaging was acquired 30 to 45 minutes after injection. On completion of rest imaging, the patient was removed from the camera and escorted to the laboratory room, where the psychological stress testing was performed. A 30-minute rest period was initiated, followed by a standard psychological stress protocol (cf. refs 17, 25) that included a formal 10-minute resting baseline condition. For the baseline condition, patients were instructed to close their eyes and imagine being in a restful setting.

After completion of baseline, the 6-minute acute psychological stress condition (PS) was initiated. For this condition, mental arithmetic—serial subtraction—was used, as it is a particularly potent stress task for both male and female patients of diverse backgrounds.[17,25] Starting with a 4-digit number, patients were instructed to subtract a specified number (eg, "7") serially. Following a standard protocol, the patient was instructed to work as quickly and accurately as they could, and they were both frequently prompted to work faster, and firmly corrected when they made errors. The frequency of prompts was titrated to incur an error rate of 1 per 10 calculations, as we have described previously (cf. refs 17, 25), and this was achieved with all patients. Approximately 1 minute into the PS condition, 30 to 32 mCi ^{99m}Tc tetrofosmin was injected, with acquisition of SPECT imaging approximately 45 to 60 minutes later.

Monitoring during the laboratory protocol was identical to that done for clinical stress testing. In brief, HR, systolic/diastolic blood pressure, and 12-lead ECG were obtained at 5-minute intervals during baseline and at 1-minute intervals

Table 1. Patient Characteristics

	Total Cohort (N=146)	New/Worse Myocardial Perfusion Defect During PS		BDI Score		
		No (N=67)	Yes (N=79)	Normal Score 0 to 4 (N=41)	Hi-Normal Score 5 to 9 (N=48)	Depressed Score ≥10 (N=57)
Age (SD)	66 (9)	66 (10)	67 (9)	65 (8)	68 (10)	66 (9)
Sex (% male)	76	77	75	77	77	74
LVEF % (SD)*	56 (11)	56 (13)	55 (10)	55 (11)	56 (10)	56 (13)
Hyperlipidemia (%)	91	91	92	95	88	93
Diabetes (%)	33	30	36	24	44	30
Hypertension (%)	83	85	81	80	83	84
Tobacco use (%)	34	39	31	39	27	38
Mean BDI score (SD)	10.5 (9.2)	8.6 (7.9)	12.0 (9.9)	2.0 (1.3)	7.0 (1.4)	19.4 (8.3)
Medications						
Aspirin (%)	78	76	79	76	85	73
Statin (%)	92	91	94	88	90	98
β-Blocker (%)	81	79	83	80	83	80
Plavix (%)	21	26	17	32	21	13
Ca-channel blocker (%)	34	31	37	37	35	32
ACE inhibitor (%)	43	42	43	41	40	46
SSRI (%)	21	16	25	0	25	33
Severity of coronary disease						
MPI defect on exercise/ Pharmacologic stress (%)	54	55	54	49	54	59
Prior ACS (%)	52	48	55	50	52	53
Prior PCI (%)	51	54	48	53	46	49
Number vessels (SD)	1.60 (0.96)	1.72 (0.89)	1.50 (1.03)	1.63 (0.97)	1.65 (0.99)	1.58 (1.01)
Prior CABG (%)	44	40	47	42	44	46
Number vessels (SD)	3.17 (1.00)	3.07 (0.99)	3.26 (1.01)	3.17 (0.98)	3.17 (0.99)	3.19 (1.02)
Months since revascularization (SD)	78 (72)	74 (73)	81 (71)	78 (72)	76 (71)	79 (82)

ACE indicates angiotensin converting enzyme; ACS, acute coronary syndrome; BDI, Beck Depression Inventory; Ca, calcium; CABG, coronary artery bypass graft surgery; LVEF, left ventricular ejection fraction; MPI, myocardial perfusion imaging; PCI, percutaneous coronary intervention; PS, psychological stress; SSRI, selective serotonin reuptake inhibitor.
*LVEF value taken from the most recent diagnostic test in the medical record (eg, resting cardiac echocardiogram/single-photon emission computed tomography MPI, cardiac catheterization).

during PS. Indication for early termination of PS likewise was identical to clinical stress testing: angina or symptom equivalent, ST-segment depression of >3 mm, drop in systolic blood pressure, or any arrhythmia, though none of these indications occurred during the protocol.

SPECT Myocardial Perfusion Imaging

Radiotracer dosing, image acquisition, and image processing were performed according to guidelines of the American Society of Nuclear Cardiology[26] and followed a protocol identical to that used clinically in the low dose/high dose single-day protocol with rest imaging performed prior to stress imaging. Gated SPECT was performed with use of a step-and-shoot acquisition on a Philips Forte gamma camera system with Gd-153 line source attenuation correction or on a GE Discovery SPECT/CT system with CT-based attenuation correction. Data were acquired over 180 degrees, with 64 frames with a 64×64 matrix, 8 frame gating, and 20% window centered on 140 keV photo peak of ^{99m}Tc.

Tomographic images were reconstructed using standard filtered backprojection and Butterworth low-pass filtering, using JET Stream platform (Philips Medical Systems, Milpitas, CA). Short- and long-axis SPECT slices were generated, along with multilevel gated cines. Reconstructed images were interpreted using AUTOQUANT (Cedars-Sinai, Los Angeles,

CA). Myocardial perfusion images were independently analyzed and interpreted by 2 experienced nuclear cardiologists (R.S., J.M.) blinded to the name and risk profile of the patients, and all other medical data, including depression status. The concordance rate was 95%, with discordant studies addressed by another joint review where consensus was reached.

Perfusion, wall motion, and wall thickening were assessed in a qualitative and a semiquantitative manner. Perfusion images were analyzed in both a gray-scale and color display. Rest and stress images were visually compared for number and severity of perfusion defects using a 17-segment model. Each segment was scored from 0 to 4, with 0 being "normal uptake" and 4 being "no uptake," yielding a total score. A reversible defect score (summed difference score) was calculated as the difference between summed PS and summed rest scores. Following published guidelines,[26] a new impairment in myocardial perfusion during PS compared with the resting baseline images in a segment was defined as a score ≥2 (definitely abnormal); a worsening impairment was defined as an increase in score ≥1 above a score of 2 or greater. If any of the 17 segments evidenced these scores, the patient was categorized as having new/worsening impairment in myocardial perfusion during PS.

Data Analysis

From the overall sample, 3 groups of patients were created based on BDI-I scores, using an approach previously reported in the literature[6,27]: those with a score <5 (not depressed), those with a score of 5 to 9 (high normal), and those with a score ≥10 (depressed), the latter range having been linked in multiple studies to risk for recurrent ACS/mortality (cf. refs 1, 2, 24). We report descriptive statistics for the total sample, and separately by depression group and for myocardial perfusion response to PS. Group differences in percentages were tested using the χ^2 test of independence; *t* tests, and 1-way ANOVA were used to test for differences in means between groups with and without new/worsening myocardial perfusion from baseline to PS, and among depression groups, respectively. Using logistic regression, we estimated and tested the unadjusted odds ratios for new/worsening impairment in myocardial perfusion from baseline to PS for those in the depressed group and the high normal group, relative to the not-depressed group. Three multiple logistic regression models were then estimated with the inclusion of the following covariates:

Model 1: ACS recurrence/mortality risk factors—age, left ventricular ejection fraction (LVEF), hypertension, hypercholesterolemia, diabetes, and tobacco use;

Model 2: medications—aspirin, statin, β-blocker, and Plavix;

Model 3: ACS recurrence/mortality risk factors and medications.

Depression status based on BDI-I score and use of an SSRI were inherently correlated ($P<0.001$), and thus we did not want to treat SSRI medication use as a potential confounder unless it was also correlated with the likelihood of a new/worsening impairment in myocardial perfusion from baseline to PS; 51.3% of the 115 participants not taking a selective serotonin reuptake inhibitor (SSRI) and 64.5% of the 31 taking an SSRI had this new/worsening impairment ($P=0.23$ by Fisher's exact test). Based on this result, SSRI use was not included in the multivariable analyses. Given the relatively small sample size, effect modification was not examined.

Finally, we performed a sensitivity analysis in which all models were re-estimated, treating depression symptoms as a continuous predictor (square-root transformed to reduce the positive skewness of the distribution).

Results

Demographics

Of the overall N=146 sample, 41 (28%) patients scored in the not-depressed range on the BDI-I, 48 scored in the high normal range (33%), and 57 (39%) in the depressed range. Figure 1 contains a histogram portraying the distribution of BDI-I scores. The average age was 66 (±9) years. Approximately 76% were male, 92% were classified as hyperlipidemic, 83% as hypertensive, 33% as diabetic, and 34% as tobacco user; 78% were taking aspirin, 92% a statin, 81% a β-blocker, 21% Plavix, 43% an angiotensin converting enzyme inhibitor, 34% a calcium channel blocker, and 21% an SSRI antidepressant. In addition, the average LVEF extracted from the medical record was 55.8%, while 52% had a previous ACS, and 51% had previous percutaneous and 44% surgical revascularization, with an average 78 months since revascularization

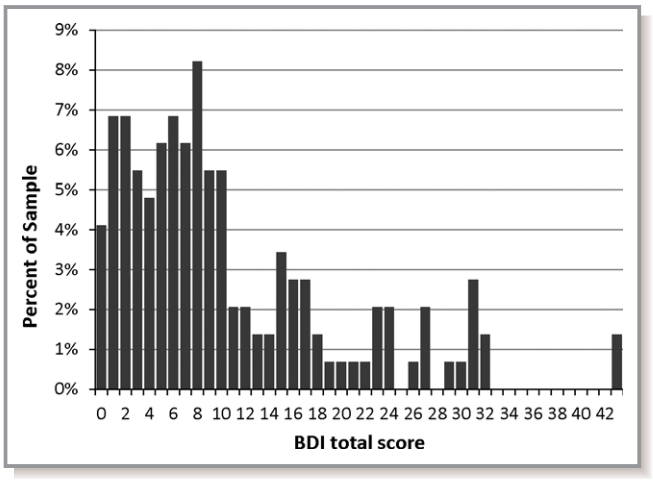

Figure 1. Distribution of Beck Depression Inventory-I (BDI-I) scores.

(Table 1). There were no statistically significant differences in these variables between those with versus without new/worsening impairment in myocardial perfusion from baseline to PS, or with the exception of SSRI, between the 3 depression groups.

Hemodynamics and SPECT-Derived LVEF

At resting baseline, the average systolic blood pressure was 133 (±20) mm Hg, average diastolic blood pressure was 73 (±12) mm Hg, and average heart rate was 59 (±12), while the average LVEF derived from SPECT myocardial perfusion imaging was 56.0 (±10.8). With PS this increased to a systolic/diastolic blood pressure of 151 (±19)/82 (±9) mm Hg, and heart rate of 67 (±11), while the SPECT myocardial perfusion imaging–derived LVEF was 56.9 (±11.6). There were no statistically significant differences in these variables between those with versus without new/worsening impairment in myocardial perfusion during PS, or between the 3 depression groups. The apparent lack of change in LVEF from baseline to PS is not surprising since the PS SPECT images were acquired 45 to 60 minutes after the stress. While the perfusion images acquired at that time reflect perfusion at the time of injection (eg, at the time of the stress) the gated wall motion images on which LVEF is derived reflect wall motion *at the time of acquisition* (eg, 45 to 60 minutes after injection), a time when any deficits in LVEF provoked by psychological stress would be expected to have normalized (Table 2).

Depression and New/Worsening Impairment in Myocardial Perfusion During PS

Overall, 79 (54%) patients demonstrated a new/worsening impairment in myocardial perfusion from baseline to PS (Table 3). This included 16 (39%) of those with BDI-I score from 0 to 4 (no depression), 26 (54%) with BDI-I score of 5 to 9 (high normal), and 37 (65%) with BDI-I score of ≥10 (depressed). The unadjusted logistic regression analysis revealed a statistically significant greater likelihood of this new/worsening impairment for those having a BDI-I score in the depressed range, compared to those with no depression (odds ratio=2.89, 95% CI: 1.26 to 6.63, *P*=0.012); the greater likelihood for those having a BDI-I score in the high normal range was consistent with a dose–response relationship, but not statistically significant (odds ratio=1.85, 95% CI: 0.79 to 4.30, ns). Having a BDI-I score in the depressed range remained a significant predictor of a new or worsening impairment in myocardial perfusion during PS in separate subsequent models controlling for (a) age, LVEF, hypertension, hypercholesterolemia, diabetes, and tobacco use (odds ratio=3.43, 95% CI: 1.43 to 8.25, *P*=0.006); (b) aspirin, statin, β-blocker, and Plavix medications (odds ratio=2.63, 95% CI: 1.11 to 6.23, *P*=0.028); and (c) with both sets of covariates in a single model (odds ratio=3.38, 95% CI: 1.35 to 8.49, *P*=0.01) (Table 4). While in each case a BDI-I score in the high normal range was not a significant predictor of impaired myocardial perfusion during PS, the increase in likelihood was approximately 50% of that for those with a BDI-I score in the depressed range. These analyses were also repeated using BDI-I score as a continuous variable, with comparable results (Table 5).

In the sensitivity analyses in which depression group was replaced by the continuous BDI-I score (square-root transformed), the association between depressive symptoms and the likelihood of a new/worsening impairment in myocardial perfusion from baseline to PS remained statistically significant (Table 5).

A locally weighted scatterplot smoothing (LOESS) curve of the bivariate relationship between BDI-I score and the

Table 2. Heart Rate, Blood Pressure, and Ejection Fraction at Resting Baseline and Acute Psychological Stress

	Heart Rate and Blood Pressure						MPI Ejection Fraction*	
	Baseline			Change With PS				
	SBP (mm Hg)	DBP (mm Hg)	HR (bpm)	SBP (mm Hg)	DBP (mm Hg)	HR (bpm)	Rest	PS
BDI score								
Normal score 0 to 4 (N=41)	136±20	74±8	59±11	16±14	9±6	8±6	55.8±10.8	57.3±11.6
Hi-Normal score 5 to 9 (N=48)	128±17	70±7	64±10	17±11	9±6	7±6	56.0±10.7	56.7±11.4
Depressed score ≥10 (N=57)	131±20	72±15	58±12	15±13	7±9	7±7	56.4±10.9	56.9±11.7
New/Worse impairment in myocardial perfusion during PS								
No (N=67)	134±21	73±10	60±11	13±12	8±6	6±6	55.80±10.19	55.44±11.06
Yes (N=79)	129±24	71±13	60±12	18±13	9±8	8±7	56.22±11.18	58.30±11.67

BDI indicates Beck Depression Inventory; bpm, beats per minute; DBP, diastolic blood pressure; HR, heart rate; mm Hg, millimeters of mercury; MPI, myocardial perfusion imaging; PS, psychological stress; SBP, systolic blood pressure.

*Ejection fraction associated with PS was obtained from gated images 45 to 60 minutes post stress; thus, any effect of stress on ejection fraction would be expected to no longer be present, and this is what was found.

Table 3. Myocardial Perfusion at Rest and During Psychological Stress

	Total	BDI Score		
		Normal Score 0 to 4	Hi-Normal Score 5 to 9	Depressed Score ≥10
New	66	9	22	35
Worse	53	7	20	26
Patients with new/worse MPI defect	(N=79)	(N=16)	(N=26)	(N=37)
SRS	3.59 (3.30)	4.25 (3.63)	2.10 (2.47)	4.20 (3.74)
SSS	9.41 (4.24)	8.38 (4.67)	9.10 (3.84)	9.00 (4.34)
SDS	5.82 (2.24)	4.13 (2.29)	7.00 (3.25)	4.80 (1.51)
Patients without new/worse MPI defect	(N=67)	(N=25)	(N=22)	(N=20)
SRS	2.66 (2.48)	2.79 (2.16)	2.90 (2.73)	2.23 (2.20)
SSS	4.13 (3.02)	3.68 (1.89)	4.55 (3.45)	4.23 (3.96)
SDS	1.47 (1.41)	0.89 (0.50)	1.65 (1.38)	2.00 (2.58)

Values for SRS, SSS, and SDS are mean (SD). BDI indicates Beck Depression Inventory-I; MPI, myocardial perfusion imaging; SDS, sum defect score; SRS, sum rest score; SSS, sum stress score.

probability of new/worsening myocardial perfusion defect from baseline to PS was generated (Figure 2). In this relatively small sample, the LOESS curve does not fit the data significantly better than a straight line (P=0.22).

Discussion

In what we believe to be the first reported test of whether the confluence of depression and acute psychological stress affects coronary vascular function, we found that a score on the BDI-I indicative of depression and previously linked to ACS recurrence and mortality risk was associated with a substantially greater likelihood (odds ratio of 2.6 to 3.4) of a new or worsening impairment in myocardial perfusion during such stress, independent of ACS recurrence risk factors and medications. We furthermore found that an intermediate score of high normal on the BDI-I increased this likelihood in a dose–response manner (odds ratio of 1.7 to 1.9), though this was not statistically significant; the study was underpowered to detect associations of this magnitude. Thus, the cur-

Table 4. Logistic Regression Models Predicting New/Worsening Impairment in Myocardial Perfusion From Baseline to PS From Depression Group, ACS Recurrence/Mortality Risk Factors, and Medications

Predictor	Unadjusted Model OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Depression group				
High normal vs Normal	1.85 (0.79 to 4.30)	1.80 (0.74 to 4.38)	1.82 (0.77 to 4.30)	1.73 (0.70 to 4.33)
Depressed vs Normal	2.89* (1.26 to 6.63)	3.43** (1.43 to 8.25)	2.63* (1.11 to 6.23)	3.38** (1.35 to 8.49)
Age (per 10-year increase)		1.00 (0.67 to 1.47)		0.99 (0.66 to 1.50)
LVEF (per 10% increase)		0.86 (0.63 to 1.18)		0.85 (0.61 to 1.18)
Hypertension		0.70 (0.26 to 1.73)		0.62 (0.23 to 1.64)
Hypercholesterolemia		1.32 (0.37 to 4.64)		1.29 (0.36 to 4.68)
Diabetes		1.23 (0.57 to 2.65)		1.18 (0.54 to 2.60)
Tobacco use		0.74 (0.35 to 1.59)		0.73 (0.33 to 1.58)
Aspirin			1.22 (0.52 to 2.82)	1.63 (0.67 to 3.94)
Statin			1.07 (0.32 to 3.56)	0.76 (0.20 to 2.84)
β-Blocker			1.43 (0.60 to 3.40)	1.47 (0.56 to 3.84)
Plavix			0.67 (0.28 to 1.56)	0.60 (0.25 to 1.47)

ACS indicates acute coronary syndrome; LVEF, left ventricular ejection fraction; OR, odds ratio; PS, psychological stress.
*P≤0.05, **P≤0.01.

Table 5. Logistic Regression Models Predicting New/Worsening Impairment in Myocardial Perfusion From Baseline to PS From Continuous BDI Score, ACS Recurrence/Mortality Risk Factors, and Medications

Predictor	Unadjusted Model OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Depressive symptom (BDI total score$^{0.5}$)	1.37* (1.07 to 1.76)	1.42** (1.09 to 1.84)	1.33* (1.03 to 1.72)	1.40* (1.07 to 1.84)
Age (per 10-year increase)		0.96 (0.65 to 1.42)		0.95 (0.63 to 1.43)
LVEF (per 10% increase)		0.85 (0.62 to 1.17)		0.84 (0.60 to 1.17)
Hypertension		0.67 (0.26 to 1.73)		0.62 (0.24 to 1.64)
Hypercholesterolemia		1.26 (0.37 to 4.35)		1.25 (0.35 to 4.43)
Diabetes		1.18 (0.56 to 2.52)		1.14 (0.52 to 2.48)
Tobacco use		0.74 (0.35 to 1.58)		0.74 (0.34 to 1.59)
Aspirin			1.24 (0.54 to 2.85)	1.58 (0.66 to 3.76)
Statin			1.04 (0.32 to 3.46)	0.83 (0.22 to 3.06)
β-Blocker			1.42 (0.60 to 3.36)	1.44 (0.56 to 3.75)
Plavix			0.66 (0.28 to 1.54)	0.58 (0.24 to 1.40)

ACS indicates acute coronary syndrome; BDI, Beck Depression Inventory-I; LVEF, left ventricular ejection fraction; OR, odds ratio; PS, psychological stress.
*$P\leq0.05$, **$P\leq0.01$.

rent findings reveal one potential and previously untested pathway—vulnerability in the coronary vasculature—that may underlie the ACS recurrence and mortality risk associated with depression.

Although depression is prevalent and marks ACS recurrence and mortality risk among patients with CHD,[1–7] an understanding of the causal pathways or mechanisms through which this risk is conferred remains elusive.[9,10] The multifactorial nature of ACS is increasingly recognized.[11] This led us to recently propose [12] that the equivocal findings in the literature regarding such factors as inflammation, platelet function, autonomic dysregulation, and medication adherence as underlying the relationship of depression to ACS recurrence and mortality risk may in part reflect a failure to consider additional, activating factors. We therefore offered a new model defined by the confluence of depression with acute psychological stress as a possible activating factor for elucidating critical pathways, and thus contributing to a more precise understanding of depression-associated risk.[12] In the current study we tested this model, specifically with regard to dynamic coronary perfusion and thus, coronary vascular processes, and the findings provide credence to the proposed paradigm and support its use in future larger studies aimed at understanding the depression-associated risk for ACS recurrence and mortality.

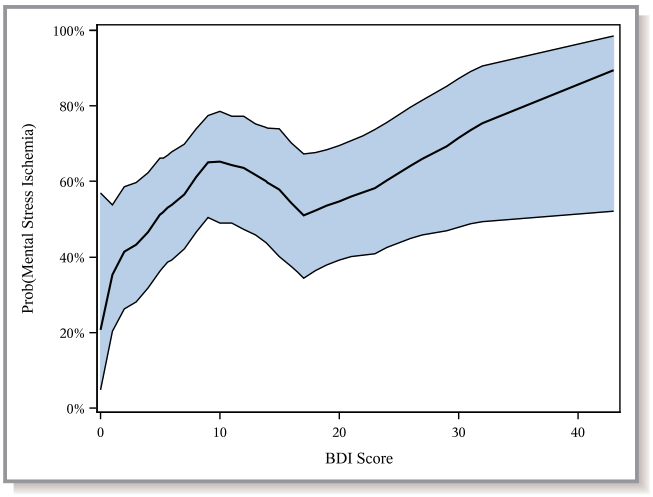

Figure 2. LOESS curve of the bivariate relationship between Beck Depression Inventory (BDI) score and the probability of new/worsening myocardial perfusion defect from baseline to psychological stress (PS). Dark black line shows the relationship between BDI score and the predicted probability of new/worsening impairment in myocardial perfusion from baseline to PS. The blue bands around this line outline the 95% CI. In this relatively small sample, the LOESS curve does not fit the data significantly better than a straight line (P=0.22). MPI indicates myocardial perfusion imaging. LOESS indicates locally weighted scatterplot smoothing curve.

Depression and Vascular Function

To understand the pathophysiological processes by which depression influences coronary vascular performance during acute psychological stress, it is essential to recognize the dynamic nature of the observed impairment in myocardial perfusion. Specifically in the current study, there were no depression-related differences—or differences between those with and without impairment in myocardial perfusion during acute psychological stress—in the prior occurrence of ACS, in prior revascularization, or in the severity of myocardial perfusion impairment with exercise or pharmacologic stress. Thus, differences in coronary anatomy are not likely to account

for the main finding. Furthermore, the increase in myocardial oxygen demand during the acute psychological stress, as reflected by increases in heart rate and blood pressure, similarly showed no difference, and indeed, was lower than the increase in demand that typically occurs during exercise-provoked impairment in perfusion. Rather, these data point to a likely *dynamic* coronary obstruction[17,28,29] whereby some aspect of underlying vulnerability in the coronary vasomotor response to psychological stress is specifically revealed among CHD patients as a function of depression.

Prior research has shown that depression is associated with disruption in vascular processes (ie, endothelial dysfunction[30] and impairment in coronary flow reserve[31]) that could account in part for the current findings and for increased ACS/mortality risk. We have shown in 1 small study of stable CHD patients that psychological versus pharmacologic stress is predominately associated with impaired coronary vascular function in coronary distributions without obstructive atherosclerotic plaques,[28] a finding that must be confirmed in larger studies. Others have demonstrated epicardial vasoconstriction during acute psychological stress at the site of epicardial coronary segments with minimal atherosclerosis.[29] Thus, impairment may be more broadly evident throughout the coronary vasculature. Furthermore, we have observed a level of endogenous endothelin-1 (ET-1) among depressed CHD patients that has previously been linked to myocardial infarction recurrence.[32] We have also observed that circulating ET-1 increases during acute psychological stress.[32–34] ET-1, the most potent endogenous vasoconstricting agent, is secreted by endothelial cells and macrophages, and in the setting of coronary atherosclerosis is responsible to the greatest extent for coronary vasoconstriction.[35] ET-1 also acts synergistically with norepinephrine,[36] to accentuate dynamic vasoconstriction, and we have previously observed that acute psychological stress provokes an increase in circulating norepinephrine among CHD patients.[17,33,34] Of note, depression is associated with autonomic dysregulation, defined in part by an increase in sympathetic activity.[37] While serological data on norepinephrine and ET-1 were not available for the current analyses, the data are nonetheless intriguing, and highlight that a consideration of stress as an "activating" process may lead to a better understanding of the link between depression and recurrent ACS/mortality, rather than the inconsistent puzzle that is defined by the literature.[12] It may be that the identification of mechanisms—and thus potential treatment targets—of depression-related ACS recurrence/mortality risk requires that we psychologically "stress" the depressed CHD patient.

Strengths

To the best of our knowledge, this is the first study to specifically examine the confluence of depression and acute psychological stress as they relate to *dynamic impairment in coronary vascular function*, a process that can serve to initiate an ACS event.[11] It is important to note that 2 earlier studies demonstrated *impairment in ventricular function* during psychological stress in relation to depression; 1 study used radionuclide ventriculography[21] and 1 used cardiac ultrasound.[22] Furthermore, a recent clinical trial of the SSRI antidepressant medication escitalopram demonstrated a benefit for this medication on mental stress–provoked impairment in ultrasound-assessed ventricular function regardless of depression status,[38] though in the current study we found no such effect for this class of medications on the likelihood of a new or worsening myocardial perfusion defect provoked by psychological stress. When viewed in the context of the current findings and prior research on the pathways responsible for "mental stress–provoked myocardial ischemia," these prior studies raise important questions.

The issue of myocardial perfusion versus ventricular function—"flow versus function"—in research concerning the effects of psychological stress on the heart has been the focus of recent editorials[39,40] and of research for approximately 30 years, since the publication by Deanfield et al[20] in which it was reported that, using positron emission tomography rubidium, psychological stress provoked a myocardial perfusion defect. Later studies by Arrighi et al using positron emission tomography,[28] and both Yeung et al[29] and Boltwood et al[41] in the cath lab, demonstrated that the static flow-limiting plaque model was at best inaccurate when applied to the effects of psychological stress, in that this form of stress caused coronary vasoconstriction. These data also helped solve the riddle of why "ischemia" during mental stress was observed in the context of a lower myocardial oxygen demand, when compared with "ischemia" during exercise/pharmacologic stress.[17,25] These data also served to highlight a pathway by which psychological stress could lead to plaque rupture (eg, through coronary vasomotion at the site of a vulnerable plaque).[11]

The issue of sensitivity/specificity as concerns "flow versus function" was further highlighted by the Psychophysiological Investigations of Myocardial Ischemia study investigators, who reported both a decrement in function during psychological stress among healthy individuals, and furthermore, an increase in peripheral resistance and thus afterload, during psychological stress; this increase in afterload is also likely to affect ventricular function, particularly among the patient population typically studied (those with already impaired ventricular function secondary to previous infarct).[42,43] We have also previously shown substantial discordance between wall motion abnormality/left ventricular dysfunction and new/worsening myocardial perfusion defect during psychological stress.[44] This discordance is not surprising, since along the ischemic cascade, an acute impairment in

myocardial blood flow is more proximal than a decrement in ventricular performance.[45] It may be that because psychological stress appears to uniquely affect dynamic coronary vasomotion versus physical or pharmacologic stress, the phenomena being indexed by myocardial perfusion versus ventricular function are somewhat distinct. This has led us to conclude that SPECT myocardial perfusion imaging may be the better choice in studies concerning the effects of psychological stress on the heart.[40]

Limitations

While the current findings lend support to the utility of a depression–acute psychological stress confluence in the effort to understand the ACS recurrence/mortality risk associated with depression, the study is not without limitations. The sample was heterogeneous, comprised stable patients who were far removed from their most recent ACS event or revascularization, and the coronary anatomy at the time of the study was not known. Thus, these findings may not be applicable to an understanding of depression-associated prognosis soon after ACS. In addition, while hemodynamic indices and detailed information regarding underlying coronary disease were available for analysis, serum markers—including of ET-1 and indices of inflammation—and other related measures of autonomic and endothelial function were not. The sample size was also relatively small, and many of the statistical tests failed to reach significance. This may have included the absence of an effect for SSRI medications on the likelihood of a psychological stress–provoked myocardial perfusion defect, and indeed, this class of medications may still be useful for cardiac patients with comorbid depression. Replication with a larger sample that is more proximal to an ACS event and that includes these measures should provide a more complete test of the stress–depression paradigm and an understanding of the depression-associated risk for poor prognosis after ACS.

An additional issue concerns whether the impairment in myocardial perfusion observed as a function of depression was because depressed patients have a lower ischemic threshold in general (eg, due to a greater vascular vulnerability). It is also possible that depressed patients are more susceptible to psychological stress (eg, that the serial subtraction task was more stressful for them). Future studies should include an exercise or pharmacologic stress condition, and should include a self-report measure of task stressfulness to address these issues.

In summary, we found that stable CHD patients with depression were more likely to demonstrate a new or worsening impairment in myocardial perfusion during acute psychological stress, with evidence of a dose–response relationship. This could not be accounted for by markers of the underlying extent of coronary atherosclerosis, medical comorbidity and traditional risk factors, or medications. These preliminary findings lend credence to a confluence of depression with acute psychological stress for understanding the contribution of depression to ACS recurrence and mortality. Future studies with larger cohorts will be able to address the question of whether this effect of acute psychological stress on myocardial perfusion accounts for the greater risk of recurrent ACS/mortality associated with depression.

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Disclosures

None.

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