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Depression Predicts Elevated Endothelin-1 in Patients with Coronary Artery Disease

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Abstract

Objectives—Depression carries an independent 2- to 4-fold increased risk of early morbidity and mortality after acute coronary syndrome (ACS). The pathway(s) linking depression to event-free survival remain to be determined. We examined the relationship of depression severity to circulating endothelin-1 (ET-1), which has previously been linked to plaque rupture and post-ACS survival.

Methods—Patients with documented history of coronary artery disease (n=101) provided a resting morning blood sample that was assayed for ET-1, and completed the Beck Depression Inventory (BDI). ET-1 was treated as a log transformed continuous variable (logET-1), and as a dichotomous variable using a post-ACS risk threshold previously reported (≥1.16 fmol/ml).

Results—BDI score was related to logET-1 in both unadjusted and adjusted models. In addition, unadjusted and adjusted logistic regression models with dichotomous ET-1 revealed that for each point increase in BDI score there was approximately a 14% increased likelihood of being at or above ET-1 risk threshold. Secondary logistic regression models demonstrated a greater than 3.5-fold likelihood of being at or above this risk threshold in association with a BDI score ≥10.

Conclusions—Depression symptom severity predicts ET-1 elevation that has previously been linked to post-ACS survival, with the greatest risk of elevation among those with worse depression symptoms. This link may identify a vulnerability to triggered ACS and poorer survival associated with depression. Future research should establish whether the observed relationship of depressive symptoms to ET-1 level mediates the link between depression and survival.

Keywords

depression; endothelin-1; acute coronary syndrome

Introduction

Acute experience of depressed mood has been identified as a trigger of incident acute coronary syndrome (ACS - e.g., myocardial infarction, unstable angina), with a 4.33-fold

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associated event risk following mood onset and lasting for at least 2-hours.[1] Furthermore, a history of depression increases risk of initial ACS, while among patients who have already experienced this catastrophic cardiac event, depression carries a 2-to 4-fold increased risk of recurrent ACS or mortality, independent of cardiac disease severity and other prognostic risk markers.[2,3] With this evidence demonstrating that depression increase risk of new onset ACS and of reduced post-ACS survival, researchers have focused attention on the possible pathway(s) by which depression may be contributing to these risks. Among the factors that have been examined are biological dysregulation of the autonomic and immune systems, and non-adherence to medication prescriptions.[4–6] While these pathways appear promising, they do not fully account for the link between depression and cardiac events.

We and others have shown that activation of negative moods in the natural environment and in the laboratory can provoke frank myocardial ischemia, with the underlying pathophysiology defined by epicardial and coronary microvascular dysfunction[7–9]. The vascular dysfunction provoked by these negative moods can last for over 90-minutes[10] - thereby mirroring the hazard period for triggered ACS associated with acute onset of depressed mood - and has been found in part to be mediated by endothelin-1 (ET-1)[11,12]. Research has also shown that in the arterial substrate defined by coronary disease (CAD), ET-1 is secreted by activated macrophages[12–16], the primary inflammatory cells found in atherosclerotic lesions. It is through this pathway that ET-1 can both promote the atherosclerotic process[14], and eventually contribute to coronary plaque rupture [17,18] and the consequent triggering of ACS events [19,20] in part by way of enhanced vasoreactivity[13–16].

In summary, depression can contribute to initial catastrophic cardiac events and to post-ACS event-free survival. Furthermore, ET-1 plays an important role in the progression of CAD and eventual plaque rupture and ACS onset. It has not however, been shown that depression is associated with higher circulating levels of ET-1. Such a finding could in part account for both the increased risk of initial ACS, and the poorer post-ACS prognosis associated with depression. We therefore examined the relationship between depression symptom severity and circulating level of ET-1 at rest among patients with chronic stable CAD.

METHODS

Subjects

Patients with chronic stable CAD (n=101), documented by history of ACS, surgical or percutaneous revascularization, and/or positive exercise myocardial perfusion study were recruited from the Cardiology outpatient clinics at Yale University Medical Center and VA Connecticut Healthcare System between January 2004 and February 2008 for a larger investigation concerning the effects of acute emotional stress modeled in the laboratory on vascular performance. Patients with a diagnosis of myocardial infarction or unstable angina 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 defibrillators, uncompensated congestive heart failure, incapacitating or life-threatening illness, diabetes mellitus (due to effects on endothelial function and vessel wall inflammation), major psychiatric disorder, substance abuse disorder (by history), cognitive impairment, pregnancy, and/or inability to speak or read English were excluded. Medical chart review and patient interview were used to obtain demographic information and determine cardiovascular risk profile. The population was homogeneous with regard to severity of CAD as determined by exercise SPECT myocardial perfusion study, with all patients demonstrating mild to moderate inducible defects. Participants with a recent history of systolic pressure >140 mm Hg or diastolic pressure >90 mm Hg, or currently taking antihypertensive medications were classified as hypertensive, while those with total cholesterol ≥200 mg/dl, LDL ≥130 mg/dl, or taking cholesterol lowering medications were

classified as having hypercholesterolemia. The study was approved by the Institutional Review Board at both medical facilities, and all patients provided informed consent. Patient characteristics are described in Table 1.

Procedures

Patients reported to the Cardiovascular Behavioral Medicine Laboratory at VA Connecticut between 9AM and 11AM on a weekday. They were instructed to take all medications as usual before reporting. On their arrival, they were asked to complete the Beck Depression Inventory (BDI), a 21-item self-report questionnaire designed to assess depression symptom severity[21,22]. 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 week. This questionnaire has been used in studies of patients with stable CAD and after ACS, and in particular, scores ≥ 10 have been linked to increased risk for major adverse cardiac events and mortality in these populations[2,3]. Cronbach's alpha for the current sample was 0.86.

Once the BDI was completed, patients were escorted to the blood draw station, and after resting quietly for 10 minutes, a 4mL blood sample was acquired with the patient sitting upright. These samples were centrifuged at 3000g for 15 min to separate plasma. Aliquots of plasma were then stored at −70° C until analysis. Enzyme-linked immunosorbent assay (ELISA) was used for assessment of ET-1 using a colorimetric sandwich kit generating absorbance at 450 nm (Biomedica Gruppe, Austria). The kit has a detection limit of 0.02 fmol/ml (0.05 pg/ml). Specificity of the antibody used in this kit has previously been described[23], as has its use in previous studies with humans by our group and others.[24,25]. All samples from a single subject were analyzed in one assay to insure against inter-assay variation.

Statistical Analysis

The distribution of ET-1 was skewed and values were thus logarithmic transformed (logET-1). The relationship of logET-1 to overall depression symptom severity - BDI score - in both univariate and multivariate models was then examined. The multivariate model controlled for factors known to influence ET-1 level including age[28], diabetes[29], hypertension[30], and the use of statins[31,32] and beta-blockers.[33]

Previous studies have reported that a threshold level of ET-1 predicts post-ACS prognosis.[20,26,27] Thus, in a second set of regression analyses, we treated ET-1 as a categorical variable, selecting for these analyses the most conservative reported risk threshold of ET-1 that was previously linked to post-ACS prognosis (ET-1 ≥1.16 fmol/ml)[26]. In the primary set of these logistic regression analyses, we examined the relationship of overall depression symptom severity - BDI score - to ET-1 risk threshold; in the secondary set of logistic regression analyses we examined the relationship of BDI score ≥10, the threshold previously linked to ACS related morbidity and mortality[2,3] to ET-1 risk threshold. In these two sets of logistic regression analyses, we first examined the relationship of depression to ET-1 in a simple model. We then followed this by an examination of the multivariate relationship of depression to ET-1, controlling for factors known to influence ET-1 level, as in the analyses with logET-1. All tests were two-sided, and analyses were performed using SAS version 9.2[34].

RESULTS

The average age of the study cohort was 66.5 years (± 8.9 years), with 3.1% female and 8.8% non-white. Mean LVEF was 52.7% (± 9.6%). Most patients had a history of

hypertension (85%), 30% were classified with diabetes, and 46.8% with a BMI over 30. Overall, 14.3% were active smokers, while 52% were on ACE inhibitors, 77% were on β-blockers, 31% on calcium channel blockers, 89% on statins, and 67% taking aspirin. Mean BDI score was 7.8 (± 5.8). The range in ET-1 was from 0.12 - to 5.14 fmol/ml, (mean=1.00, SD=0.93), and approximately 25% of patients demonstrated values at or above the risk threshold of 1.16 fmol/ml. (see Table 1).

In regression analysis, logET-1 was related to depression symptom severity – total BDI score ($t=2.69$, $p<0.001$). Total BDI score remained significant ($t=2.54$, $p<0.0129$) in a multivariate regression model that controlled for age, diabetes, hypertension, and the use of statins and beta-blockers (full model not presented).

High Risk ET-1 Level

In the primary logistic regression models, depression symptom severity significantly predicted the probability of having resting level of ET-1 in the high risk range. Specifically, as a continuous measure of symptom severity, total BDI score was associated with an odds ratio of 1.14 (95% CI [1.05–1.24], $p<0.002$), indicating a 14% increased likelihood of being in the high risk ET-1 group for each point increase in BDI score. This odds ratio increased slightly to 1.15 (95% CI [1.05–1.25], $p<0.002$) in the multivariate logistic model that controlled for age, diabetes, hypertension, and use of beta-blockers and statins (see Table 2).

In the secondary logistic regression models utilizing the dichotomous measure of depression-associated risk for ACS events, a score on the BDI>10 substantially increased the likelihood of being in the high risk ET-1 group. Specifically, BDI>10 was associated with an odds ratio of 3.55 (95% CI [1.42–8.87] $p<0.007$). This odds-ratio increased to 3.89 (95% CI [1.47–10.31] $p<0.007$) in the multivariate logistic model that controlled for age, diabetes, hypertension, and use of beta-blockers and statins. Thus in both uncontrolled and controlled logistic models, there was greater than a 3.5-fold increased likelihood of being in the high risk ET-1 group associated with a BDI score previously found to predict CAD related prognosis (see Table 2).

Discussion

Research conducted over the past 30 years has consistently demonstrated that depression, whether indexed according to diagnostic criteria or as a threshold of symptom severity, independently contributes to poorer prognosis for patients with CAD[2,3]. These findings have recently led to the recommendation that routine screening for depression be conducted with medical patients[35,36]. Research on the process(es) by which depression contributes to increased risk for triggered ACS and for early morbidity and mortality has identified several factors that may be involved, including inflammation[37] and dysregulated platelet function[4], autonomic dysregulation[5], and medication nonadherence[6], though the literature is not consistent, and different pathways may provide independent links[37]. The current study extends these findings by demonstrating that depression symptom severity is related to the resting level of ET-1, a protein involved in the regulation of vascular compliance, and directly linked to plaque rupture.[17,18] Each point increase in depression severity independently increased by 14% the likelihood of a patient evidencing a resting level of ET-1 in a range previously found to predict post-ACS morbidity and mortality[26,27]. When a threshold of depressive symptoms that has repeatedly been linked to post-ACS prognosis was utilized, this likelihood increased to 3.75-fold.

The current finding thus expands the range of pathways that may link depression and post-ACS survival to include ET-1. This peptide, the most potent endogenous vasoconstrictor, is typically secreted by the vascular endothelium. Most relevant to the current discussion, it is

also prominently found in the intima of atherosclerotic coronary arteries, particularly in areas with significant macrophage infiltration[12,14,16]. In this setting, ET-1 contributes to risk of coronary plaque rupture and triggered ACS[17–20]. Furthermore, ET-1 enhances the vasoconstrictive effects of norepinephrine and serotonin[38], thereby also contributing to arrhythmogenesis and consequent risk of fatal arrhythmia[39]. It is important to note that depression is associated with dysregulation in the bioavailability of both norepinephrine[40] and serotonin[41]. Thus, elevated ET-1 could in combination with these two agents, synergistically contribute to pronounced vasoconstriction, with localization of more pronounced effects at the site of vulnerable or active atherosclerotic plaques. In this way, ET-1 may contribute to the poorer post-ACS prognosis associated with depression[1–3].

While the process(es) by which depression may contribute to elevated ET-1 remain to be elucidated, the autonomic nervous system may play an important role. For example, macrophage production and secretion of pro-inflammatory cytokines has recently been demonstrated by Tracey and colleagues to be in part under the influence of cholinergic regulation[42–44]. Through this pathway acetylcholine, the principal neurotransmitter of the vagus nerve, binds nicotinic cholinergic receptors on macrophages, and thereby inhibits synthesis of TNF-α. In the presence of an appropriate pro-inflammatory stimulus, Tracey et al found that blockade or down-regulation of vagal input results in an increased production and release of these cytokines by macrophages, while enhancement of this input has the opposite effect. The heart is well enervated by the vagus, and low parasympathetic tone is both a well-described predictor of early post-MI mortality[45], and associated with depression. Indeed, the autonomic imbalance seen in depression - largely characterized by chronically reduced parasympathetic activity – is thought in part to contribute to the poorer prognosis of CHD patients with depression[5]. Macrophages that reside in the myocardial vasculature are a main source of TNF-α[46,47]. Furthermore, TNF-α has been shown to promote secretion of ET-1 by macrophages[48,49]. As parasympathetic activity is reduced in depression, secretion of TNF-α by macrophages may be disinhibited, and thus enhance the additional release of ET-1. Through this pathway, circulating levels of ET-1 at rest could be higher among patients with depression.

The current findings on depression and ET-1 provide a potentially important pathway to enhance our understanding of how depression contributes to triggered events and post-ACS survival. It is important to note however, that the study was cross sectional, and the population was relatively small and predominantly male, which may skew the results since the level of ET-1 is generally lower in pre-menopausal females, possibly due to protective effects of estrogen[50]. The size of the sample also limited the number of covariates that could be considered, and thus unanticipated confounding of results may be present. Furthermore, we did not assess inflammatory or platelet factors in relation to depression in this sample and thus cannot rule out the possibility that the relationship of ET-1 to depression would be mitigated by the inclusion of these other biomarkers. In addition, while the value of ET-1 on which we grouped patients was selected as the more conservative among values previously found to predict post-ACS prognosis[26], a normal value range for this biomarker has not yet been established.

The population was heterogeneous with regard to length of history of CAD, ranging from several months to several years, though severity of CAD and ischemic burden - as determined by exercise perfusion study - was largely equivalent, and radionuclide assessed ventricular function was largely within normal ranges for all patients. This overall stable nature of the population may therefore at least in part limit the generalizability of the current findings to other populations (e.g., those immediately post-ACS), though the proximity of this class of event for many in the study population was within the range described in studies concerning depression and post-ACS prognosis. Longer term follow-up data are not yet

available for the study cohort and thus we are not able to determine whether ET-1 mediates the relationship of depression to prognosis. Furthermore, prior research has shown that depression is associated with reduced nitric oxide bioavailability[51]. Thus, the observations reported here may touch on a more complex pathophysiology that involves several contributors to vaso-motor regulation, interacting with ET-1 in the determination of plaque vulnerability. Unfortunately, assessment of nitric oxide was beyond the scope of the current exploration.

In summary, depression symptom severity predicted an ET-1 elevation that prior research has shown to predict post-ACS survival. Furthermore, the greatest risk of this ET-1 elevation was observed among patients whose depression severity was consistent with poorer post-ACS prognosis. The link between depression severity and ET-1 may identify a vulnerability to triggered ACS and poorer survival associated with depression. Future research should extend these findings to a more heterogeneous post-ACS population that includes longer term follow-up. In addition, future research should test the relationship of depression to ET-1 and other biomarkers concurrently so as to establish both whether the observed relationship of depressive symptoms to level of ET-1 mediates the link between depression and post-ACS survival, and whether other factors such as inflammatory processes, platelet function, and/or nitric oxide bioavailability play a complementary role.

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Abbreviations

ACS	acute coronary syndrome
BDI	Beck Depression Inventory
β-blocker	beta-blocking medication
CAD	coronary artery disease
ELISA	enzyme-linked immunosorbent assay
ET-1	endothelin-1
fmol/ml	fentomole per milliliter
LVEF	left ventricular ejection fraction
logET-1	log transformed ET-1
pg/ml	pictogram per milliliter
SAS	statistical analysis software
tnf-α	tumor necrosis factor alpha

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Table 1

Patient Characteristics

		ET-1 Risk Group (fmol/ml)	
Variable	**Total Cohort (N=101)**	**Low (N=76) (0.12-1.15)**	**High (N=25) (1.16–5.14)**
Age, mean (SD), years	67.0 (9.0)	66.4 (8.7)	69.2 (10.2)
Female	3.1%	2.6%	6.0%
Non White Race	8.8%	9.0%	8.0%
History of Hypertension	85%	83%	94%
Active smokers	14.3%	14.0%	14.6%
LVEF, mean (SD)	52.7 (9.6)	54 (8.6)	46.2 (11.2)
Obesity (BMI >30)	46.8%	49%	37%
Diabetes	30%	29%	32%
Mean BDI Score (SD)	8.1 (5.9)	7.44 (5.20)	10.77 (7.95)
Medications			
Ace inhibitors	52%	48%	63%
Beta-Blockers	77%	78%	77%
Aspirin	67%	68%	63%
Calcium Channel Blocker	31%	30%	32%
Statins	89%	89%	89%

ET-1 = Endothelin-1

fm/ml = fentomole/milliliter

LVEF = left ventricular ejection fraction

BMI = body mass index

BDI = Beck Depression Inventory

Table 2

Logistic Regression Models Predicting ET-1 Risk Elevation

Variable	Point Estimate	95% Wald Confidence Limits		P-Value
Model 1				
BDI Score - Continuous	1.14	1.05	1.24	0.002
Model 2				
BDI[1] Score - Continuous	1.15	1.05	1.25	0.002
Use of Beta-Blockers	0.51	0.15	1.71	0.28
Diabetes	0.80	0.28	2.31	0.68
Age	1.04	0.98	1.10	0.18
Use of Statins	0.77	0.13	4.45	0.70
Hypertension	0.44	0.12	1.67	0.77
Model 3				
BDI[1] Score ≥ 10	3.55	1.42	8.87	0.007
Model 4				
BDI[1] Score ≥ 10	3.89	1.47	10.31	0.007
Use of Beta-Blockers	0.65	0.20	2.07	0.46
Diabetes	0.86	0.30	2.45	0.77
Age	1.04	0.98	1.09	0.21
Use of Statins	0.79	0.14	4.48	0.79
Hypertension	3.87	0.67	22.23	0.13

ET-1 = endothelin-1

BDI = Beck Depression Inventory