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Severe Depressive Symptoms are Associated with Elevated Endothelin-1 in Younger Patients with Acute Coronary Syndrome

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Abstract

Objective—To explore the relationship of depressive symptom severity to circulating Endothelin (ET) – 1 in younger patients with acute coronary syndrome (ACS). Younger patients report greater depressive symptom severity, which predicts poorer post-ACS prognosis. The pathways linking depression to post-ACS prognosis require further elucidation. ET-1 is a potent endogenous vasoconstrictor which has been previously linked to adverse post-ACS outcomes.

Methods—The sample (n=153) included males 50 years of age and females 55 years of age who participated in a larger study. Blood samples for ET-1 assessment were collected within 2–3 hours of ACS admission. Depressive symptoms were assessed with the Beck Depression Inventory (BDI) II within 2–5 days of admission. ET-1 was treated as a transformed continuous variable (ET-1T). BDI-II scores were classified into four categories using conventional thresholds demarcating mild, moderate, and severe levels of depressive symptoms. The relationship of classified BDI-II score to ET-1T was examined in simple and multivariable linear regression models.

Results—Classified BDI-II score was related to ET-1T in both unadjusted ($\chi^2 = 9.469$, $p = 0.024$) and multivariable ($\chi^2 = 8.430$, $p = 0.038$) models, with ET-1T being significantly higher in patients with severe depressive symptoms than in those with mild and moderate depressive symptoms.

Conclusions—In this sample of younger post-ACS patients, severe depressive symptoms were associated with elevated ET-1. We acknowledge that the observed association could be eliminated

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by the inclusion of some unmeasured variable(s). Longitudinal research should examine whether ET-1 mediates the relationship of depressive symptoms to long-term post-ACS outcomes.

Keywords

Acute Coronary Syndrome; Depression; Depressive Symptoms; Endothelin; Myocardial Infarction; Younger Patients

Introduction

Epidemiologic evidence demonstrates a consistent relationship between depression and acute coronary events (i.e. myocardial infarction [MI], unstable angina). In multiple investigations, depression, whether indexed as a syndrome of major depressive disorder or as a threshold of self-reported depressive symptoms, has been shown to increase the risk of acute coronary events and to contribute to poor post-event prognosis [1–3]. According to a recent meta-analysis, post-coronary event depression is associated with a 1.6- to 2.7-fold increased risk of adverse outcomes, including all-cause mortality, cardiac mortality and recurrent cardiac events within 24 months following index admission [4]. Although the link between depression and post-event prognosis has been established, the exact pathophysiological pathways by which depression contributes to subsequent morbidity and mortality require further elucidation. A better understanding of these pathways may facilitate the development of mechanism-specific therapies to decrease cardiovascular risk in depressed persons [1].

Endothelin (ET) -1 is a 21-amino acid peptide secreted by endothelial cells [5] and activated macrophages [6]. ET-1 is the major form of ET produced in humans and is the most potent endogenous vasoconstrictor. The peptide acts in the peripheral and coronary circulations by binding to ET-A and ET-B receptors. Binding of ET-1 to ET-A receptors induces vasoconstriction, whereas binding of ET-1 to ET-B receptors generally promotes ET-1 clearance, inhibition of ET-1 converting enzyme, and release of the vasodilatory mediators, including nitric oxide (NO) and prostacyclin [7–9]. In addition to its potent vasoconstrictive effects, ET-1 exhibits mitogenic properties, contributing to endothelium-dependent growth and vascular wall remodeling via promotion of smooth muscle cell proliferation [10]. Dysregulation of vascular growth and homeostasis and enhanced vasoreactivity are believed to comprise the principal pathways by which elevated ET-1 levels contribute to the progression of coronary artery disease (CAD) and to plaque rupture and acute coronary event onset [7, 10–12]. The role of ET-1 following acute coronary events can be detrimental [13, 14]; by virtue of its pronounced vasoconstrictive properties, post-event elevated ET-1 may contribute to increased afterload and myocardial ischemia [6]. In a study of MI patients who underwent primary percutaneous coronary intervention, elevated ET-1 during early hours of MI was found to strongly predict adverse clinical outcomes, including congestive heart failure and 30-day mortality [15].

To date, only one study has reported the relationship of depression to ET-1 in cardiac patients, and this was in a heterogeneous group of stable patients with previous acute coronary syndrome (ACS), surgical or percutaneous revascularization, and/or effort angina

controlled by medication [16]. While these findings provide important data, the results may not be extrapolated to other subgroups, including patients immediately post-ACS. Examination of the relationship between depressive symptoms and circulating ET-1 in post-ACS patients could, given the important role of ET-1 in post-event prognosis, aid in identification of patients at risk for post-ACS morbidity and mortality.

While ACS occurs more frequently at an older age, younger patients (males 50 years of age and females 55 years of age) constituted 20% of the total sample in a recent large study (n=1140) of consecutively admitted ACS patients (age range 26–96 years), [17]. This is an important finding, given the results of the few studies of ACS patients that specifically examined younger patients. In particular, these younger patients apparently differ from their older counterparts with respect to psychosocial characteristics [17, 18]. In one study, younger ACS patients were significantly more likely to report greater depressive symptom severity on the Beck Depression Inventory (BDI) II questionnaire and to report feeling depressed in the year preceding the index event ($p<0.001$ for each), compared to their older counterparts [17]. In another recent study [19], depressive symptoms (i.e. somatic symptoms and hopelessness) independently predicted adverse post-MI prognosis (composite of recurrent MI and mortality during a mean follow-up of 2.1 years) in participants younger than 70 years of age (mean age = 55 years). In that same study, depressive symptoms did not independently predict poor post-MI outcomes in older participants (patients 70 years of age, mean age = 76 years). The differences in depression measures and depression-related post-event prognosis among younger and older patients, coupled with the overall paucity of research involving younger patients undergoing acute coronary events underscore the importance of exploring the relationship between psychosocial risk, post-acute event prognosis, and the mechanisms involved in these links in younger subgroups.

The specific aim of this cross-sectional study was, therefore, to examine the relationship between depressive symptom severity and circulating ET-1 in younger ACS patients. It was hypothesized that depressive symptom severity would be positively associated with plasma ET-1 level.

Methods

Participants

The sample consisted of 153 patients admitted to two large tertiary care hospitals in a major U.S. city with a diagnosis of ACS. Patients were admitted between the years of 2007 through 2011 and were among participants of a larger longitudinal investigation on interactive effects of genetics and depression on ACS outcomes. ACS was defined as hospitalization for chest pain or symptoms suggestive of ACS lasting more than 15 minutes with new, transient or persistent ST segment ischemic electrocardiogram (ECG) changes [20] and ultimate disposition as acute MI, including STEMI and NSTEMI; unstable angina; or angina requiring emergent revascularization. One intention of this larger investigation was to test for inflammatory processes; therefore, patients with medical conditions and/or taking medications that can affect inflammatory processes were excluded. The specific exclusion criteria were: HIV, malignancy, hepatic or chronic renal disease or dialysis, recent surgery or trauma (>2 months), inflammatory bowel disease, rheumatoid arthritis, chronic

obstructive pulmonary disease, hepatitis, systemic lupus, myocarditis, pericarditis, Crohn's disease or recent (within the previous 2 months) coexisting infections as noted in the patient record. Patients being treated with immunosuppressants or systemic steroids, or those who had recently had antibiotic therapy (i.e., within the past two months) were also excluded, as were patients with active sepsis.

The criteria for participation in the present study were: 1) males 50 years of age and females 55 years of age who participated in the aforementioned larger study on interactive effects of genetics and depression on ACS outcomes; 2) accrued by July, 2011; 3) have a completed BDI-II screening questionnaire; and 4) have an available stored plasma sample for ET-1 analysis. The larger study and the present study were approved by the Committee for the Protection of Human Subjects associated with the hospitals and university. Informed consent was obtained from all participants of the larger study. At the time of informed consent participants were informed that their plasma samples, clinical data, and DNA would be stored indefinitely for use in future medical research investigations.

Procedures

Patient interview and medical chart review were utilized to obtain information on demographics, previous hospitalization(s), cardiovascular risk factors, medication use, and family health history. Depressive symptom severity was assessed with the BDI-II questionnaire [21, 22] which was administered by the research nurse during the patients' hospital stay, within 2–5 days of admission for ACS. BDI-II is 21-item self-report questionnaire designed to assess depression symptom severity. Each of the items in this questionnaire describes a symptom characteristic of the depression, and respondents indicate on a 0 to 3 scale the intensity with which they have experienced the symptom during the past two weeks. The total BDI-II score is the sum of all items from 0 to 63. The BDI-II had been previously used in ACS population and had been shown to have high internal consistency reliability [23, 24]. Cronbach's alpha for the current sample was 0.92.

Blood samples were drawn within 2–3 hours of ACS admission to emergency department. Samples were stored on ice immediately after collection and transported to the University of Texas Health Science Center at Houston, School of Nursing Bioscience Laboratory (Houston, TX). The samples were then centrifuged and separated; and the plasma layer of each tube was transferred to labeled aliquot tubes and frozen at -80° . The samples remained frozen until analysis. ET-1 assessment was performed at the Atherosclerosis Clinical Research Laboratory located at the Baylor College of Medicine (Houston, TX). ET-1 analysis was conducted via enzyme linked immunosorbent assay, using a colorimetric sandwich kit (R&D Systems Inc., Minneapolis, MN). The kit has a sensitivity of 0.207 pg/mL and can be used to measure ET-1 in human cell culture supernates, serum, plasma, and urine samples. Intra-assay and inter-assay coefficients of variation for the current sample were 4.0% and 3.9%, respectively.

Statistical Analyses

The distribution of ET-1 was skewed (skewness=3.98, SE=0.96), and values were thus transformed using square root of logarithmic transformed ($ET-1T = \sqrt{\log_{10}(1+ET-1)}$).

The transformed variable did not differ significantly from normality under Shapiro-Wilk test. For further analyses, the BDI-II scores and ET-1T values were initially introduced as continuous variables. Using local regression (LOESS curve), the linearity of the relationship between the BDI-II scores and ET-1T was then examined and not found to be satisfactory. To correct for the nonlinearity, the BDI-II scores were classified into four categories using established values that represent no depression, mild, moderate, and severe levels of depressive symptoms - the scores of 14, 20, and 29, respectively [21]. The association between classified BDI-II score and ET-1T was then calculated in both simple and multivariable linear regression models. The multivariable model controlled for factors that have the potential of influencing ET-1 level, i.e. left ventricular ejection fraction [LVEF] [15], hypertension [25], diabetes [26], use of beta-blockers [27] and statins [28], current smoking, age [29], race/ethnicity and gender [30]. Descriptive statistics and multivariable models of ET-1T were examined using SPSS 19 statistical package for Windows (SPSS Inc, Chicago, Illinois). All statistical tests were two-tailed with alpha level set at 0.05.

Results

The average age of the study sample was 45.9 years (SD=5.97 years), with 44.4% female; 45% of the participants were White, 23.5% were Black, 24.2% were Hispanic, and 7.2% were of other race/ethnicity (Table 1). Overall, more than 40% of the participants had a history of previous MI, almost 36% were active smokers, 60% had a body mass index ≥ 30 , 30% were diabetic, 63% were hypertensive, 58% were dyslipidemic. With respect to medications, 76% of the patients were taking aspirin, 35% were taking beta-blockers, 45% were taking angiotensin converting enzyme inhibitors, 39% were taking statins, and 16% were taking anti-depressants. Almost 27% of the participants reported ever being diagnosed with depression, and 43% reported feeling depressed in the year preceding their admission for ACS. Mean BDI-II score was 13.67 (SD=10.76). The distribution of the BDI-II scores is shown in Figure 1.

The range in ET-1 was 0.402 pg/mL – 10.00 pg/mL (mean=1.68; SD=1.04, median=1.42, inter-quartile range: 1.09, 2.08). The mean ET-1 was 1.618 pg/mL, 1.516 pg/mL, 1.533 pg/mL, and 2.521 pg/mL in patients with no depressive symptoms, mild, moderate, and severe depressive symptoms, respectively.

In unadjusted regression analyses, ET-1T was related to classified BDI-II score ($\chi^2(3) = 9.469$, $p = 0.024$; Table 2, Unadjusted Model). Post hoc tests with sequential Sidak correction for multiple comparisons indicated that ET-1T differed significantly among patients with severe depressive symptoms (BDI-II score ≥ 29) and those with any of the other level of depressive symptoms ($p = 0.035$ for each). Parameter estimates for each level of depressive symptoms severity for the unadjusted regression model are shown in Table 3.

The classified BDI-II score remained significant ($\chi^2(3) = 8.430$, $p = 0.038$) in the multivariable regression model that adjusted for LVEF, hypertension, diabetes, use of betablockers and statins, current smoking, age, race/ethnicity, and gender (Table 2, Adjusted Model).

Discussion

Evidence accumulated over the last three decades has consistently demonstrated that depression is associated with poor post-acute coronary event prognosis [1–3]. These findings have led researchers to focus their efforts on understanding the mechanisms by which depression contributes to adverse post-event outcomes. Some plausible biological pathways include platelet hyper-reactivity, inflammation, autonomic dysregulation, hypothalamic-pituitary axis imbalance and endothelial dysfunction. Potential behavioral pathways include poor adherence to pharmacological therapy and therapeutic lifestyle changes [1]. In the current study we found that severe depressive symptoms were associated with elevated ET-1. These results extend the findings of Burg et al. [16] to another CAD subgroup, by demonstrating that the level of circulating ET-1 in younger post-ACS patients was significantly higher in persons with severe depressive symptoms than in those with mild and moderate depressive symptoms.

The current finding adds to the previous knowledge regarding the pathways that may link depression to post-ACS morbidity and mortality. Following acute cardiac events, elevated plasma ET-1 may contribute to increased coronary and peripheral resistance, leading to increased afterload and myocardial ischemia [6]. Of particular relevance to the current discussion, ET-1 has been shown to augment the vasoconstrictive effects of norepinephrine and serotonin [38, 39]. Depression is associated with an imbalance of both of these hormones; thus ET-1, by virtue of its independent vasoconstrictive properties and in synergy with norepinephrine and serotonin, may lead to pronounced vasoconstriction, thereby contributing to poor post-ACS prognosis associated with depression.

Although the processes by which depression may contribute to elevation in circulating ET-1 are yet to be definitively determined, potential mediators may include reduced NO bioavailability, decreased parasympathetic activity, and increased levels of pro-inflammatory cytokines. Reduced bioavailability of NO in depression has been previously demonstrated [31, 32]. As ET-1 inhibition is largely influenced by NO, reduced NO availability could disinhibit secretion of ET-1, leading to a perturbation in vascular homeostasis. It has also been demonstrated that depression is associated with the reduced cardiac vagal control [1], which has been shown to increase ET-1 dynamically [33]. Lastly, secretion of the pro-inflammatory cytokine, tumor necrosis factor (TNF) – α , which is both associated with depression [34] and enhanced by withdrawal of cardiac vagal control [35], promotes ET-1 release by macrophages [36, 37]. Thus, a number of pathways involved in the regulation of ET-1 are also activated in concordance with depression, thus providing multiple avenues by which depression could lead to an increase in circulating ET-1.

The mean BDI-II in this study was high – 13.47. This is probably due to the younger age of the study participants. Indeed, in our previous investigation (n=1140) [17], compared to their older counterparts, younger ACS patients (males 50 years of age and females 55 years of age) were significantly more likely to have a higher BDI-II depression score, and to feel depressed during the year preceding their admission for ACS. Importantly, in one study [19], after adjustment for disease severity and comorbidities, somatic symptoms of depression and hopelessness were associated with poor post-MI prognosis in younger, but

not in older patients. In general, the research exploring the links between depression and coronary events/post-event prognosis in younger patients is scarce. Future research should continue exploring the relationship between psychosocial factors, post-coronary event prognosis, and the mechanisms involved in these links in younger subgroups.

Strikingly, with the 40% history of previous MI, only 35% of the participants were taking beta-blockers and 39% were taking statins prior to hospital admission. This discrepancy is likely to be a multifactorial issue, related to lack of access to care, medication costs, and noncompliance, among other issues. Lack of access to care and medication costs are particularly compelling reasons, given that 76% of the participants reported taking aspirin. The aforementioned explanations are, however, speculative, and we do not have specific data to support them.

Limitations

The participants of the present study were recruited from hospitals located in a prominent medical center of a large city. Moreover, due to the nature of the larger investigation, patients with certain medical characteristics, such as those with active inflammatory illness among others, were excluded. Taken together, the resulting sample may not be entirely representative of the hospitalized population of younger individuals with ACS and thus caution should be utilized when generalizing the findings of this investigation.

A limitation of this study is its cross-sectional design. Therefore, examination of whether ET-1 mediates the relationship of depression to post-ACS outcomes was not possible. In addition, the number of covariates accessible for analysis was limited; as for example, data regarding ACS severity (i.e. peak troponin levels) were not available, raising a chance of an undetected confounding. Furthermore, assessment of additional biomarkers, i.e. proinflammatory cytokines, platelet factors, or other markers of vasomotor tone in relation to depression was not performed. Thus the possibility that the observed association between depression and circulating ET-1 could be eliminated by inclusion of these other markers does exist. The aforementioned limitations will be in part addressed in our future study which will examine the relationship between depressive symptoms, ET-1, markers of inflammation, and long-term post-ACS outcomes in younger ACS patients.

Some [41] but not all [42] studies have reported that depression is associated with a delay in seeking treatment for MI symptoms. At the same time, studies show that during MI, ET-1 is secreted in a dynamic fashion, being markedly elevated within hours following MI and peaking at 6 hours [40]. Due to the potential delay in seeking care, it is thus conceivable that depressed participants of this study presented to the emergency department closer to ET-1 peak time. Unfortunately, data regarding the time that had elapsed since ACS onset were not obtained in the parent study. Our inability to include these data could have introduced bias into the present investigation.

Conclusions

In summary, this study found that circulating ET-1 in younger post-ACS patients with severe depressive symptoms (BDI-II score ≥ 29) was significantly higher than that in patients

with mild and moderate depressive symptoms. The present study is unique in a) being the first investigation to examine the relationship between severity of depressive symptoms and ET-1 in post-ACS patients and b) one of the few investigations involving a younger and racially/ethnically diverse ACS cohort. Despite the potential limitations, the findings of this study provide valuable preliminary data regarding the relationship between depressive symptom severity and plasma ET-1 in a younger ACS sample.

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Abbreviations

ACS	acute coronary syndrome
BDI	Beck Depression Inventory
BMI	body mass index
CAD	coronary artery disease
ET-1	endothelin - 1
ET-1T	transformed ET-1
LVEF	left ventricular ejection fraction
MI	myocardial infarction
NO	nitric oxide
pg/ml	pictogram per milliliter
TNF-α	tumor necrosis factor – α

References

1. Huffman JC, Celano CM, Januzzi JL. The relationship between depression, anxiety, and cardiovascular outcomes in patients with acute coronary syndromes. *Neuropsychiatr Dis Treat*. 2010 May 6;6:123–136. [PubMed: 20505844] Khawaja IS, Westermeyer JJ, Gajwani P, Feinstein RE. Depression and coronary artery disease: The association, mechanisms, and therapeutic implications. *Psychiatry (Edmont)*. 2009 Jan; 6(1):38–51. [PubMed: 19724742]
2. Khawaja IS, Westermeyer JJ, Gajwani P, Feinstein RE. Depression and coronary artery disease: The association, mechanisms, and therapeutic implications. *Psychiatry (Edmont)*. 2009 Jan; 6(1):38–51. [PubMed: 19724742]
3. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: A meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur Heart J*. 2006 Dec; 27(23):2763–2774. [PubMed: 17082208]
4. Meijer A, Conradi HJ, Bos EH, Thombs BD, van Melle JP, de Jonge P. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: A meta-analysis of 25 years of research. *Gen Hosp Psychiatry*. 2011 May-Jun;33(3):203–216. [PubMed: 21601716]

5. Winkles JA, Alberts GF, Brogi E, Libby P. Endothelin-1 and endothelin receptor mRNA expression in normal and atherosclerotic human arteries. *Biochem Biophys Res Commun.* 1993 Mar 31; 191(3):1081–1088. [PubMed: 8466485]
6. Ehrenreich H, Anderson RW, Fox CH, Rieckmann P, Hoffman GS, Travis WD, Coligan JE, Kehrl JH, Fauci AS. Endothelins, peptides with potent vasoactive properties, are produced by human macrophages. *J Exp Med.* 1990 Dec 1; 172(6):1741–1748. [PubMed: 1701822]
7. Khan IA. Role of endothelin-1 in acute myocardial infarction. *Chest.* 2005 May; 127(5):1474–1476. [PubMed: 15888812]
8. Kinlay S, Behrendt D, Wainstein M, Beltrame J, Fang JC, Creager MA, Sekwyn AP, Ganz P. Role of endothelin-1 in the active constriction of human atherosclerotic coronary arteries. *Circulation.* 2001 Sep 4; 104(10):1114–1118. [PubMed: 11535565]
9. Yanagisawa M, Kurihara H, Kimura S, Tomobe Y, Kobayashi M, Mitsui Y, Yasaki Y, Goto K, Masaki T. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature.* 1988 Mar 31; 332(6163):411–415. [PubMed: 2451132]
10. Chabrier PE. The role of endothelin in the vessel wall. *Baillieres Clin Haematol.* 1993 Sep; 6(3): 577–591. [PubMed: 8025344]
11. Lerman A, Holmes DR Jr, Bell MR, Garratt KN, Nishimura RA, Burnett JC Jr. Endothelin in coronary endothelial dysfunction and early atherosclerosis in humans. *Circulation.* 1995 Nov 1; 92(9):2426–2431. [PubMed: 7586341]
12. Zeiher AM, Goebel H, Schachinger V, Ihling C. Tissue endothelin-1 immunoreactivity in the active coronary atherosclerotic plaque. A clue to the mechanism of increased vasoreactivity of the culprit lesion in unstable angina. *Circulation.* 1995 Feb 15; 91(4):941–947. [PubMed: 7850978]
13. Katayama T, Yano K, Nakashima H, Takagi C, Honda Y, Suzuki S, Iwasaki Y. Clinical significance of acute-phase endothelin-1 in acute myocardial infarction patients treated with direct coronary angioplasty. *Circ J.* 2005 Jun; 69(6):654–658. [PubMed: 15914941]
14. Omland T, Lie RT, Aakvaag A, Aarsland T, Dickstein K. Plasma endothelin determination as a prognostic indicator of 1-year mortality after acute myocardial infarction. *Circulation.* 1994 Apr; 89(4):1573–1579. [PubMed: 8149523]
15. Yip HK, Wu CJ, Chang HW, Yang CH, Yu TH, Chen YH, Hang CL. Prognostic value of circulating levels of endothelin-1 in patients after acute myocardial infarction undergoing primary coronary angioplasty. *Chest.* 2005 May; 127(5):1491–1497. [PubMed: 15888819]
16. Burg MM, Martens EJ, Collins D, Soufer R. Depression predicts elevated endothelin-1 in patients with coronary artery disease. *Psychosom Med.* 2011 Jan; 73(1):2–6. [PubMed: 20947777]
17. Yammine L, Frazier L. Comparison of demographic, psychosocial, and clinical characteristics among younger and older persons with acute coronary syndrome. *J Am Acad Nurse Pract.* 2013 Feb; 25(2):103–108.
18. Lavie CJ, Milani RV. Adverse psychological and coronary risk profiles in young patients with coronary artery disease and benefits of formal cardiac rehabilitation. *Arch Intern Med.* 2006 Sep 25; 166(17):1878–1883. [PubMed: 17000945]
19. Denollet J, Freedland KE, Carney RM, de Jonge P, Roest AM. Cognitive-affective symptoms of depression after myocardial infarction: Different prognostic importance across age groups. *Psychosom Med.* 2013 Sep; 75(7):701–708. [PubMed: 23873711]
20. Valgimigli M, Agnoletti L, Curello S, Comini L, Francolini G, Mastrorilli F, et al. Serum from patients with acute coronary syndromes displays a proapoptotic effect on human endothelial cells: A possible link to pan-coronary syndromes. *Circulation.* 2003 Jan 21; 107(2):264–270. [PubMed: 12538426]
21. Beck, AT.; Steer, RA. Manual for the Beck Depression Inventory. San Antonio, TX: Psychological Corporation; 1993.
22. Beck AT, Ward CH, Mendelson M. An inventory for measuring depression. *Arch Gen Psychiatry.* 1961; 4:561–571. [PubMed: 13688369]
23. Di Benedetto M, Lindner H, Hare DL, Kent S. Depression following acute coronary syndromes: A comparison between the cardiac depression scale and the beck depression inventory II. *J Psychosom Res.* 2006 Jan; 60(1):13–20. [PubMed: 16380305]

24. Dias CC, Mateus PS, Mateus C, Bettencourt N, Santos L, Adao L, Sampaio F, Fonseca C, Simoes L, Coelho R, Ribeiro VG. Acute coronary syndrome and depression. *Rev Port Cardiol.* 2005 Apr; 24(4):507–516. [PubMed: 15977775]
25. Shreenivas S, Oparil S. The role of endothelin-1 in human hypertension. *Clin Hemorheol Microcirc.* 2007; 37(1–2):157–178. [PubMed: 17641406]
26. Kim JA, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction: Molecular and pathophysiological mechanisms. *Circulation.* 2006 Apr 18; 113(15):1888–1904. [PubMed: 16618833]
27. Virdis A, Ghiadoni L, Taddei S. Effects of antihypertensive treatment on endothelial function. *Curr Hypertens Rep.* 2011 Aug; 13(4):276–281. [PubMed: 21499710]
28. Mraiche F, Cena J, Das D, Vollrath B. Effects of statins on vascular function of endothelin-1. *Br J Pharmacol.* 2005 Mar; 144(5):715–726. [PubMed: 15678081]
29. Kanaya AM, Barrett-Connor E, Wassel Fyr CL. Endothelin-1 and prevalent coronary heart disease in older men and women (the rancho bernardo study). *Am J Cardiol.* 2007 Feb 15; 99(4):486–490. [PubMed: 17293190]
30. Yammine L, Kang DH, Baun MM, Meininger JC. Endothelin-1 and psychosocial risk factors for cardiovascular disease: A systematic review. *Psychosom Med.* 2014 Feb; 76(2):109–121. [PubMed: 24434952]
31. Chrapko W, Jurasz P, Radomski MW, Archer SL, Newman SC, Baker G, Lara N, Le Melleo GM. Alteration of decreased plasma NO metabolites and platelet NO synthase activity by paroxetine in depressed patients. *Neuropsychopharmacology.* 2006 Jun; 31(6):1286–1293. [PubMed: 16319917]
32. Chrapko WE, Jurasz P, Radomski MW, Lara N, Archer SL, Le Melleo JM. Decreased platelet nitric oxide synthase activity and plasma nitric oxide metabolites in major depressive disorder. *Biol Psychiatry.* 2004 Jul 15; 56(2):129–134. [PubMed: 15231445]
33. Burg MM, Soufer A, Lampert R, Collins D, Soufer R. Autonomic contribution to endothelin-1 increase during laboratory anger-recall stress in patients with coronary artery disease. *Mol Med.* 2011 May-Jun; 17(5–6):495–501. [PubMed: 21267513]
34. O'Brien SM, Scott LV, Dinan TG. Cytokines: Abnormalities in major depression and implications for pharmacological treatment. *Hum Psychopharmacol.* 2004 Aug; 19(6):397–403. [PubMed: 15303243]
35. Marsland AL, Gianaros PJ, Prather AA, Jennings JR, Neumann SA, Manuck SB. Stimulated production of proinflammatory cytokines covaries inversely with heart rate variability. *Psychosom Med.* 2007 Nov; 69(8):709–716. [PubMed: 17942840]
36. Kahaleh MB, Fan PS. Effect of cytokines on the production of endothelin by endothelial cells. *Clin Exp Rheumatol.* 1997 Mar-Apr; 15(2):163–167. [PubMed: 9196868]
37. Woods M, Mitchell JA, Wood EG, Barker S, Walcot NR, Rees GM, Warner TD. Endothelin-1 is induced by cytokines in human vascular smooth muscle cells: Evidence for intracellular endothelin-converting enzyme. *Mol Pharmacol.* 1999 May; 55(5):902–909. [PubMed: 10220569]
38. Goddard AW, Ball SG, Martinez J, Robinson MJ, Yang CR, Russell JM, Shekhar A. Current perspectives of the roles of the central norepinephrine system in anxiety and depression. *Depress Anxiety.* 2010 Apr; 27(4):339–350. [PubMed: 19960531]
39. Yang ZH, Richard V, von Segesser L, Bauer E, Stulz P, Turina M, Luscher TF. Threshold concentrations of endothelin-1 potentiate contractions to norepinephrine and serotonin in human arteries. A new mechanism of vasospasm? *Circulation.* 1990 Jul; 82(1):188–195. [PubMed: 2194695]
40. Stewart DJ, Kubac G, Costello KB, Cernacek P. Increased plasma endothelin-1 in the early hours of acute myocardial infarction. *J Am Coll Cardiol.* 1991 Jul; 18(1):38–43. [PubMed: 2050938]
41. Bunde J, Martin R. Depression and prehospital delay in the context of myocardial infarction. *Psychosom Med.* 2006 Jan-Feb; 68(1):51–57. [PubMed: 16449411]
42. Schlyter M, Andre-Petersson L, Engstrom G, Tyden P, Ostman M. The impact of personality factors on delay in seeking treatment of acute myocardial infarction. *BMC Cardiovasc Disord.* 2011 May 19; 11:2261–11-21.

Highlights

- Endothelin (ET)-1 is a potent endogenous vasoconstrictor
- ET-1 has been previously linked to adverse post-ACS outcomes
- We examined the relationship of depressive symptoms to ET-1 in younger ACS patients
- Severe depressive symptoms were associated with elevated ET-1 in the study sample

Figure 1.
Distribution of BDI-II scores
Abbreviation: BDI = Beck Depression Inventory

Table 1**Patient Characteristics**

Variable	Total Cohort (n=153)
Age, mean (SD), years	45.9 (5.97)
Female (%)	44.4
Race/Ethnicity (%)	
White	45.1
Black	23.5
Hispanic	24.2
Other	7.2
LVEF (%)	
<35	10.3
35–39	2.2
40–54	35.3
55	52.2
Hx of Previous MI (%)	40.5
Diabetes (%)	30.1
Hypertension (%)	63.4
Dyslipidemia (%)	57.5
Obesity (BMI ≥30) (%)	60.1
Current Smoking (%)	35.9
Medications (%)	
Beta-blockers	34.6
ACE inhibitors	45.1
Statins	39.2
Aspirin	75.8
ET-1, mean (SD), pg/mL	1.68(1.04)
Depression Related Variables	
Depression ever been diagnosed or treated (%)	26.8
Depression feeling in the last year (%)	42.7
Currently taking anti-depressants (%)	16.3
Mean BDI-II score (SD)	13.67 (10.76)
Depressive symptom severity, BDI-II (%):	
Mild	14.4
Moderate	17.6
Severe	9.8

Abbreviations: ACE = angiotensin converting enzyme; BDI = Beck Depression Inventory; BMI = body mass index; ET = endothelin; Hx = history; LVEF = left ventricular ejection fraction; MI = myocardial infarction; SD = standard deviation

Table 2

Unadjusted and Adjusted Regression Models

Variable	df	Wald Chi-Square	p-value
Unadjusted model			
BDI-II Score	3	9.469	.024
Adjusted model			
BDI-II Score	3	8.430	.038
Race/ethnicity	3	1.605	.658
Gender	1	3.113	.078
Age	1	.643	.423
LVEF	3	20.524	.000
Hypertension	1	.629	.428
Diabetes	1	.711	.399
Use of Beta-blockers	1	.971	.160
Use of Statins	1	.193	.660
Current Smoking	1	.209	.647

Abbreviations: BDI = Beck Depression Inventory, LVEF = Left Ventricular Ejection Fraction

Table 3

Variation of transformed ET-1 with depressive symptoms severity levels

Predictor	Parameter estimate	95% Confidence Interval		p-value
		Lower	Upper	
Intercept	.624	.603	.644	.000
Mild depressive symptoms	-.015	-.062	.031	.511
Moderate depressive symptoms	.001	-.044	.045	.977
Severe depressive symptoms	.087	.032	.142	.002

Abbreviation: ET = endothelin

Note: "No depression" is used as the reference value