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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 h 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 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.

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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

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.

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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. An 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 the participants of a larger longitudinal investigation on the 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 min 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 the 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 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 the 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 h of ACS admission to the 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, and 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 the square root of logarithmic transformed $\left(\text{ET-1T} = \sqrt{\log_{10}(1 + \text{ET-1})}\right)$. The transformed variable did not differ significantly from normality under the 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

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