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Relationship of depression, stress and endothelial function in stable angina patients

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HIGHLIGHTS

- We studied relationships between EPCs, FMD and DASS in stable angina patients.
- A high depression or stress score was associated with impaired brachial FMD.
- A high depression or stress score was related to depletion of circulating EPCs.
- Stress was only related to depletion of mature, but not immature circulating EPCs.
- A high depression score was an independent predictor for impaired brachial FMD.

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ABSTRACT

Endothelial dysfunction has been considered as one of potential mechanisms by which depression and stress might contribute to the development of coronary artery disease (CAD). Recent studies suggest that circulating endothelial progenitor cells (EPCs) and brachial artery flow-mediated dilation (FMD) are related to endothelial function and progression of CAD. We investigated the relationships between the level of circulating CD34/KDR$^+$ EPCs and CD133/KDR$^+$ EPCs, brachial FMD, and scores of depression and stress measured with the Depression Anxiety Stress Scales in 288 stable angina patients without major psychiatric disorders. As defined by the ≥75th percentile, 100 (35%) subjects had high depression score (≥8), and 84 (29%) subjects had high stress score (≥10). Subjects with high depression or stress score had significantly lower FMD (1.86 ± 0.14 vs. 3.63 ± 0.17%, $p < 0.001$; 2.05 ± 0.18 vs. 3.48 ± 0.17%, $p < 0.001$) and percentage of circulating CD34/KDR$^+$ EPCs (0.97 ± 0.11 vs. 1.94 ± 0.17%, $p < 0.001$; 1.09 ± 0.13 vs. 1.68 ± 0.16%, $p = 0.005$), but not CD133/KDR$^+$ EPCs (0.52 ± 0.04 vs. 0.66 ± 0.06%, $p = 0.057$; 0.61 ± 0.05 vs. 0.59 ± 0.05%, $p = 0.833$), as compared with subjects with normal depression or stress score. Multivariate regression analysis indicated that high depression score (OR 1.09, 95% CI: 1.04–1.15, $p < 0.001$), but not stress score or percentage of circulating EPCs, independently predicted impaired brachial FMD. In conclusions, our results demonstrated that in stable angina patients without major psychiatric disorders, a high depression or stress score was related to attenuated brachial FMD and depletion of circulating EPCs. However, only the depression score, but not the stress score or the level of EPCs, was an independent predictor for decreased brachial FMD.

1. Introduction

Depression and stress are associated with the development of coronary artery disease (CAD) and are major risk factors for adverse outcomes of CAD [1,2]. Previous studies have demonstrated that depression and CAD have a bidirectional relationship, i.e., CAD can cause depression and depression is an independent risk factor for CAD [3]. Among different psychiatric disorders and environmental factors, depression and stress are more prominent risk factors associated with the pathogenesis of CAD [4,5]. Although the potential mechanism remains unclear, one possibility is that depressive and stress symptoms contribute to CAD by fostering endothelial dysfunction [6,7].

Endothelial progenitor cells (EPCs) are immature cells with a capability to differentiate into mature endothelial cells. They originate from the bone marrow and can be mobilized into the bloodstream to participate in the repair of damaged vascular endothelium and contribute to neovascularization and reendothelialization [8]. EPCs express distinct biomarkers in different stages of their maturation. Mature EPCs present CD34 marker and immature EPCs express CD133 marker on

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the surface of cells [9]. Previous studies have shown that EPCs are correlated with endothelial function and independently predict cardiovascular events [10]. Furthermore, recent data from both experimental and clinical studies have demonstrated that the number of circulating EPCs is reduced in patients with stable CAD, but increased in those with unstable angina and acute myocardial infarction [11–14]. Moreover, a recent study has shown that the number of circulating EPCs is reduced in patients with a current episode of major depression [15].

Brachial artery flow-mediated dilation (FMD) has been established as a common noninvasive assessment of vascular endothelial function [16]. Previous studies have demonstrated that impaired FMD is correlated with prognosis of CAD patients and even predicts outcomes for patients with low risk of cardiac events [17,18]. Furthermore, recent studies have shown that stress attenuates FMD in normal subjects [19,20]. Moreover, therapies which improve stress management can also improve cardiac function and FMD [21,22]. A recent study has also reported that CAD patients with significant depressive symptomatology showed attenuated FMD, and the use of antidepressant medication was associated with improved FMD [23]. These findings suggest that endothelial dysfunction may be one of the potential mechanisms by which depression and stress can contribute to the development of CAD.

However, there is little data on the relationships between the level of circulating EPCs, endothelial function, and depression and stress. Therefore, we aimed to determine the relationships between mature and immature circulating EPCs, endothelial function, and depressive and stress symptoms in stable angina patients.

2. Methods

2.1. Subjects

We studied 288 consecutive patients with stable angina who were recruited from the cardiology department of Beijing Anzhen Hospital, Capital Medical University, from August 2011 to September 2012. The age of the subjects ranged from 45 to 78 years, and 228 (79%) of them were men. Subjects were eligible to participate in the study if they had ≥50% stenosis in at least one coronary artery as detected by coronary angiography, based on effort angina symptoms consistent with coronary computed tomography, or evidence of exercise induced ischemia by treadmill or cardiac perfusion testing. Subjects with unstable angina, acute myocardial infarction, cardiogenic shock, cardiomyopathy, heart failure, valvular heart disease, cardiac arrhythmias, history of myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft surgery, resting blood pressure >200/120 mm Hg, serum creatinine level >2.5 mg/dl (if male) or >2.0 mg/dl (if female), alanine aminotransferase or aspartate aminotransferase 3 times that of normal, metabolic, neoplastic, or systemic illnesses and recent infection, febrile illness or inflammatory disease within the past 3 months were excluded. Those patients whose medical history did contain any major psychiatric disorders and/or who had a clinical diagnosis of a current psychiatric disorder were also excluded. Subjects in this study were all of Chinese ethnicity. This study was approved by the Research Ethics Board of Beijing Anzhen Hospital and informed written consent was obtained from all subjects before their participation.

2.2. Study design

All the subjects' baseline demographic and clinical characteristics, blood sampling and vascular ultrasound were obtained on the same day. Cardiovascular risk factors, including tobacco smoking, hypertension, diabetes mellitus, and hypercholesterolemia, were evaluated. The body height and weight, blood pressure and body mass index (BMI) of all the subjects were measured as previously described [24]. Hypertension was defined as either resting systolic or diastolic blood pressure of ≥140/90 mm Hg at two different times or on medications. Diabetes mellitus was defined as a fasting serum glucose level of ≥7.1 mmol/l or on medications. Hypercholesterolemia was defined as a fasting total serum cholesterol level of ≥4.9 mmol/l or on medications. Smoking status was recorded as either smoker (past and current) or nonsmoker. Fasting blood samples were obtained from all subjects to determine the levels of serum creatinine, glucose and lipid.

2.3. Flow cytometry

The circulating EPCs were defined by the expression of surface markers CD34/KDR$^+$ and CD133/KDR$^+$, and their numbers were measured by fluorescence-activated cell analysis of peripheral blood sample. As previously described [24], 100 μl of peripheral blood was incubated with a phycoerythrin-conjugated monoclonal antibody against human KDR (Sigma, St Louis, MO, USA), followed by a fluorescein isothiocyanate (FITC)-conjugated CD34 and CD133 antibodies (Beckman Coulter, Fullerton, CA, USA). FITC-labeled anti-human CD45 antibody was used for differential gating during flow analysis. FITC labeled IgG1a (Beckman Coulter) and phycoerythrin-labeled IgG2b (Becton Dickinson, Franklin Lakes, NJ, USA) served as the isotypic control for color compensation. Analysis was conducted with an automated fluorescence-activated cell counter (Elite, Beckman Coulter) in which 1,000,000 events were counted. The percentages of all the measured components defined as the absolute cell counts divided by the lymphocyte counts were calculated.

2.4. Brachial endothelial function

Vascular ultrasound was conducted using a high-resolution ultrasound system (Agilent Sonos 5500; Philips, Andover, MA, USA) with the use of a 7.5-MHz linear array transducer by 2 experienced operators without knowledge of the subjects. All of the scanned images were stored digitally and analyzed offline by the same operators, who were not informed of the identity of the studied subjects. All the subjects were studied in the fasting state, and all vasoactive medications (including beta-blockers, calcium channel blockers, and nitrates) were withheld for ≥12 h before the study. As described previously [25,26], longitudinal scans of the brachial artery were obtained at rest, and then brachial FMD was induced by the inflation of a pneumatic tourniquet placed on the forearm to a pressure of 250 mm Hg for 5 min. Then, the cuff was released, and serial imaging of the brachial artery was recorded for 5 min. FMD was defined as the percentage change in brachial artery diameter from the baseline scan to 1 min after cuff deflation.

2.5. Assessment of depression and stress status

Depression and stress scores were assessed using Depression Anxiety Stress Scales (DASS), which is a 21-item questionnaire of self-reported measure of depressive, anxiety, and stress symptomatology [27]. In brief, the DASS is separated into 3 dimensions: depression, anxiety and chronic stress. Each dimension is subsequently divided into scores that reveal (1) Normal, (2) Mild, (3) Moderate, (4) Severe and (5) Extremely Severe. Although the clinical diagnosis of depression cannot be based on this questionnaire, it is commonly used by psychiatrists to evaluate subjects' depression status as a reliable and valid instrument [28]. This study only assessed the scores of depression and stress, which are more prominent risk factors for cardiovascular diseases than anxiety [5].

2.6. Statistical analysis

Continuous variables were expressed as mean ± SEM. Depression and stress scores were categorized by the tertile distribution of the study population in analysis. Categorical data were expressed as frequencies and percentages. Comparisons between groups were performed using Student's t test or Mann–Whitney test, as appropriate. Comparisons of