



# Effect of anxiety and depression on endothelial function and inflammation degree of coronary heart disease patients with angina pectoris

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## ABSTRACT

**Objective:** To study the effect of anxiety and depression on endothelial function and inflammation degree of coronary heart disease patients with angina pectoris. **Methods:** 80 cases of patients diagnosed with angina pectoris of coronary heart disease in our hospital from May 2012 to August 2014 were enrolled for study; anxiety and depression were judged by anxiety subscale (HADS-a) and depression subscale (HADS-d). Endothelial progenitor cell and endothelial microparticle contents in peripheral blood as well as serum ET-1, CGRP, IL-6, IL-6R, IL-18, ADAMTS-1 and NO contents were detected. **Results:** EPC, NO and CGRP contents of angina pectoris patients with anxiety were lower than those of angina pectoris patients without anxiety, and EMP, ET-1, IL-6, IL-6R, IL-18 and ADAMTS-1 contents were higher than those of angina pectoris patients without anxiety; EPC, NO and CGRP contents of angina pectoris patients with depression were lower than those of angina pectoris patients without depression, and EMP, ET-1, IL-6, IL-6R, IL-18 and ADAMTS-1 contents were higher than those of angina pectoris patients without depression. **Conclusions:** Angina pectoris of coronary heart disease patients complicated with anxiety and depression have endothelial dysfunction and inflammatory reaction activation; endothelial dysfunction and inflammatory reaction activation are possible pathways that anxiety and depression cause the progression of coronary heart disease.

## 1. Introduction

Angina pectoris of coronary heart disease is a common cardiovascular system disease and its development process will be accompanied by anxiety, depression and other negative emotions. Existing clinical research shows that negative emotional reaction and mental state have a negative impact on angina pectoris of coronary heart disease, easily lead to disease progression and increase the risk of unstable angina pectoris, myocardial infarction and other serious cardiovascular events[1]. Relationship between anxiety, depression and progression of angina pectoris of coronary heart disease has received more and more recognition and attention, but intrinsic molecular mechanism that connects the two remains to be elucidated. Endothelial dysfunction and inflammatory reaction

activation are important pathological features of coronary heart disease patients with angina pectoris[2]. In the following research, the effect of anxiety and depression on endothelial function and inflammation degree of coronary heart disease patients with angina pectoris was analyzed.

## 2. Case information and research materials

### 2.1. Case selection

A total of 80 cases of patients diagnosed with angina pectoris of coronary heart disease in our hospital from May 2012 to August 2014 were selected for study. Including criteria are as follows: (1) first diagnosis and without history of drug therapy for coronary heart disease; (2) meeting the diagnosis of stable angina pectoris; (3) coronary angiography confirmed stenosis of one or more than one major coronary arteries was more than 50%. Excluding criteria were as follows: (1) unstable or variant angina pectoris patients; (2)

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taking glyceryl trinitrate, isosorbide dinitrate, and other drugs before; (3) complicated with cerebral vascular diseases.

## 2.2. Materials

Flow cytometer was from Beckman Company in the US and ELIASA was from Bio-tek Company in the US; FITC and PE labeled monoclonal antibodies as well as negative control IgG were from Sigma Company, ELISA kits and NO detection kits were from Roche Company.

## 2.3. Anxiety and depression evaluation methods

Same group of doctors determined whether patients had depression or/and anxiety through core symptom inquiry methods; then anxiety subscale (HADS-a) and depression subscale (HADS-d) in HADS scales were combined for further evaluation of patients' anxiety and depression, HADS-a 8 points was determined as with anxiety and HADS-d 8 points was determined as with depression. 31 cases were complicated with anxiety and 33 cases were complicated with depression.

## 2.4. Endothelial progenitor cell (EPC) detection methods

Peripheral venous blood was drawn to incubate FITC labeled CD34 antibodies and PE labeled VEGFR2 antibodies respectively for 15min at room temperature away from light; red cell lysate was added and then centrifugation was done for 5 min with 300 g, supernatant was discarded and then the rest was washed twice with special washing fluid for flow cytometer, finally fixative was added and the percentage of CD34/VEGFR2 double positive cells was detected in flow cytometer.

## 2.5. Endothelial microparticle (EMP) detection methods

Peripheral venous blood was drawn, added to vacuum citrate anticoagulation tube and centrifuged for 10 min with 160 g, platelet-rich plasma was obtained and centrifuged for 6 min with 1 000 g, platelet-poor plasma was obtained to incubate PE labeled CD31 antibodies and FITC labeled CD42 antibodies for 30 min, and then flow cytometer detection was carried out; when detected, standard microspheres with a diameter of 1.0  $\mu\text{m}$  were taken as FSC gate, microparticle inside the gate was  $<1.0 \mu\text{m}$ , FITC and PE fluorescence intensity at 525 nm and 575 nm was analyzed, and then number of endothelial microparticles was calculated.

## 2.6. Serum index evaluation methods

Peripheral blood of enrolled patients was collected and centrifuged to get serum, ELISA kits were used to detect ET-1, CGRP, IL-6, IL-6R, IL-18 and ADAMTS-1 contents, and colorimetry kits were used to detect NO contents. All operations followed the operation steps of kits.

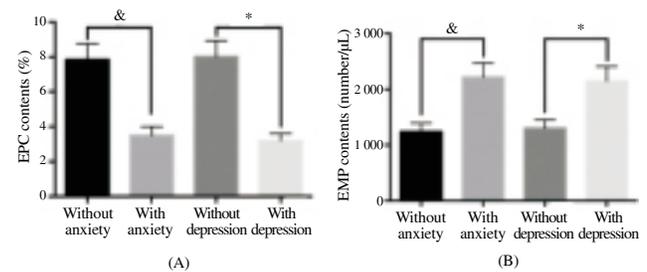
## 2.7. Statistical analysis methods

Detected data was input and analyzed by SPSS21.0 software and comparison of measurement data between two groups was by *t* test. Differences were considered to be statistically significant at a level of  $P < 0.05$ .

## 3. Results

### 3.1. Endothelial injury degree

EPC and EMP contents were detected, and analysis of angina pectoris patients with and without anxiety showed that EPC contents of angina pectoris patients with anxiety were lower than those of angina pectoris patients without anxiety and EMP contents were higher than those of angina pectoris patients without anxiety; analysis of angina pectoris patients with and without depression showed that EPC contents of angina pectoris patients with depression were lower than those of angina pectoris patients without depression and EMP contents were higher than those of angina pectoris patients without depression (Figure 1).



**Figure 1.** Comparison of EPC and EMP contents of angina pectoris patients with different emotional states.

Left figure was for EPC contents and right figure was for EMP contents. &: angina pectoris patients without anxiety vs angina pectoris patients with anxiety; \*: angina pectoris patients without depression vs angina pectoris patients with depression.

### 3.2. Endothelial function related factors

ET-1, NO and CGRP are active substances synthesized and secreted by endothelial cells and they can regulate vascular endothelial function. ET-1, NO and CGRP contents were detected, and analysis of angina pectoris patients with and without depression showed that ET-1 contents of angina pectoris patients with depression were higher than those of angina pectoris patients without depression, NO and CGRP contents were lower than those of angina pectoris patients without depression, and details were shown in Table 1; analysis of angina pectoris patients with and without anxiety showed that ET-1 contents of angina pectoris patients with anxiety were higher than those of angina pectoris patients without anxiety, NO and CGRP contents were lower than those of angina pectoris patients without

anxiety, and details were shown in Table 2.

**Table 1**

Effect of depression on contents of endothelial function related factors of coronary heart disease patients with angina pectoris.

Patients	Case No.	ET-1 (ng/L)	NO ( $\mu$ mol/L)	CGRP (mg/L)
Without depression	47	70.28 $\pm$ 9.59	409.44 $\pm$ 52.34	42.32 $\pm$ 4.42
With depression	33	134.95 $\pm$ 16.53	223.12 $\pm$ 31.23	19.59 $\pm$ 2.34
<i>t</i>		10.192	8.696	14.484
<i>P</i>		<0.05	<0.05	<0.05

**Table 2**

Effect of anxiety on contents of endothelial function related factors of coronary heart disease patients with angina pectoris.

Patients	Case No.	ET-1 (ng/L)	NO ( $\mu$ mol/L)	CGRP (mg/L)
Without anxiety	49	73.17 $\pm$ 8.79	398.59 $\pm$ 45.45	43.18 $\pm$ 5.02
With anxiety	31	128.49 $\pm$ 14.23	231.29 $\pm$ 33.69	17.98 $\pm$ 1.94
<i>t</i>		11.398	7.988	15.049
<i>P</i>		<0.05	<0.05	<0.05

### 3.3. Inflammatory factors

IL-6, IL-6R, IL-18 and ADAMTS-1 are inflammatory factors closely related to angina pectoris of coronary heart disease. IL-6, IL-6R, IL-18 and ADAMTS-1 contents were detected, and analysis of angina pectoris patients with and without depression showed that IL-6, IL-6R, IL-18 and ADAMTS-1 contents of angina pectoris patients with depression were higher than those of angina pectoris patients without depression, details shown in Table 3; analysis of angina pectoris patients with and without anxiety showed that IL-6, IL-6R, IL-18 and ADAMTS-1 contents of angina pectoris patients with anxiety were higher than those of angina pectoris patients without anxiety, details shown in Table 4.

## 4. Discussion

Depression and anxiety are the most common mental disorders in general hospitals. In the progression process of coronary heart disease, incidence of anxiety and depression reaches 15%–20%, and anxiety and depression related symptoms reach 40%. In recent years, lots of studies have proved that anxiety and depression are independent risk factors in development process of coronary heart

disease, and have significant impact on the prognosis of disease[3]. In healthy people, anxiety and depression are risk factors that predict the occurrence of coronary heart disease; in coronary heart disease patients, anxiety and depression are one of the bases that judge prognosis, and also risk factors that increase case fatality rate[4]. At present, the mechanisms how anxiety and depression affect coronary heart disease progression have not been fully elucidated. Related studies believe that endothelial dysfunction and inflammatory reaction activation may be the pathways that connect the pathological process of angina pectoris of coronary heart disease to anxiety and depression, but specific molecules involved in the process are still in an unknown state[5].

Endothelial progenitor cell (EPC) is a type of progenitor cell that can differentiate into mature endothelial cell, it plays an important regulating role in self repair of dysfunctional blood vessel segments as well as endothelial cell homing and differentiation, and it is an important pathway that maintains steady state of vascular endothelium[6]. The number of EPC can directly reflect endothelial self repair ability, and thereby indirectly reflect endothelial function[7]. Endothelial microparticle (EMP) is submicron particle falling from cell membrane under the effect of different physical and chemical injury factors[8]. Recent studies have proved that EMP has the effect of promoting inflammation and inhibiting the synthesis of vasodilative factor NO, and its content can directly reflect endothelial dysfunction degree[9]. In the research, detection of EPC and EMP contents showed that EPC contents of coronary heart disease patients with anxiety and depression significantly decreased and EMP contents significantly increased, which indicated that anxiety and depression would increase endothelial dysfunction of coronary heart disease patients.

Vascular endothelial cell itself can secrete a variety of active substances to maintain its normal function, including calcitonin gene-related peptide (CGRP), nitric oxide (NO), endothelin 1 (ET-1), and so on. CGRP is currently the most powerful vasodilative molecule, and can antagonize the effect of a variety of vasoconstrictive molecules. NO not only has direct vasodilative effect, but also has a certain degree of anti-platelet aggregation and inhibiting vascular smooth muscle cell proliferation effect, and can confront coronary

**Table 3**

Effect of depression on contents of inflammatory factors of coronary heart disease patients with angina pectoris.

Patients	Case No.	IL-6 (ng/L)	IL-6R (ng/L)	IL-18 (ng/L)	ADAMTS-1 (ng/mL)
Without depression	47	67.65 $\pm$ 7.87	197.49 $\pm$ 24.19	225.85 $\pm$ 29.14	7.94 $\pm$ 0.91
With depression	33	120.12 $\pm$ 13.52	332.40 $\pm$ 39.52	378.39 $\pm$ 42.95	13.04 $\pm$ 1.86
<i>t</i>		9.650	8.484	9.218	9.823
<i>P</i>		<0.05	<0.05	<0.05	<0.05

**Table 4**

Effect of anxiety on contents of inflammatory factors of coronary heart disease patients with angina pectoris.

Patients	Case No.	IL-6 (ng/L)	IL-6R (ng/L)	IL-18 (ng/L)	ADAMTS-1 (ng/mL)
Without anxiety	49	71.43 $\pm$ 7.87	191.93 $\pm$ 22.49	230.48 $\pm$ 28.48	7.28 $\pm$ 0.86
With anxiety	31	112.45 $\pm$ 12.69	351.28 $\pm$ 41.39	362.38 $\pm$ 44.18	13.94 $\pm$ 2.01
<i>t</i>		7.687	9.484	8.586	10.384
<i>P</i>		<0.05	<0.05	<0.05	<0.05

microthrombosis and duct cavity constriction[10]. ET is a class of endogenous long-acting vasoconstrictor, it includes three subtypes ET-1, ET-2 and ET-3, and mature vascular endothelial cell can only synthesize and secrete ET-1; ET-1 has the function of promoting vasoconstriction, increasing microthrombosis and inducing cell proliferation, and it has a promoting effect on the pathological process of coronary lesions[11]. In the research, detection of endothelium related molecules showed that CGRP and NO contents of coronary heart disease patients complicated with anxiety and depression significantly decreased and ET-1 contents significantly increased, which indicated that anxiety and depression would tip the balance between vasoconstrictive molecules and vasodilative molecules.

In recent years, more and more studies have realized that systemic and local inflammation plays an important role in the pathogenesis of angina pectoris of coronary heart disease, and a variety of inflammatory factors are involved in the development of coronary heart disease. Generation of endothelial microparticles may increase inflammation degree, and the presence of anxiety and depression may also affect endocrine balance and activate inflammatory reaction. IL-18 is a type of pro-inflammatory factor with the effect of promoting atherosclerosis progression, changing plaque nature and accelerating vulnerable plaque formation[12]; ADAMTS-1 is a member of metalloproteinase family, has disintegrin structure and thrombin-sensitive structure, and can regulate adhesion of inflammatory cells and matrix, degrade matrix and thereby cause thinner fiber cap and unstable plaque[13]; IL-6 combination with receptor IL-6R can activate leukocytes to accumulate in vessel wall, promote vascular smooth muscle proliferation and thereby cause vascular stenosis through gp130 signaling pathway[14,15]. In the research, analysis of serum inflammatory factor contents showed that IL-6, IL-6R, IL-18 and ADAMTS-1 contents of coronary heart disease patients complicated with anxiety and depression significantly increased, which indicated that anxiety and depression might promote the progression of angina pectoris by means of increased inflammation.

Based on the above discussions, it is concluded that angina pectoris of coronary heart disease patients complicated with anxiety and depression have endothelial dysfunction and inflammatory reaction activation; endothelial dysfunction and inflammatory reaction activation are possible pathways that anxiety and depression cause the progression of coronary heart disease.

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