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Research Papers

The impact of major depression on heart rate variability and endothelial dysfunction in patients with stable coronary artery disease

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ABSTRACT

Background: Depression is an independent risk factor in cardiovascular diseases. Changes in the cardiac autonomic functions and pro-inflammatory processes are potential biological factors. Endothelial dysfunction plays an important role in the etiopathogenesis of atherosclerosis. Our objective was to evaluate the impact of major depression on heart rate variability and endothelial dysfunction in patients with stable CAD.

Methods: The study group included 65 CAD patients with a diagnosis of major depression and 54 CAD patients without major depression. All study population underwent transthoracic echocardiography, measurement of flow mediated dilatation (FMD) and 24-h holter recording for heart rate variability (HRV). Blood samples were drawn to determine the inflammatory parameters. Severity of depressive episode was assessed by Montgomery-Asberg Depression Scale (MADRS).

Results: The distribution of age and sex was similar in the patient and control groups ($P = 0.715$, 0.354, respectively). There was no significant difference in medications used between the groups. Echocardiographic parameters were similar between the groups. Inflammatory parameters were also similar between the groups. HRV parameters were significantly lower in the patient group than controls. The absolute FMD value and percentage FMD were significantly lower in the patient group than controls ($P < 0.001$). The MADRS score correlated with pNN50 in both groups ($P < 0.05$), and with FMD in the control group ($P < 0.001$), even after adjusting for age and gender ($P < 0.001$).

Conclusions: MADRS score was an independent predictor of pNN50 level, percentage and absolute FMD values regardless of age and gender. Clinician should pay more attention for evaluation of depressive patients with CAD.

1. Introduction

Depression is an independent risk factor in cardiac diseases and death in patients with coronary artery disease (CAD) [1,2]. Potential biological factors include changes in the cardiac autonomic functions and pro-inflammatory and pro-coagulant processes [3,4]. The relationship between CAD and autonomous nervous system has a form of mutual interaction. While stimulation of the sympathetic nervous system is associated with myocardial ischemia, myocardial ischemia is associated with neurohormonal activation, which, in turn, increases cardiac norepinephrine (NE) release and circulatory catecholamine levels.

Impaired autonomous nervous system alters the autonomic tone, promoting coagulation and inflammation, and leading to endothelial dysfunction which leads to cardiac events and accelerates the course of CAD [5,6]. Heart rate variability (HRV) is defined as cyclic changes in sinus rate over time; it is an index of sympathetic and/or inadequate parasympathetic tone. There are studies which have demonstrated that depression caused reduction in HRV following myocardial infarction (MI) and during stable periods of CAD [7,8].

Coronary artery disease is an atherosclerotic process. Chronic inflammatory process is one of the causes underlying endothelial damage in atherosclerosis [9,10]. Inflammation is a complex process involving many different types of cells and molecules. The proteins whose plasma levels are increased (positive acute phase protein), and reduced (negative acute phase protein) at least by 25% during the inflammatory process are called acute phase proteins. Most acute phase proteins have the potential to influence one or more stages of the inflammation. Depressive symptoms are closely related with immune system parameters, which include increased acute phase proteins (e.g., C-reactive protein (CRP), fibrinogen). When coagulation mechanisms are considered, there are data indicating that depression is a condition increasing coagulation of the blood. Four studies examining coagulation factors in depression showed that increases were seen in the factors, while one study found that fibrinolysis capacity remained unchanged [11]. However, previous study suggested that the relationship between

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depression scores and fibrinogen may be associated with cardiovascular risk factors [12].

Endothelial dysfunctions have been shown to play a major role in the etiopathogenesis of atherosclerosis. As described above, depression is closely related with the neurohormonal system. Similarly, neurohormonal system is also expected to have an effect on the nitric oxide (NO) metabolism [13]. There is a strong correlation between NO metabolism and endothelial dysfunction. Depression is related with endothelial dysfunction, which is a potential outcome of impairment in the neurohormonal activity through NO. There is limited number of studies available on this subject. In one study, depressive patients were treated with brachial artery flow-mediated dilation (FMD) method, a non-invasive technique, to evaluate endothelial function, and the endothelial function was significantly lower compared to the control group [14]. Based on prior research, our objective was to evaluate the impact of major depression on heart rate variability and endothelial dysfunction in patients with stable CAD.

2. Material and methods

2.1. Study population

The study group included 65 coronary artery disease patients with a diagnosis of major depression according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) diagnostic criteria [15] who presented to our cardiology outpatient clinic, and provided an informed written consent. The control group included 54 coronary artery disease patients without major depression according to the DSM-IV-TR diagnostic criteria. Inclusion criteria for the study were as follows: to accept participation and provide an informed written consent and to have a stable coronary artery disease (those who were diagnosed with CAD by physical examination, electrocardiography, echocardiography, treadmill test, cardiac scintigraphy, cardiac markers (CK, CK-MB, Troponin) or coronary angiography). Exclusion Criteria for the study were as follows: to be younger than 18 and older than 65 years of age, to have a diagnosis of mental impairment, dementia or other cognitive impairment that can interfere with the interview, to have a concomitant psychiatric diagnosis, presence of acute myocardial infarction and unstable angina, signs of active congestive heart failure, presence of a concomitant severe heart valve disease prior, to have a neurological, endocrine, pulmonary, gastrointestinal, hepatic, renal, immunological or hematological disease and organic brain disease, and to have systemic diseases leading to cognitive impairment or physical diseases affecting visual, auditory and motor skills. We screened 138 patients with stable CAD. 6 patients were excluded for congestive heart failure, 5 patients were excluded for severe heart valve disease, and 8 patients were excluded for the presence of psychiatric diagnosis from the study.

2.2. Study procedure

The study was carried out by a single interviewer. Each patient was questioned for presence of any systemic illness with history taking. Blood samples were drawn to determine CRP and fibrinogen levels. Patients underwent transthoracic echocardiography, and FMD measurements were performed from the brachial artery with a linear probe. After completion of the examination, patients underwent a 24-h Holter recording for HRV analysis.

2.3. Sociodemographic data

It is a form filled out by the interviewer to have background information from a patient about his/her age, gender, education level, employment status, marital status, socioeconomic level, place of residence and social support.

2.1. Structured clinical interview scale for DSM-IV Axis I Disorders - Clinical Version (SCID-I/CV)

The patients meeting the inclusion criteria were administered the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I) to ascertain the diagnosis [16]. SCID-I is a semi-structured interview form that was developed by First et al. in 1997 for DSM-IV for making present and lifetime first axis diagnoses. It was translated into Turkish by Özkürkçügil et al. [17], and it has been already validated. It consists of six modules including mood episodes, psychotic and associated symptoms, differential diagnosis of psychotic disorders, mood disorders, alcohol and other substance use disorders, anxiety and other disorders.

2.2. Montgomery-Asberg Depression Rating Scale (MADRS)

The interviewer administered the Montgomery-Asberg Depression Scale (MADRS) to patients to evaluate the severity of depressive episode [18]. The MADRS was developed to measure the overall severity of disorder in patients diagnosed with depression. It is a standard scale used for determining the severity of depression in clinical trials. In the 10-item questionnaire, the interviewer determines ratings for each item lying on well-defined severity steps (0-2-4-6) or between them (1-3-5). Higher scores indicate increasing severity of the symptom. The lowest score on the scale is 0 while the highest score is 60. The sensitivity of the scale for depression severity was assessed by Kearns et al. [19].

2.3. Assessment of heart rate variability

Heart rate variability was assessed using the 24-h Holter electrocardiography monitoring. Holter WIN-PV plus software was used for Holter recordings. For HRV analysis, Holter recordings of all patients were evaluated manually in order to remove artefacts, and then 'time domain' HRV variables were automatically identified. For assessment, variables of 24-h SDNN (standard deviation of all normal R-R intervals), SDNN5 (the mean of all the 5-min standard deviations of all R-R intervals), SDANN (standard deviation of all the 5-min R-R interval means), pNN50 (percentage of adjacent RR intervals > 50 ms different), and RMSSD (root of mean squared differences of successive R-R intervals) were selected respectively.

2.4. Measurements of brachial artery flow and diameter

Flow mediated dilation method was used to assess endothelial functions of the patients. Imaging was performed using a linear transducer with Vivid 7 (GE) ultrasound system. Imaging procedure for all patients was carried out by the same blinded cardiologist. Patients were allowed to rest approximately for 12 min at the room temperature before the imaging procedure. The brachial artery images were obtained above the antecubital fossa using B-mode imaging in the longitudinal plane of the artery. First the baseline diameter of the brachial artery was measured by magnifying this part of the artery. Then, the blood pressure cuff was placed on the proximal forearm, and it was inflated to 50 mmHg above the systolic blood pressure to occlude arterial flow for 5 min. The brachial artery diameter was measured at 30 s after releasing the cuff. The highest value obtained during ischemia-induced hyperemia was used for calculating the FMD ratio [(maximum diameter − baseline diameter) / baseline diameter × 100].

2.5. Acute phase proteins

Among laboratory variables, fibrinogen was assessed using a Dade Thrombin Reagent kit on the Dade Behring analyzer. Fibrinogen level was automatically measured by diluting the plasma 1:10 with a Dade* Owren's Veronal buffer. CRP level was automatically measured using the BioSystems' CRP latex kit with A&B reagents in the test protocol.