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Original Article

Serum oxidative stress level correlates with epicardial adipose tissue thickness in heart failure-reduced ejection fraction patients

Gokhan Ceyhun[1], Mutlu Buyuklu[2], Ergun Kutlusoy[2]

[1]Ataturk University, Faculty of Medicine, Department of Cardiology, Erzurum, Turkey
[2]Erzincan Binali Yildirim University, Faculty of Medicine, Department of Cardiology, Erzincan, Turkey

Abstract

Aim: In the course of heart failure, various inflammatory cytokines are secreted and oxidative stress occurs. The source of some produced cytokines is epicardial fat tissue (EFT). There is a positive correlation between EFT thickness and metabolic activity. In this study, we aimed to investigate the relationship between oxidative stress and epicardial fat tissue thickness in patients with heart failure.

Material and Methods: A total of 36 patients with heart failure-reduced ejection fraction as study group and 36 subjects without heart failure as control group were included in the study. Biochemical blood analyses and echocardiographic examinations were performed.

Results: The NT-proBNP level in the heart failure-reduced ejection fraction group was significantly higher than the control group (6506.8±11214.3, 116.5±185.6, respectively, p<0.001). The total oxidant status level in the heart failure-reduced ejection fraction group was significantly higher than the control group (14.5±3.7, 10.3±2.0, respectively, p<0.001). The total antioxidant capacity level in the heart failure-reduced ejection fraction group was significantly lower than the control group (7.2±2.8, 14.4±8.7, respectively, p<0.001). The EFT thickness level in the heart failure-reduced ejection fraction group was significantly higher than the control group (0.78 / (0.67-0.85), 0.51 / (0.37-0.66), respectively, p<0.001).

Conclusions: Oxidative stress was higher in patients with heart failure and similarly the EFT thickness was found to be increased.

Keywords: Epicardial fat tissue thickness; heart failure; oxidative stress

INTRODUCTION

Heart failure (HF) is a significant health problem in all societies with incidence increasing globally and high mortality/morbidity rates. The prevalence of HF is 1-2% in developed countries and as it is commonly observed in the elderly population, especially (above 70 years ≥ 10%) the increase in health expenditure, in addition to the search for medical and interventional treatment, keep it on the agenda (1,2)

Heart failure is a clinical syndrome characterized by typical symptoms and findings, occurring as a result of structural and/or functional abnormalities of the heart, with increased intracardiac pressure during rest or exercise and/or reduction in beat volume (3).

Visceral fat tissue is more active metabolically compared to subdermal fat tissue. When this fat tissue surrounds the heart it is known as epicardial fat tissue (EFT) and is nearly 5 mm thick in health individuals (4,5). The most important characteristic separating EFT from other visceral fat tissues is that in addition to systemic effects, it releases many proinflammatory and proatherogenic molecules and may affect myocardium and coronary artery paracrine (6).

Studies to date have shown that oxidative stress (OS) plays a role in the pathogenesis of HF and at the same time that reactive oxygen molecules (ROM) are produced by damaged myocardial tissue (7,8).

In this study, we aimed to investigate the correlation between epicardial fat tissue thickness (EFTT) and oxidative stress in reduced ejection fraction HF patients.

MATERIAL and METHODS

Study Population

This study prospectively included patients applying to Erzincan University Mengücek Gazi Education and

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Corresponding Author: Gokhan Ceyhun, Ataturk University, Faculty of Medicine, Department of Cardiology, Erzurum, Turkey
E-mail: gokhanceyhun@gmail.com

Research Hospital Cardiology clinic from May 2016 to June 2017. Before beginning the study participants gave oral and written consent. The study group included 36 heart failure patients with left ventricular ejection fraction (LVEF) <40%, New York Heart Association (NYHA) class 1, 2 and 3 on echocardiography investigations and the study group included 36 cases without heart failure.

Cases with smoking habit, thyroid function disorder, using any medication that may affect oxidative stress parameters, history of acute coronary syndrome in the last 21 days, hemorrhagic disorders, infection, malignancy, and rheumatological diseases were excluded from the study.

Biochemical Analysis

For biochemical measurements blood samples were taken from all 72 cases from the antecubital vein after 10 hours starvation. Plasma N-terminal brain natriucetic peptide (NT-proBNP), C-reactive protein (CRP), routine biochemistry tests, hemogram and sedimentation rate were studied. For total antioxidant capacity (TAC) and total oxidant status (TOS) parameters, blood was emptied into biochemistry tubes by removing the needle tip from the injector. Tubes were centrifuged in a cooled centrifuge at 3000 rpm for 10 minutes. The obtained serums were divided into small portions in Eppendorf tubes and stored at -80 °C in a deep freezer until laboratory analysis. Samples were studied once as a group for TAC and TOS levels at Atatürk University Faculty of Veterinary Biochemistry laboratory.

Serum TAC level was determined with an ELISA kit (Sunred Biological Technology, Shanghai, China) using an automatic measurement method based on the characteristic color formed by the 2,2'-azino-bis (3-ethylbenz-thiazoline- 6-sulfonic acid) radical when the antioxidants in the sample are added. Results were determined as unit/ml.

Serum TOS level was again studies with ELISA kits (Sunred Biological Technology, Shanghai, China) with the oxidants in the sample transforming ferrous ion-o-dianicidine complex to ferric ions. The ferric ion forms a color complex with xylenol orange in an acidic environment. The intensity of the spectrophotometrically measured color is related to the total amount of oxidant molecules in the sample. Results were determined as pg/ml.

Echocardiographic Investigation

Echocardiographic investigations of patients included in the study were completed with a Philips Epiq 7c brand device. LVEF was measured with the modified Simpson's method. EFTT measurements on two-dimensional echocardiographic investigation were measured from the window of the parasternal long axis, with thickness of the low-density area adjacent to the right free wall measured perpendicular to the aorta annulus in 3 cardiac cyclus at the end of systole. Assessments were analyzed by two independent operators.

Statistical Analysis

Data obtained were uploaded to the SPSS 20.0 (SPSS Inc., Chicago, IL, USA) in a computer environment for analysis. The statistical methods of tabulation, frequency distribution, descriptive statistics and appropriate parametric or nonparametric tests were used. Compliance of numerical variables with normal distribution was tested with the Kolmogorov-Smirnov Z test. As the variables bilirubin, CRP, NT-proBNP, TAC and EFTT values were not normally distributed, comparisons between the groups had the Mann Whitney U test. Comparison of other parametric variables used the independent samples t test, with comparisons of categorical variables completed with the chi-square test. Statistical significance level was accepted as $p<0.05$.

RESULTS

This study included a total of 72 patients with 36 in the HF-REF and 36 in the control group. Table 1 shows the basic characteristics of the groups. Both groups were not statistically different in terms of age, gender, hyper tension (HT), diabetes mellitus (DM), and angiotensin converting enzyme inhibitor (ACEI) use. There were significant differences between the two groups in terms of presence of Coronary artery disease (CAD), and use of spironolactone, furosemide, ivabradine and digoxin. The mean age in the HF-REF group was 69.8 ± 10.6 years, while in the control group it was 56.6 ± 12.6 years (p=0.188). In the HF-REF group, the HF etiology was ischemic dilated cardiomyopathy (DCMP). Of patients, more than 70 % were receiving optimal HF treatment.

Table 1. Basic characteristics of cases

Variables	HF-REF patients (n = 36)	Control group (n = 36)	P value
Age (year)	69.8+10.6	56.6+12.6	0.188
Male (%)	26 (72.2 %)	20 (55.6 %)	0.141
Hypertension (%)	15 (41.6 %)	13 (36.1 %)	0.089
Diabetes Mellitus (%)	10 (27.7 %)	8 (22.2 %)	0.265
CAD (%)	25 (69.4 %)	4 (11.1 %)	<0.001
ASA usage (%)	25 (69.4 %)	4 (11.1 %)	<0.001
Beta Blocker usage (%)	36 (100 %)	6 (16.7 %)	<0.001
ACEI usage (%)	12 (33.3 %)	5 (13.8 %)	0.102
ARB usage (%)	19 (52.7 %)	7 (19.4 %)	<0.001
Spiranolactone usage (%)	25 (69.4 %)	0	<0.001
Furosemid usage (%)	10 (27.7 %)	0	<0.001
Ivabradin usage (%)	10 (27.7 %)	0	<0.001
Digoxin usage (%)	10 (27.7 %)	0	<0.001

CAD: Coronary Artery Disease; ACEI; Angiotensin Converting Enzyme Inhibitor; ARB; Angiotensin Receptor Blocker

Table 2. Variability of biochemical and echocardiographic of cases

Variables	HF-REF patients (n = 36)	Control group (n = 36)	P value
Systolic BP (mmHg)	110.4±7.5	109.1±7.3	0.567
Diastolic BP (mmHg)	72.1±6.2	71.2±6.2	0.651
Heart rate (pulse/min)	85.6±11.1	84.2±9.7	0.435
LVDD (mm)	65.0±6.2	49.1±3.4	<0.001
LVDV (ml)	134.4±31.8	44.3±5.9	<0.001
LVSV (ml)	192.7±30.8	124.3±6.4	<0.001
LVEF (%)	30.7±5.2	64.4±3.6	<0.001
Hemoglobin (g/dL)	13.8±2.1	14.6±2.1	0.799
Leukocyte (x10^3/mm^3)	7.8±2.0	7.3±1.3	0.023
Creatinine (mg/dL)	1.2±0.5	0.9±0.1	0.026
AST (U/L)	22.6±5.3	22.1±6.4	0.708
ALT (U/L)	21.7±11.8	21.0±9.9	0.767
Sodium (mmol/L)	135.7±2.1	136.6±1.5	0.019
Potassium (mmol/L)	4.2±0.5	4.3±0.3	0.433
Ferritin (mg/dL)	111.3±107.8	54.6±46.8	0.004
Bilirubin mg/dL [median (IQR)]	0.96 / (0.51-1.31)	0.62 / (0.45-0.80)	0.011
CRP [median (IQR)]	4.4 / (3.0-12.9)	3.0 / (3.0-3.5)	0.005
NT-proBNP (pg/ml) [median (IQR)]	1375.0 / (916.0-4902.5)	64.5 / (38.0-134.0)	<0.001
TAC (U/ml) [median (IQR)]	6.8 / (4.9-9.2)	13.2 / (9.2-14.7)	<0.001
TOS(pg/ml)	14.5±3.7	10.3±2.0	<0.001
EFTT (cm) [median (IQR)]	0.7 / (0.6-0.8)	0.5 / (0.3-0.6)	<0.001

LVDD; Left Ventricle End-Diastolic Diameter, LVDV; Left Ventricle End-Diastolic Volume, LVSV; Left Ventricle End-Systolic Volume, LVEF; Left Ventricular Ejection Fraction, CRP; C-Reactive Protein, NT-proBNP; N-Terminal Brain Natriucetic Peptide, TAC; Total Antioxidant Capacity, TOS; Total Oxidant Status, EFTT; Epicardial Fat Tissue Thickness

Table 2 shows the clinical, biochemical and echocardiographic characteristics of the HF-REF and control groups. There was no statistically significant difference between the two groups in terms of systolic blood pressure, diastolic blood pressure, heart rate, Hgb, AST, ALT and potassium levels. However, there were statistically significant differences between the two groups in terms of Left ventricle end-diastolic diameter (LVDD), Left ventricle end-diastolic volume (LVDV), left ventricle end-systolic volume (LVSV), SVEF, white cells, sodium, creatinine, ferritin, bilirubin, CRP, NT-proBNP, TAC, TOS and EFTT levels.

DISCUSSION

In the current study, we demonstrated that the oxidative stress marker of TOS level was high and the antioxidant system marker of TAC level was significantly suppressed in the HF-REF group. At the same time we determined the HF-REF group had significantly increased EFTT. Again, in the HF-REF group we identified that the NT-proBNP level indicating the severity of HF and the CRP level showing inflammation were significantly high.

Heart failure is a syndrome affecting many systems. The antioxidant and oxidant systems are among these affected systems. The antioxidant system is suppressed, with the increase in the oxidant system causing oxidative stress (OS). In HF, the most important mechanism causing suppression of the antioxidant system is the increase in activity of the neurohumoral and sympathetic system and the tissue damage caused by this (9,10). As a result unwanted situations for HF like worsening myocardial remodeling, increased apoptosis of myocytes, endothelial dysfunction, and excitation-contraction dysfunction occur. The increase in oxidative stress in HF has been shown by many studies (11-14) Arai et al (15). showed heart failure after myocardial infarction was associated with suppressed antioxidant system and increased oxidative stress. Another study by Hill and Singal (16) mentioned that in addition to suppression of the antioxidant system

in HF developing after myocardial infarction it may be associated with increased myocardial oxidative stress. In this study, similar to previous studies, the oxidative stress marker of TOS was significantly higher in the HF group compared to the control group and we observed the antioxidant system marker of TAC was lower.

Echocardiographic measurement of epicardial fat tissue thickness is a simple and practical method related to cardiovascular and metabolic diseases (17). The association between EFT and cardiovascular diseases is related to the anatomic and functional proximity of EFT to the myocardial tissue and its metabolic activity. A variety of mechanisms have been proposed to explain the production of inflammatory cytokines by epicardial fat tissue. In response to regional ischemia and reduced myocardial function, increased production of oxygen radicals may activate oxidant-sensitive inflammatory signals within visceral fat tissue in neighboring fat stores. The presence of increased inflammatory cells in epicardial fat tissue may reflect a similar response to advanced atherosclerotic lesions, neighboring adventisia and inflammatory infiltrates in perivascular regions. Increased oxidative stress has been shown in a variety of diseases, with the increase in EFTT shown in a variety of studies. A study by Demir et al. (18) identified increased EFTT in metabolic syndrome patients, a situation progressing with elevated oxidative stress. Again, another study by Demir et al. (19) identified that OS was high in the patient group with polycystic ovarian syndrome and EFTT was increased. Aydoglu et al. (20) identified that OS and EFTT were high in the subclinical hypothyroid patient group and that these values reduced after treatment. In this study, similar to previous studies, EFTT was identified to be significantly high in the HF-REF group.

CONCLUSION

In conclusion, it was determined that OS was elevated and similarly EFTT was increased in HF-REF. As a result, EFTT is an easy, cheap and repeatable simple method that may be recommended for use to identify OS elevation in this type of patient group.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: This study was approved by the Institutional Ethics Committee and conducted in compliance with the ethical principles according to the Declaration of Helsinki.

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