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Original Article

# Epicardial fat thickness is associated with oxidative stress index in cardiac syndrome X

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## Abstract

**Aim:** We aimed to investigate the relationship between oxidative parameters- total oxidant status (TOS), total antioxidant capacity (TAC), and oxidative stress index (OSI)- and EFT in patients with CSX. Without clinically significant coronary artery disease, cardiac syndrome X (CSX) is characterized by cardiac ischemia, and chest pain. However, there is some evidence about increased oxidative stress in CSX patients; the relationship between oxidative stress parameters and epicardial fat thickness (EFT) is not well established in this population.

**Material and Methods:** : One hundred and twenty-two patients with normal coronary arteries (73 female, 49 males, mean age 56.71 ± 10.69 years) were enrolled in the study. The study population was divided into two groups according to their OSI. Oxidative stress index below the median was defined as the OSI low group and equal or higher than the median was defined as the OSI high group.

**Results:** EFT was higher in the high OSI group than the low OSI group (6 (3.9 – 8.9) vs. 5.4 (0.56 – 7.2), p= 0.032). In bivariate correlation analysis EFT was positively correlated with OSI and TOS (r=0.242, p=0.036 and r=0.234, p=0.025 respectively). In binary logistic regression analysis, EFT was found to be an independent predictor of OSI.

**Conclusion:** : In our study, EFT was independently associated with OSI in CSX patients. This finding suggests that EFT may be a marker of increased oxidative stress in CSX.

**Keywords:** Antioxidants; microvascular dysfunction; oxidative stress

## INTRODUCTION

Without clinically significant coronary artery disease (CAD), cardiac syndrome X (CSX) is characterized by chest pain and cardiac ischemia. Oxidative stress is one of the several postulated mechanisms for the pathogenesis of CSX, and the relationship between these parameters is well established in the literature (1).

Epicardial fat tissue is a visceral fat surrounding the heart and major coronary vessels. Epicardial fat tissue produces several proatherogenic and proinflammatory substances increasing oxidative stress (2). Epicardial fat thickness (EFT) is associated with increased collateral formation (3) and extent of CAD in acute myocardial infarction patients (4) and decreased coronary flow reserve in patients with normal coronary arteries (5). Epicardial fat thickness is found to be higher in CSX patients compared with the control group (6).

However, there is some evidence about increased oxidative stress parameters in CSX patients (7,8), the relationship between oxidative stress parameters and EFT is not well established in this population. We aimed to investigate the relationship between oxidative parameters- total oxidant status (TOS), total antioxidant capacity (TAC), and oxidative stress index (OSI)- and EFT in patients with CSX.

## MATERIAL and METHODS

### Study Population

One hundred and twenty-two patients who underwent coronary angiography due to typical chest pain on exertion and an abnormal stress test with normal coronary arteries were enrolled between June 2017 and September 2017. All patients had a treadmill stress test using the Bruce protocol. Horizontal or downsloping ST segment depression equal to or more than 1 mm at 80 ms of the J point in one or more leads considered positive.

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The study was carried out in accordance with the Helsinki declaration. All participants read and understood the study protocol and gave consent. The local ethics committee approved the test protocol.

Patients were excluded if they had a history of diabetes, uncontrolled hypertension, cancer, inflammatory bowel disease, coronary artery disease, chronic kidney disease, peripheral artery disease, and significant valvular disease. Patients who take drugs exerting antioxidant effects such as diuretics, statins, beta-blockers (carvedilol, nebivolol), angiotensin-converting enzyme inhibitors (captopril, zofenopril), and vitamins (such as C and E) xenobiotics and alcohol were not eligible for the study. Patients taking drugs which are proved to alter EFT (atorvastatin, pioglitazone, sitagliptin, insulin detemir) were also excluded from the study (2). Patients taking beta-blockers and angiotensin-converting enzyme inhibitors not showing antioxidant activity were not excluded.

Transthoracic echocardiography was performed on the next day of coronary angiography. Blood pressure was measured two times after five minutes of rest, and measurements were averaged. A measuring tape was used to obtain anthropometric measures like weight, height, and waist circumference. Body mass index was calculated as body weight divided by height squared.

Blood samples were obtained after twelve hours of fasting to measure plasma levels of glucose, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) cholesterol, triglyceride (TG). Blood samples were drawn during coronary angiography for the measurement of TOS and TAC.

**Echocardiography**

Standard two-dimensional and Doppler echocardiographies were performed using a commercially available echocardiographic machine (EPIQ 7, Philips Healthcare, Andover, MA, USA) with a 2.0–3.5- MHz transducer in the left lateral decubitus position. Epicardial fat appears as an echo-lucent space between the linear echo-dense parietal pericardium and the right ventricular epicardium. EFT was measured as the vertical distance of this echo-lucent space. The mediastinal fat above the parietal pericardium is not included in the measurement. EFT thickness was measured at end-diastole from parasternal long-axis images by two echocardiographers who were blinded to coronary angiography and clinical data of study participants. The Simpson method was used to measure left ventricular ejection fraction (9).

**Measurement of TAC and TOS**

Total antioxidant capacity was measured using an automated new generation, more stable, colored 2,2-azinobis-(3-ethyl benzothiazoline-6-sulfonic acid) radical cation (ABTS). The ABTS is decolorized by antioxidants according to their concentrations, and antioxidant capacities, and this change was measured spectrophotometrically at 660 nm. This process was applied to an automated analyzer (10)., and the assay was calibrated with Trolox. The results were expressed as mmol Trolox equivalent/L. Analytical sensitivity was found to be 0.11 Absorbance/Amount, [AX (mM)-1] for the TAC (11).

An automated measurement method was used to measure TOS. The oxidants in the sample oxidize the ferrous ion-o-dianisidine complex to ferric ion. The ferric ion, together with xylenol forms an orange-colored complex and the color intensity measured by spectrophotometry gives the total amount of oxidant molecules. The assay was calibrated with hydrogen peroxide ($H_2O_2$), and the results were expressed as mmol $H_2O_2$ equivalent/L. Analytical sensitivity was found to be 0.0076 Absorbance/Amount [AX $(\mu M)^{-1}$] for the TOS (11). Precision values are lower than 3% for both TOS and TAC (10,11). The oxidative stress index was calculated by dividing TOS to TAC (10).

**Coronary Angiography Data**

Coronary angiography was performed using the modified Seldinger technique via the femoral approach with Judkins catheters from conventional views. Vasodilator drugs such as nitrates, calcium channel blockers, and adenosine were stopped for at least one week before the angiography. Slow-flow without any atherosclerotic lesion was also considered as abnormal and excluded from the study. Coronary artery spasm was tested by administration of methylergonovine and more than 50% narrowing of an epicardial coronary artery lumen upon administration was considered positive and excluded from the study (12). Coronary angiographic images were assessed by two experienced cardiologists blinded to patient characteristics and laboratory data.

**Statistical Analysis**

All analyses were performed using the SPSS software (Statistical Package for the Social Sciences, Version 17.0, SSPS Inc., Chicago, IL, USA). Normality analysis was performed using the Shapiro Wilk test. Normally distributed continuous variables were expressed as mean values ± SD, non-normally distributed variables were expressed as median and rank and categorical variables as number and percentages. A comparison among multiple groups was performed by one-way analysis of variance (ANOVA) with Scheffe or Tamhane post hoc test for continuous variables. Comparison of categorical variables between the groups was performed using the chi-square test. Binary logistic regression analysis was used to analyze the independent relationship between EFT and OSI. A p-value of less than 0.05 considered statistically significant. The variables with a p-value lower than 0.25 in bivariate analysis were included in the binary logistic regression model. These variables were hyperlipidemia, HDL cholesterol (r= 0.135, p= 0.241) and EFT. However, age, smoking status, waist circumference, and BMI were similar among groups with a p-value higher than 0.25; they were included in the multivariate analysis because in literature they were shown to alter oxidative status (13).

## RESULTS

One hundred and twenty-two patients with normal coronary arteries (73 female, 49 male mean age 56.71±10.69 years) were enrolled in the study. Median OSI was 3.04 (range 1.10 – 12.18). The study population was divided into two groups according to their OSI. The oxidative stress index below or equal to the median was defined as the OSI low group and higher than the median was defined as the OSI high group. Seventy-six patients (62.30%) entered the OSI low group, and 46 (37.7%) entered the OSI high group (Table 1).

Age, gender, systolic and diastolic blood pressure, hypertension frequency, total cholesterol, HDL cholesterol, LDL cholesterol and TG levels, BMI, waist circumference, acetylsalicylic acid, beta-blockers, ace inhibitor, and angiotensin receptor blocker usages were similar among groups. Hyperlipidemia frequency was higher in the OSI high group than the OSI low group (10 (21.73%) vs. 5 (6.58 %), p= 0.013). Epicardial fat thickness was higher in the high OSI group than the low OSI group (6 (3.9 – 8.9) vs. 5.4 (0.56 – 7.2), p= 0.032) (Table 1).

**Table 1. Comparison of clinical and laboratory variables between Oxidative Stress Index groups**

| Variable | OSI low group (n=76) | OSI high group (n=46) | p |
|---|---|---|---|
| Age, (years) | 56.86 ± 10.98 | 56.45 ± 10.29 | 0.847 |
| Gender, male, n (%) | 30.00 (39.47 %) | 19.00 (41.30 %) | 0.841 |
| Body mass index, kg/m$^2$ | 28.92 ± 5.05 | 28.79 ± 6.07 | 0.904 |
| Hypertension, n (%) | 24 (31.58 %) | 14.00 (30.43 %) | 0.894 |
| Smoking habit, n (%) | 22 (28.95 %) | 12 (26.08 %) | 0.732 |
| Hyperlipidemia, n (%) | 5 (6.58 %) | 10 (21.73 %) | 0.013 |
| Office SBP, (mmHg) | 121.53 ± 12.07 | 118.75 ± 15.17 | 0.284 |
| Office DBP, (mmHg) | 76.92 ± 8.49 | 75.23 ± 8.15 | 0.302 |
| Waist circumference, (cm) | 104.34 ± 14.35 | 104.51 ± 19.85 | 0.963 |
| Total cholesterol, (mg/dL) | 190.05 ± 40.36 | 187.73 ± 40.71 | 0.769 |
| Low density lipoprotein, (mg/dL) | 135.95 ± 103.55 | 118.30 ± 33.00 | 0.297 |
| High density lipoprotein, (mg/dL) | 47.11 ± 26.41 | 47.03 ± 11.24 | 0.985 |
| Triglyceride, (mg/dL) | 146.5 (20.3 - 327) | 155 (51.9 - 363) | 0.571 |
| Acetylsalicylic acid, n (%) | 6 (7.89 %) | 5 (10.86 %) | 0.578 |
| ACE inhibitors, n (%) | 2 (2.63%) | 2 (4.34 %) | 0.605 |
| ARB, n (%) | 12 (15.79 %) | 5 (10.86 %) | 0.446 |
| Beta blockers, n (%) | 12 (15.79 %) | 4 (8.69 %) | 0.260 |
| Ca antagonist, n (%) | 7 (9.21%) | 3 (6.52 %) | 0.599 |
| Epicardial fat thickness, mm | 5.4 (0.56 - 7.2) | 6 (3.9 - 8.9) | 0.032 |

ACE: Angiotensin converting enzyme, ARB: Angiotensin receptor blocker, Ca: Calcium, DBP: Diastolic blood pressure, SBP: Systolic blood pressure, Student's t test, Mann Whitney U and Chi-square tests were used

In bivariate correlation analysis EFT was positively correlated with OSI and TOS (r=0.242, p=0.036 and r=0.234, p=0.025 respectively) (Table 2 and Table 3).

In binary logistic regression analysis, OSI was found to be independently associated with EFT and hyperlipidemia (Table 4).

**Table 2. Bivariate correlations of Oxidative Stress Index**

| Variable | r | p |
|---|---|---|
| Age (years) | 0.042 | 0.716 |
| Body mass index (kg/m$^2$) | 0.043 | 0.709 |
| Waist circumference (cm) | 0.002 | 0.983 |
| Total cholesterol, (mg/dL) | 0.046 | 0.692 |
| Low density lipoprotein, (mg/dL) | 0.132 | 0.254 |
| High density lipoprotein, (mg/dL) | 0.135 | 0.241 |
| Triglyceride, (mg/dL) | 0.077 | 0.506 |
| Epicardial fat thickness (mm) | 0.242 | 0.036 |

Pearson and Spearman correlation tests were used

**Table 3. Bivariate correlations of Epicardial Fat thickness**

| Variable | r | p |
|---|---|---|
| Age (years) | 0.192 | 0.027 |
| Body mass index (kg/m$^2$) | 0.137 | 0.120 |
| Waist circumference (cm) | 0.227 | 0.011 |
| Total oxidant stress | 0.234 | 0.025 |
| Total antioxidant capacity | 0.127 | 0.147 |

Pearson and Spearman correlation tests were used

**Table 4. Multivariate regression analysis of Oxidative Stress Index**

| | Exp(B) | 95% CI for Exp (B) | p |
|---|---|---|---|
| Hyperlipidemia | 4.599 | 1.389 – 15.228 | 0.012 |
| Epicardial fat thickness | 1.629 | 1.068 – 2.490 | 0.024 |

$R^2$ = 0.146. Binary logistic regression analysis was used
Adjusted for HDL

## DISCUSSION

According to our study, EFT was higher in the high OSI group, EFT was directly correlated with TOS and OSI, and OSI was independently associated with hyperlipidemia and EFT. However separate studies are showing increased EFT (6) and oxidative stress (7,8) levels in CSX, according to our knowledge, this is the first study to find an independent relationship between EFT and OSI in this study population. This finding infers a causal relationship or coexistence between the pathogenetic processes involving in the oxidation and visceral adiposity in CSX patients. We assert that EFT is directly proportional to the epicardial fat volume and, therefore, directly proportional to the levels of proinflammatory and proatherogenic molecules which in turn increase the TOS and OSI.

Systemic oxidative stress occurs as a consequence of accumulating reactive oxygen species (ROS; superoxide, peroxynitrite, hydrogen peroxide) in the body, which mainly generated by natural biochemical reactions such as mitochondrial electron transport chain (14). Superoxide ($O2^-$), which is produced by the reduction of molecular oxygen (O2) is the precursor of other ROSs. Superoxide is produced mainly by NADPH oxidase in mitochondria, where oxidative phosphorylation takes place. In oxidative phosphorylation electrons pass through a series of proteins (oxidation-reduction) to produce ATP. Under normal conditions at the end of the chain, electrons pass to oxygen molecules to produce water, however in a small percentage (0.1-2%) of electrons incompletely reduce oxygen and produce superoxide radicals (15,16). Hydrogen peroxide occurs as a result of dismutation of superoxide and can be reduced to either hydroxyl or water (14,17). In addition to NADPH oxidase, uncoupled nitric oxide synthase, xanthine oxidase, and cyclooxygenase are other sources of superoxide radical in the heart. Smoking, radiation, pollution, drugs, xenobiotics are exogenous sources of ROS (18).

There are endogenous antioxidant defenses restricting the effects of ROS, such as glutathione peroxidase, superoxide dismutase, and catalase in the body. Superoxide dismutase inactivates superoxide by dismutation, glutathione peroxidase, and catalase inactivates hydrogen peroxide by reduction. There are also exogenous molecules exerting antioxidant properties like vitamin A, vitamin E, and vitamin C (18). When the balance between these two counteracting mechanisms disrupted in favor of ROS, oxidative stress occurs. Oxidative stress causes lipid peroxidation, cellular damage, apoptosis, and programmed cell death (13). The relationship between atherosclerosis and oxidative stress is also well known in the literature (19).

Epicardial fat tissue not only secretes proinflammatory and proatherogenic but also secretes antiatherogenic and anti-inflammatory adipokines such as adrenomedullin and adiponectin (20). Adiponectin has anti-inflammatory and antiatherogenic actions and improves insulin sensitivity. Adrenomedullin is a powerful vasodilator, angiogenic, and anti-inflammatory factor. However, factors influencing

the balance between these counteracting factors in an individual is not fully understood (21), there is some evidence suggesting that in unstable coronary artery disease patients, secretion of proinflammatory cytokines is dominant and suppresses the production of adiponectin and adrenomedullin (20,22). In a study by Yun et al., in stable CAD patients, adiponectin levels were negatively correlated with EFT and independently predicted the obstructive coronary artery disease presence (23). These findings suggest a similar balance in favor of atherogenic and proinflammatory effects may exist in stable patients as well. In a recently published study on patients with suspected coronary artery disease and negative $^{82}$Rb PET/CT results showed that epicardial fat tissue volume was independently and inversely related to myocardial perfusion reserve in patients with coronary artery calcium score 0. This study indicates that epicardial adipose tissue volume is independently associated with microvascular dysfunction (24). Our study subjects are clinically stable and do not have any significant atherosclerotic coronary artery disease. The positive relationship between EFT and OSI found in our study may be attributable to the increased proinflammatory and proatherogenic cytokine levels. According to our knowledge, this is the first study to show such a relationship. From this point of view, EFT may be considered as a marker of increased oxidative stress in CSX patients.

Two-dimensional transthoracic echocardiography is a non-invasive, safe, and reproducible instrument for measurement of EFT. However, CT and MRI allow measurement of epicardial fat volume rather than thickness, which more accurately reflects the cardiovascular risk, echocardiographic measurement of EFT is safer, cheaper, and less time-consuming method (25).

In our article we assert that EFT is directly proportional to the epicardial fat volume and, therefore directly proportional to the levels of proinflammatory and proatherogenic molecules. We measured the thickness of epicardial fat by echocardiography, not by CT or MRI which allows epicardial fat volume measurement. Epicardial fat volume measurement would be more appropriate than the EFT to make such a suggestion.

We used the exercise treadmill test to identify Cardiac Syndrome X patients. However, exercise treadmill test is enough to make the diagnosis of CSX, the sensitivity and specificity of this test is low for diagnosing ischemia (1). Besides, measuring coronary flow reserve (CFR) or fractional flow reserve (FFR) would more precisely establish the diagnosis of microvascular dysfunction. These tests were not available in our catheter laboratory. These are the main limitations of our study.

## CONCLUSION

In our study, EFT was independently associated with OSI in CSX patients. This finding suggests that EFT may be a marker of increased oxidative stress in CSX. Further studies with higher patient numbers are needed to reach a definitive conclusion in this matter.

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

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