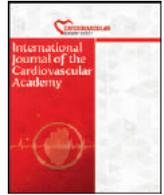




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Case report

Relationship between epicardial fat tissue thickness and breast arterial calcifications in premenopausal women☆

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Objective

Epicardial fat tissue (EFT) is located between myocardium and visceral pericardium. It has the same embryologic origin with the mesenteric omental fat tissue. It is very close to the myocardium and shares the same microcirculation.¹ EFT functions as a mechanical buffer against coronary arterial wave torsion, plays an important role in maintaining fatty acid homeostasis and is thought to contribute coronary artery remodeling.² EFT secretes several proinflammatory cytokines such as angiotensin II, tumor necrosis factor- α , monocyte chemoattractant protein-1, interleukin-6, resistin and plays an active role in inflammatory and atherosclerotic processes.^{3,4}

Breast arterial calcifications (BAC) are a type of medial calcification detected at mammography. Its prevalence ranges between 1% and 49% in female population.⁵ Age, race and ethnicity are the most important factors influencing the prevalence of BAC.⁶ BAC have been associated with hypertension,⁷ diabetes mellitus,⁷ coronary artery disease⁸ and are a risk marker for future cardiovascular disease events.⁹ Women with mammography-detected BAC are more likely to have coronary artery calcification which is an early sign of coronary artery disease.¹⁰

In this study starting with the possibility of existence of correlation between EFT thickness and BAC, we aimed to investigate the relationship between EFT thickness and BAC in premenopausal women.

Methods

Among 756 premenopausal women who underwent diagnostic mammography between November 2015 and March 2016, 171 of these premenopausal women enrolled in this prospective study. Clinical indication for mammography was either routine screening mammography for women with no presenting complaints or diagnostic mammography for women with suspicious findings on breast ultrasound. The study protocol was approved by the Medipol University Ethics Committee and all subjects gave informed consent prior to participation. The study group consisted of 80 women with mammography detected BAC and the control group consisted of 86 women without BAC (an example of BAC is shown in Fig. 1.) Women with hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease, congestive heart failure, thyroid dysfunction, anemia, renal or hepatic failure, stroke or other chronic medical disorders were excluded from the study.

Blood samples were collected from antecubital vein after an overnight fast. Serum total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting glucose were analysed.

Each subject underwent a full-field digital mammographic examination using a Mammomat 3000 Nova equipment (Siemens AG, Germany). All mammograms had craniocaudal and mediolateral oblique images of the two breasts. All images were interpreted by an experienced radiologist who was blinded to the echocardiography results. BAC were described as deposits of parallel lines of calcium when the arterial wall was imaged longitudinally or as calcific rings when the arterial wall was imaged transversely.¹¹

All the subjects underwent full transthoracic echocardiographic examination using Vivid 3 pro (GE Vingmed Ultrasound AS, Horten, Norway) in accordance with the recommendations of the American Society of Echocardiography.¹² Left ventricular ejection fraction (LVEF) was measured by using Simpson rule. Epicardial fat tissue was identified as echo free space between myocardium and visceral pericardium and its thickness was measured perpendicularly on the free wall of right ventricle from parasternal long-axis and short axis views at end diastole by an experienced cardiologist who was blinded to the clinical results of the patients.¹³ The average of three measurements was used for statistical analysis.

☆ Conflict of interest: None declared.

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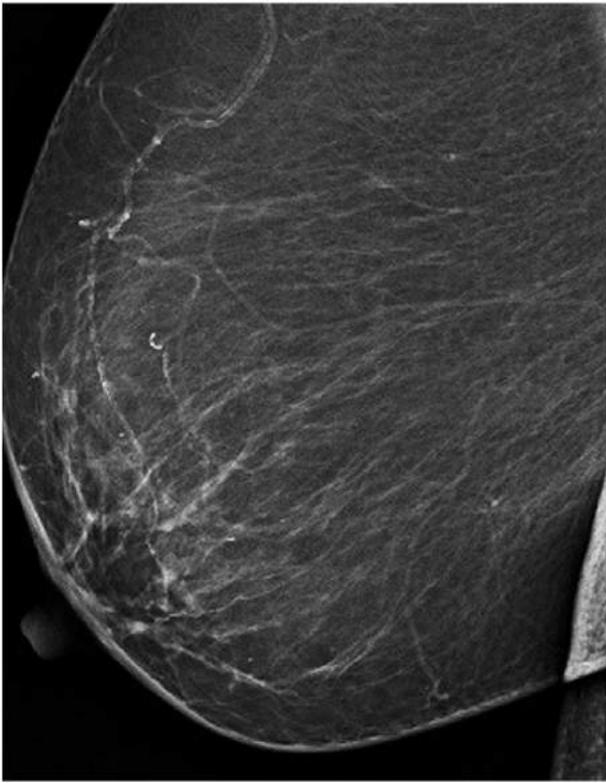


Fig. 1. An example of BAC.

Statistical analysis

Continuous variables were expressed as mean and standard deviation. Categorical variables were expressed as percentages. Parametric continuous variables and categorical variables were compared by Student's *t*-test and, the chi square test respectively. Multiple regression analysis was used to evaluate the possible associations of weight, BMI, glucose, LDL-C, HDL-C, TC, TG, EFT with BAC. *P* values <0.05 were considered significant. All statistical studies were carried out by using the SPSS program (version 15.0; SPSS Inc., Chicago, Illinois, USA).

Results

Among 756 women who underwent screening and diagnostic mammography, 168 subjects met the entry criteria and were enrolled in the study. 80 women with BAC were accepted as the study group, and 86 women without BAC were accepted as the control group. No significant difference was detected between the two groups with respect to age, weight, height, BMI, LVEF, fasting glucose, TC, HDL-C and TG levels. LDL-C level and EFT thickness were statistically significantly higher in the study group compared to the control group (3.65 ± 0.73 mm vs. 2.94 ± 0.67 mm, $p < 0.001$, respectively). Clinical and biochemical parameters of the patients are shown in Table 1.

Multiple regression analysis showed that EFT thickness, TC, LDL-C and BMI were important associations of BAC (Table 2).

Discussion

Our study showed an association between EFT thickness and BAC in patients without structural heart disease. EFT thickness was significantly higher in patients with BAC. There was a strong association between EFT thickness and BAC. We also found positive associations between EAT thickness and TC, BMI, LDL-C.

Anatomically EFT, located between myocardium and visceral pericardium, is mainly concentrated in the atrioventricular and interventricular

Table 1
Clinical and biochemical parameters of the patients.

	Study group (n = 80)	Control group (n = 86)	P
Age	44.7 ± 3.7	45.1 ± 3.3	0.36
Height (m)	1.64 ± 0.08	1.65 ± 0.07	0.37
Weight (kg)	74.3 ± 10.7	72.8 ± 9.2	0.33
BMI	27.8 ± 5.1	26.8 ± 4.1	0.16
Smokers, n (%)	15 (18)	18 (20.4)	0.44
Alcohol, n (%)	8 (9.6)	9 (10.2)	0.57
Fasting Glucose (mg/dl)	99.7 ± 10.3	96.9 ± 8.3	0.06
TC (mg/dl)	190.7 ± 36.7	188.3 ± 26.6	0.64
LDL-C (mg/dl)	133.7 ± 25.9	125.1 ± 27.8	0.04
HDL-C (mg/dl)	43.4 ± 9.8	41.8 ± 9.9	0.30
TG (mg/dl)	157.2 ± 58.9	156.6 ± 59.3	0.94
SBP (mmHg)	131.4 ± 11.6	130.1 ± 18.2	0.59
DBP (mmHg)	81.8 ± 8.7	82.3 ± 8.1	0.72
LVEF (%)	62.7 ± 4.1	63.3 ± 3.5	0.36
EFT thickness (mm)	3.65 ± 0.73	2.94 ± 0.67	<0.001

TC: Total cholesterol; LDL-C: Low density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol; TG: Triglyceride; SBP: Systolic blood pressure DBP: Diastolic blood pressure; LVEF: Left ventricular ejection fraction; EFT: Epicardial Fat tissue.

grooves and shares the same microcirculation with the myocardium and coronary arteries.¹⁴ EFT has paracrine and vasocrine activities, have both harmful and protective effects on heart through release of variety of adipocytokines.¹⁵ Recently, it has been demonstrated that increased EFT thickness occurs with disorders such as hypertension,¹⁶ insulin resistance,¹⁷ metabolic syndrome,¹⁸ and coronary atherosclerosis.⁴ Several studies have assessed the relationship between EFT and coronary artery disease.^{3,4,15,19} The pathophysiological mechanisms responsible for CAD development through EFT are not clearly elucidated. In patients with CAD, inflammatory pathways within EFT are activated and EFT secretes more chemokines and cytokines that mediate inflammation.²⁰ EFT may act as an endocrine organ by secreting various factors in the circulation thus contributing coronary lesion formation.

Vascular calcifications occur in the intima or media layers of the vessel wall. Intimal calcification is almost always associated with atherosclerosis, whereas BAC are a form of medial arterial sclerosis which is independent of atherosclerosis.^{21,22} These two types of calcification represent pathophysiological different mechanisms. Intimal calcification is related to chronic inflammatory changes which involve growth factors, inflammatory cells, lipid deposition and macrophage accumulation.²¹ Medial arterial calcification is almost always associated with aging, chronic renal failure or diabetes and involves the differentiation of vascular smooth muscle cells into osteoblast like cells.²² BAC are correlated with subsequent development of coronary artery calcifications,^{23–25} Kemmeren et al. found that presence of BAC was associated with a 30% and 90% increase in cardiovascular mortality in non-diabetic and diabetic women, respectively.²⁶ Rotter et al. showed that mammographically detected BAC was associated with an increased prevalence of cardiovascular risk factors and cardiovascular morbidity.¹¹ A recent study has shown that presence of BAC are stronger risk factor than other cardiovascular risk factors such as diabetes, hypertension and hyperlipidemia for coronary artery calcification.²⁷

Until several decades ago, it had been thought that coronary artery disease was primarily a man's disease. Today, it is recognised that this

Table 2
Parameters that have associations with BAC.

	OR	95% C.I.	P
TC	0.962	0.938–0.986	0.002
LDL-C	0.955	0.924–0.987	0.007
BMI	0.631	0.510–0.782	<0.001
EFT thickness	869.4	97.91–7719.8	<0.001

BAC: Breast arterial calcifications; BMI: Body mass index; TC: Total cholesterol; LDL-C: Low density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol; TG: Triglyceride.

belief is not true, as cardiovascular disease is the most common cause of death among women throughout the world; In addition cardiovascular mortality rate among young women is still on the rise. Prevention and diagnosis of coronary artery disease are of great importance, because not only it increases the chances of cure, but it also reduces the major complications that could be avoided at an early stage. Traditional risk factors such as hyperlipidemia, hypertension, family history, diabetes mellitus and smoking are commonly used to assess the cardiovascular disease risk. Besides traditional risk factors, several new coronary risk factors have been identified and play significant roles in the atherosclerosis development.^{28,29} One of those risk factors is BAC. Recent studies have shown that presence of BAC on mammograms indicates a greater risk for coronary artery disease.²⁷ As the EFT thickness was positively correlated with BAC and LDL-C levels, risk factors for coronary artery disease, in our study, EFT thickness measurement might play an important role in coronary artery risk stratification for premenopausal women in clinical practice.

Study limitations

Visual scoring of conventional mammography was applied in BAC assessment, the calcification mass scoring which is used at the digital mammography was not performed.

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