# Correlation of echocardiographic epicardial fat thickness with severity of coronary artery disease-an observational study

## *Koroner arter hastalığının şiddeti ile ekokardiyografik epikardiyal yağ kalınlığının ilişkisi-gözlemsel bir çalışma*

*Hasan Shemirani, Meysam Khoshavi*

From Department of Cardiology, Faculty of Medicine, Isfahan University of Medical Sciences, Noor Hospital, Isfahan-*Iran*

## ABSTRACT

**Objective:** Epicardial fat is an indirect contact with coronary arteries. There are some studies about the relationship between this fat and metabolic syndrome and it has considered as an indicator of cardiovascular risk. Several studies have addressed the association between epicardial fat thickness (EFT) and coronary artery disease (CAD) with conflicting results. The aim of our study was to evaluate the hypothesis that echocardiographic EFT thickness could be a marker severe CAD.

**Methods:** Overall, 315 cases who underwent coronary angiography were classified in two groups: Normal and CAD. Measurement of EFT was done with echocardiography. The difference between mean EFT in two groups was analyzed. Califf scoring considered for severity of CAD. Then the relationship between EFT and age, sex, body mass index (BMI), serum lipids and severity of CAD was evaluated. The obtained data were compared by using ANCOVA test, Pearson and Spearman's partial correlation analyses.

**Results:** The EFT in CAD group was significantly higher than in normal group (5.4±1.9 mm vs 4.4±1.8mm, p=0.0001). EFT had a positive relationship with Califf scoring of diseased coronary arteries (r=0.158 p=0.04), low-density lipoprotein cholesterol (p=0.04), female gender (p=0.02), BMI (p=0.001) and serum triglyceride levels (p=0.04).

**Conclusion:** This study shows an association between EFT thickness and severity of CAD. *(Anadolu Kardiyol Derg 2012; 12: 200-5)*

**Key words:** Epicardial fat, coronary artery disease, echocardiography

## ÖZET

**Amaç:** Epikardiyal yağ koroner arterle doğrudan temas halindedir. Bu yağ ve metabolik sendrom arasındaki ilişki hakkında bazı çalışmalar vardır ve kardiyovasküler riskin bir göstergesi olarak ele alınmıştır. Çeşitli çalışmalar, çelişkili sonuçları olan koroner arter hastalığı (KAH) ve epikardiyal yağ kalınlığı (EYK) arasındaki ilişkiyi ele almaktadır. Böylece, bizim çalışmamız, ekokardiyografik EYK'nın ciddi KAH belirteci olabileceği hipotezini değerlendirmektedir.

**Yöntemler:** Koroner anjiyografi uygulanan 315 olgu iki gruba sınıflandırıldı: Normal ve KAH. Gruplarda EYK ölçümü ekokardiyografi ile yapıldı. Ortalama epikardiyal yağ kalınlıkları arasındaki fark iki grupta da analiz edildi. KAH'ın şiddeti için Califf skorlaması kullanıldı. Sonra, EYK ve yaş, cinsiyet, vücut kitle indeksi (VKİ), serum lipitleri ve KAH şiddeti arasındaki ilişki değerlendirildi. Elde edilen veriler ANCOVA test, Pearson ve Spearman kısmi korelasyon analizleri kullanılarak karşılaştırıldı.

**Bulgular:** KAH grubunda EYK normal gruptan önemli derecede yüksekti (4.4±1.8 mm`ye karşın 5.4±1.9 mm, p=0.0001). Epikardiyal yağ kalınlığı, koroner arter hastalığının Califf skorlaması (r=0.158 p=0.04), düşük-dansiteli lipoprotein kolesterol (p=0.04), kadın cinsiyet (p=0.02), VKİ (p=0.001) ve serum trigliserid düzeyleri (p=0.04) ile pozitif ilişkiye sahiptir.

**Sonuç:** Bu çalışma, KAH'ın ciddiyeti ve EYK kalınlığı arasındaki ilişkiyi göstermektedir. *(Anadolu Kardiyol Derg 2012; 12: 200-5)*

**Anahtar kelimeler:** Epikardiyal yağ, koroner arter hastalığı, ekokardiyografi

## Introduction

Visceral adiposity is a fat deposition around internal organs. It is metabolically active and is an important risk factor for developing the metabolic syndrome (MS) (1-4). It is widely recognized that accumulation of abdominal visceral fat is strongly related to the development of coronary artery disease (CAD) (4-9). It suggested that epicardial fat thickness (EFT) may reflect the amount of visceral fat, which is associated with insulin resistance and inflammation (10). EFT is also known to be a rich source of free fatty acids and a number of bioactive molecules and inflammatory cytokines (11-14). Visceral adipose tissue thickness is associated with hip and thigh circumference or subcutaneous fat thickness (15). EFT was significantly higher in patients with nonalcoholic fatty liver disease (16). Pathological investigations revealed EFT and the adventitia of coronary arteries or myocardium to be contiguous, with no intervening structures (10).

Some reports have suggested a crucial role of EFT in the development of CAD through changes in adipokine expressions in EFT, which promote pro-inflammatory characteristics, thereby possibly facilitating the progression of coronary atherosclerosis (12-15).

Transthoracic echocardiography enables non-invasive assessment of EFT (3, 14). Conceptually, this peri-coronary fat might be most interesting because of its close anatomic relation with the coronary arteries. EFT was significantly increased in women with microvascular dysfunction (17) and individual with a higher detectable carotid atherosclerosis (18). But some studies suggested correlation between severity of obstructive coronary artery stenosis and EFT (19, 20). Several investigations of the relation between EFT and the severity of coronary stenosis in patients have produced conflicting results (20-22). Califf scoring is a reliable system for the quantification of jeopardized myocardium and severity of coronary stenosis (23, 24). Yet correlation between severity of coronary artery stenosis and EFT with this scoring system was not done.

Therefore, the aim of our study was to evaluate the hypothesis that echocardiographic EFT thickness could be a marker for severity of CAD.

## Methods

### Study design

The study was designed as an observational cross-sectional study.

This study has been confirmed by the Ethic Committee of Esfahan Medical Sciences University and all the participants were informed of its objectives before the study and signal a letter of consent in accordance with the Helsinki Declaration Standards.

### Patients

In a cross-sectional study, 315 patients who were candidate for coronary angiography due to chest pain (e.g. acute coronary syndrome and/ or chronic stable angina) and/or an abnormal stress test were selected.

The inclusion criteria were: normal respiration, normal anatomical chest, and stable sinus rhythm.

Patients were excluded if they had abnormal images on transthoracic echocardiography or poor echo window, a history of coronary artery bypass graft surgery (CABG), percutaneous coronary intervention (PTCA), chronic kidney disease, pericardial and/or pleural effusion.

### Variables

Body mass index (BMI) was calculated as body weight divided by height squared. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or requirement for antihypertensive medication (25). Diabetes mellitus was defined according to the criteria of the American Diabetes Association (26), or requirement for insulin or oral hypoglycemic drugs. Hyperlipidemia was defined as use of a lipid-lowering agent, low-density lipoprotein cholesterol (LDL) cholesterol equal or greater than 160 mg/dl, or total cholesterol higher than 220 mg/d or triglycerides ≥150 mg/dl (27). CAD was defined with presence of 75 percent cross-sectional stenosis or more of at least one major coronary artery. Height (m) and weight (kg) were used to calculated body mass index. Obesity was defined as having a BMI ≥30 kg/m$^2$ (27).

### Protocol of the study

After coronary angiography, all patients underwent transthoracic echocardiography. Systolic and diastolic blood pressures were measured after 5 min of rest. Height, waist circumference (WC), weight and body fat ratio (Tanita TBF 534, Japan) were measured during a fasting period.

### Echocardiographic measurement

Transthoracic echocardiography provides a reliable measurement of EFT (14). Epicardial fat appears as an echo free space on left and right ventricles and if it is massive, is a hyperechoic space. In this apace there is a scattered reflection that is adjacent to ventricles and move with them. This is characteristic of epicardial fat. The highest diameter of this fat is on right ventricular free wall. The subcostal four chamber and parasternal long and short axis echocardiogram views show this finding in best way (28, 29). A normal upper-limit value for EFT has not been established yet (30).

Differentiation from pericardial effusion is done with location and density of echo.

Echocardiography was performed by only one operator using Vivid- 3, GE (United States, probe number 2.5) instrument, which has a 3.5 MHZ transducer and is capable of M-mode, 2D and Doppler study. The operator and the subjects did not know the results of coronary angiography (normal or diseased coronary arteries) at the time of echocardiography.

The subjects lied on left lateral decubitus position and the fat thickness was measured on free wall of right ventricle at end systole because of: 1. this point has highest absolute epicardial fat layer thickness and 2. parasternal long- and short -axis views allow the most accurate measurement of epicardial fat on right ventricle with optimal cursor beam orientation. The average value from 3 cardiac cycles for each echocardiographic view

was used for the statistical analysis (30) (Fig. 1). To assess the reproducibility of the echocardiographic measurements, EFT thickness was measured by two independent echocardiographers in 22 randomly selected patients and inter-observer correlation coefficients were calculated. In the same group of patients, echocardiographic measurements were repeated 1 day later to calculate intra-observer correlation coefficients. Variability of measurements were also calculated as the mean of differences in measurements.

### Coronary angiography data

All cases undergo diagnostic coronary angiography. Major coronary vessels were defined as the left main, left anterior descending, circumflex, and right coronary artery. Patients with slow flow in the absence of any discernible lesions were also excluded. By considering cut-off point 75% for the definition of significant stenosis, Califf scoring was appropriate for defining severity of CAD (31). Califf scoring system for purposes of determining the severity of Coronary stenosis is considered as six arterial segments the left anterior descending artery, major diagonal, the first major septal branch, the left circumflex artery, the major obtuse marginal and the right coronary artery. In patients with a left dominant system, RCA is assigned no points. Each segment with a 75% or greater stenosis is given a score of 2 points. Each vessel distal to a 75% or greater stenosis is also given a score of 2 points (31). Coronary angiograms were interpreted by two independent invasive cardiologists. Interobserver agreement of the angiographic interpretation was assessed with a between-observer coefficient of variation. However, there is significant intra- and interobserver agreement with regard to angiographic evaluation of the extent of coronary stenosis.
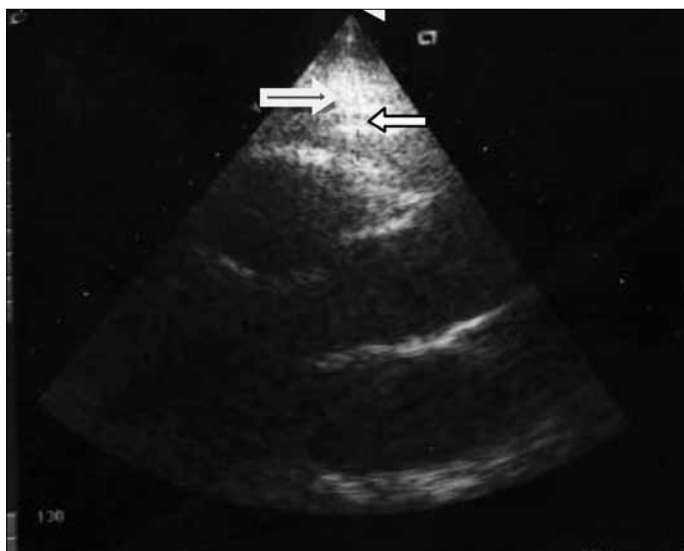


**Figure 1. Echocardiographic epicardial fat thickness (EFT). EFT (thick arrow) can be identified as the echo free space between outer wall of the myocardium and visceral layer of pericardium (thin arrow) in the parasternal long-axis view. EFT is measured during end-systole at the point on the free wall the right ventricle along the midline of the ultrasound beam, with the best effort to be perpendicular to the aortic annulus, used as an anatomic landmark**

### Statistical analysis

Statistical analysis was done using SPSS 16.0 for Windows software (SPSS Inc., Chicago, IL, US). All data were expressed as mean±standard deviation. The difference of mean EFT in normal and CAD groups were compared with unpaired Student's t test and with 95 percent confidence interval. Pearson correlation analysis was used for analysis of correlation between EFT and age, BMI, serum lipids and WC. The effect of EFT on the presence and severity (Califf scoring) of CAD was assessed using analysis of covariance (ANCOVA) and Spearman's partial correlation analysis, controlling for the intervening factors including: diabetes, sex, age, smoking, LDL, BMI. Distribution of diabetes, hypertension and smoking in normal and CAD group was analyzed with Chi-square test. Statistical significance was set at <0.05.

## Results

### Demographic features

Of the 315 patients 23 cases were excluded, 15 cases because of poor echocardiographic window and 8 cases because of pericardial effusion.

Finally, 292 subjects in the range of 32-85 years were included. Mean ages of Normal and CAD groups were 54±8.6 and 59±10 years, respectively with statistical significant difference (p=0.001). Overall, 64 (51.2%) and 111 (64.9%) males were in normal and CAD groups respectively so there was a gender difference (p=0.02) in two groups (Table 1).

### Cardiovascular risk factors distribution in groups

Distribution of diabetes (p=0.03), and smoking (p=0.001) in two groups was significantly different (Table 1), but hypertension did not differ (p=0.3).

Mean of serum LDL level was significantly higher in CAD group (p=0.04) as compared to Normal group.

### EFT and clinical variables

Epicardial fat thickness varied between 1-13.5 mm. Mean of thickness in normal group was 4.4±1.8 mm and in CAD group 5.4±1.9 mm (Fig. 2) that was statistically significant (p=0.0001). Additional ANCOVAs in both groups (normal and CAD), with discussion of diabetes, sex, age, smoking, LDL, BMI, as dependent variables, showed that the differences in EFT between both groups had significantly influenced the CAD presence (p=0.0001) (Table 2). EFT had a positive correlation with LDL, BMI (p=0.001), serum triglyceride (p=0.04) and WC (p=0.04) (Table 3). Epicardial fat thickness was higher in females (Table 4).

### Correlation EFT and severity of coronary diseases

Correlation EFT with severity of CAD with Spearman's analysis (Spearman r=0.3, p=0.0001) is defined but despite confounding variables again EFT had positive correlation with the severity of coronary diseases (Califf scoring) by controlling (partial correlation) confounding variables (Spearman r=0.213 p=0.002). Mean of Califf scoring in CAD group was 6.2.

## Discussion

This study shows the association of EFT with severity of CAD. EFT may thus be increased in the presence of atherosclerotic plaque. In addition, it may be related to cardiovascular risk factors and metabolic syndrome (MS) (4). Our study showed correlation between cardiovascular risk factors (smoking, diabetes, obesity, hyperlipidemia, age) and EFT. Distribution of traditional risk factors such as age, male sex, diabetes, smoking and serum LDL had significant difference in normal and CAD groups. This subject may have confounding effect on our results, but by controlling (ANCOVA test) these factors, the correlation between EFT and presence of CAD was defined (p=0.0001) independently.

EFT thickness emerged as an independent predictor of CAD among other well- known risk factors (32).
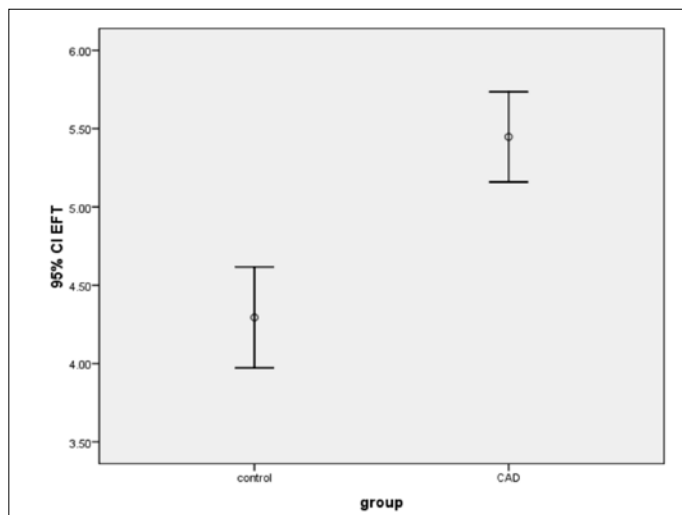


**Figure 2. Mean values of EFT in normal (control) and CAD groups**
CAD - coronary artery disease, EFT - epicardial fat thickness

**Table 1. Demographic characteristics and risk factors of patients classified according to CAD and control groups**

| Variables | CAD group | Control group | *p |
|---|---|---|---|
| Sex (male/female), n (%) | 111(64.9)/60(35.1) | 62(51.2)/59(48.8) | 0.01 |
| Age, years | 54±8.6 | 59±10 | 0.02 |
| DM, n (%) | 48/(28.1) | 21 (17.4) | 0.03 |
| Smoking, n (%) | 39 (22.8) | 8 (6.6) | 0.001 |
| HT, n (%) | 81 (47.4) | 50 (41.3) | 0.3 |
| LDL, mg/dl | 143±24 | 138±23 | 0.04 |
| Tg, mg/dl | 159.4±35 | 158.4±37 | 0.8 |
| EFT, mm | 5.4±1.9 | 4.4±1.8 | 0.0001 |
| Califf scoring, points | 6.2 | 0 | |

Data are presented as mean±SD and number/percentage
*Chi-square and unpaired Student's t-tests
CAD - coronary artery diseases, DM - diabetes mellitus, EFT - epicardial fat thickness, HT-hypertension, LDL - low - density lipoprotein, Tg - triglyceride

Two potential mechanisms for this association have been proposed: first, EFT is a component of visceral adiposity and is related to metabolic syndrome and cardiovascular risk factors (1-4), secondly, EFT has paracrine and endocrine functions. It can secrete numerous bioactive molecules (adipokines) such as adiponectin, resistin and inflammatory cytokines (interleukin -1b, interleukin -6, tumor necrosis factor- $\alpha$) (13, 33). Interestingly, inflammatory mediators originating outside the coronary artery are also capable of including compositional changes in the inner layer of intima (34, 35).

There is a growing evidence that the changes in or perivascular tissue surrounding epicardial coronary arteries could alter vascular homeostasis and contribute to endothelial dysfunction, amplification of vascular inflammation, intimal lesions, plaque progression by an "outside-to-inside"x signaling mechanism (34-37). Atherosclerosis and atherothrombosis have been identified as an inflammatory disease (38) Sacks et al. (10) pointed out the paracrine and vasocrine signaling effects of epicardial adipokines for the development of atherogenesis.

**Table 2. ANCOVA analysis result for both groups (normal and CAD), with confounding factors including of diabetes, sex, age, smoking, LDL**

| Confounding factors | **df | *F | ***p |
|---|---|---|---|
| Age | 1 | 1.01 | 0.315 |
| Sex | 1 | 11.8 | 0.001 |
| Smoking | 1 | 1.18 | 0.013 |
| DM | 1 | 6.3 | 0.27 |
| LDL | 1 | 3.3 | 0.6 |

Dependent variable= EFT
*F=F-test assumes that the errors are normally distributed and homoscedastic
**df=degrees of freedom
***p value
CAD - coronary artery diseases, DM - diabetes mellitus, EFT - epicardial fat thickness, LDL - low density lipoprotein

**Table 3. Spearman and Pearson correlation analyses for relationship of epicardial fat and clinical variables**

| Variables | r | p |
|---|---|---|
| Age | 0.148 | 0.01 |
| BMI | 0.551 | 0.001 |
| Tg | 0.487 | 0.001 |
| LDL | 0.309 | 0.001 |
| Califf Score | 0.158 (Spearman) | 0.042 |

BMI - body mass index, EFT - epicardial fat thickness, LDL - low - density lipoprotein, Tg - triglyceride

**Table 4. Gender difference in EFT in all cases**

| Gender | Number | Mean thickness | SD | *p |
|---|---|---|---|---|
| Female | 119 | 5.3 | 1.9 | 0.01 |
| Male | 173 | 4.6 | 1.9 | |

Data are presented as mean±SD and number
Unpaired Student's t-test
EFT - epicardial fat thickness

It seems that EFT is a part of active adipose tissue that can affects the coronary circulation via secretion of inflammatory mediators and adipokines (12).

However, there is a substantial amount of data demonstrating associations between increased EFT thickness and volume as assessed by echocardiography and coronary atherosclerosis. It is of note that some of the studies indicate that an increased amount of EFT is either not related to CAD or is merely a marker of visceral and overall adiposity and that adding it to the already existing cardiovascular risk assessment models does not enhance their predictive capabilities (39, 40).

These discrepancies may be to some extent the result of varying methodologies and study populations. We also showed that EFT independently was related to severity (p=0.042) of CAD.

The correlation between EFT thickness and the severity of CAD has been addressed previously (19, 20). However, the results of these studies are conflicting, as they did not assess patients with normal coronary arteries.

Ahn et al. (10) showed that EFT was thicker in subjects with CAD than in those without CAD, and that it might provide additional information for assessing CAD risk and predicting the extent and activity of CAD.

In this study, we defined that increased EFT correlated with multiple and severe coronary artery stenosis without confounding effect of dependent variables.

In our study, EFT on the right ventricle varied between 1 and 13.5 mm, which was similar to those reported in a recent study (1.8-16.5mm) (14). Epicardial fat thickness was higher in females (Table 4) that may be because of higher BMI in females than in men.

Inflammation has been identified as a potential target for therapeutic intervention in patients with CAD (39). Inflammatory mediators-derived EFT was favorable target for preventive intervention and novel therapeutic strategies, that these interventions (such as aspirin, angiotensin-converting enzyme inhibitor, statin, and specially exercise and weight loss) may also have anti- inflammatory effect and decreasing epicardial fat volume, but more studies are required for approving this hypothesis.

### Study limitations

To further clarify the possible relation between fat surrounding, coronary arteries and the development of CAD, it is important to reliably quantify this adipose tissue. In a few studies, adipose tissue around the heart has been measured by magnetic resonance imaging (MRI), computed tomography (CT) or echocardiography (41-44). Furthermore, there are differences in anatomic description (pericardial versus epicardial fat) and measurement techniques (volume or thickness) (41, 42, 44).

A measurement of adipose tissue directly surrounding the coronary arteries has not been published.

We could not confirm epicardial fat using the standard MRI and CT methods. Echocardiography was a relatively simple and inexpensive method, but the accuracy and reproducibility should be further tested. In addition, as epicardial adipose tissue has a 3-dimensional distribution, 2-dimensional echocardiography may not completely assess the total amount of epicardial adiposity. Further study will be necessary.

### Conclusion

In our study, thickness of epicardial fat layer was higher in CAD group than in normal group. EFT measured using transthoracic echocardiography significantly correlated with the severe multiple of coronary artery stenosis in patients with known coronary artery disease. Also, epicardial fat thickness as a marker of severity of coronary lesions. These findings may enhance the utility of echocardiography as an assessment tool for patients' adiposity and, if confirmed, can assist in the risk stratification of patients with coronary artery disease. Complementary studies in this field are recommended.

### References

1. Peiris AN, Sothmann MS, Hoffmann RG, Hennes MI, Wilson CR, Gustafson AB, et al. Adiposity, fat distribution and cardiovascular risk. Ann Intern Med 1989; 110: 867-72.
2. Folsom AR, Kushi LH, Anderson KE, Mink PJ, Olson JE, Hong CP, et al. Associations of general and abdominal obesity with multiple health outcomes in older women: the Iowa Women's Health Study. Arch Intern Med 2000; 160: 2117-28. **[CrossRef]**
3. Rexrode KM, Buring JE, Manson JE. Abdominal and total adiposity and risk of coronary heart disease in men. Int J Obes Relat Metab Disord 2001; 25: 1047-56. **[CrossRef]**
4. Iacobellis G, Ribaudo MC, Assael F, Vecci E, Tiberti C, Zappaterreno A, et al. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. J Clin Endocrinol Metab 2003; 88: 5163-8. **[CrossRef]**
5. Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, et al. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. Lancet 2005; 366: 1640-9. **[CrossRef]**
6. Carr DB, Utzschneider KM, Hull RL, Kodama K, Retzlaff BM, Brunzell JD, et al. Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. Diabetes 2004; 53: 2087-94. **[CrossRef]**
7. Rexrode KM, Carey VJ, Hennekens CH, Walters EE, Colditz GA, Stampfer MJ, et al. Abdominal adiposity and coronary heart disease in women. JAMA 1998; 280: 1843-8. **[CrossRef]**
8. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu CY, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. Circulation 2007; 116: 39-48. **[CrossRef]**

9.   Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002; 105: 1135-43. **[CrossRef]**
10.  Ahn SG, Lim HS, Joe DY, Kang SJ, Choi BJ, Choi SY, et al. Relationship of epicardial adipose tissue by echocardiography to coronary artery disease. Heart 2008; 94: 7. **[CrossRef]**
11.  Mazurek T, Zhang L, Zalewski A, Mannion JD, Diehl JT, Arafat H, et al. Human epicardial adipose tissue is a source of inflammatory mediators. Circulation 2003; 108: 2460-6. **[CrossRef]**
12.  Iacobellis G, Pistilli D, Gucciardo M, Leonetti F, Miraldi F, Brancaccio G, et al. Adiponectin expression in human epicardial adipose tissue in vivo is lower in patients with coronary artery disease. Cytokine 2005; 29: 251-5.
13.  Baker AR, Silva NF, Quinn DW, Harte AL, Pagano D, Bonser RS, et al. Human epicardial adipose tissue expresses a pathogenic profile of adipocytokines in patients with cardiovascular disease. Cardiovasc Diabetol 2006; 5: 1. **[CrossRef]**
14.  Iacobellis G, Assael F, Ribaudo MC, Zappaterreno A, Alessi G, Di Mario U, et al. Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. Obes Res 2003; 11: 304-10. **[CrossRef]**
15.  Sacks HS, Fain JN. Human epicardial adipose tissue: a review. Am Heart J 2007; 153: 907-17. **[CrossRef]**
16.  Yılmaz Y, Kurt R, Gürdal A, Alahdab YO, Yonal O, Senates E, et al. Circulating vaspin levels and epicardial adipose tissue thickness are associated with impaired coronary flow reserve in patients with nonalcoholic fatty liver disease. Atherosclerosis 2011; 217: 125-9. **[CrossRef]**
17.  Sade LE, Eroğlu S, Bozbaş H, Özbiçer S, Hayran M, Haberal A, et al. Relation between epicardial fat thickness and coronary flow reserve in women with chest pain and angiographically normal coronary arteries. Atherosclerosis 2009; 204: 580-5. **[CrossRef]**
18.  Nelson MR, Mookadam F, Thota V, Emani U, Al Harthi M, Lester SJ, et al. Epicardial fat: an additional measurement for subclinical atherosclerosis and cardiovascular risk stratification? J Am Soc Echocardiogr 2011; 24: 339-45. **[CrossRef]**
19.  Jeong JW, Jeong MH, Yun KH, Oh SK, Park EM, Kim YK, et al. Echocardiographic epicardial fat thickness and coronary artery disease. Circ J 2007; 71: 536-9. **[CrossRef]**
20.  Iwasaki K, Matsumoto T, Aono H, Furukawa H, Samukawa M. Relationship between epicardial fat measured by 64-multidetector computed tomography and coronary artery disease. Clin Cardiol 2011; 34: 166-71. **[CrossRef]**
21.  Chaowalit N, Somers VK, Pellikka PA, Rihal CS, Lopez-Jimenez F. Subepicardial adipose tissue and the presence and severity of coronary artery disease. Atherosclerosis 2006; 186: 354-9. **[CrossRef]**
22.  Eroğlu S, Sade LE, Yıldırır A, Bal U, Özbiçer S, Özgül AS, et al. Epicardial adipose tissue thickness by echocardiography is a marker for the presence and severity of coronary artery disease. Nutr Metab Cardiovasc Dis 2009; 19: 211-7. **[CrossRef]**
23.  Candell-Riera J, JCastell-Conesa J, Aguadé-Bruix S. Myocardium at risk and viable myocardium: evaluation by SPET. 2001, 130-3.
24.  Candell-Riera J, Santana-Boado C, Castell-Conesa J, Aquade-Bruix S, Olona-Cabeses M, Domingo E, et al. Culprit lesion and jeopardized myocardium: correlation between coronary angiography and single-photon emission computed tomography. Clin Cardiol 1997; 20: 345-50. **[CrossRef]**
25.  Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003; 289: 2560-72. **[CrossRef]**
26.  Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997; 20: 1183-97.
27.  National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in adults (Adult Treatment Panel III): final report. Circulation 2002; 106: 3143-421.
28.  Hagan AD, Demaria AN. Clinical applications of two-dimensional echocardiography and cardiac Doppler. 2nd ed. Boston: Little Brawn Company; 1989.
29.  Schejbal V. Epicardial fatty tissue of the right ventricle-morphology, morphometry and functional significance. Pneumologie 1989; 43: 490-9.
30.  Iacobellis G, Willens HJ, Barbaro G , Sharma AM. Threshold values of high-risk echocardiographic epicardial fat thickness. Obesity (Silver Spring) 2008; 16: 887-92. **[CrossRef]**
31.  Califf RM, Phillips HR 3rd, Hindman MC, Mark DB, Lee KL, Behar VS, et al. Prognostic value of a coronary artery jeopardy score. J Am Coll Cardiol 1985; 5: 1055-63. **[CrossRef]**
32.  Shemirani H, Hosseini K. The relationship between echocardiographic epicardial fat thickness and coronary artery disease. Journal of Isfahan Medical School 2004; 21: 35-7.
33.  Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. Nat Clin Pract Cardiovasc Med 2005; 2: 536-43. **[CrossRef]**
34.  Miyata K ,Shimokawa H, Kandabashi T, Higo T, Morishige K, Eto Y, et al. Rho-kinase is involved in macrophage -mediated formation of coronary vascular lesions in pigs in vivo . Arterioscler Thromb Vas Biol 2000; 20: 2351-8. **[CrossRef]**
35.  Shimokawa H, Ito A , Fukumoto Y, Kadokami T, Nakaike R, Sakata M, et al . Chronic treatment with interleukin -1 induces coronary intimal lesions and vasospastic responses in pig in vivo. The role of platelet-derived growth factor. J Clin Invest 1996; 97: 769-76. **[CrossRef]**
36.  Pagano PJ, Clark JK, Cifuentes-Pagano ME, Clark SM, Callis GM, Quinn MT, et al. Localization of a constitutively active, phagocyte-like NADPH oxidase in rabbit aortic adventitia: enhancement by angiotensin II. Proc Natl Acad Sci U S A 1997; 94: 14483-8. **[CrossRef]**
37.  Wang HD, Pagano PJ, Du Y, Cayatte AJ, Quinn MT, Brecher P, et al. Superoxide anion from the adventitia of the rat thoracic aorta inactivates nitric oxide. Circ Res 1998; 82: 810-8.
38.  Morrow DA, De Lemos JA, Sabatine MS, Wiviott SD, Blazing MA, Shui A, et al. Clinical relevance of C-reactive protein during follow -up of patients with acute coronary syndromes in the Aggrastat-to-Zocor Trial .Circulation 2006; 114: 281-8. **[CrossRef]**
39.  de Vos AM, Prokop M, Roos CJ, Meijs MF, van der Schouw YT, Rutten A, et al. Peri-coronary epicardial adipose tissue is related to cardiovascular risk factors and coronary artery calcification in post-menopausal women. Eur Heart J 2008; 29: 777-83. **[CrossRef]**
40.  Rosito GA, Massaro JM, Hoffmann U, Ruberg FL, Mahabadi AA, Vasan RS, et al. Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community- based sample: the Framingham Heart Study. Circulation 2008; 117: 605 -13. **[CrossRef]**
41.  Wheeler GL, Shi R, Beck SR, Langefeld CD, Lenchik L, Wagenknecht LE, et al. Pericardial and visceral adipose tissues measured volumetrically with computed tomography are highly associated in type 2 diabetic families. Invest Radiol 2005; 40: 97-101. **[CrossRef]**
42.  Taguchi R, Takasu J, Itani Y, Yamamoto R, Yokoyama K, Watanabe s, et al. Pericardial fat accumulation in men as a risk factor for coronary artery disease. Atherosclerosis 2001; 157: 203-9. **[CrossRef]**
43.  Abbara S, Desai JC, Cury RC, Butler J, Nieman K, Reddy V. Mapping epicardial fat with multi-detector computed tomography to facilitate percutaneous transepicardial arrhythmia ablation. Eur J Radiol 2006; 57: 417-22. **[CrossRef]**
44.  Flüchter S, Haghi D, Dinter D, Heberlein W, Kühl HP, Neff W, et al. Volumetric assessment of epicardial adipose tissue with cardiovascular magnetic resonance imaging. Obesity (Silver Spring) 2007; 15: 870-8. **[CrossRef]**