Association Between Epicardial Fat Thickness and Premature Coronary Artery Disease: A Case Control Study

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Background: The association between epicardial fat thickness (EFT) and premature coronary artery disease (CAD) has not been elaborately studied.

Objectives: In the present study, we sought whether such a relationship between EFT and CAD exists.

Patients and Methods: Sixty-two consecutive subjects, under 50 years of age, who underwent coronary angiography (CAG) with the aspect of CAD, were included in this case control study. They were divided into two groups of 31 subjects, namely CAD (cases) and non-CAD (controls) group, according to CAG data. Presence of conventional coronary risk factors, drug history, and anthropometric data were recorded. Then, each subject underwent standard transthoracic echocardiography for measuring EFT in the proximal part of right ventricular outflow tract in the parasternal long axis view at end diastole, as well as other parameters of systolic and diastolic function, and left ventricle (LV) mass. Images were stored for offline analysis when the echocardiocardiographers were blind to CAG data.

Results: Among baseline characteristics, waist circumference, triglyceride levels, cigarette smoking and history of statin use were significantly higher in the CAD group. The body mass index (BMI) was significantly higher in the non-CAD group. According to echocardiographic data, the EFT with a cut off value of 2.95 mm could well differentiate subjects in each group. The LV mass and E/e were significantly higher in CAD group, in addition to EFT. Also, there was a significant correlation between EFT and waist circumference, as well as LV mass. However, no significant relation was between EFT and LV systolic and diastolic function.

Conclusions: The EFT, as measured by echocardiography, with a cut off value 2.95 mm has a strong association with premature CAD.

Keywords: Coronary Angiography; Coronary Artery Disease; Echocardiography

1. Background

A number of studies have put question marks against metabolic syndrome, as a risk marker of coronary artery disease (CAD). Such controversy is based on the fact that, although most definitions of metabolic syndrome include the measurement of central obesity, none of the current criteria focuses on direct measurement of visceral fat deposition, which is known to be a risk factor for dysmetabolism (1). Therefore, estimation of visceral adipose tissue seems to be a key issue and several methods are being applied for this measurement. Epicardial adipose tissue is a type of visceral fat deposited around the heart, particularly around subepicardial coronary vessels, and that has been shown to be implicated in the development of CAD (2). Several studies have also shown the association between the severity of CAD and epicardial fat thickness (EFT), measured by echocardiography, although, to the extent of our knowledge, none of them has evaluated this association with premature CAD (defined as occurrence of atherosclerosis in men under 55 and in women under 65 years of age) (3-5).

2. Objectives

The aim of our study was to evaluate the EFT in the population affected by premature CAD, in the context of reports that have shown that this adipose tissue, as a source of inflammatory mediators, can trigger atherosclerosis (6).

3. Patients and Methods

3.1. Subjects

Sixty-three consecutive subjects under 50 years of age, who underwent coronary angiography (CAG), with the impression of CAD, in our center, from October to December 2013, were included in this case control study, from which about the half were referred from other cities. The CAG data were collected by reviewing CAG films and CAD
was defined as at least one vessel disease, with diameter of stenosis of 50% or greater. According to that criteria, the subjects were divided in two groups, namely CAD (31 cases) and non-CAD (31 controls).

Power analysis was done according to measuring the difference between means of EFT of two groups and the required parameters were adopted from the pilot study ($\alpha = 2$ mm, $\beta = 4$ mm), which allowed to estimate the subjects in each group to be 31.

3.1.1. Inclusion Criteria

Subjects under 50 years old, who underwent CAG due to acute coronary syndrome occurrence, ST segment elevation myocardial infarction, high risk noninvasive studies, or symptoms, which made the impression of CAD highly probable.

3.1.2. Exclusion Criteria

Patients with non-atherosclerotic forms of CAD, severe valvular heart disease, cardiomyopathies, pericardial effusion, and those with poor image quality were excluded from the study.

3.2. Methods

Subjects were interviewed regarding the presence of conventional coronary risk factor (diabetes mellitus, hyperlipidemia, hypertension, smoking, and a family history of CAD) and present medication use. Height and weight (for calculation body surface area (BSA) and body mass index (BMI) according to appropriate formulas), waist circumference, blood pressure, fasting blood sugar and lipid profiles were also recorded.

All patients underwent transthoracic echocardiography in the following day after CAG. Echocardiograms were performed with the VIVID 7 (General Electric Company, Fairfield, CT, USA) instrument, using standard techniques and with patients in left lateral decubitus position. The images were stored and offline measurements were performed by two echocardiographers, who were blind to angiographic data and to the results of each other.

We measured EFT (which is identified as the echo free space between the outer layer of myocardium and the visceral layer of pericardium, to be differentiated from pericardial fat (which lies between the two layers of pericardium)). Measurements were made on the free wall of proximal right ventricular outflow tract in parasternal long axis view, along the midline of the ultrasound beam, perpendicular to the aortic annulus at end diastole (marked by R wave on ECG) and the average value from three cardiac cycles was used (Figure 1).

Other echocardiographic measurements were performed in conformity to the American Society of Echocardiography guidelines, including ejection fraction (EF), left atrial volume (by volumetric biplane Simpson method), cardiac output, left ventricular (LV) mass, diastolic parameters (E, A, DT, E/A, E/e) and they were indexed by BSA, when necessary.

3.3. Statics

Statistical analyses were performed using SPSS version 18 for Windows (SPSS Inc., Chicago, IL, USA). Baseline qualitative data were expressed as percentile and quantitative data were shown as Mean ± SD. All interval data were tested for normal distribution, with one sample Kolmogorov Smirnov test. Subjects’ characteristics, according to CAD and non-CAD groups, were compared using independent T (or Mann–Whitney U) tests and the chi square test.

The optimum sensitivity and specificity of threshold values of EFT to show significant CAD were tested using the receiver operating curve (ROC). Inter- and intraobserver variability for measuring EFT by echocardiography were evaluated using the Bland-Altman plot.

Correlation between EFT and quantitative variables were evaluated using Pearson (or Spearman) tests. Multivariate analysis was performed to determine the factors independently related to significant CAD, by using logistic regression. Comparison of EFT in different groups of CAD patients (groups with one vessel, two vessel, or three vessel disease) was done using one way analysis of variance (ANOVA) test.

4. Results

Except only one subject, who was excluded from the study because of poor image quality, we had two groups (CAD and non-CAD) of 31 subjects.

4.1. Baseline Characteristics of the Groups

Among baseline characteristics, BMI, waist circumference (WC), blood triglyceride (TG) levels, cigarette smoking and statin use were significantly different between the groups and all of these variables, except BMI, were higher in the CAD group (Table 1).

4.2. Echocardiographic Findings

4.2.1. Epicardial Fat Thickness

Our special focus was on the evaluation of the association between premature CAD and EFT, which is evidenced by the results in Table 2 and Figure 2. We also discovered a cutoff value of 2.95 mm of EFT, regarding this association, with a sensitivity of 83%, specificity of 75%, 95% confidence interval (CI 95%) of 0.69–0.93 and accuracy of 0.81, using the ROC (Figure 3). The EFT = 2 mm was 87% sensitive and 36% specific, while EFT = 4 mm was 51% sensitive and 94% specific, for the detection of this association. It is also important to mention that intra-observer and inter-observer variability for measuring EFT were ideal, according to Bland-Altman plot, with non-significant P values (Figure 4).
Table 1. Comparison of Clinical and Paraclinical Data Between the Coronary Artery Disease and Non-coronary Artery Disease Groups

| Variables                      | Non-CAD | CAD       | P Value |
|--------------------------------|---------|-----------|---------|
| Age, y                         | 45 ± 4  | 46 ± 3    | 0.45    |
| Male, %                        | 58.1    | 74.2      | 0.18    |
| BMI, kg/m²                     | 28.8 ± 4.3 | 26.29 ± 4.26 | 0.047   |
| Waist circumference, cm        | 88 ± 4.5 | 92 ± 4.4 | < 0.001 |
| HTN, %                         | 25.8    | 22.6      | 0.76    |
| Cigarette smoking, %           | 19.4    | 45.2      | 0.03    |
| Family history, %              | 9.7     | 29.0      | 0.054   |
| DM, %                          | 12.9    | 25.8      | 0.19    |
| Total cholesterol, mg/dL       | 151 ± 41 | 157 ± 40 | 0.55    |
| HDL, mg/dL                     | 41 ± 6  | 38 ± 6    | 0.07    |
| LDL, mg/dL                     | 83 ± 27 | 86 ± 28   | 0.61    |
| TG, mg/dL                      | 135 ± 119 | 185 ± 161 | 0.036   |
| ACEI/ARB, %                    | 19.4    | 29.0      | 0.37    |
| Beta blocker, %                | 32.3    | 51.6      | 0.12    |
| Statin, %                      | 12.9    | 54.8      | < 0.001 |
| ASA, %                         | 41.9    | 48.4      | 0.61    |

\[Abbreviations: ACEI/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor blockers; ASA, acetylsalicylic acid; BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; HDL, high density lipoprotein; HTN, hypertension; LDL, low density lipoprotein; Non-CAD, non-coronary artery disease; TG, triglyceride.\]

Table 2. Comparison of Epicardial Fat Thickness Between Coronary Artery Disease and Non-Coronary Artery Disease Groups

| Variable            | Non-CAD | CAD       | P Value |
|---------------------|---------|-----------|---------|
| Epicardial fat thickness, mm | 2.6 ± 1.2 | 4.2 ± 1.4 | < 0.001 |

\[Abbreviations: CAD, coronary artery disease; Non-CAD, non-coronary artery disease.\]
4.3. Values of Other Echocardiographic Findings

The LV mass and E/e were also significantly higher in the CAD group (Table 3).

4.4. Correlation Between Epicardial Fat Tissue and Other Parameters

There were significant correlations between EFT and WC, as well as LV mass. However, there were no significant correlations between EFT and lipid profile and parameters of systolic and diastolic function (Table 4).

4.5. Regression Model for Evaluation of Independent Risk Markers of Coronary Artery Disease

By including age, WC, BMI, smoking, DM, statin use, and EFT in regression models, we found that WC, BMI, EFT and statin therapy had independent association with premature CAD with significant P values (Table 5).

4.6. Differences of Epicardial Fat Tissue in Subgroups of Coronary Artery Disease

There were no significant differences between EFT in the subgroups of CAD, based on subjects with one, two, or three vessel disease (P value = 0.7).

Table 3. Comparison of Echocardiographic Data Between Coronary Artery Disease and Non-coronary Artery Disease Groups a

| Variables                        | Non-CAD   | CAD       | P Value |
|----------------------------------|-----------|-----------|---------|
| EF, %                            | 49 ± 9    | 46 ± 13   | 0.19    |
| Cardiac output, L/min            | 5.4 ± 1.7 | 5.7 ± 1.8 | 0.4     |
| Cardiac index, L/m²              | 3.09 ± 0.95 | 3.01 ± 1.02 | 0.7    |
| LV mass, gr                      | 163 ± 48  | 195 ± 45  | 0.008   |
| LV Mass index, gr/m²             | 92 ± 25   | 101 ± 25  | 0.25    |
| LA volume index, cc/m²           | 23 ± 6    | 24 ± 8    | 0.8     |
| E/A                              | 1.2 ± 0.6 | 1.5 ± 1.6 | 1       |
| DT(msec)                         | 197 ± 42  | 195 ± 50  | 0.9     |
| E/e                              | 8 ± 3.6   | 11 ± 5    | 0.001   |

a Abbreviations: CAD, coronary artery disease; DT, deceleration time; EF, ejection fraction; LA, left atrium; LV, left ventricle; Non-CAD, non-coronary artery disease.

Table 4. Correlation Between Epicardial Fat Tissue and Clinical, Laboratory and Echocardiographic Parameters a

| Variable                        | r     | P Value |
|---------------------------------|-------|---------|
| Age and anthropometric data     |       |         |
| Age                             | 0.2   | 0.1     |
| WC                              | 0.3   | 0.01    |
| BMI                             | -0.02 | 0.8     |
| Lipid profile                   |       |         |
| HDL                             | -0.09 | 0.47    |
| LDL                             | 0.12  | 0.33    |
| TG                              | 0.09  | 0.45    |
| Total cholesterol               | 0.04  | 0.7     |
| Echocardiographic data          |       |         |
| EF                              | -0.19 | 0.13    |
| Cardiac output                  | 0.03  | 0.8     |
| Cardiac index                   | 0.003 | 0.98    |
| LV mass                         | 0.26  | 0.03    |
| LV mass index                   | 0.23  | 0.06    |
| LA volume index                 | 0.03  | 0.18    |
| E/A                             | -0.15 | 0.23    |
| DT                              | 0.08  | 0.5     |
| E/e                             | 0.17  | 0.18    |

a Abbreviations: BMI, body mass index; DT, deceleration time; EF, ejection fraction; HDL, high density lipoprotein; LA, left atrium; LDL, low density lipoprotein; LV, left ventricle; TG, triglyceride; WC, waist circumference.
4. Discussion

At present, magnetic resonance imaging (MRI) is accepted as a gold standard method for measuring EFT (7). However, in 2003, Iacobellis et al. showed that echocardiographic measurements of EFT had good correlations with epicardial fat measured by MRI (8, 9).

Twenty percent of all coronary events are reported to occur in patients without classic risk factors. At present, the search for novel and reproducible cardiovascular risk prediction methods is continuing and seems very promising. Several studies have reported the correlation between EFT and the severity of CAD, and also between EFT and fatal and nonfatal coronary events, previously (4, 5, 10). Nevertheless, to the best of our knowledge, the present study is the first clinical study to show the association between EFT and premature CAD. We also found that the cut off value of 2.95 mm for EFT, in our patients, had strong association with premature CAD, with good sensitivity, specificity and accuracy. We believe that our findings could introduce a new applicable and readily accessible risk assessment method of atherosclerosis that offers good reliability and reproducibility, as well as low cost and noninvasiveness. As only one subject was excluded from our study, because of poor image quality, there is a rational for introducing it into routine echocardiographic studies.

Because an appreciable number of our subjects were referred from other cities for CAG, we think our results are generalizable. We also found a positive relationship between EFT and WC and also between EFT and LV mass, which is in accordance with the previous studies (4, 11). Nevertheless, to the best of our knowledge, the present study, perhaps due to a lower incidence of CAD in women, for predicting metabolic syndrome. Therefore, we believe future studies should focus on the development of a standardized technique for evaluating this parameter. Another point concerns distinguishing epicardial fat (which lies between the myocardium and visceral pericardium) from the pericardial fat (between the two layers of pericardium) that may also make differences in the ranges claimed by the authors. In summary, we were able to find an association between EFT and premature CAD and propose that further prospective studies are needed for introducing high risk EFT, as a CAD risk factor.

5.1. Limitations

We should have in mind that epicardial fat has a 3D distribution and that 2D echocardiography cannot assess the total amount of epicardial fat. Also, defining cutoff values based on gender requires recruiting larger number of females, which were under represented in our study, perhaps due to a lower incidence of CAD in women in the selected age range of our study.

Measuring EFT by echocardiography is a feasible, affordable, reliable, and reproducible method of CAD risk assessment and high risk EFT has a greatly acceptable sensitivity and specificity for the presence of CAD.

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### Table 5. Logistic Regression Analysis Indicating Independent Risk Markers of Coronary Artery Disease a

| Variable       | Unstandardized Coefficients | B Standard Error | P Value | Odds Ratio | 95% CI (Lower-Upper) |
|----------------|----------------------------|------------------|---------|------------|---------------------|
| EFT            | 0.94                       | 0.4              | 0.019   | 2.572      | 1.17 - 5.66         |
| Cigarette smoking | 0.51                      | 0.97             | 0.6     | 1.658      | 0.25 - 11.01        |
| Atorvastatin   | 2.7                        | 1.2              | 0.025   | 15.158     | 1.41 - 163.42       |
| Age            | 0.14                       | 0.33             | 0.271   | 1.152      | 0.89 - 1.48         |
| WC             | 0.59                       | 0.39             | 0.002   | 1.798      | 1.23 - 2.61         |
| BMI            | -0.42                      | 0.16             | 0.01    | 0.66       | 0.48 - 0.91         |
| TG             | 0.002                      | 0.005            | 0.622   | 1.002      | 0.99 - 1.01         |
| DM             | 2.92                       | 2.44             | 0.232   | 18.625     | 0.15 - 2242.07      |

a Abbreviations: BMI, body mass index; DM, diabetes mellitus; EFT, epicardial fat tissue; TG, triglyceride; WC, waist circumference.
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Authors’ Contributions

Study concept and design: Mozhgan Parsaee, Sedigheh Saedi, Ali Vasheghani Farahani. Acquisition of data: Mozhgan Parsaee, Shadi Faghihi. Drafting of the manuscript: Shadi Faghihi, Sedigheh Saedi. Critical revision of the manuscript for important intellectual content: Sedigheh Saedi, Shadi Faghihi. Statistical analysis: Behshid Ghadrdoost, Shadi Faghihi. Administrative, technical, material support: Mozhgan Parsaee, Ali Vasheghani Farahani. Study supervision: Mozhgan Parsaee.

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