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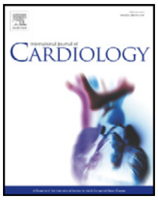

Echocardiographic epicardial fat thickness is associated with arterial stiffness

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ABSTRACT

Background: Epicardial adipose tissue represents visceral adiposity, the early detection of which could be helpful for assessing subclinical target organ damage. Although previous studies have reported a relationship between epicardial fat thickness (EFT) and carotid intima-media thickness, there have been no studies detailing the relationship between EFT and brachial–ankle pulse wave velocity (baPWV).
Methods: We consecutively enrolled 655 subjects (445 men, 55 ± 9 years) who underwent echocardiography and baPWV and had an ankle–brachial index greater than 0.95. The subjects were divided into four quartile groups depending on EFT. Subjects were also classified into two groups according to baPWV: group I (324 subjects), baPWV ≤ 1366 cm/s, and group II (331 subjects), baPWV > 1366 cm/s.
Results: The EFT in group II was significantly higher than in group I (4.2 mm vs. 3.7 mm, $p<0.001$). There were significant differences in baPWV values among the EFT quartile groups (quartile I, 1327 ± 148.8 cm/s; quartile II, 1371 ± 215.0 cm/s; quartile III, 1434 ± 228.3 cm/s; quartile IV, 1507 ± 233.1 cm/s; p-value < 0.001). In multivariate regression models, the highest quartile groups of EFT had higher odds ratios (ORs) for increased baPWV compared with that of the lowest quartile group (OR [95% confidence interval (CI)]: 2.19[1.21–3.95]), irrespective of confounding factors. Moreover, EFT was an independent determinant of baPWV (standard $\beta=0.113$, $p=0.001$).
Conclusions: This study demonstrates an independent relationship between EFT and arterial stiffness, suggesting that echocardiographic EFT measurement could be an easy-to-measure tool for early detection of subclinical target organ damage.

1. Introduction

Epicardial adipose tissue consists of visceral fat deposited around the heart between the myocardium and visceral pericardium and has been considered a metabolically active organ that secretes several bioactive molecules [1,2]. Recently, with the progress of imaging modalities, epicardial fat can be easily measured by echocardiography, multi-detector computer tomography (MDCT), or cardiac magnetic resonance imaging (MRI). Although echocardiographic epicardial fat thickness (EFT) measurement has some limitations, in that it might not reflect the variability of fat thickness or total epicardial fat volume, and the accuracy of the measurement is highly dependent on acoustic window, echocardiographic measurements are widely used, due to low cost and easy availability.

Assessment of subclinical vascular damage including carotid intima-media thickness, coronary artery calcification, and arterial stiffness is commonly performed for public health care screening and also helpful for risk stratification of future cardiovascular disease. Among them, brachial–ankle pulse wave velocity (baPWV), an index of arterial stiffness, has been widely used to assess atherosclerotic vascular damage in the general population in East Asian countries. In addition, previous studies have reported that baPWV is associated with oxidative stress, albuminuria, cardiovascular morbidity, and mortality [3–6].

Recently, several studies have reported that epicardial fat is associated with insulin resistance [7], increased cardiometabolic risk [8], inflammatory markers [9–13] and coronary artery disease [14,15]. Furthermore, some studies reported that epicardial adipose tissue is related to subclinical target organ damage such as carotid intima-media thickness [16] or carotid plaque [17]. However, no studies have been performed regarding the association between EFT and baPWV.

The present study was designed to evaluate whether echocardiographic EFT is associated with increased arterial stiffness independent of other coexisting risk factors.

2. Materials and methods

2.1. Study population

A total of 699 individuals, none of whom had any history of peripheral artery disease, had echocardiography and brachial–ankle pulse wave velocity (baPWV) measurements performed at the health promotion center at the Kangbuk Samsung Hospital between 2008 and 2009. Among the individuals screened, a total of 655 subjects (age: 55 ± 8.8 years, men: 445 subjects) with an ankle–brachial index (ABI) greater than 0.95 were enrolled for this analysis.

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Medical and medication histories, alcohol consumption (≥three times per week), smoking status (current- or non-smoker), and physical activity (≥three times per week) were assessed using standard questionnaires. Height and weight were measured using automatic instruments with participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters squared). Waist circumference was measured at the midlevel between the lowest rib and the iliac crest with the subject standing and breathing normally. Systolic and diastolic blood pressures (SBP and DBP) and heart rate (HR) were measured by a trained nurse using a mercury sphygmomanometer on the right arm of subjects in a seated position after they had rested for 5 min or longer.

A morning blood sample was collected after at least 12 h of fasting. Serum glucose, alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), serum total cholesterol, triglycerides, low density lipoprotein (LDL) cholesterol, and high density lipoprotein (HDL) cholesterol concentrations were measured using an autoanalyzer (Advia 1650 Autoanalyzer, Bayer Diagnostics, Leverkusen, Germany). Fasting insulin concentration was measured by immunoradiometric assay (Biosource, Nivelles, Belgium), and hemoglobin $_{A1c}$ (Hb_{a1c}) was measured using an immunoturbidimetric assay with a Cobra Integra 800 automatic analyzer (Roche Diagnostics, Basel, Switzerland) with a reference value range of 4.4% to 6.4%.

Serum creatinine and uric acid levels were determined using the Jaffe reaction method (Advia 1650 kit, Bayer Corp., Pennsylvania, USA) and the uricase EMST method, respectively.

High sensitivity C-reactive protein (hs-CRP) concentration was measured using particle-enhanced immunonephelometry, with a lower limit of detection of 0.175 mg/L after a 1:20 sample dilution (Behring Nephelometer II, Dade Behring, Marburg, Germany).

Insulin resistance was measured by homeostasis model assessment-insulin resistance (HOMA-IR) and obtained using the following formula: HOMA-IR = [fasting insulin (uIU/mL) × fasting blood glucose (mmol/l)]/22.5.

Metabolic syndrome was defined using the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria, and was confirmed when at least three of the following five components were present: abdominal obesity (waist circumference >90 cm for men and >80 cm for women), triglyceride concentration 1.70 mmol/l (150 mg/dl) or more, HDL cholesterol less than 1.04 mmol/l (40 mg/dl) for men and less than 1.3 mmol/l (50 mg/dl) for women, systolic blood pressure/diastolic blood pressure (SBP/DBP) 130/85 mm Hg or more, and fasting glucose 5.545 mmol/l (100 mg/dl) or more. In addition, participants met the criteria for elevated blood pressure or fasting glucose concentration if they were currently receiving antihypertensive or antidiabetic medication, respectively.

Hypertension was defined as SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg or current use of medication for hypertension. Diabetes mellitus was defined as a fasting blood glucose of 126 mg/dl or greater, Hba1c of 6.5% or greater, or current use of medication for diabetes.

2.2. Measurements of pulse wave velocity

Measurement of baPWV was performed as described in our previous studies [3,4]. Briefly, bilateral brachial and ankle blood pressures and arterial pulse waves were simultaneously measured using an automatic waveform analyzer (VP-1000, Omron Healthcare, Kyoto, Japan). Subjects were examined in the supine position after at least 5 min of bed rest. Pneumatic cuffs were wrapped around both upper arms and ankles and connected to a plethysmographic sensor to determine the volume pulse waveform. Bilateral brachial and posterior tibial artery pressure waveforms were stored for 10 s sample times with automatic gain analysis and quality adjustment. The baPWVs were recorded and calculated using the formula $L1 - L2/T$; in which, L1 and L2 were defined as the distance from the heart to the ankle and from the heart to the brachium, respectively, and T was defined as the transit time between the brachial and posterior tibial artery waveforms. The baPWV reference value was ≤1366 cm/s. The average baPWVs from the left and right sides were used for the analysis. ABI was defined as the bilateral ratio of the systolic BP of the posterior tibial artery to that of the brachial artery.

2.3. Measurement of echocardiographic epicardial fat thickness

Two-dimensional transthoracic echocardiography was performed (Vivid 7; GE, Milwaukee, USA). Images from standard parasternal long- and short-axis views were digitally stored and reviewed by a single echocardiologist blinded to the clinical data. The maximum epicardial fat thickness was measured at the point on the free wall of the right ventricle at end-systole, perpendicular to the aortic annulus for parasternal long-axis view, and perpendicular to the interventricular septum at midchordal and tip of the papillary muscle level for parasternal short-axis view. Epicardial fat was defined as the relatively echo-free space between the outer wall of the myocardium and the visceral layer of the pericardium. The average value of three cardiac cycles from each echocardiographic view was determined as epicardial fat thickness. EFT in 50 randomly selected subjects was re-measured by the same echocardiologist one week later. The coefficient of intra-observer variation was 2.3%.

2.4. Statistical analyses

Data are expressed as mean ± standard deviation (SD) or median and interquartile range for continuous variables and as percentages (%) for categorical variables. Among the variables, serum triglyceride, serum creatinine, serum fasting glucose, HOMA-IR, hs-CRP concentration, and epicardial fat thickness were log-transformed for analysis to correct for skewed distributions; values in tables are expressed as untransformed data for ease of interpretation. Subjects were classified into two groups according to baPWV value, group I with baPWVs ≤ 1366 cm/s and group II with baPWVs > 1366 cm/s. In addition, subjects were categorized into quartiles according to EFT: ≤3.40, 3.42–3.90, 3.92–4.65, and ≥4.66 millimeter (mm). The comparisons of the characteristics between the two groups of baPWVs were assessed using either the Student's *t*-test or Chi-square test. The differences in characteristics among the EFT quartile groups were determined using one-way ANOVA or the Chi-square test. Associations among baPWV, EFT, and other variables were identified using Pearson's correlation analyses. Multivariate linear or logistic regression analyses were performed for the effect of EFT quartile on the absolute values or two groups of baPWVs; model 1 was adjusted for age, sex, lifestyle status (alcohol, smoking, and exercise), and waist circumference; model 2 was adjusted for model 1, and for systolic blood pressure and heart rate; and model 3 was adjusted for model 2, and for serum fasting glucose, TG, HDL cholesterol, HOMA-IR and hsCRP. Regression analyses were also performed for subjects not taking anti-hypertensive or antidiabetic medication.

Statistical analyses were performed using PASW version 18.0 (SPSS Inc., Chicago, IL, USA), in which p values of <0.05 were considered statistically significant. This research protocol was approved by the Ethical Committee of Kangbuk Samsung Hospital.

3. Results

The mean age (± standard deviation) of 655 individuals was 55 ± 8.8 years, and 445 of the subjects were men (68%). Among the total population, the prevalence of hypertension and diabetes mellitus was 17% and 13%. The increased baPWV group (Group II, baPWV of >1366 cm/s) included 331 subjects (51%).

Comparative analyses between the two groups according to baPWV showed that group II subjects were older and had higher prevalence of diabetes mellitus, hypertension, and metabolic syndrome. Group II also demonstrated higher measurements for waist circumference, SBP/DBP, heart rate, serum TG, serum fasting glucose and insulin, Hb_a1c, HOMA-IR, hs-CRP, and epicardial fat thickness (group I vs. group II, 3.73[3.17, 4.33] mm vs. 4.20[3.57, 4.88] mm, $p < 0.001$) compared to those of group I (Table 1).

Comparisons of the characteristics of the EFT quartile groups are presented in Table 2.

Age, BMI and waist circumference, SBP/DBP, heart rate, serum creatinine and uric acid, triglycerides, HDL cholesterol, fasting insulin, HOMA-IR, and GGT were significantly different among the EFT quartile groups. The prevalence of men and metabolic syndrome, as well as the frequency of alcohol consumption, increased with increasing quartile of EFT, and baPWV also increased with increasing quartile of EFT (lowest, second, third, and highest quartiles: 1327 ± 148.8 cm/s, 1371 ± 215.0 cm/s, 1434 ± 228.3 cm/s, 1507 ± 233.1 cm/s, respectively; $p < 0.001$).

Correlation analyses among baPWVs, EFT, and other variables are presented in Table 3. The absolute EFT value was significantly associated with baPWV level ($r = 0.327$, $p < 0.001$). Furthermore, EFT and baPWVs were significantly correlated with several factors related to cardiometabolic risk.

In the age- and sex-adjusted logistic regression analyses, the highest EFT quartile group had a higher odds ratio (OR) for increased baPWV compared to that of the lowest quartile group (OR [95% confidence interval (CI)], 2.74[1.67–4.50], $p < 0.001$). The ORs in the multivariate regression models were slightly attenuated but remained significant (2.58[1.49–4.47], 2.26[1.26–4.06], and 2.19[1.21–3.95] in models 1, 2, and 3, respectively) (Table 4). When the presence or absence of metabolic syndrome was taken into account in model 3, the ORs were similar (2.19[1.21–3.95], $p = 0.010$). Moreover, increasing EFT quartile was associated with increased baPWV (p for trends <0.001, 0.001, 0.007, and 0.010 in age-and sex-adjusted, models 1, 2, and 3, respectively) (Table 4).

When EFT quartile and baPWV each were replaced with absolute values, the multiple linear regression analyses also showed that the association between EFT value and baPWV remained significant (standard $\beta = 0.171$, $p < 0.001$ in the age-and sex-adjusted model; standard $\beta = 0.167$, $p < 0.001$ in model 1; standard $\beta = 0.118$, $p = 0.001$ in model 2; standard $\beta = 0.113$, $p = 0.001$ in model 3) (Table 5). The results