Nutrition, Metabolism & Cardiovascular Diseases (2016) xx, 1–7

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Epicardial adipose tissue is related to cardiac function in elderly women, but not in men

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Received 1 June 2016; received in revised form 13 October 2016; accepted 2 November 2016
Available online ■ ■ ■

KEYWORDS
Adipose tissue;
Cardiac function;
Women;
Difference

Abstract *Background and aim:* Epicardial adipose tissue (EAT) is easily quantifiable visceral adipose tissue that is closely associated with cardiometabolic disease including heart failure with preserved left ventricular (LV) ejection fraction. As body fat distribution and metabolism are different between men and women, we evaluated the sex difference in EAT thickness and its relationship to cardiac function.

Methods and results: A total of 152 consecutive patients (76 men) with mean age of 62 ± 9 years were enrolled. Conventional echocardiography was performed and EAT thickness was measured perpendicularly on the right ventricular free wall at end systole.

Mean EAT thickness in all patients was 6.5 ± 2.0 mm. EAT thickness was associated with patient age, body mass index, and the presence of hypertension. EAT thickness was not different by sex in patients younger than 60 years (men, 6.4 ± 2.0 mm; women, 6.2 ± 1.8 mm, $p = 0.716$); however, among patients aged 60 years or older, EAT thickness was significantly greater in women than men (men, 6.0 ± 1.7 mm; women 7.7 ± 2.1 mm, $p < 0.001$). LV function represented by E/e′ and s′ was significantly related to EAT thickness only in women (E/e′, $\beta = 0.330$, $p = 0.002$; lateral s′, $\beta = -0.225$, $p = 0.042$).

Conclusion: EAT thickness was greater in women than men after 60 years old and its relationship with LV function was significant only in women. Greater increase in EAT thickness in elderly women after menopause might partially account for this difference.

Background

Heart failure with preserved ejection fraction (HFpEF) more frequently develops in elderly women with hypertension [1]. In contrast to male patients, many of the female patients with HFpEF show left ventricular (LV) concentric remodeling [2]. Obesity is one of the most important risk factors for the development of hypertension and HFpEF [3,4], and common in these patients. Increased body mass is related to the development of HFpEF [5,6], and central obesity accelerates LV concentric remodeling in patients with hypertension [7,8]. However, these factors do not directly explain the relationship between obesity and development of HFpEF in elderly women.

Even in individuals with the same body mass index, adiposity is different between men and women; lean body mass is greater in men and women have more subcutaneous adipose tissue [9]. The body fat distribution is also

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http://dx.doi.org/10.1016/j.numecd.2016.11.001
0939-4753/

Please cite this article in press as: Kim S-A, et al., Epicardial adipose tissue is related to cardiac function in elderly women, but not in men, Nutrition, Metabolism & Cardiovascular Diseases (2016), http://dx.doi.org/10.1016/j.numecd.2016.11.001

different between men and women. Men are more likely to have adipose tissue in the abdomen in the form of visceral adipose tissue, whereas women are more likely to have adipose tissue in the subcutaneous area; this difference is partly influenced by sex hormones [10]. Moreover, in women, the pattern of body fat distribution and fat metabolism change after menopause [11].

Epicardial adipose tissue (EAT), one of the most easily measurable forms of visceral adipose tissue [12], is metabolically bioactive and closely related to insulin resistance and free fatty acid generation [11]. Therefore, EAT thickness has been used as a quantifiable marker of visceral adiposity in many studies and it has shown a positive association with the development of cardiometabolic diseases including metabolic syndrome, atherosclerosis, and coronary artery disease [13–15]. Moreover, EAT covers the ventricular free wall and directly releases inflammatory cytokines into the LV. The paracrine effect of EAT might have a synergistic effect on LV function and the development of coronary artery disease [16].

We hypothesized that the difference in EAT thickness and the different relationships between EAT thickness and LV function in men and women explain the higher prevalence of HFpEF in elderly women. Therefore, we evaluated EAT thickness using echocardiography and analyzed its relationships with cardiometabolic disease and cardiac function. We also investigated the sex difference in EAT thickness and its relationship to cardiac function.

Methods

Study population

Patients with normal sinus rhythm and LV ejection fraction (EF) $>$ 50% who underwent echocardiography for any cause were consecutively enrolled. We excluded patients who had a history of significant cardiac arrhythmia, valvular heart disease, or coronary artery disease diagnosed by clinical symptoms, electrocardiogram, or conventional echocardiography. Blood pressure (BP) was measured according to the standard procedure with a sphygmomanometer, and hypertension was defined as systolic BP $\geq$ 140 mmHg or diastolic $\geq$ 90 mmHg, or use of antihypertensive drugs. Diabetes mellitus was defined as fasting glucose greater than 125 g/dL, HbA1c greater than 6.5%, or use of oral hypoglycemic agents or insulin. Dyslipidemia was defined as the total cholesterol level greater than 220 mg/dL or use of any cholesterol lowering agent. All patients provided informed consent, and study approval was obtained from the Institutional Review Board of Korea University College of Medicine.

Conventional echocardiography

All echocardiographic measurements were acquired with a commercially available ultrasound system (Acuson SC 2000, Siemens Medical Solutions, USA, Inc.) equipped with a 4V1c transducer. Chamber quantification was performed directly from 2-dimensional echocardiographic images, and LV mass index was evaluated with linear measurements using the formula recommended by the American Society of Echocardiography [17]. Mitral inflow was obtained by pulsed-wave Doppler echocardiography during early diastole (E). Early diastolic septal and lateral mitral annular velocities (e′) were obtained from pulse wave velocity measured by spectral tissue Doppler imaging. Systolic mitral annular velocity (s') was obtained at the septal and lateral mitral annulus. Global longitudinal strain of LV was also analyzed. LV diastolic function was assessed following the updated recommendation of American society of Echocardiography at 2015 [18]. Patients with more than 2 positive parameters among average E/e′$>$ 14, septal e′ velocity $<$ 7 cm/s or lateral e′ velocity $<$ 10 cm/s, left atrial volume index $>$ 34 ml/m^2, and maximal velocity of tricuspid regurgitation $>$ 2.8 m/sec were regarded to have the possibility of abnormal LV diastolic function.

Epicardial adipose tissue thickness measurements

Standard parasternal long-axis and short-axis images were acquired from 2-dimensional echocardiography. EAT was generally identified as the relatively echo-free space between the outer wall of the myocardium and the visceral layer of the pericardium. In the parasternal long-axis view, the maximal thickness of EAT was measured on the right ventricular free wall perpendicular to the aortic annulus. In the mid ventricular parasternal short axis view, maximum EAT thickness was measured on the right ventricular free wall along the midline of the ultrasound beam perpendicular to the interventricular septum at the mid-chordal or tip of the papillary muscle level. Both values were measured at end systole in three cardiac cycles and the six values were averaged [19]. Intraobserver variability and interobserver variability was evaluated from randomly collected 30 samples of echocardiographic images.

Statistical analysis

SPSS software (version 20.0) was used for statistical analysis. All results are expressed as mean $\pm$ standard deviation. The differences in EAT thickness and echocardiographic parameters between male and female patients, patients with and without cardiovascular disease, and patients younger than 60 years and patients aged 60 years or older were tested by independent samples t-tests, and the differences in the presence of cardiovascular risk between patients were tested by chi-square test. The correlation between EAT thickness and cardiac function assessed by echocardiography was evaluated with the correlation analysis, and the significance of correlation between EAT thickness and cardiac function was determined by multivariate linear regression analysis. P value $<$ 0.05 was considered to be statistically significant. The reproducibility of EAT thickness measurements was evaluated using Bland–Altman plot.

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