ORIGINAL RESEARCH

Diagnostic Values of Epicardial Adipose Tissue Thickness with Right Common Carotid Artery Elasticity and Intima-Media Thickness for Middle-Aged and Elderly Patients with Coronary Heart Disease

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Background: Coronary heart disease (CHD) is the most common cardiovascular disease which greatly threatens the health of middle-aged and elderly people.

Objective: To explore the correlations of epicardial adipose tissue (EAT) thickness with right common carotid artery elasticity and intima-media thickness (IMT) in middle-aged and elderly patients with CHD by ultrasound.

Methods: A total of 132 patients diagnosed with CHD by coronary angiography (CAG) from February 2019 to August 2020 were enrolled and divided into single-vessel disease group (n=38), double-vessel disease group (n=52), and three-vessel disease group (n=42), and 52 healthy subjects were selected as control group. Their general data, biochemical indices, EAT thickness, right common carotid artery elasticity indices, and IMT were compared. The correlations of EAT thickness with right common carotid artery elasticity indices and IMT were studied by Pearson's analysis. The predictive values of EAT thickness and IMT for CHD were analyzed by receiver operating characteristic curves.

Results: With increasing number of diseased branches, EAT thickness, stiffness parameters β (β), strain elastic modulus (Ep), pulse wave velocity β (PWV-β) and IMT increased, arterial compliance (AC) decreased (P<0.05), but argumentation index (AI) did not change significantly. EAT thickness had significant positive correlations with β, Ep, PWV-β and IMT, negative correlation with AC, and no significant correlation with AI. The areas under the curves of EAT thickness and IMT for predicting CHD were 0.806 and 0.784, respectively.

Conclusion: EAT thickness is significantly correlated with right common carotid artery elasticity and IMT in middle-aged and elderly patients with CHD, and EAT thickness and IMT have high predictive values. The three indices are crucial for CHD diagnosis.

Keywords: ultrasound, coronary heart disease, epicardial adipose tissue, right common carotid artery elasticity, intima-media thickness

Introduction

With the acceleration of aging, the incidence rate of cardio-cerebrovascular diseases closely related to the middle-aged and elderly population is gradually increasing.[1] Coronary heart disease (CHD) is the most common cardiovascular disease which greatly threatens the health of middle-aged and elderly people.[2] CHD means that in the case of abnormal lipid metabolism, blood lipids deposit on the artery intima and

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gradually accumulate to form white plaques that lead to arterial stenosis and obstruction of blood flow, resulting in myocardial ischemia and angina pectoris.[3] The incidence, disability and mortality rates of CHD are rising annually.[4] Epicardial adipose tissue (EAT) refers to the adipose tissue between the visceral layer of the pericardium and the outer surface of the myocardium, surrounding the coronary arteries, and there is no fascia to separate them.[5] EAT is able to secrete multiple inflammatory and anti-inflammatory cytokines to maintain vascular homeostasis,[6] but increase in its thickness induces changes in the paracrine function of adipocytes, releasing a large number of inflammatory cytokines to form an inflammatory state.[7] The increase in EAT thickness also raises the risk of cardiovascular diseases, which may be a risk factor for atherosclerotic diseases.[8] It is easy to detect the common carotid artery that is in a relatively superficial position, which is often used to reflect the degree of arteriosclerosis.[9] The common carotid artery intima-media thickness (IMT) is closely associated with CHD.[10] Echo-tracking (ET) technique is a new non-invasive ultrasound method that can accurately determine the indices reflecting common carotid artery elasticity and IMT.[11] The present study aimed to explore the correlations of EAT thickness with right common carotid artery elasticity and IMT in middle-aged and elderly patients with CHD by ultrasound.

Patients and Methods
General Information
A total of 132 patients diagnosed with CHD by coronary angiography (CAG) from February 2019 to August 2020 in our hospital were enrolled. According to the number of diseased branches, the patients were divided into single-vessel disease group (n=38), double-vessel disease group (n=52), and three-vessel disease group (n=42). In single-vessel disease group, there were 18 males and 20 females aged 45–73 years old, with an average age of 62.41±8.12 years. In the double-vessel disease group, there were 24 males and 28 females aged 46–75 years old, with an average age of 64.35±7.23 years. In the three-vessel disease group, there were 19 males and 23 females aged 46–78 years old, with an average age of 63.58±6.95 years. Meanwhile, 52 healthy subjects physically examined in our hospital were selected as control group, including 18 males and 24 females aged 45–76 years old, with an average age of 63.74±8.26 years.

Inclusion criteria: a) patients who were diagnosed with CHD by CAG, b) those with at least one diseased coronary artery stenosis of more than 50%, c) those who had quit smoking for more than 5 years or had no history of smoking, d) those aged 45–80 years old, and e) those with complete clinical data.

Exclusion criteria: a) patients with unclear ultrasound images, b) those whose pericardial effusion or EAT could not be identified, c) those with congenital heart disease, thyroid disease, severe liver or kidney insufficiency, or diseases in vital organs, d) those with common carotid artery stenosis, e) those who were pregnant or had endocrine disorders, f) those with mental disorders or infectious diseases, g) those with poor compliance, or h) presence of morphologic/functional EAT changes such as aortic valve stenosis, atrial fibrillation or heart failure.

This study was approved by the Ethics Committee of The Second Affiliated Hospital of Zhejiang University School of Medicine and was conducted in accordance with the Declaration of Helsinki. All patients and their families signed the informed consent.

Collection of Baseline Clinical Data
The general data of patients were collected through electronic medical records. After admission, gender and age (years old) were recorded, height (m) and weight (kg) were measured to calculate body mass index (BMI=weight/height^2), and systolic blood pressure (mmHg) and diastolic blood pressure (mmHg) were measured.

Measurement of Biochemical Indices
In the early morning of the next day after admission, 5 mL of fasting venous blood was drawn from every patient and placed in a serum separation tube, followed by centrifugation at 3000 rpm for 10 min. Subsequently, the serum was collected to detect fasting blood glucose (FBG), total cholesterol (TC), triacylglycerol (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels.

Measurement of EAT Thickness
Voluson E8 color Doppler ultrasound system (USA) was utilized to measure EAT thickness (frequency: 2.5 MHz) according to previous literature.[12] EAT thickness between the free wall of right ventricle and the visceral layer of pericardium was measured as follows (Figure 1): an M5S probe was positioned on the parasternal long-axis section,
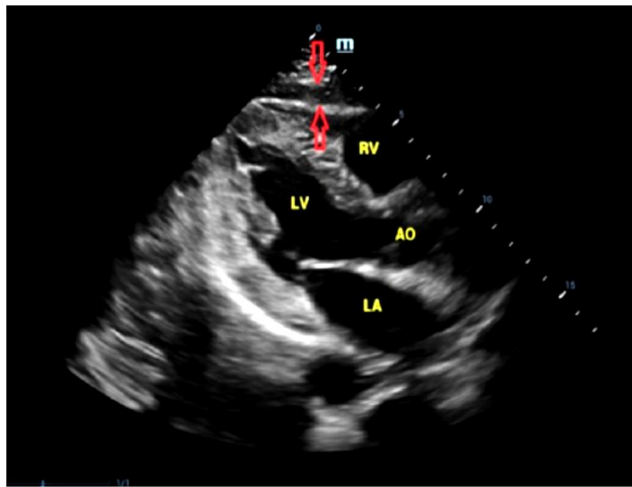
Figure 1 EAT measurement. EAT of the anterior wall of the right ventricle appears as a hypoechoic zone between the epicardium (red arrow below) and pericardium visceral layer (red arrow above).

the image was frozen at end-diastole, and then the sampling line was perpendicular to the free wall of the right ventricle and fixed at the aortic valve annulus. Besides, the M5S probe was positioned at the level of the papillary muscle, the image was frozen at end-diastole, and then the sampling line was perpendicular to the interventricular septum. Three dynamic images of the cardiac cycle were captured to obtain the average, and the average of EAT thicknesses of the two sections was calculated.

Measurement of Right Common Carotid Artery Elasticity and IMT

The vascular elasticity of right common carotid artery was determined by L11-3 probe with a frequency of 7–13 MHz combined with ET technique. Firstly, after resting for 5–10 min, blood pressure was measured from the right upper limb of the patient. The patient was kept in a supine position, with the neck fully exposed. Subsequently, the morphology and thickness of the intima-media of right common carotid artery were examined by ultrasound, and IMT was measured in the middle of right common carotid artery. Then ECG was connected, and M-type sampling line was adjusted to be perpendicular to the common carotid artery wall. At 2.0 cm below the lower edge of right carotid sinus, the sampling gates were placed at the junctions of the anterior and posterior walls of the common carotid artery, respectively, avoiding the internal jugular vein as much as possible. The trajectory of the anterior and posterior

walls of the blood vessel was tracked in real time and recorded during systole and diastole, and then more than five continuous change curves of the inner diameter of the common carotid artery were obtained. Next, the systolic and diastolic blood pressures were loaded, and the clear images of 5–6 cardiac cycles were selected for offline analysis. Finally, the indices reflecting right common carotid artery elasticity were determined and calculated, including stiffness parameters (β), strain elastic modulus (Ep), pulse wave velocity β (PWV-β), arterial compliance (AC), and argumentation index (AI). All data were measured 3 times to obtain the average. Ep (kPa) = (SP-DP)/[(Ds-Dd)/Dd]; β = ln(SP/DP)/[(Ds-Dd)/Dd]; AC (mm^2/kPa) = π(Ds^2-Dd^2)/[4(SP-DP)]; PWV-β (m/s) = ($\beta \times$DP/2p)1/2; AI (%) = Dp/PP. Where SP is the systolic pressure, DP is the diastolic pressure, PP is the pulse pressure, Dp is the difference between the peak systolic pressure and the pressure at break point, Ds is the maximum diameter of the carotid artery, Dd is the minimum diameter of the carotid artery, and p is the blood density.[13]

Statistical Analysis

SPSS 19.0 software was adopted to conduct one-way analysis of variance. GraphPad Prism 5.0 software was utilized for plotting. The differences between two groups were compared by t-test, and the differences among multiple rates or constituent ratios were compared by Chi-squared test. The correlations of EAT thickness with right common carotid artery elasticity indices and IMT were studied by Pearson's analysis. The predictive values of EAT thickness and IMT for CHD were analyzed by receiver operating characteristic (ROC) curves. P<0.05 indicated that the difference was statistically significant.

Results
General Information and Biochemical Indices

The four groups had similar age, gender, BMI, systolic blood pressure, diastolic blood pressure, as well as FBG, TC, TG, HDL-C, and LDL-C levels (P>0.05) (Table 1).

EAT Thickness

EAT thickness was significantly higher in the three-vessel disease group than those in double-vessel disease group, single-vessel disease group, and control group in turn (P<0.05) (Table 2).

Table 1 General Information and Biochemical Indices

Group	Control Group (n=52)	Single-Vessel Disease Group (n=38)	Double-Vessel Disease Group (n=52)	Three-Vessel Disease Group (n=42)	F	P
Age (years)	63.74±8.26	62.41±8.12	64.35±7.23	63.58±6.95	0.725	>0.05
Male/female	18/24	18/20	24/28	19/23	0.728	>0.05
BMI (kg/m^2)	24.37±3.28	24.65±3.62	25.02±3.85	25.14±3.19	0.363	>0.05
Systolic blood pressure (mmHg)	126.94±9.27	128.74±9.52	133.41±11.02	136.12±12.05	1.951	>0.05
Diastolic blood pressure (mmHg)	81.37±7.26	83.42±10.28	84.56±9.65	85.62±8.37	1.622	>0.05
FBG (mmol/L)	5.24±0.72	5.43±0.75	5.64±0.81	5.56±0.84	0.672	>0.05
TC (mmol/L)	4.45±0.92	4.51±1.02	4.55±1.32	4.63±0.95	0.381	>0.05
TG (mmol/L)	1.42±0.43	1.56±0.48	1.61±0.58	1.64±0.56	1.024	>0.05
HDL-C (mmol/L)	1.35±0.24	1.43±0.25	1.37±0.24	1.45±0.30	1.341	>0.05
LDL-C (mmol/L)	2.24±0.65	2.22±0.61	2.45±0.82	2.37±0.61	0.192	>0.05

Table 2 EAT Thickness

Group	Control Group (n=52)	Single-Vessel Disease Group (n=38)	Double-Vessel Disease Group (n=52)	Three-Vessel Disease Group (n=42)
EAT thickness (mm)	2.12±1.24	6.45±1.69[a]	7.58±2.32[ab]	11.82±2.85[abc]

Notes: [a]P<0.05 vs control group, [b]P<0.05 vs single-vessel disease group, [c]P<0.05 vs double-vessel disease group.

Right Common Carotid Artery Elasticity Indices and IMT

With increasing number of diseased branches, right common carotid artery elasticity indices β, Ep, PWV-β and IMT significantly increased, and AC decreased (P<0.05). No significant difference was found in AI among the four groups (P>0.05) (Table 3).

Correlation Analysis Results

The results of Pearson's correlation analysis displayed that EAT thickness had significant positive correlations with β,

Ep, PWV-β, AC and IMT (P<0.05), negative correlation with AC (P<0.05), and no significant correlation with AI (P>0.05) (Table 4 and Figure 2).

ROC Curve Analysis Results

To assess the predictive values of EAT thickness and IMT for CHD, the optimal cut-off values were obtained by plotting ROC curves. The optimal cut-off values of EAT thickness and IMT for predicting CHD were 4.28 and 0.73, respectively. The areas under the curves were 0.806 [95% confidence interval (CI): 0.735–0.863, P<0.001] and

Table 3 Right Common Carotid Artery Elasticity Indices and IMT

Group	Control Group (n=52)	Single-Vessel Disease Group (n=38)	Double-Vessel Disease Group (n=52)	Three-Vessel Disease Group (n=42)	F	P
β	4.24±1.08	7.13±1.92	9.08±2.75	12.48±3.24	5.42	<0.05
Ep (kPa)	57.50±12.42	98.65±31.42	125.08±45.68	182.69±64.38	7.53	<0.05
PWV-β (m/s)	4.82±0.83	6.24±1.32	7.62±1.15	9.14±2.25	3.85	<0.05
AC (mm^2/kPa)	1.42±0.53	1.02±0.41	0.74±0.33	0.43±0.24	4.25	<0.05
AI (%)	14.49±8.36	14.92±8.65	15.28±8.73	15.06±7.93	1.28	>0.05
IMT (mm)	0.62±0.14	0.85±0.16	0.97±0.42	1.28±0.76	2.95	<0.05

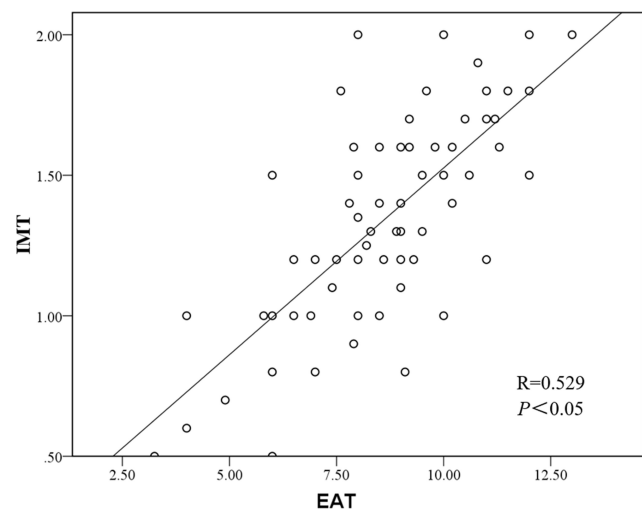**Table 4** Correlations Between EAT Thickness and Right Common Carotid Artery Elasticity Indices

Index	EAT Thickness	
	r	P
β	0.582	0.018
Ep (kPa)	0.523	0.025
PWV-β (m/s)	0.496	0.032
AC (mm²/kPa)	−0.552	0.021
AI (%)	0.162	0.065

0.784 (95% CI: 0.716–0.824, P<0.001), respectively, suggesting high predictive values (Table 5 and Figure 3).

Figure 2 Correlation between EAT thickness and IMT.

Discussion

CHD is a common cardiovascular disease in middle-aged and elderly people, which is mainly caused by coronary atherosclerosis which is the most common type of arteriosclerosis.[14] Possibly, CHD occurs because the branches of coronary arteries are multi-directional and close to the ventricle, and bear huge blood flow shear stress and systolic pressure impact.[15] Considerable complex carbohydrates and lipids are deposited in the intima of the involved artery, inducing fibrous tissue hyperplasia and calcium deposition, and even vascular occlusion and wall rupture and bleeding.[16] As the gold standard for CHD diagnosis, CAG is an invasive and expensive examination method.[17] Thus, it is necessary to find non-invasive and highly predictive diagnostic indices. EAT thickness has a close relationship with CHD and has high predictive value for it.[18] Besides, it is easy to detect the common carotid artery which is in a relatively superficial position, so related indices have often been utilized to reflect the degree of arteriosclerosis in recent years.[19]

EAT accumulates on the surface of the heart and originates from brown adipose tissue together with visceral adipose tissues such as the greater omentum and mesentery.[20] About 80% of the surface of an adult heart is covered by EAT, mostly covering the right ventricle.[21]

As an independent risk factor for CHD, the increase in EAT thickness can reflect severity.[22] Given the fact that the echo of EAT notably differs from those of surrounding tissues during ultrasound examination, it is easy to accurately measure EAT thickness through echocardiography.[23] Moreover, due to non-invasiveness, simple operation and no economic burden to patients, echocardiography for EAT examination is well-accepted by patients. In the present study, EAT thickness was significantly higher in the three-vessel disease group compared with double-vessel disease group, single-vessel disease group, and control group in turn. The common carotid artery, a crucial blood vessel that supplies blood to the head and neck, is superficial and convenient for detection, so it has always been considered as a "window" to reflect the degree of arteriosclerosis. ET is a non-invasive ultrasound technique to examine vascular function, which can accurately measure common carotid artery elasticity indices including β, Ep, PWV-β, AC, and AI as well as IMT.[24] Ren et al reported that common carotid artery elasticity and IMT were closely associated with CHD.[10] In this study, with increasing number of diseased branches, β, Ep, PWV-β,

Table 5 Predictive Values of EAT Thickness and IMT for CHD

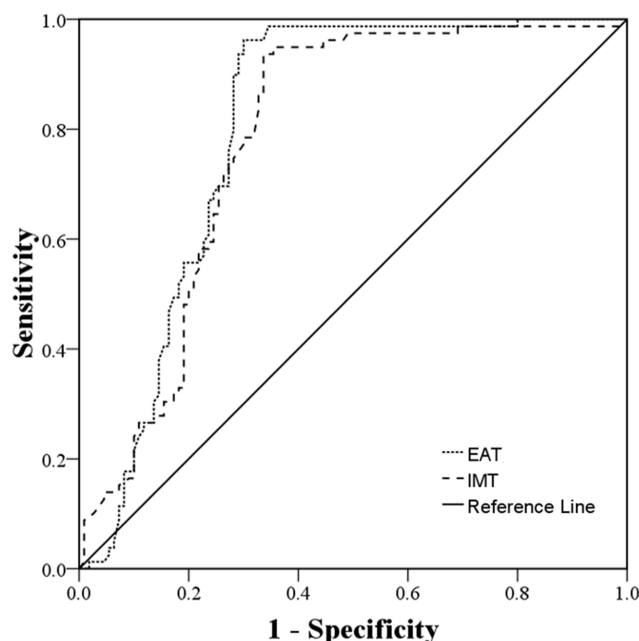| Diagnostic Index	AUC	Optimal Cut-Off	P	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
EAT thickness	0.806	4.28	<0.001	69.78	75.65	74.13	87.02
IMT	0.784	0.73	<0.001	66.25	72.42	71.72	85.04

Figure 3 ROC curve analysis of predictive values of EAT thickness and IMT for CHD.

and IMT significantly increased, and AC decreased. No significant difference was found in AI.

EAT thickness, right common carotid artery elasticity, and IMT are all measured by ultrasound, so the procedure is non-invasive and simple. Since the three indices are closely related to CHD, they can work as predictors for early CHD and reflect the severity and therapeutic effect.[10] EAT thickness has significant correlations with right common carotid artery elasticity and IMT.[25] In the present study, EAT thickness had significant positive correlations with β, Ep, PWV-β and IMT, negative correlation with AC, and no significant correlation with AI. With high predictive values for CHD, EAT thickness and IMT are crucial for diagnosing and evaluating the therapeutic effects of CHD.[5] Herein, the optimal cut-off values of EAT thickness and IMT for predicting CHD were 4.28 and 0.73, respectively, and the areas under the curves were 0.806 and 0.784, respectively, suggesting their high predictive values.

Conclusion

In conclusion, given the high correlations of EAT thickness with right common carotid artery elasticity and IMT in middle-aged and elderly patients with CHD and the high predictive values of EAT thickness and IMT for CHD, the three indices are of significance in CHD diagnosis.

Disclosure

The authors declare no conflicts of interest in this work.

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