The association between epicardial adipose tissue thickness and left atrial phasic function in patients with non-valvular atrial fibrillation

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Abstract

Abstract Purpose: The purpose of our study was to explore the relationship between EAT thickness and left atrial phasic function in patient with non-valvular atrial fibrillation (NVAF). **Methods:** 100 NVAF patients were enrolled, including 50 patients with paroxysmal AF and 50 patients with persistent AF. Another 50 patients without AF in sinus rhythm were selected as the control group. EAT thickness in front of the right ventricular free wall was measured using transthoracic echocardiography(TTE) at end-systole, while left atrial phasic function parameters were measured by Real-time three-dimensional echocardiography(RT-3DE) and two-dimensional speckle tacking imaging(2D-STI), including left atrial total emptying fraction(LATEF), left atrial active emptying fraction(LAAEF), left atrial passive emptying fraction(LAPEF), left atrial reservoir strain(LASr), left atrial contraction strain(LASct) and left atrial conduit strain(LAScd). Subsequently, we compared EAT thickness and left atrial phasic function parameters in each group, and analyzed the relationship between EAT thickness and left atrial phasic function parameters. **Results:** Compared with control group, patients with paroxysmal AF and persistent AF groups had sequentially greater EAT thickness and left atrial diameter (LAD), but sequentially lower left atrial phasic function parameters (LATEF, LAAEF, LAPEF, LASr, LASct, LAScd) (all p<0. 001). By Pearson and Spearman Correlation Coefficient, EAT thickness was significantly positively correlated with LAD and negatively correlated with left atrial phasic function parameters (all p<0. 001). **Conclusions:** EAT thickness in front of the ventricular free wall measured by TTE was significantly correlated with left atrial phasic function in patients with NVAF, which could effectively reflect the trend of left atrial function changes, thus providing some reference for clinical practice and early intervention of left atrial remodeling.

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Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Statement of Ethics

Since this study did not involve operations such as drugs that may affect the human body and ultrasonography is a non-invasive test, we followed the principles of the Declaration of Helsinki, and the echocardiography and clinically relevant data were collected after informed consent of patients.

Author Contributions

You Yang and Biaohu Liu made significant contributions to the design, data acquisition, statistical analysis and data interpretation. You Yang drafted this study and completed the manuscript. And further improved and revised the article under the guidance of Biaohu Liu. Biaohu Liu and Deguo Wang made significant contributions to the funds collection of the study. Jing Ding, Shanqiang Tao and Feifei Lian contributed to data acquisition and statistical analysis. Wenyan Ji made significant contributions to the literature search and revision of the important content of this study.

Abstract

Purpose: The purpose of our study was to explore the relationship between EAT thickness and left atrial phasic function in patient with non-valvular atrial fibrillation (NVAF).

Methods: 100 NVAF patients were enrolled, including 50 patients with paroxysmal AF and 50 patients with persistent AF. Another 50 patients without AF in sinus rhythm were selected as the control group. EAT thickness in front of the right ventricular free wall was measured using transthoracic echocardiography(TTE) at end-systole, while left atrial phasic function parameters were measured by Real-time three-dimensional echocardiography(RT-3DE) and two-dimensional speckle tacking imaging(2D-STI), including left atrial total emptying fraction(LATEF), left atrial active emptying fraction(LAAEF), left atrial passive emptying fraction(LAPEF), left atrial reservoir strain(LASr), left atrial contraction strain(LASct) and left atrial conduit strain(LAScd). Subsequently, we compared EAT thickness and left atrial phasic function parameters in each group, and analyzed the relationship between EAT thickness and left atrial phasic function parameters.

Results : Compared with control group, patients with paroxysmal AF and persistent AF groups had sequentially greater EAT thickness and left atrial diameter (LAD), but sequentially lower left atrial phasic function parameters (LATEF, LAAEF, LAPEF, LASr, LASct, LAScd) (all $p<0.\ 001$). By Pearson and Spearman Correlation Coefficient, EAT thickness was significantly positively correlated with LAD and negatively correlated with left atrial phasic function parameters (all $p<0.\ 001$).

Conclusions: EAT thickness in front of the ventricular free wall measured by TTE was significantly correlated with left atrial phasic function in patients with NVAF, which could effectively reflect the trend of left atrial function changes, thus providing some reference for clinical practice and early intervention of left atrial remodeling.

Keywords

Epicardial Adipose Tissue, Atrial Fibrillation, Left Atrial

1 Introduction

The relationship between epicardial adipose tissue (EAT) and atrial fibrillation (AF) has become a topic of great interest. Previous studies have demonstrated that EAT is associated with the development of AF [1,2]. Excessive EAT promotes adipose infiltration and fibrosis of myocardial, and affects cardiac electrophysiological function through pathophysiological processes such as inflammation and oxidative stress, thus contributing to the occurrence and development of AF [3]. Magnetic resonance imaging (MRI) and computed tomography (CT) can be used for EAT examination, but their examination time is long and cost is high, and CT has certain radiation, so it is difficult to be popularized in clinical practice. The use of ultrasound to measure EAT thickness is a more convenient and economical method, that is easy to be promoted and has good reliability compared with MRI in measuring EAT thickness [4]. To further explore the relationship between EAT and AF, our study applied TTE to measure EAT thickness anterior the right ventricular free wall in NVAF patients and analyzed its relationship with left atrial phasic function to explore the possible mechanism between EAT and AF.

2 Materials and Methods

2.1 Study population

From January 2021 to April 2022, 100 patients with NVAF who were treated at the First Affiliated Hospital of Wannan Medical College were selected. Among them, there were 68 males and 32 females with an average age of 59.36±7.70 years. They were divided into paroxysmal AF group and persistent AF group according to the duration of AF, with 50 patients in each group. The inclusion criteria were as follows: (1) NVAF; (2) good image quality. And the exclusion criteria included rheumatic heart disease, heart failure (left ventricular ejection fraction, LVEF<50%), cardiac valve repair or replacement, AF radiofrequency ablation, hyperthyroidism, and severe liver and kidney dysfunction. In addition, 50 non-AF patients in sinus rhythm treated in our hospital during the same period were selected as the control group, and the exclusion criteria were consistent with the case group. Among them, there were 34 males and 16 females with an average age of 59.34±7.05 years. The basic clinical information of the above 150 patients was recorded, such as age, gender, body mass index (BMI), body surface area (BSA), smoking and drinking history, some comorbidities, and some laboratory parameters. Ultimately, 150 patients were included in our study (shown in Fig. 1). Since this study did not involve operations such as drugs that may affect the human body and ultrasonography is a non-invasive test, we followed the principles of the Declaration of Helsinki, and the echocardiography and clinically relevant data were collected after informed consent of patients.

2.2 Echocardiographic image acquisition

All patients were examined with the Philips EPIQ 7C ultrasound system, and the require image were collected by S5-1 and X5-1 probes. During the examination, all patients in the control and paroxysmal AF groups had sinus rhythm and heart rate <100 beats/min, while the average ventricular rate <100 beats/min in the persistent AF group. First, after connecting the ECG, the patient was placed in the left lateral position, and the S5-1 probe was used to observe the parasternal-long axis view. Subsequently, the near-field area was enlarged and the image gain was appropriately adjusted to fully display EAT, which located in front of the right ventricular free wall and beneath the pericardium. Using the aortic annulus as a reference, the reference line was placed across the aortic annulus and the right ventricular free wall, and EAT thickness was measured vertically in front of the right ventricular free wall at end-systole. Then, the parasternal-long axis view and apical two-chamber and four-chamber views were collected, and four cardiac cycles were continuously recorded to obtain LAD and LVEF which was analyzed by the biplane Simpson's method. Finally, the X5-1 probe was used to display the apical four-chamber view, and the "full-volume" mode was selected to record four cardiac cycles continuously to obtain the three-dimensional volume of left atrium.

2.3 Echocardiographic image analysis

(1) RT-3DE: Philips Qlab 10. 4 software was used to off-line analyze the full-volume image. In the 3DQA mode, the left atrial volume curve was obtained, and we recorded the maximal, minimal and pre-atrial contraction left atrial volume (LAVmax, LAVmin, LAVp). Then, each left atrial volume index (LAVImax, LAVImin, LAVIp) was obtained by normalizing BSA. Finally, we calculated LATEF, LAAEF and LAPEF. the calculation method was as follows: LATEF= (LAVImax-LAVImin)/LAVImax×100%; LAAEF= (LAVIp-LAVImin)/LAVIp×100%; LAPEF= (LAVImax-LAVIp)/LAVImax×100%. (2) 2D-STI: Off-line analysis of apical two-chamber and four-chamber images of four consecutive cardiac cycles using Philips Qlab 10. 4 software. In the aCMQ mode, we recorded the intima of the left atrium and plotted the region of interest to obtain the left atrial strain curve. LASr, LASct and LAScd were recorded respectively, and the strain values of the the two views were added together and included in the analysis after averaging. The mean peak strain during left atrial systole, late diastole and early diastole respectively represents LASr, LASct and LAScd. Where LASr is positive, LASct and LAScd are both negative, so the absolute value was taken and analyzed.

2.4 Statistical analysis

Statistical analysis of all data was performed using SPSS 25. 0. The continuous variables were tested for normality using the Shapiro-Wilks test. When the continuous variables were conformed to normal distributions, they were expressed as mean±SD, and the date with skewed distributions were expressed as medians with 25% and 75% interquartile ranges. Categorical variables were expressed as numbers with percentages. The continuous variables conforming to normal distribution between three groups were compared by F-test or Welch's test. When at least one of three groups of continuous variables conforms to skewed distribution, the kruskal-Wallis test was used. Then, we performed multiple comparisons between groups. Categorical variables between three groups were compared by Chi-square test. Pearson and Spearman Correlation Coefficient were used to determine the correlation between EAT thickness and LAD, as well as the correlation between EAT thickness and left atrial phasic function in patients with AF. Intra-class correlation coefficient (ICC) was used to test the reproducibility of measurement of EAT thickness and left atrial phasic function parameters within and between operators. For all tests, a $p<0.05$ was defined as statistically significant.

3 Results

3.1 Baseline clinical and echocardiographic characteristics

All baseline parameters are summarized in Table 1. A total of 150 patients were included in our study, with 50 patients in each group. 16 (32%) were female in control group with an average age of 59.34±7.05 years, 17 (34%) were female in paroxysmal AF group with an average age of 57.78±8.36 years and 15 (30%) were female in persistent AF group with an average age of 60.94±6.70 years. In our study, EAT thickness differed significantly among control group (3.51±0.29mm), paroxysmal AF group (5.11±0.84mm) and persistent AF group (6.26±0.80mm). And compared with control group, LAD in paroxysmal AF group and persistent AF group increased in turn. However, there was no significant difference in LVEF among three groups. The baseline clinical characteristics among three groups also had no statistical difference, such as age, gender, BMI, BSA and so on.

3.2 RT-3DE and 2D-STI parameters

The parameters obtained by RT-3DE are shown in Table 2. Compared with control group, LAVImax, LAVIp and LAVImin in paroxysmal AF group and persistent AF group increased in turn, but LATEF, LAAEF and LAPEF decreased in turn. The left atrial volume curves obtained by RT-3DE among the three groups are shown in Figure 2.

Left atrial strain measured by 2D-STI among the three groups are shown in Table 2. The LASr, LASct and LAScd of patients in persistent AF group were significantly lower than those in paroxysmal AF group, while the left atrial strain of patients in paroxysmal AF group were significantly lower than those in control group. Figure 3 shows the left atrial strain curves obtained by 2D-STI among the three groups.

3.3 The correlation analysis of EAT thickness with LAD and left atrial phasic function in patients with AF

EAT thickness was significantly positively correlated with LAD, LAVImax, LAVIp and LAVImin ($r=0.936$, 0.778, 0.837 and 0.865, all $p<0.001$).

EAT thickness was significantly negatively correlated with LATEF, LAAEF and LAPEF ($r=-0.877$, -0.782 and -0.816, all $p<0.001$;). And EAT thickness was significantly negatively correlated with LASr, LASct and LAScd ($\rho=-0.844$, -0.746 and -0.816, all $p<0.001$) (shown in Fig.4).

3.4 Reproducibility analysis of EAT thickness and left atrial phasic function parameters

15 patients were randomly selected for reproducibility analysis of EAT thickness and left atrial phasic function parameters. Two experienced ultrasound physicians used TTE to measure the images respectively, and analyzed the Interobserver agreement. One week later, the images were measured again by one of the physicians and analyzed the Intraobserver agreement. The analysis results are shown in Table 3.

4 Discussion

Our study mainly found that EAT thickness in front of the right ventricular free wall measured by TEE was significantly positively correlated with left atrial size, but significantly negatively correlated with left atrial phasic function.

EAT is biologically active tissue that is unevenly distributed between the myocardial and the visceral pericardium. There is no fascial barrier between EAT and myocardial, so local EAT can slow down conduction through fat infiltration, damage to the myocardial interstitium, and self-tissue fibrosis, thereby affecting myocardial electrophysiology [5]. EAT also promotes adjacent myocardial fibrosis by paracrine release of multiple adipose cytokines [6]. Similarly, there are no fascial boundaries between the atrium and the ventricles, thus, multiple adipose cytokines secreted by EAT around the left ventricle can reach the atrium and affect atrial fibrosis [7]. A variety of inflammatory mediators secreted by EAT are also closely related to the occurrence of AF [8]. In addition, EAT is rich in autonomic ganglion plexus, and the excitation of sympathetic and parasympathetic nerves can increase intracellular calcium concentration and shorten action potential duration, thus promoting the occurrence and development of AF [9]. Left atrial remodeling is crucial in the occurrence and development of AF, and EAT participates in this process through the above various pathophysiological mechanisms. Moreover, left atrial remodeling is also an important indicator of the prognosis of AF [10]. Therefore, early identification of left atrial remodeling and timely intervention may slow or even reverse this pathophysiological process, while improving prognosis. Our study found that compared with control group, EAT thickness in paroxysmal AF group and persistent AF group increased sequentially, and the difference was statistically significant. This is consistent with the findings of previous studies [11]. Similarly, van Rosendael et al. [12]applied CT to quantitatively assess EAT around the left atrium and found that it was independently associated with AF. Through above studies, we found that EAT was closely related to the occurrence and development of AF.

In the occurrence and development of AF, the pathological changes caused by initial trigger factors cause atrial remodeling through the formation of functional AF matrix [13]. The enlargement of left atrium indicates that atrium has remodeled. Wong et al. [14] found that pericardial fat volume by MRI was positively correlated with left atrial volume in patients with AF. Yorgun et al. [15] used CT to measure EAT thickness and found that it was correlated with the presence and type of AF, and significantly related to the LAD. Our study showed that LAD, LAImax, LAVIp and LAVImin increased sequentially in control group, paroxysmal AF group and persistent AF group, and EAT thickness was significantly positively correlated with left atrial size. Those results were consistent with previous studies. According to our studies, the increase of EAT thickness may cause structural changes in left atrium, which can reflect the structural change trend of left atrium.

Left atrial phasic function is a sensitive parameter that reflects the changes in left atrial structure and function, and can early detect myocardial motion changes caused by left atrial remodeling. It mainly includes reservoir function, booster function and conduit function. LATEF and LASr represent reservoir function; LAAEF and LASct represent booster function; LAPEF and LAScd represent conduit function.

Our study demonstrated that the left atrial reservoir function, booster function and conduit function were sequentially decreased in control group, paroxysmal AF group and persistent AF group. Hopman et al. [16] found that compared with the control group, the left atrial reservoir strain, conduit strain and systolic strain in AF group were significantly reduced, and the left atrial strain in the persistent AF group was lower than in paroxysmal AF group, but there was no significant difference between the two groups, which is slightly different from the results of our study, and may be affected by different subjects. In addition, in order to further study the relationship between EAT and left atrial, and to deeply explore the mechanism of EAT leading to left atrial remodeling. Our study attempted to analyze the correlation between EAT thickness and left atrial phasic function. The results showed that EAT thickness was significantly negatively correlated with left atrial reservoir function, booster function and conduit function. The above studies all confirmed that with the increase of EAT thickness, left atrial function showed a downward trend. Compared with LAD, our study comprehensively assessed the left atrial phasic function by RT-3DE and 2DD-STI, which more accurately reflected the changes of left atrial structure and function. And the results of our study showed that both LAD and more sensitive left atrial phasic function were significantly correlated with EAT thickness. Combined with the results of our study and previous studies, it is further confirmed that there is a certain connection between EAT and left atrium of patient with AF. The increased thickness of EAT may be one of the important mechanisms of left atrial remodeling.

The result of this study showed that EAT thickness measured by TTE and left atrial phasic function assessed by RT-3DE and 2D-STI had good reproducibility and reliability. At present, the evaluation of left atrial size is generally based on LAD measured by TTE, but the irregular remodeling of left atrium makes it difficult to accurately assess left atrial size. With the development of three-dimensional technology, RT-3DE has achieved accurate assessment of left atrial structure and function. MRI is the gold standard to evaluate left atrial structure and function. Mor-Avi et al. [17] used the left atrial function parameters measured by MRI as reference, and found that RT-3DE and MRI had a better correlation in evaluating left atrial function, and they were more accurate than two-dimension echocardiographic parameters. In addition, 2D-STI is also widely used in the evaluation of early changes in myocardial function, which can sensitively detect myocardial strain damage in the early stage of the disease and quantitatively evaluate the changes in left atrial function. Therefore, our study selected RT-3DE and 2D-STI to comprehensively assess left atrial phasic function. With the deepening of research on EAT, noninvasive examination has become the main way to evaluate EAT, mainly including MRI, CT and TTE. Compared with MRI and CT, TTE is more convenient, economical, and easier to popularize in clinical practice.

Our study also has a few limitations. First, the research subjects included in this study were relatively small. Second, EAT thickness measured by TTE was not compared with other techniques, such as MRI and CT. Therefore, the follow-up will continue to expand the sample size and combine other techniques to further explore the mechanism of EAT on the left atrial structure and function in patients with AF.

5 Conclusion

Our study found that left atrial phasic function was significantly impaired in patients with AF, and patients with persistent AF were more severely damaged than those with paroxysmal AF. The combination of RT-3DE and 2D-STI can more comprehensively evaluate left atrial structure and function. EAT thickness was significantly negatively correlated with left atrial reservoir function, booster function and conduit function. EAT thickness measured by TTE can effectively reflect the change trend of left atrial structure and function in patients with AF, thereby providing a certain reference for clinical practice.

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Figure

Fig. 1. Flowchart of patient enrollment in the study.

Fig. 2. Left atrial volume curves. a control group, b paroxysmal AF group, c persistent AF group.

Fig. 3. Left atrial strain curves. a control group, b paroxysmal AF group, c persistent AF group.

Fig. 4. The scatterplot and regression lines of individual values of EAT thickness(x-line) and corresponding values of left atrial phasic function parameters(y-lines) in patients with AF. LATEF and LASr represent reservoir function; LAAEF and LASct represent booster function; LAPEF and LAScd represent conduit function.

Table

Table 1. Baseline clinical and echocardiographic characteristics.

Table 2. RT-3DE and 2D-STI parameters.

Table 3. Intraobserver and Interobserver variability of EAT thickness and left atrial phasic function parameters.

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