The relationship between epicardial fat tissue thickness and frequent ventricular premature beats

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Abstract

Background: Ventricular premature beats (VPBs) are one of the most common rhythm abnormalities. Structural heart diseases such as myocardial hypertrophy and left ventricular dysfunction are associated with VPBs. However, the exact mechanism of VPBs in patients without structural heart disease has not been revealed yet. Epicardial fat tissue (EFT) is a visceral fat around the heart. Increased EFT thickness is associated with myocardial structural and ultrastructural myocardial abnormalities, which may play a role in the development of VPBs.

Aims: To evaluate the possible relationship between EFT thickness and frequent VPBs.

Methods and results: The study population consisted of 50 patients with VPBs and 50 control subjects. Frequent VPBs were defined as the presence of more than 10 beats per hour assessed by 24-h Holter electrocardiography monitoring. EFT thickness was measured by transthoracic echocardiography. Multivariable logistic regression analysis was used to assess factors related with frequent VPBs. Baseline demographic and biochemical features including age, gender, and rates of hypertension and diabetes mellitus were similar in both groups. EFT thickness was significantly higher in patients with frequent VPBs than in controls (3.3 ± 1.3 mm vs. 2.2 ± 0.8 mm, p < 0.001). In multivariable logistic regression analysis, EFT thickness was independently associated with VPB frequency (B = 1.030, OR = 2.802, p < 0.001).

Conclusions: Patients with frequent VPBs had increased EFT thickness compared to control subjects. EFT thickness was independently associated with frequent VPBs.

Key words: ventricular premature beat, ventricular arrhythmia, epicardial fat tissue

INTRODUCTION

Ventricular premature beat (VPB) is an extra heart beat that causes symptoms including palpitation and feeling of a pause in heart beating, VPBs can lead to some adverse cardiovascular effects such as systolic and diastolic dysfunction of the left ventricle (LV) and decreased exercise capacity [1–3]. Frequent VPBs is also related to myocardial infarction (MI) and all cause mortality in apparently healthy individuals [4, 5]. Although some predisposing disorders such as myocardial hypertrophy, cardiomyopathy, LV dysfunction, myocardial ischaemia, and MI have been defined in patients with structural heart disease, factors associated with VPBs have not been completely revealed in patients without structural heart disease [6–8].

Epicardial fat tissue (EFT) is a kind of visceral fat located around the heart [9]. There is a close anatomical and functional relationship between EFT and myocardium. It is associated with both structural and ultrastructural changes in myocardium, such as increased LV mass, atrial enlargement, and diastolic dysfunction [10–12]. This change is also associated with the development of VPBs. EFT also has many biochemical effects...
on the cardiovascular system, including insulin resistance, high free fatty acid levels, beta-adrenergic activity, and local and systemic inflammation [9–11, 13]. However, the relationship between EFT and VPB has never been investigated. Hence, the purpose of this study was to evaluate this possible relationship in patients without structural heart disease.

**METHODS**

**Patient selection**

The study population consisted of 50 patients without structural heart disease, who had frequent VPBs detected by ambulatory 24-h Holter monitoring, and 50 age- and sex-matched controls without VPBs. A frequency of VPBs of more than 10 per hour was defined as frequent VPBs [14]. VPB was also classified to right ventricular/right ventricular outflow tract (RV/RVOT) or left ventricular/left ventricular outflow tract (LV/LVOT) origin by using electrocardiographic features (right or left bundle branch morphology in lead V1, and inferior axis in lead D, D1, and aVF, respectively). Exclusion criteria were the presence of structural heart disease including heart failure (ejection fraction [EF] < 50%), dilated or hypertrophic cardiomyopathy, known coronary artery disease (angina pectoris, previous MI, percutaneous coronary intervention, and coronary by-pass), valvular disease (except mild form), valve replacement, and poor echocardiographic imaging. In the case of suspicion of clinically significant coronary artery disease assessed by history, electrocardiography (ECG) or echocardiography and exercise testing was made. Patients with positive exercise testing were also excluded from the study. The presence of blood pressure > 140/90 mm Hg or the use of antihypertensive medication was defined as hypertension. Demographic data, biochemical blood tests, and ECG were obtained from the entire study population. Body mass index (BMI) was calculated as weight (kilograms) divided by the square of height (metres squared). The study protocol was approved by the Institutional Ethics Committee.

**Echocardiographic examination**

**Baseline echocardiography.** All echocardiographic measurements were performed by two independent investigators who were unaware of the patient’s clinical data. Each member of the study population underwent a baseline echocardiographic evaluation using a commercially available system (Vivid 7, GE Vingmed Ultrasound AS, Horten, Norway). Subjects were examined in left lateral recumbent position using standard parasternal views (short and long axis) and apical views (two chamber, four chamber, and long axis). LV end-systolic (LVESD) and end-diastolic (LVEDD) dimensions, LV wall thicknesses, left atrial diameter (LA), early (E) and late (A) diastolic mitral inflow velocities, systolic mitral annular velocity (Sm), and early (Em) and late (Am) diastolic mitral annular velocities were measured by two-dimensional guided M-mode echocardiography. E/A and E/Em ratios were computed. LV function was assessed by EF using the modified biplane Simpson’s rule. LV mass index (LVMI) was calculated using the Devereux formula [15].

**Assessment of epicardial adipose tissue.** EFT thickness was evaluated by transthoracic echocardiography. EFT was defined as an echo-free space in front of the RV free wall on transthoracic parasternal long-axis images according to a predefined method (Fig. 1) [16]. The measurement of EFT thickness was made to be perpendicular on the free wall of RV at end-diastole [16]. The aortic annulus was used as an anatomical reference to standardise the measurement point.

All measurements were performed for three consecutive cardiac cycles and an average value was obtained. Reproducibility, which refers to the degree of agreement between measurements and the ability of study to be reproduced, was assessed by Bland-Altman method for EFT thickness [17, 18]. Echocardiographic images were digitally recorded and stored on the device. The recorded data of 20 patients were evaluated by two cardiologists. Then, intra- and inter-observer variability for EFT were computed as 4.7% and 5.8%, respectively.

**Statistical analysis**

Continuous variables were described as mean ± standard deviation. Normal distributions of values were assessed by using Kolmogorov-Smirnov test and histogram. Mann-Whitney U and student-t test were used for analysis of continuous variables when appropriate. Categorical variables were expressed as percentage values. They were analysed by using $\chi^2$ or Fisher’s exact test. Multivariable logistic regression analysis was performed to determine the factors that are independently associated with frequent VPBs. Variables that have a significant relationship with frequent VPBs in the univariate logistic regression analysis were included the multivariable regression analysis. A p value < 0.05 was considered statistically significant. All statistical analyses were performed by SPSS software program (SPSS, 13.0, Inc, Chicago, Illinois).
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RESULTS

Demographic and echocardiographic features

Baseline demographic and biochemical and electrocardiographic parameters of the patients and the control groups are shown in Table 1. EFT thickness and baseline echocardiographic parameters of both groups are given in Table 2. Patients with frequent VPBs and controls had similar demographic findings, including age, sex, rate of hypertension and diabetes mellitus, smoking, and BMI. The average number of VPBs was 4793 ± 5815 (range 246–27541). Forty-one (82%) patients had unifocal VPBs (31 [62%] patients had RVOT-VPB, 10 [20%] patients had non RVOT-VPB), and nine (18%) patients had multifocal VPBs. Mean EFT thickness was 3.3 ± 1.3 mm in patients with VPBs and 2.2 ± 0.8 mm in controls (range 1–6 mm). EFT thickness, LVEDD, and LWMI were significantly higher in patients with VPBs than in controls (Tables 1, 2). EFT thickness was similar in patients with unifocal VPB and in those with multifocal VPBs (3.3 ± 1.3 mm vs. 3.8 ± 1.3 mm, p = 0.32). There was no EFT thickness difference between patients with VPBs originating from RVOT and non-RVOT (3.2 ± 1.3 vs. 3.4 ± 1.2 mm, respectively, p = 0.84).

Relationship VPB and EFT

Demographic (age, gender, hypertension, diabetes mellitus, smoking, and BMI) and echocardiographic (LVESD, LVEDD, EF, LVMI, LA, E, A, Sm, Em, Am, E/A, and E/Em) parameters were assessed by univariate logistic regression analysis. In univariate analysis, EFT thickness (OR = 2.840, p < 0.001, 95% CI 1.007–1.257), LVEDD (OR = 1.125, p = 0.038, 95% CI 1.007–1.257), LVEDD (OR = 1.165, p = 0.014, 95% CI 1.032–1.316), and LVMI (OR = 1.028, p = 0.014, 95% CI 1.006–1.052) were related with frequent VPBs. However, in multivariable logistic regression model, only EFT thickness was independently associated with the presence of frequent VPBs (Table 3).

DISCUSSION

In this study a possible relationship between EFT and frequent VPBs was assessed in patients without structural heart disease. We found that EFT thickness was significantly higher in patients with VPBs than in controls. There was also an independent relationship between EFT thickness and frequent VPBs.

VPB is one of the most common types of arrhythmia in clinical practice. Some disorders such as ischaemia, myocardial hypertrophy, and cardiomyopathy are defined as predisposing for VPBs [6–8]. However, factors associated with VPBs could not be described exactly in apparently healthy subjects or patients without structural heart disease.

EFT has recently been a subject of interest because of its adverse effects on the cardiovascular system mediated by inflammation, insulin resistance, high free fatty acid levels, and beta-adrenergic activity [9–11, 13]. Recently, a variety of disorders such as atherosclerosis, hypertension, arterial stiffness, impaired coronary flow reserve, and microvascular function, enlarged atrial and ventricular dimensions, atrial fibrillation, increased LV mass, and diastolic dysfunction have been reported to be associated with EFT [10, 12, 19, 20–24]. However, the relationship between EFT and VPBs has never been investigated.
Some potential mechanisms can be proposed to explain the relationship between EFT thickness and frequent VPBs. The effect of EFT, which can lead to both structural and ultrastructural changes in myocardium, might be considered as a possible mechanism. Iacobellis et al. [10, 25] reported that increased EFT thickness is associated with structural changes such as LV mass, and atrial and RV cavity size. Increased LV mass might predispose the heart to arrhythmias by means of three different ways: increased fibrosis, electrophysiological changes, and calcium handling of myocardium [26]. In our study, LVMI was higher in patients with VPBs than controls, and it was also associated with frequent VPBs in univariate analysis. Therefore, we considered that increased LVMI may play a role in the development of VPBs.

EFT also releases inflammatory cytokines such as tumour necrosis factor-α, interleukin-1β, and interleukin-6 and is associated with both local and systemic inflammation, which can lead to cardiac ultrastructural remodelling including myocardial fibrosis [9, 13]. Myocardial remodelling and fibrosis may produce some changes in action potential characteristics and predispose the heart to VPBs [27]. Voulgari et al. [28] showed that LV arrhythmogeneity was associated with low-grade inflammation in patients with metabolic syndrome. Duncan et al. [29] reported that tumour necrosis factor-α and interleukin-1β also lead to increased ventricular arrhythmia susceptibility in patients with sepsis. Therefore, it has been proposed that inflammatory processes including bioactive molecules, inflammatory cytokines, cell infiltration and myocardial remodelling may play a role in the development of VPBs.

Limitations of the study
First, our study population had a relatively small number of patients. Second, no evaluation of magnetic resonance imaging (MRI) or computed tomography (CT) was performed to assess EFT. However, they are not applicable for routine clinical use because MRI is expensive and time consuming and CT is an imaging method based on radiation. Two-dimensional echocardiography, which was used in this study, is an accepted method for the assessment of EFT thickness as is highly correlated with MRI. It is also reliable, practical, and less time consuming [11]. Third, in this study, EFT thickness was less than in some previous studies [12, 16, 19, 25]. However, it should be stated here that our study population was different from those of previous studies that included patients with obesity and atherosclerosis. Obesity is almost a prototype situation for increased EFT thickness. In our study, both BMI and prevalence of obesity were lower than previous studies. In addition, the presence of known atherosclerotic disease is an exclusion criterion for this study, and patients with obvious atherosclerotic disease were excluded from the study. Fourth, patients with asymptomatic coronary artery disease, which correlates with EFT, were not excluded from the study. Lastly, blood levels of inflammatory markers and cytokines were not obtained. Therefore, our study results should be confirmed by a further study.

CONCLUSIONS
EFT thickness increased in patients with VPBs. There is also an independent relationship between EFT thickness and frequent VPBs. EFT thickness may be a new mechanism to explain the pathogenesis of VPBs.

Conflict of interest: none declared

References

Table 3. Results of multivariate logistic regression analysis between ventricular premature beat and other variables

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>OR</th>
<th>P</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV ESD</td>
<td>0.071</td>
<td>1.074</td>
<td>0.43</td>
<td>0.901 — 1.280</td>
</tr>
<tr>
<td>LV EDD</td>
<td>0.071</td>
<td>1.074</td>
<td>0.5</td>
<td>0.878 — 1.313</td>
</tr>
<tr>
<td>LV mass index</td>
<td>0.05</td>
<td>1.005</td>
<td>0.7</td>
<td>0.978 — 1.033</td>
</tr>
<tr>
<td>EFT thickness</td>
<td>1.030</td>
<td>2.802</td>
<td>&lt; 0.001</td>
<td>1.703 — 4.611</td>
</tr>
</tbody>
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DD — end-diastolic diameter; EFT — epicardial fat tissue; LV — left ventricular; ESD — end-systolic diameter; OR — odds ratio
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Zależność między grubością nasierdziowej tkanki tłuszczowej a występowaniem częstych przedwczesnych pobudzeń komorowych

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S t r e s z c z e n i e

Wstęp: Pobudzenia przedwczesne komorowe (VPB) to jedne z najczęstszych zaburzeń rytmu. Choroby strukturalne serca, takie jak przerost mięśnia sercowego i dysfunkcja lewej komory, wiążą się z VPB. Jednak dotychczas nie wyjaśniono dokładnie mechanizmu powodującego VPB u pacjentów bez strukturalnej choroby serca. Nasierdziowa tkanka tłuszczowa (EFT) jest zlokalizowana wokół serca, a jej zwiększona grubość wiąże się z występowaniem strukturalnych i ultrastrukturalnych zaburzeń mięśnia sercowego, które mogą przyczyniać się do rozwoju VPB.

Cel: Badanie przeprowadzono w celu oceny możliwych zależności między grubością EFT a częstymi VPB.

Metody i wyniki: Badana populacja składała się z 50 chorych z VPB i 50 osób stanowiących grupę kontrolną. Częste VPB definiowano jako obecność ponad 10 pobudzeń na godzinę ocenianych w całodobowym monitorowaniu elektrokardiograficznym metodą Holtera. Grubość EFT mierzyła się w echokardiografii przezklatkowej. Do oceny czynników związanych z częstymi VPB zastosowano wielozmiennową analizę regresji logistycznej. Wyjściowe dane demograficzne i biochemiczne, w tym wiek, płeć, odsetek osób z nadciśnieniem tętniczym i cukrzycą, były podobne w obu grupach. Grubość EFT była istotnie większa u chorych z częstymi VPB niż u osób z grupy kontrolnej (3,3 ± 1,3 mm vs. 2,2 ± 0,8 mm; p < 0,001). W wielozmiennowej analizie regresji logistycznej wykazano, że grubość EFT była niezależnie związana z częstością VPB (B = 1,030; OR = 2,802; p < 0,001).

Wnioski: U chorych z VPB grubość EFT była większa niż u osób z grupy kontrolnej. Grubość EFT była niezależnie związana z częstymi VPB.

Słowa kluczowe: pobudzenie komorowe przedwczesne, arytmia komorowa, nasierdziowa tkanka tłuszczowa

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