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The relationship of epicardial fat and atrial high-rate episodes in patients with permanent pacemaker

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ABSTRACT

Objectives: Atrial high-rate episodes (AHRE) can occur in patients who have permanent pacemakers (PPM). AHRE is classified as subclinical atrial fibrillation (AF). Also, AHRE is related to clinical AF. Epicardial fat tissue (EFT) thickness is linked to AF. The purpose of this study was to examine the relation between AHRE and EFT thickness in PPM patients.

Methods: Forty patients with dual-chamber PPM were enrolled. Transthoracic echocardiography was used to measure the thickness of the EFT. Patients were examined in 2 groups according to whether there was AHRE in the records: group 1 (AHRE) and group 2 (AHRE-free). A high atrial rate of more than 175 beats per minute for more than 5 minutes was defined as AHRE. The findings of the standard 2-dimensional echocardiography and the Doppler echocardiography were all recorded. A statistical relationship between EFT thickness and the development of AF was investigated.

Results: Group 1 had ten patients, while Group 2 included thirty individuals. When the demographic features of the two groups were compared, they were similar. Both groups had similar 2-D echocardiographic and Doppler results. The difference in EFT thickness between groups 1 (2.0 ± 1.1 mm) and 2 (2.9 ± 1.8 mm) was not statistically significant ($p = 0.138$).

Conclusions: In patients with PPM, AHRE may develop after implantation and may be detected asymptomatically in periodic follow-up. In this population, we did not observe a significant association between EFT thickness and the development of AF.

Keywords: Epicardial fat, atrial high rate, atrial fibrillation

In patients with permanent pacemakers (PPM) atrial fibrillation may occur with overt clinical manifestations, or it may sometimes be detected as "silent-subclinical" with an AF complication such as stroke or tachycardiomyopathy. Sometimes it can be identified even in the absence of clinical signs. For this reason, the detection and appropriate treatment of AF in these patients is a critical problem awaiting a solution. Detection of clinical AF requires documentation of a 12-lead electrocardiogram (ECG) or AF electrocardiographic features on a rhythm strip of at least 30 seconds [1]. Pacemaker telemetry can record AF episodes, enabling diagnosis and quantification of the AF burden [2]. Recent studies have investigated the

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link between AF and epicardial fat tissue (EFT) thickness, which has endocrine properties. [3, 4]. It has been shown that EFT can be found in the atrioventricular and interventricular groove, right ventricular free wall, left-right ventricular apical, around the atrium and appendage, outside the adventitia of the coronary arteries [5]. In the study in which Mazurek and his colleagues demonstrated the inflammatory activity of EFT with positron emission tomography, it was noted that EFT showed more inflammatory properties in patients with AF [6]. According to Iacobellis *et al*., EFT thickness is greater in chronic AF patients than in paroxysmal AF patients [7].

An atrial high-rate episode (AHRE) is characterized by tachycardia episodes lasting more than 5 minutes with an atrial rate greater than 175 beats per minute (b.p.m) recorded by cardiac implantable devices. The presence of AHRE is considered as a subclinical AF [8] and it increases the risk of clinical AF by 5.66 times and stroke by 2.41 times [9]. There has been significant research on the link between the thickness of the EFT and AF [10], but less is known about the link between EFT and AHRE.

Our understanding of the causes of AHRE, which is a common finding in patients with PPM and has been linked to an increased risk of stroke and systemic embolism when it occurs frequently and for prolonged periods [11], remains limited. To address this knowledge gap, we conducted a study to investigate whether there is a relationship between EFT thickness (a known risk factor for AF) and AHRE, and by extension, the development of AF in patients with PPM.

METHODS

The local Clinical Research Ethics Committee gave their approval to the study (07.04.2014/03). This study adheres to all institutional and/or national research committee and Helsinki statement of 1964 ethical standards. All subjects were informed about the research and granted their consent.

Study Population

The research was involved 40 subjects who were presented for periodic PPM follow-up, provided written consent, m*et al*l inclusion criteria, and had a conventional dual-chamber PPM (DDD-PPM) implanted but no history of permanent AF. Indications for PPM implantation were sick sinus syndrome (25%, n = 10), complete heart block (27.5%, n = 11) and other causes (47.5%, n = 19). The following were the research's exclusion criteria: Patients with > 50% stenosis of a coronary artery, hyperthyroidism, severe valvular disease (moderate-severe), hypertrophic cardiomyopathy, and systolic HF (Ejection fraction < 50%).

In the study, only patients with DDD-PPM were included. If the patient requires a pacemaker and the sinus node is intact, a DDD-mode PPM is usually implanted because it is more physiological. These pacemakers also record AHRE or other arrhythmic events. The presence of an atrial rate of > 175 b.p.m. lasting > 5 minutes was defined as AHRE [1, 8]. Since AHRE is highly correlated with AF [8], two separate groups were formed according to those with and without AF detected in the pacemaker interrogation. The group with AHRE constituted the group 1, and the group with AHRE-free patients formed group 2.

Concurrent medical conditions and medication use were recorded. The height and weight of the patients were recorded. After 5 minutes of rest, the patients' blood pressure (BP) was recorded as the average of two measures taken on the right arm while seated.

Echocardiographic Measurements

Echocardiographic measurements were performed with Vivid 7 (GE, Norway) echocardiography machine in all patients. On parasternal long axis imaging, left atrial (LA) diameter, LV end-systolic and end-diastolic diameters, interventricular septum and posterior wall thicknesses (IVS and PW), and EFT thickness were measured using 2-dimensional echocardiography. EFT thickness was measured as the echo-free space in front of the right ventricular free wall on transthoracic parasternal long-axis images according to the predefined technique [12]. The LV volumes, maximum and minimum LA volumes, right atrium and right ventricular diameters were all measured using apical four-chamber imaging. The modified Simpson's method was used to calculate left ventricular ejection fraction (EF) and LV volumes. Early diastolic wave (E) and late diastolic wave (A) were measured 1 cm distal to the mitral valve leaflets in apical four-chamber imaging with Doppler echocardiog-

raphy. In tissue Doppler examination, the sample volume was placed in the lateral mitral annulus and early (E'), late (A') diastolic and systolic (S') waves were measured. TAPSE (tricuspid annular plane systolic excursion) was measured using M-mode by placing the sample volume on the tricuspid valve's lateral annulus.

Statistical Analysis

All values were presented as the mean plus the standard deviation. Using the Kolmogorov-Smirnov test, the normality of the distribution was determined. The Student's t-test was used to evaluate continuous variables with a normal distribution, whereas the Mann-Whitney U test was used to evaluate continuous variables with a non-normal distribution. Pearson Chi-Square or Fisher Exact test was applied to categorical variables expressed as a percentage, depending on the sample size. *P* values under 0.05 were considered statistically significant. SPSS (13.0, Inc., Chicago, Illinois) software was applied for statistical analysis.

RESULTS

Forty patients with DDD PPM participated in the trial. Those with AHRE (group 1, n = 10) and those without AHRE (group 2, n = 30) were split into two groups. Sick sinus syndrome (n = 10) and third degree AV block (n = 11) were the most common indications for PPM. There was no statistical difference between the groups in terms of age. The male gender was more prevalent in both groups, but gender distribution was similar. There was no difference between the two groups regarding smoking, HT, DM and atherosclerosis history. The BP values measured at rest were similar between the two groups. While the resting heart

Table 1. Demographic characteristics of the patients

	Group 1 (AHRE) n = 10	Group 2 (AHRE-free) n = 30	*p* value
Age (year) (mean ± SD)	57.8 ± 17.0	60.5 ± 1.7	0.609
Gender, n (%)			0.858
Male	6 (60)	17 (56.7)	
Female	4 (40)	13 (43.6)	
Pacemaker indication, n (%)			0.590
Sick sinus syndrome	3 (30)	7 (23.3)	
AV complete block	3 (30)	8 (26.7)	
Other	4 (40)	15 (50)	
Hypertension, n (%)	3 (30)	17 (56.7)	0.152
Diabetes Mellitus, n (%)	1 (10)	1 (3.3)	0.415
Coronary artery disease, n (%)	2 (20)	6 (20)	0.707
Smoking, n (%)	1 (10)	3 (10)	1.0
Body Mass Index (kg/m²) (mean ± SD)	26 ± 3.8	28 ± 3.1	0.104
Aspirin, n (%)	4 (40)	10 (33.3)	0.711
Statin, n (%)	0	6 (20)	0.132
Beta blocker, n (%)	4 (40)	11 (36.7)	0.855
Calcium channel blocker, n (%)	1 (10)	7 (23.3)	0.374
ACE inhibitor/ARB, n (%)	1 (10)	11 (36.7)	0.117
Amiodarone, n (%)	1 (10)	2 (6.7)	0.737
Systolic BP (mmHg) (mean ± SD)	126 ± 16.3	119 ± 16	0.184
Diastolic BP (mmHg) (mean ± SD)	76.0 ± 9.7	73.7 ± 6.1	0.031

ACE = Angiotensin-converting enzyme, AHRE = Atrial high rate episode, ARB = Angiotensin receptor blocker, AV = Atrioventricular, BP = Blood pressure, SD = Standard deviation

rate was 74.5 ± 8.8 b.p.m. in group 1, it was 71.8 ± 14.8 b.p.m. in group 2, and there was no difference between the groups. Also, there was no difference in drug use and BMI values between the two groups. Baseline demographic characteristics of patients in group 1 and 2 are shown in Table 1. The demographic characteristics of the patients were similar in both groups. Left ventricular diameters and volumes, wall thicknesses, LVM index and LA diameter, which are the basic echocardiographic parameters, were similar between groups. Although LA minimum and maximum volumes were higher in group 1, this difference was not statistically significant. TAPSE was also similar in both groups (p = 0.44). Doppler and tissue Doppler findings were similar in both groups. Two-dimensional M-mode, Doppler and tissue Doppler findings echocardiography results are shown in Table 2. While the mean EFT thickness was 2.0 ± 1.1 mm in group 1, it was 2.9 ± 1.8 mm in group 2; this difference between the two groups was not statistically significant. There were three patients with EFT thickness ≥ 3 mm and AF. Epicardial fat thickness was < 3 mm in

Table 2. Echocardiographic 2D, M mode, Doppler findings of the study population

	Group 1 (AHRE) n = 10 Mean ± SD	Group 2 (AHRE-free) n = 30 Mean ± SD	*p* value
Left atrium			
Diameter (mm)	35.5 ± 4.5	36.1 ± 5.5	0.771
Maximum volume (ml)	52.6 ± 22.1	45.2 ± 17.3	0.282
Minimum volume (ml)	24.5 ± 12.4	18.9 ± 9.9	0.152
Left ventricle			
ESD (mm)	29.5 ± 5.1	29.9 ± 6.4	0.301
EDD (mm)	47.6 ± 3.9	48.5 ± 5.1	0.603
ESV (ml)	40.0 ± 13.5	38.4 ± 13.8	0.751
EDV (ml)	88.9 ± 30.7	87.5 ± 33.6	0.908
Ejection fraction (%)	60.6 ± 6.7	59.5 ± 5.4	0.592
IVS (mm)	12.2 ± 3.2	11.7 ± 2.5	0.591
PW (mm)	9.8 ± 1.3	10.4 ± 1.7	0.351
Right atrium diameter (mm)	40.3 ± 5.7	38.0 ± 5.3	0.245
Right ventricular diameter (mm)	33.1 ± 6.8	35.3 ± 5.2	0.283
LVM index (gr/m²)	101.5 ± 6.3	107.4 ± 5.0	0.617
E (cm/s)	58.9 ± 18.1	65.7 ± 17.2	0.333
A (cm/s)	68.2 ± 23.9	70.6 ± 19.3	0.772
E' (cm/s)	10.4 ± 4.2	9.6 ± 3.8	0.616
A' (cm/s)	11.6 ± 2.9	10.7 ± 3.2	0.772
TAPSE (mm)	21.6 ± 5.1	23.1 ± 5.2	0.449
Epicardial fat tissue (mm)	2.0 ± 1.1	2.9 ± 1.8	0.138

A = Late mitral diastolic filling velocity, A' = Mitral annular late diastolic wave, AHRE = Atrial high rate episode, E = Early mitral diastolic filling velocity, E' = Mitral annular early diastolic wave, EDD = end-diastolic diameter, EDV = end-diastolic volume, ESD = end-systolic diameter, ESV = end-systolic volume, IVS = Interventricular septum thickness, LVM = Left ventricular mass, PW = Left ventricular posterior wall thickness, S' = Mitral annular systolic wave, SD = Standard deviation , TAPSE = Systolic movement of the tricuspid annular plane

Table 3. Characteristics of patients according to EFT thickness

	EFT thickness ≥ 3 mm (n = 17)	EFT thickness < 3 mm (n = 23)	*p value*
AHRE, n (%)	3 (17.6)	7 (30)	-
Age (years) (mean ± SD	62.9 ± 12.5	57.6 ± 15.5	0.266
HT, n (%)	17 (42.5)	23 (57.5)	0.806
LA diameter (mm) (mean ± SD	35.7 ± 4.7	36.1 ± 5.7	0.672
LVM index (gr/m²) (mean ± SD	104.1 ± 25.2	107.3 ± 33.1	0.617

AHRE = Atrial high rate episode, EFT = Epicardial fat tissue, HT = Hypertension, LA = Left atrium, LVM = Left ventricular mass, SD = Standard deviation

the other seven patients with AF. While mean EFT thickness was 2.7 ± 0.8 mm in 6 patients with a BMI ≥ 30, it was 2.7 ± 1.8 mm in those with a body mass index < 30, and there was no significant difference between the two groups. Characteristics of patients according to EFT thickness are shown in Table 3. Atrial fibrillation was detected in the ECGs of three patients at the time of enrollment (Paroxysmal AF). In the other seven patients, sinus rhythm was present in the ECG, but AHRE was detected in the recordings of the pacemaker telemetry.

The lowest EFT thickness was measured as 1 mm in the whole population, and the maximum was 8 mm. Epicardial fat thickness was ≥ 3 mm in 17 (42.5%) patients and < 3 mm in 23 (57.5%) patients.

DISCUSSION

In this research article, we investigated the association between AHRE detection and EFT thickness in DDD PPM patients. AHRE was detected in 25% of patients with DDD PPM. However, no statistically significant difference was found in terms of EFT thickness between those with and without AHRE.

AHRE is not uncommon in patients with PPM. According to the literature, 10-30% AHRE has been reported in patients with PPM who were not previously known to have AF. [13]. In the earlier MOST study, 51.3% of patients with PPM were found to have an AHRE of > 220 beats/min lasting longer than 5 minutes within 27 months of follow-up. [14]. In the ASSERT study, which enrolled 2580 patients aged > 65 years, with a PPM and without a history of AF, it was determined that subclinical AHRE developed at a rate of 10.1% in a 3-month follow-up. These tachycardia episodes were associated with clinical AF, and the risk of AF development increased to 36% within 2.8 years of follow-up. In addition, subclinical AF was related with an increased risk of ischemic stroke or systemic embolism, as demonstrated by this study [15]. In our study, the incidence of AHRE in patients with PPM was 25%. Since our patients in the study population were younger than other studies, AHRE was evaluated with a one-time measurement, and comorbid conditions that could lead to AF were less in our patients, the AHRE rate may have been found to be lower.

Epicardial fat tissue functions as a paracrine organ and has been shown to cause AF via various mechanisms. A significant risk factor for AF is inflammation, which is caused by the release of inflammatory cytokines and markers in the blood from EFT. Obesity, metabolic syndrome, and atherosclerosis are also associated with EFT [7, 12, 16]. According to the findings of a cardiac tomography study, EFT is thicker in patients with persistent AF than in patients without AF [17]. Based on previous studies examining the relationship between EFT and AF, we hypothesized that EFT may also be associated with AHRE. But we found no statistically significant difference existed between the groups. Possible explanations for this finding include the relatively young age and low rates of comorbid diseases such as diabetes in group 1, as well as the slightly lower mean BMI in the AF group, although this difference was not statistically significant.

Limitations

Our study was not prospective. However, the prospective study will require a long time and increase

costs. The relatively small number of patients is also a significant limitation. However, the effect of this restriction on the results was tried to be eliminated by strictly applying exclusion criteria in patient selection and including the patient population with one type of PPM (the type of PPM most associated with AF). Finally, the evaluation of AF only with the presence of AHRE obtained from PPM records is another limiting factor of the study. Implantable loop recorders, smartwatches or smart devices also could be used to detect AF, but these technologies would also increase costs.

CONCLUSION

According to the findings of this study, the hypothesis that EFT thickness could be a predictor of AF in patients with PPM was evaluated. Still, EFT thickness was not associated with AF in this particular population. More research is needed to determine the predictors of the development of AF in patients with PPM.

Authors' Contribution

Study Conception: YH, AK; Study Design: YH, AK; Supervision: FA, AK; Funding: N/A; Materials: YH, FA; Data Collection and/or Processing: YH, FA; Statistical Analysis and/or Data Interpretation: YH, FA; Literature Review: YH, FA; Manuscript Preparation: YH, FA and Critical Review: YH, AK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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