

# AMCoR

Asahikawa Medical University Repository <http://amcor.asahikawa-med.ac.jp/>

International heart journal (2013) 54卷5号:297-303.

Epicardial adipose tissue is associated with prevalent atrial fibrillation in patients with hypertrophic cardiomyopathy

Muhib S, Fujino T, Sato N, Hasebe N

# Epicardial Adipose Tissue Is Associated With Prevalent Atrial Fibrillation in Patients With Hypertrophic Cardiomyopathy

Sharifi MUHIB,<sup>1\*</sup> MD, Takayuki FUJINO,<sup>1\*</sup> MD, Nobuyuki SATO,<sup>1</sup> MD, and Naoyuki HASEBE,<sup>1</sup> MD

## SUMMARY

Prevalent atrial fibrillation (AF) in patients with hypertrophic cardiomyopathy (HCM) represents an important issue with regard to stroke events caused by embolization and is associated with high mortality. Increased epicardial adipose tissue (EAT), which shows high metabolic activity, can locally influence the activity of the autonomic ganglia, enhancing autonomic dysregulation and increasing the likelihood of AF. We tested the hypothesis that EAT is associated with prevalent AF in HCM patients. Sixty-two patients with idiopathic HCM diagnosed on the basis of ultrasound cardiography findings and histopathological evaluation of myocardium obtained by right ventricular biopsy underwent cardiac magnetic resonance imaging to estimate the extent of EAT. EAT area was significantly higher in the group with AF episodes than in the group without. An increased incidence of AF was found to be significantly related to an increase in EAT, and this association persisted after adjustment for body mass index, sex, and age. Time domain measures of heart rate variability measured by Holter electrocardiography, standard deviation of normal to normal, and standard deviation of the average of normal to normal were negatively related to EAT area. EAT was positively correlated with intraventricular septal thickness and cystatin C level and negatively correlated with the 24-hour creatinine clearance rate. Increased EAT area in HCM patients is significantly related to the presence of AF, which is associated with changes in baseline autonomic nervous tone, left ventricular mass, and chronic kidney disease. (*Int Heart J* 2013; 54: 297-303)

**Key words:** Heart rate variability, Cardiac magnetic resonance imaging

Epicardial adipose tissue (EAT) is unique because of its proximity to cardiac structures and its shared blood supply with the cardiac microcirculation.<sup>1,2)</sup> EAT is the true visceral fat of the heart, and its regional distribution and function is of growing scientific and clinical interest. Being a metabolically active organ and a source of several bioactive molecules, EAT may exert protective as well as unfavorable effects on the heart. EAT covers 80% of the heart's surface and constitutes 20% of its total weight. It is located in the atrioventricular and interventricular grooves, along the major branches of the coronary arteries, around the atria, over the free wall of the right ventricle (RV), and over the apex of the left ventricle (LV). Growing evidence indicates that EAT may substantially affect cardiovascular morphology and function, eg, EAT was found to be related to LV mass in a previous report.<sup>1)</sup> However, little is known about changes in EAT in relation to the development of cardiac hypertrophy in patients with hypertrophic cardiomyopathy (HCM).

Atrial fibrillation (AF) is expected to affect many individuals in Western countries and Japan and is associated with significant morbidity and mortality.<sup>3)</sup> Obesity represents an important risk factor for new-onset AF.<sup>4,5)</sup> The association between pericardial fat and AF was recently evaluated in a study population from the Framingham study.<sup>6)</sup> Prevalent AF in HCM patients is an important issue with regard to stroke

events caused by cardiogenic embolization. Autonomic dysregulation at baseline, as reflected by altered heart rate variability (HRV), is associated with the risk of AF.<sup>7)</sup> This suggests that autonomic nervous tone fluctuations measured by HRV precede episodes of paroxysmal AF. Increased EAT, which shows high metabolic activity, can locally influence these autonomic ganglia, enhancing autonomic dysregulation and increasing the likelihood of AF, which may be a potential mechanism by which obesity increases the risk of AF. It remains unclear whether the association between EAT and prevalent AF in HCM patients is independent of the systemic effects of obesity.

This study aimed to evaluate EAT area as assessed by cardiac magnetic resonance (CMR) imaging, investigate its relationship with the presence of AF and cardiovascular parameters in HCM patients, and investigate the mechanisms related to baseline autonomic nervous tone associating pericardial fat with AF.

## METHODS

**Study population:** Between April 2005 and November 2010, we retrospectively analyzed consecutive Japanese HCM patients who underwent coronary angiography and demonstrated

From the <sup>1</sup> Department of Internal Medicine, Cardiovascular Respiratory and Neurology Division, Asahikawa Medical University, Hokkaido, Japan.

\*These authors contributed equally to this work.

Address for correspondence: Takayuki Fujino, MD, Department of Internal Medicine, Cardiovascular Respiratory and Neurology Division, Asahikawa Medical University, Midorigaoka Higashi 2-1-1-1, Asahikawa, Hokkaido 078-8510, Japan.

Received for publication December 14, 2012.

Revised and accepted April 1, 2013.

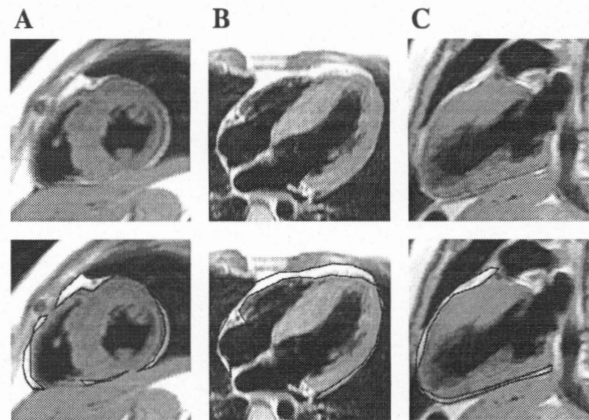
the absence of ischemic heart disease and the presence of epicardial coronary arteries with  $\geq 75\%$  stenosis or a history of myocardial infarction or coronary revascularization. The diagnosis of HCM was based on ultrasound cardiography (UCG) findings and the presence of asymmetrical LV hypertrophy on B-mode and two-dimensional (2D) Doppler echocardiography, a demonstrable wall thickness of end-diastolic phase  $> 11$  mm, and a disrupted myofibrillar pattern and interstitial fibrosis in the myocardium on RV biopsy. A total of 62 consecutive patients (36 males and 26 females) with idiopathic HCM were investigated. The exclusion criteria were as follows: history of coronary artery bypass graft surgery, incomplete measurement of epicardial fat area, and other missing data.

Ventricular hypertrophy and dimensions and LV function were assessed by UCG and cardiac catheter examination. Standard 2D measurements of LV diastolic and systolic dimensions, ventricular septum and posterior wall thickness, and left atrial (LA) diameter were obtained. The LV ejection fraction (EF) was calculated using the modified Simpson method. LA dimensions were measured at end systole. Mitral inflow velocity was traced and the following variables obtained: peak velocity of early (E) and late (A) filling and deceleration time of E-wave velocity. To estimate cardiac function, patients underwent pressure studies of right heart catheterization and left ventriculography. For the indices of LV function, LV ejection fraction (LVEF), LV end-diastolic volume (LVEDV), and LV end-systolic volume (LVESV) were analyzed by the area-length method using right anterior oblique views of the left ventriculogram.

Risk factor and covariate assessment were performed as previously described.<sup>8)</sup> Informed consent was obtained from all patients, and the study protocol conformed to the ethical guidelines of our institution's human research committee and was in accordance with the 1975 Declaration of Helsinki.

**Assessment of EAT area by CMR:** All studies were performed using a 1.5-Tesla whole-body imaging system (Magnetom Sonata, Siemens Medical Systems, Erlangen, Germany). For the assessment of EAT, we used a dark blood-prepared, T1-weighted, multislice, turbo spin-echo pulse sequence with a water suppression pre-pulse to obtain transverse 4-chamber and vertical 3-chamber views and short-axis images (Figure 1). While imaging was performed, patients were required to hold their breath at the end of expiration. Low-resolution axial survey images were first obtained, and pseudovertical long-axis images were acquired from the axial survey images. Horizontal long-axis (4-chamber) images were planned according to the pseudovertical long-axis images obtained, and vertical long-axis (2-chamber) images were planned according to these horizontal long-axis images. Short-axis images were planned according to horizontal long-axis images. In total, 7–13 images of each patient's LV were obtained so as to include the entire ventricle.

EAT area was measured using manual planimetry (GE Yokogawa Medical Co., Ltd, Tokyo) by an observer blinded to all patient details. The contours of EAT are outlined in end diastole in the views shown in Figure 1. For EAT determination, the area subtended by the manual tracings was determined in each slice. In the short-axis plane at the mid-ventricular level (Figure 1A), EAT area in the superior interventricular and inferior interventricular grooves and over the right and left ventricular walls was measured. At sites in the horizontal long-axis



**Figure 1.** Volumetric measurement of EAT with outlines of its contours in end-diastolic images of the short axis (A), horizontal long axis (B), and vertical long axis (C) covering the left and right ventricles in patients with hypertrophic cardiomyopathy. EAT indicates epicardial adipose tissue.

plane (Figure 1B), EAT area in the grooved segments (right and left atrioventricular grooves) and periatrial and right and left ventricular walls was measured. At sites in the vertical long-axis plane (Figure 1C), EAT area in the apical and free walls and inferior wall segments of the LV was measured. Total EAT area was obtained after data summation from slices of the short, horizontal long, and vertical long axes. EAT area was then expressed in  $\text{mm}^2$ .

**Assessment of AF:** Prevalent AF was defined on the basis of any confirmed episode of paroxysmal atrial flutter or AF on electrocardiography (ECG) or Holter report. ECGs and Holter records were also obtained from hospital records. AF events were confirmed by at least 2 cardiologists.

**Cardiac autonomic functions derived from HRV recordings:** All subjects underwent 24-hour Holter ECG monitoring. The recordings were analyzed and interpreted by one experienced cardiologist and one research fellow. Each beat was classified and labeled with respect to origin using template-matching techniques. HRV was determined from 24-hour Holter records using 4 time domain HRV measures [root mean square of successive normal sinus RR interval differences (rMSSD), percentage of successive normal sinus RR intervals  $> 50$  ms (pNN50), standard deviation of all normal sinus RR intervals during a 24-hour period (SDNN), and standard deviation of averaged normal sinus RR intervals for all 5-minute segments (SDANN)].

**Statistical analysis:** The Mann–Whitney *U* test was used to compare variables between the 2 groups and Pearson's chi-square test was used for comparison of discrete variables between the 2 groups. Logistic regression analysis was used to determine the relationship between 2 variables and multivariate logistic regression analysis was used to determine the relationship among multiple variables. Estimates also were adjusted for AF risk factors (age, sex, P–R interval, hypertension, hypertension treatment, and clinically significant valvular disease) and were entered into the multivariate model on the basis of the reported Framingham AF risk score.<sup>8)</sup> The results are expressed as the mean  $\pm$  standard error of the mean (SEM). Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). Analyses were performed using add-in statisti-

cal software from Excel (Ekuseru Toukei 2010, Social Survey Research Information Co., Ltd., Tokyo). A 2-tailed probability value of < 0.05 was considered statistically significant.

**RESULTS**

**Relation between AF presence and EAT area:** The baseline characteristics of all study patients are shown in Table I. The study comprised 36 men and 26 women (mean age, 56.8 ± 14.0 years), 10 (16%) of whom had prevalent AF (Table I).

There were no significant differences in age, body mass index (BMI), prevalence of hypertension or diabetes mellitus, smoking history, and lipid profile between HCM patients with

a history of AF episodes (AF<sup>+</sup> group) and those with no such history (AF<sup>-</sup> group; Table I). No differences in baseline medications were noted between the 2 groups (Table I).

With regard to the comparison of cardiac catheter data between the 2 groups, the AF<sup>+</sup> group showed a significantly higher pulmonary capillary wedge pressure (PCWP) compared with the AF<sup>-</sup> group; however, there were no differences in the other measured parameters between the 2 groups (Table II).

In comparison with the AF<sup>-</sup> group, the AF<sup>+</sup> group showed a significantly higher EAT area (Table III). Next, unadjusted and multivariate-adjusted associations between EAT and AF were examined (Table IV). Unadjusted linear regression analysis showed that prevalent AF significantly increased with increasing EAT area (Table IV). According to the multi-

**Table I.** Characteristics of Patients With Hypertrophic Cardiomyopathy With and Without a History of AF Episodes

Characteristics	AF <sup>+</sup> (n = 10)	AF <sup>-</sup> (n = 52)	P
Age, years	61.0 (2.3)	57.0 (1.8)	0.11
Body mass index, kg/m <sup>2</sup>	23.1 (0.9)	24.0 (0.7)	0.52
Hypertension, n (%)	6 (60)	26 (50)	0.67
Systolic blood pressure, mmHg	134 (13)	126 (3)	0.78
Diabetes mellitus, n (%)	4 (40)	12 (23)	0.16
Smoking, n (%)	7 (70)	32 (62)	0.97
Total cholesterol (mg/dL)	191 (14)	192 (6)	0.94
HDL-cholesterol (mg/dL)	54 (5.7)	53 (1.9)	0.83
Triglycerides (mg/dL)	138 (24)	125 (6)	0.81
LDL-cholesterol (mg/dL)	113 (10)	117 (5)	0.67
Serum creatinine (mg/dL)	0.83 (0.05)	0.85 (0.06)	0.65
Cystatin C (mg/L)	1.05 (0.09)	0.91 (0.04)	0.08
24-hour Ccr (mL/minute/1.73 m <sup>2</sup> )	76.6 (9.1)	80.9 (5.1)	0.73
Renin angiotensin inhibitor	5 (50)	14 (27)	0.79
Beta-blocker	4 (40)	14 (27)	0.61
Calcium blocker	4 (40)	14 (27)	0.70
Diuretics	4 (40)	13 (25)	0.79
Anti-platelet	2 (20)	9 (17)	0.71
Statin	1 (10)	8 (15)	0.80

Data are presented as mean ± standard error of the mean. Data regarding medications are presented as number (%). AF<sup>+</sup> and AF<sup>-</sup> indicate the group with and without a history of atrial fibrillation (AF) episodes, respectively; and HDL or LDL, high or low-density lipoprotein.

**Table II.** Cardiac Catheter Data for the Groups With and Without a History of AF Episodes

	AF <sup>+</sup> (n = 10)	AF <sup>-</sup> (n = 52)	P
RA	5.7 (0.6)	5.1 (0.4)	0.35
RVEDP	7.6 (0.6)	7.7 (0.5)	0.74
Mean PA	21.9 (2.7)	17.3 (1.1)	0.09
PCWP	14.5 (2.5)	10.3 (0.7)	0.03
LVEDP	15.3 (2.0)	13.1 (0.8)	0.16
Mean Ao	99 (7.6)	97 (3.3)	0.88
CI	3.2 (0.3)	3.2 (0.1)	0.54
LVEDV	143 (22)	143 (7)	0.66
LVESV	74 (19)	72 (6)	0.77
SV	71 (13)	72 (21)	0.93

AF<sup>+</sup> and AF<sup>-</sup> indicate the group with and without a history of atrial fibrillation (AF) episodes, respectively; RA, right atrial pressure (mmHg); RVEDP, right ventricular end-diastolic pressure (mmHg); PA, pulmonary pressure (mmHg); PCWP, pulmonary capillary wedge pressure (mmHg); mean Ao, mean aortic pressure (mmHg); CI, cardiac index (L/minute/m<sup>2</sup>); LVEDV, left ventricular end-diastolic volume (mL); LVESV, left ventricular end systolic volume (mL); and SV, stroke volume (mL). Data are presented as mean ± standard error of the mean.

**Table III.** Epicardial Adipose Tissue Area and Other Parameters in the Groups With and Without a History of AF Episodes

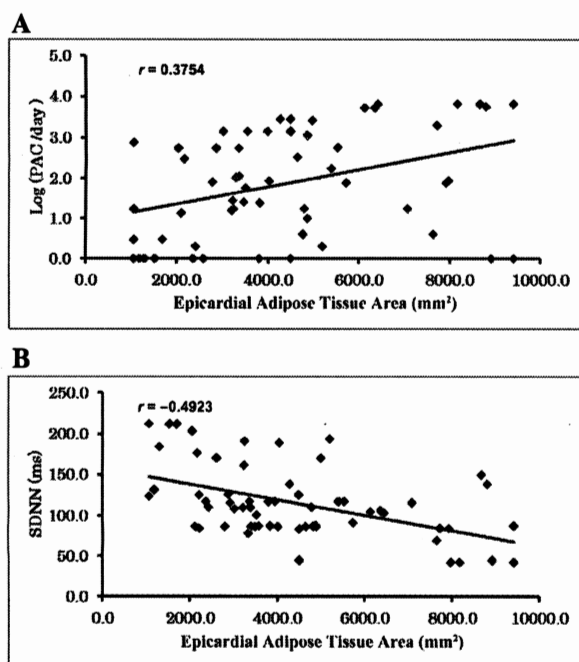
	AF <sup>+</sup> (n = 10)	AF <sup>-</sup> (n = 52)	P
Epicardial adipose tissue, mm <sup>2</sup>	5881 (544)*	4168 (369)	0.04
PR interval, ms	160 (19)	174 (5)	0.52
Brain natriuretic peptide, pg/mL	350 (82)*	135 (27)	0.002
Cardio-thoracic ratio, %	59.2 (1.7)*	50.5 (0.9)	0.0005
LVEF, %	49 (4.7)	54 (2.3)	0.32
%Fractional shortening	25 (3.4)	30 (1.6)	0.17
LA dimension, mm	48 (4.3)*	39 (1.1)	0.04
LV diastolic dimension, mm	52 (3.4)	52 (1.2)	0.96
Interventricular septal thickness, mm	11.5 (0.76)*	9.9 (0.37)	0.04
Posterior wall thickness, mm	9.9 (0.69)	9.2 (0.24)	0.35

Data represent mean ± standard error of the mean (SEM). AF<sup>+</sup> and AF<sup>-</sup> indicate the group with and without a history of atrial fibrillation (AF) episodes, respectively.

**Table IV.** Association Between Regional Epicardial Adipose Tissue Area and Prevalent AF

	OR (95% CI)	P
Unadjusted OR (95% CI)	1.30 (1.05–1.60)	0.02*
AF Risk Factor-Adjusted OR (95% CI)	1.28 (1.03–1.58)	0.03*
BMI-Adjusted OR (95% CI)	1.28 (1.01–1.63)	0.04*

\*Adjusted for the following covariates of AF risk factors: age, sex, systolic blood pressure, blood pressure treatment, PR interval, clinically significant valvular disease (defined as grade  $\geq 3$  systolic murmur or any diastolic murmur). \* $P < 0.05$ .



**Figure 2.** Correlation of epicardial adipose tissue volume with the number of PACs per day (A) and SDNN values (B). PAC indicates premature atrial contraction; vertical axis of (A), log (PACs/day); and SDNN, standard deviation of all normal sinus RR intervals during a 24-hour period.

variate-adjusted model, this association persisted after adjustment for body weight, sex, and age (Table IV). The OR per one standard deviation (SD) of EAT area after adjustment for BMI was also statistically significant (Table IV). In multivariate-adjusted models accounting for AF risk factors, pericardial fat was found to be significantly associated with AF (Table IV). The number of premature atrial contractions (PACs) per day was significantly correlated with EAT area (Figure 2A). These findings suggest that prevalent AF is significantly related to increased EAT area in HCM patients.

**Correlation between parameters of LV function and EAT:** When compared with the AF<sup>-</sup> group, the AF<sup>+</sup> group showed significantly higher brain natriuretic peptide (BNP) levels, cardiothoracic ratios, LA dimensions, and LVH (Table III). The logistic regression model was applied to test the relationships among the parameters of cardiac function and morphology and EAT. Increased EAT area was found to be associated with increased LA dimensions and LVH (Table V).

While investigating the correlation between EAT area and the parameters of LV function, no correlation was found be-

**Table V.** Correlation Between Epicardial Adipose Tissue Area and Cardiovascular Parameters

	r	P
BNP, pg/mL	0.103	0.468
CTR (%)	0.57	0.023*
LA dimension, mm	0.606	0.017*
Interventricular septal thickness, mm	0.599	0.018*
Posterior wall thickness, mm	0.455	0.046*
LVEF (%)	0.287	0.30
LV diastolic dimension, mm	-0.009	0.976
Serum creatinine (mg/dL)	0.349	0.022*
Cystatin C (mg/L)	0.531	0.001*
24-hour Ccr (mL/minute/1.73 m <sup>2</sup> )	-0.352	0.021*

\* $P < 0.05$ .

**Table VI.** Effects of Prevalent AF on Time Domain Parameters of Heart Rate Variability

HRV parameters	AF <sup>+</sup> (n = 10)	AF <sup>-</sup> (n = 52)	P
rMSSD (ms)	23.8 (5.7)	30.0 (2.1)	0.38
pNN50 (%)	7.8 (5.7)	10.9 (1.8)	0.23
SDNN (ms)	89.7 (7.8)	128 (7.3)	0.04*
SDANN (ms)	77.3 (4.2)	114 (7.3)	0.02*

Data represent mean  $\pm$  standard error of the mean. AF<sup>+</sup> and AF<sup>-</sup> indicate the group with and without a history of AF episodes, respectively; rMSSD, root mean square of the successive normal sinus RR interval difference; pNN50, percentage of successive normal sinus RR intervals  $> 50$  ms; SDNN, standard deviation of all normal sinus RR intervals during a 24-hour period; and SDANN, standard deviation of the averaged normal sinus RR intervals for all 5-min segments. \* $P < 0.05$ .

tween indexed EAT area and LVEF or percentage fractional shortening (FS). There is a parallel correlation between increases in EAT area and LV thickness in HCM patients (Table V), suggesting that increased pericardial fat is also associated with significantly increased LV mass.

A parallel correlation was found between increases in EAT area and increased serum creatinine and cystatin C levels and a decreased 24-hour serum creatinine clearance rate, suggesting that a decrease in renal function is significantly related to an increase in EAT area in HCM patients (Table V). In multivariate analysis, cystatin C level was correlated with EAT area after adjustment for age, sex, and BMI. Cystatin C level, however, was not significantly correlated with AF episodes (data not shown).

We examined the relationship between EAT area and myocardial cell diameter on the basis of the pathological findings of RV. The mean myocardial cell diameter for all subjects was  $18.8 \pm 4.0 \mu\text{m}$ , with no intergroup difference noted (AF<sup>+</sup>,  $20.2 \pm 1.73 \mu\text{m}$ ; AF<sup>-</sup>,  $18.5 \pm 0.64 \mu\text{m}$ ). In linear regression analysis, there was no significant correlation between EAT area and myocardial cell diameter ( $P = 0.453$ ,  $r = 0.143$ ).

**Relationship of HRV with prevalent AF and EAT area:** Autonomic nervous control of the heart is markedly deranged in patients with AF and HCM; in addition, HRV is decreased.<sup>9)</sup> We tested the relationships among HRV and EAT and prevalent AF. The AF<sup>+</sup> group showed consistently lower SDNN and SDANN values compared with the AF<sup>-</sup> group (Table VI). In logistic regression analysis, SDNN and SDANN were negatively related to AF episodes (SDNN,  $r = -0.21$ ,  $P = 0.04$ ; SDANN,  $r = -0.25$ ,  $P = 0.04$ ). In addition, in logistic regres-

sion analysis, SDNN (Figure 2B) and SDANN values ( $r = -0.434$ ,  $P = 0.008$ ) were negatively related to EAT area. From these findings, a relative suppression of baseline HRV was observed in patients with increased EAT area and history of AF episodes. The values of rMSSD and pNN50, which are specifically influenced by vagal tone, tended to be lower in the AF<sup>+</sup> group than in the AF<sup>-</sup> group (Table VI), and rMSSD ( $r = -0.165$ ,  $P = 0.30$ ) and pNN50 ( $r = -0.01$ ,  $P = 0.60$ ) were not significantly related to history of AF episodes. Furthermore, rMSSD ( $r = -0.300$ ,  $P = 0.077$ ) and pNN50 ( $r = -0.324$ ,  $P = 0.054$ ) were not significantly related to EAT area.

## DISCUSSION

We showed that EAT is associated with AF, even after adjustment for known AF risk factors in HCM patients. In addition, the present study determined the relationships among EAT area, prevalent AF, and baseline autonomic functions through analyses of HRV determined by 24-hour Holter ECG monitoring using 4 standard time domain measures in HCM patients. Furthermore, univariate linear regression analysis revealed significant correlations among EAT area and LA dimensions, intraseptal thickness, and low glomerular filtration ratio in HCM patients.

The major strengths of the present study were the relatively homogeneous sample drawn from a hospital-based cohort and the use of a highly reliable CMR-based quantification of fat deposits. EAT area was assessed by numerous imaging modalities. A volumetric measurement of EAT using CMR turned out to be less influenced by individual cardiac anatomy and fat distribution compared with echocardiographic measurements at single points; therefore, it was used for the assessment of EAT area in our study. We were also able to adjust odds ratio estimates using risk factors based on the Framingham AF risk score.<sup>8</sup> To our knowledge, the present study provides the first report of an association between cardiac adiposity (as measured by pericardial fat) and AF in HCM patients using CMR-based quantification of pericardial fat.

**Relationship between prevalent AF and EAT area:** Patients with HCM and a history of AF episodes exhibited significantly increased EAT area compared with patients with no such history. Prevalent AF in HCM patients was associated with stroke events caused by embolization and with mortality. Using necropsy data of various diseases, Shirani, *et al*<sup>10</sup> showed that interatrial fat correlated closely with epicardial fat thickness over the atrioventricular groove and RV. Larger fat deposits in the atrial septum were associated with a significantly higher prevalence of atrial arrhythmias. Of 80 patients with increased interatrial fat, 20 had atrial arrhythmias, 7 of which were AF. Heyer, *et al*,<sup>11</sup> in a CT-based study, reported that 75% patients (21/28) with lipomatous septal hypertrophy had increased amounts of pericardial fat; of these 21 patients, 13 had ECG abnormalities and 8 had atrial arrhythmias. Pericardial fat is significantly correlated with localized atrial septal fat, a finding known as lipomatous septal hypertrophy, which has been historically associated in several small studies with sick sinus syndrome and atrial arrhythmias.<sup>11</sup> When epicardial fat deposits enlarge, they are associated with marked fatty infiltration of the ventricular myocardium and atrial septum;<sup>12</sup> this may lead to electromechanical changes in the atrial tissue. Pericardial

fat, because of its contiguity with atrial tissue, may also cause local effects and result in AF.

### Relationship of low HRV with EAT area and prevalent AF:

The findings of the present study revealed a novel and intriguing relationship between EAT area and changes in autonomic function, defined on the basis of the 4 time domain measures of HRV in HCM patients. These findings support the hypothesis that prevalent AF depends on the attenuation of baseline autonomic function, particularly from the findings of lower SDNN and SDANN values in HCM patients. Pericardial fat may modulate the activity of the intrinsic autonomic nervous system, which is known to increase the likelihood of AF. The relationship between the autonomic nervous system and the onset of paroxysmal atrial fibrillation (PAF) is well known. Little is known, however, about prevalent AF-related changes in autonomic function, partly because very few studies have included HCM patients. The autonomic nervous system, particularly the adrenergic/cholinergic balance, has a profound influence on the occurrence of AF.<sup>13</sup> In contrast, in most patients with organic heart diseases, PAF episodes appear to be more dependent on the sympathetic nervous system.<sup>13</sup> A shift toward an increase in sympathetic tone or loss of vagal tone has been observed before postoperative PAF, before the onset of atrial flutter, and before the occurrence of PAF during sleep,<sup>13</sup> whereas a shift toward vagal predominance has been observed in young patients with lone AF and nocturnal episodes of PAF.<sup>14</sup>

It has been reported that SDNN and SDANN values in the 5 minutes preceding AF were significantly lower than those over the 60 minutes preceding AF or the SDNN values over the 24-hour recording period.<sup>7</sup>  $\beta$ -Adrenergic blockers also increase SDNN and SDANN values and decrease the incidence of paroxysmal AF or its relapse after electrical or pharmacological cardioversion.<sup>15</sup> In the UK-HEART prospective study of patients with CHF, SDNN was a significant predictor of all-cause mortality; the risk ratio for a 41.2-ms decrease in SDNN was 1.62 (95% CI, 1.16–2.44).<sup>16</sup> Among patients with idiopathic cardiomyopathy, those with SDNN < 50 ms exhibited a significantly lower survival rate, irrespective of the presence or absence of progressive heart failure, compared with those with SDNN > 50 ms.<sup>17</sup> From these findings, lower SDNN associated with increased EAT area may contribute to increased AF incidence and can be associated with a greater risk of heart failure.

It has been hypothesized that unlike large deposits of visceral abdominal fat, which act systemically, pericardial fat probably acts locally through mechanostructural or paracrine mechanisms.<sup>18,19</sup> Increased EAT area can also serve as a scavenger of excess free fatty acids that interfere with the generation and propagation of the contractile cycle of the heart, may cause ventricular arrhythmias, and are presumed to alter cardiac repolarization.<sup>20,21</sup> The epicardial autonomic ganglia contribute to sympathetic innervation of the heart. From these findings, increased pericardial fat may locally influence these autonomic ganglia, decreasing baseline autonomic tone and increasing the likelihood of AF.

**Association between cardiac structure and pericardial fat in HCM patients:** Under physiological conditions, EAT is presumed to act as a buffering system between the myocardium and the local vascular bed,<sup>22</sup> suggesting a possible local cardiovascular effect of this depot. In this study, EAT area was sig-



nificantly correlated with LV hypertrophy, which accords well with the findings of previous studies<sup>23)</sup> that showed a close relationship between ventricular muscle mass and EAT. Iacobellis, *et al*<sup>24)</sup> have shown that increased EAT is associated with significant increases in LV mass and impaired diastolic function. From the pathological findings of the RV in our study, no difference in myocardial cell diameter was found between the 2 groups and no significant correlation was found between EAT area and myocardial cell diameter, although an increase in EAT area was associated with increased LVH as estimated by UCG parameters. These findings suggest that an association between increased pericardial fat and increased LV mass may be dependent on increased fibrosis around myocytes.

It has been shown that increased pericardial fat is also associated with changes in cardiac structures and, particularly, increased LA dimensions.<sup>25)</sup> These findings were corroborated by the findings of our study, where LA diameter was found to be well correlated with EAT area. Taken together, increased pericardial fat appears to be associated with significant structural and functional changes that can affect the likelihood of AF.

**Study limitations:** Our study has a number of limitations. First, autonomic nervous system activity was indirectly evaluated by an analysis of HRV parameters on Holter ECG recordings. HRV measures relative, rather than absolute, changes in sympathetic or parasympathetic discharges in the autonomic nerve system. Change in HRV could also have resulted from lifestyle modifications (eg, increased exercise and caloric restriction programs). The SDNN index is modulated predominantly by low-frequency cyclical changes that partly reflect thermoregulatory mechanisms, fluctuation in activity of the renin-angiotensin system, functioning of peripheral chemoreceptors,<sup>27)</sup> and respiratory patterns. Second, the exact mechanism by which initiators of AF are triggered via accumulation of EAT has not been elucidated. We also acknowledge that our cases of prevalent AF were heterogeneous in origin; given their small number, we were unable to conduct several important analyses, including the relationship of pericardial fat with specific forms of AF and the anatomic distribution of pericardial fat (anterior versus posterior). Third, our sample primarily comprised middle-aged to elderly Japanese individuals; therefore, our results may not be generalized to other ethnicities or age groups. Fourth, because of limited power, the confidence intervals for the association between AF and EAT area were not small. More detailed analyses of larger samples to evaluate the potential causal explanations of the observed correlations are required in further studies, which may prove to be challenging. Fifth, in multivariate analysis, cystatin C level was correlated with EAT area after adjustment for age, sex, and BMI. Cystatin C level, however, was not correlated significantly with AF episodes, possibly because of underpowering and small sample size.

**Conclusions:** Increased EAT area represents a marker for low HRV and the predictive incidence of paroxysmal AF in HCM patients.

## REFERENCES

- Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. *Nat Clin Pract Cardiovasc Med* 2005; 2: 536-43. (Review)
- Mazurek T, Zhang L, Zalewski A, *et al*. Human epicardial adipose tissue is a source of inflammatory mediators. *Circulation* 2003; 108: 2460-6.
- Miyasaka Y, Barnes ME, Gersh BJ, *et al*. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006; 114: 119-25.
- Wang TJ, Parise H, Levy D, *et al*. Obesity and the risk of new-onset atrial fibrillation. *JAMA* 2004; 292: 2471-7.
- Watanabe H, Tanabe N, Watanabe T, *et al*. Metabolic syndrome and risk of development of atrial fibrillation: the Niigata preventive medicine study. *Circulation* 2008; 117: 1255-60.
- Thanassoulis G, Massaro JM, O'Donnell CJ, *et al*. Pericardial fat is associated with prevalent atrial fibrillation: the Framingham Heart Study. *Circ Arrhythm Electrophysiol* 2010; 3: 345-50.
- Bettoni M, Zimmermann M. Autonomic tone variations before the onset of paroxysmal atrial fibrillation. *Circulation* 2002; 105: 2753-9.
- Schnabel RB, Sullivan LM, Levy D, *et al*. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet* 2009; 373: 739-45.
- Counihan PJ, Fei L, Bashir Y, Farrell TG, Haywood GA, McKenna WJ. Assessment of heart rate variability in hypertrophic cardiomyopathy. Association with clinical and prognostic features. *Circulation* 1993; 88: 1682-90.
- Shirani J, Roberts WC. Clinical, electrocardiographic and morphologic features of massive fatty deposits ("lipomatous hypertrophy") in the atrial septum. *J Am Coll Cardiol* 1993; 22: 226-38.
- Heyer CM, Kagel T, Lemburg SP, Bauer TT, Nicolas V. Lipomatous hypertrophy of the interatrial septum: a prospective study of incidence, imaging findings, and clinical symptoms. *Chest* 2003; 124: 2068-73.
- Shirani J, Berezowski K, Roberts WC. Quantitative measurement of normal and excessive (cor adiposum) subepicardial adipose tissue, its clinical significance, and its effect on electrocardiographic QRS voltage. *Am J Cardiol* 1995; 76: 414-8.
- Schotten U, Verheule S, Kirchhof P, Goette A. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. *Physiol Rev* 2011; 91: 265-325. (Review)
- Herweg B, Dalal P, Nagy B, Schweitzer P. Power spectral analysis of heart period variability of preceding sinus rhythm before initiation of paroxysmal atrial fibrillation. *Am J Cardiol* 1998; 82: 869-74.
- Workman AJ. Cardiac adrenergic control and atrial fibrillation. *Naunyn Schmiedeberg Arch Pharmacol* 2010; 381: 235-49. (Review)
- Nolan J, Batin PD, Andrews R, *et al*. Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-heart). *Circulation* 1998; 98: 1510-6.
- Fauchier L, Babuty D, Cosnay P, Autret ML, Fauchier JP. Heart rate variability in idiopathic dilated cardiomyopathy: characteristics and prognostic value. *J Am Coll Cardiol* 1997; 30: 1009-14.
- Rosito GA, Massaro JM, Hoffmann U, *et al*. Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community-based sample: the Framingham Heart Study. *Circulation* 2008; 117: 605-13.
- Pou KM, Massaro JM, Hoffmann U, *et al*. Patterns of abdominal fat distribution: the Framingham Heart Study. *Diabetes Care* 2009; 32: 481-5.
- Manzella D, Grella R, Marfella R, Giugliano D, Paolisso G. Elevated post-prandial free fatty acids are associated with cardiac sympathetic overactivity in Type II diabetic patients. *Diabetologia* 2002; 45: 1737-8.
- Paolisso G, Gualdiro P, Manzella D, *et al*. Association of fasting plasma free fatty acid concentration and frequency of ventricular premature complexes in nonischemic non-insulin-dependent diabetic patients. *Am J Cardiol* 1997; 80: 932-7.
- Yudkin JS, Eringa E, Stehouwer CD. Vasocrine" signaling from

- perivascular fat: a mechanism linking insulin resistance to vascular disease. *Lancet* 2005; 365: 1817-20.
23. Corradi D, Maestri R, Callegari S, *et al.* The ventricular epicardial fat is related to the myocardial mass in normal, ischemic and hypertrophic hearts. *Cardiovasc Pathol* 2004; 13: 313-6.
  24. Iacobellis G, Ribaldo MC, Zappaterreno A, Iannucci CV, Leonetti F. Relation between epicardial adipose tissue and left ventricular mass. *Am J Cardiol* 2004; 94: 1084-7.
  25. Fox CS, Gona P, Hoffmann U, *et al.* Pericardial fat, intrathoracic fat, and measures of left ventricular structure and function: the Framingham Heart Study. *Circulation* 2009; 119: 1586-91.
  26. Baber U, Howard VJ, Halperin JL, *et al.* Association of chronic kidney disease with atrial fibrillation among adults in the United States: REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Circ Arrhythm Electrophysiol* 2010; 4: 26-32.
  27. Mortara A, Sleight P, Pinna GD, *et al.* Abnormal awake respiratory patterns are common in chronic heart failure and may prevent evaluation of autonomic tone by measures of heart rate variability. *Circulation* 1997; 96: 246-52.