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Arrhythmia/Electrophysiology

Effect of the Epicardial Adipose Tissue Volume on the Prevalence of Paroxysmal and Persistent Atrial Fibrillation

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Background: Although increasing evidence suggests that epicardial adipose tissue volume (EATV) is associated with atrial fibrillation (AF), it is controversial whether there is a dose-response relationship of increasing EATV along the continuum of AF. We evaluated the effect of the EATV on the prevalence of paroxysmal AF (PAF) and persistent AF (PeAF) and the relationships with cardiac structure and functional remodeling.

Methods and Results: Subjects who underwent multidetector computed tomography (MDCT) coronary angiography because of symptoms suggestive of coronary artery disease were divided into sinus rhythm (SR) (n=112), PAF (n=133), and PeAF (n=71) groups. The EATV index (EATV/body surface area, mL/m^2) was strongly associated with the prevalence of PAF and PeAF on the model adjusted for known AF risk factors. The effect of the EATV index on the prevalence of PeAF, but not on that of PAF, was modified by the left atrial (LA) dimension, suggesting that extension of the LA dimension is related to EATV expansion in PeAF. The cutoff value of the EATV index for the prevalence was higher in PeAF than in PAF (64 vs. 55 mL/m^2, P<0.01).

Conclusions: The EATV index is associated with the prevalence of PAF and PeAF, and its cutoff values are predictive for PAF and PeAF development independently of other AF risk factors.

Key Words: Atrial fibrillation; Epicardial adipose tissue volume; Obesity

Obesity is an important risk factor for atrial fibrillation (AF),[1,2] and recent evidence suggests that obesity-related diseases can be mediated more intensely by ectopic fat deposits than by entire-body adiposity.[3–5] Epidemiological and clinical studies have demonstrated that epicardial fat, a local adipose tissue deposit surrounding the heart, which can be assessed using non-invasive imaging techniques, is consistently associated with the presence, severity, and recurrence of AF.[6–8] Wong et al compared the associations of the prevalence of AF with the epicardial adipose tissue (EAT) and measures of abdominal and overall adiposities in a meta-analysis of observational studies; the EAT volume (EATV) was associated with a 2.6-fold higher odds ratio (OR) of the prevalence of AF (2.61 per SD increase), which contradicts the finding that the associations of abdominal and overall adiposities with the prevalence of AF were lesser (OR per SD: 1.32 for waist circumference, 1.11 for waist/hip ratio, and 1.22 for body mass index [BMI]).[7]

As just noted, the associations of the prevalence of AF with the EATV seem convincing; however, several important issues remain unresolved. It is controversial whether there is a dose-response relationship of increasing EATV along the continuum of no AF, paroxysmal AF (PAF),

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Table 1. General Characteristics of Patients

Parameters	Overall	SR	Paroxysmal AF	Persistent AF	P for trend	All AF	P vs. SR
n	316	112	133	71		204	
Age (years)	63 (12)	62 (15)	64 (11)	63 (9)	0.290	64 (10)	0.134
Male sex, n (%)	207 (66)	59 (53)	93 (70)	55 (78)	0.001	148 (72)	0.001
Anthropometry							
Body height (cm)	161 (9.5)	160 (10)	162 (10)	164 (9)	0.042	162 (9)	0.038
Body weight (kg)	66.8 (14.9)	64.4 (17.4)	66.9 (13.6)	70.4 (12.3)	0.027	68.1 (13.2)	0.032
BMI (kg/m^2)	25.5 (4.4)	24.9 (5.1)	25.5 (3.9)	26.3 (3.7)	0.110	25.8 (3.8)	0.086
Blood measurements							
BNP (pg/mL)	52 [23.0, 107.6]	28.6 [13.0, 57.9]	45.0 [21.5, 103.5]	95.0 [55.5, 156.0]	<0.001	66.5 [31.0, 129.3]	0.002
Log BNP (pg/mL)	1.70 (0.48)	1.47 (0.44)	1.68 (0.51)	1.99 (0.33)	<0.001	1.79 (0.48)	<0.001
Comorbidities							
Smoking history, n (%)	39/112 (35)	39/112 (35)	53/132 (40)	31/71 (44)	0.462	84/203 (41)	0.279
Hypertension, n (%)	215/316 (68)	80/112 (71)	86/133 (65)	49/71 (69)	0.520	135/204 (66)	0.378
T2DM, n (%)	83/315 (26)	31/111 (28)	34/133 (26)	18/71 (25)	0.900	52/204 (25)	0.689
Dyslipidemia, n (%)	206/316 (65)	77/112 (69)	89/133 (67)	40/71 (56)	0.290	129/204 (63)	0.388
BMI ≥25 kg/m^2, n (%)	153/316 (48)	46/112 (41)	64/133 (48)	43/71 (61)	0.037	107/204 (52)	0.060
EAT measurements							
EATV (mL)	120.3 (47.5)	103.8 (46.1)	126.5 (47.9)	134.7 (41.8)	<0.001	129.3 (46.0)	<0.001
EATVI (mL/m^2)	69.4 (26.1)	62.1 (26.0)	72.6 (26.6)	74.9 (22.9)	0.001	73.4 (25.3)	0.000
Echocardiography							
LAd (mm)	38.7 (6.2)	37.5 (6.1)	38.2 (6.2)	41.5 (5.6)	<0.001	39.3 (6.2)	0.012
LAV (mL)	45 [20, 68]	16.5 [12.4, 20.2]	53 [42, 69]	69 [54, 88]	<0.001	60 [45, 76]	<0.001
LAVI (mL/m^2)	31 [24, 41]	27 [22, 32]	32 [24, 41]	40 [30, 48]	<0.001	34 [20, 44]	<0.001
LVDd (cm)	46.9 (5.5)	46.6 (5.1)	47.11 (5.75)	46.80 (5.42)	0.730	47.0 (5.6)	0.491
LVDs (cm)	29.7 (5.6)	29.1 (4.9)	29.6 (5.8)	31 (5.9)	0.078	29.1 (4.9)	0.164
IVS thickness (cm)	8.82 (1.83)	8.65 (1.91)	8.88 (1.75)	8.97 (1.84)	0.450	8.91 (1.78)	0.222
Posterior wall thickness (cm)	8.58 (1.39)	8.57 (1.32)	8.52 (1.50)	8.70 (1.30)	0.673	8.59 (1.43)	0.941
LVM (g)	140 [114, 177]	134 [110, 161]	139 [112, 180]	148 [119, 185]	0.127	144 [116, 181]	0.049
LVMI (g/m^2)	82 [67, 99]	82 [68, 96]	82 [66, 99]	87 [71, 103]	0.658	83 [67, 100]	0.369
LVEF (%)	65 (8)	65 (5)	67 (9)	62 (10)	<0.001	65 (9)	0.370
E (cm/s)	74.0 (20.7)	66.7 (17.7)	71.5 (18.1)	91.9 (20.4)	<0.001	78 (21)	<0.001
Septal e' (cm/s)	7.15 (2.30)	6.88 (2.37)	6.99 (2.11)	7.89 (2.40)	0.010	7.30 (2.25)	0.127
Lateral e' (cm/s)	9.80 (3.15)	9.07 (2.98)	9.93 (2.98)	11.44 (3.37)	<0.001	10.40 (3.17)	0.001
Septal E/e'	11.34 (4.17)	10.68 (4.76)	11.30 (3.42)	12.52 (4.27)	0.016	11.7 (3.8)	0.036
Lateral E/e'	8.24 (3.09)	7.92 (2.61)	8.42 (2.95)	8.68 (4.34)	0.311	8.50 (3.43)	0.145

Data are expressed as mean (SD), median [IQR] or n (%). P values calculated by one-way ANOVA. AF, atrial fibrillation; BMI, body mass index; BNP, B-type natriuretic peptide; BSA, body surface area; EATV, epicardial adipose tissue volume; EATVI, EATV index=EATV/BSA; EF, ejection fraction; IVS, interventricular septum; LAd, left atrial dimension; LAV, LA volume; LAVI, LAV index; LVDd and LVDs, LV diastolic and systolic dimensions; LVM, LV mass; LVMI, LVM index; LV, left ventricular; SR, sinus rhythm; T2DM, type 2 diabetes mellitus.

persistent AF (PeAF), and long-lasting persistent (permanent) AF.[9–11] Previous studies showed that the EATV was associated with measures of the left ventricular (LV) structure and diastolic dysfunction;[12] however, the causality of the EATV-associated LV structure and functional remodeling on AF prevalence has not been clarified.[4]

In this study, we evaluated: (1) the effect of the EATV on the prevalence of PAF and PeAF and the relationships with LV structure and functional remodeling; and (2) the cutoff value for estimating the prevalence of PAF and PeAF using the receiver-operating characteristic (ROC) curve method.

Methods

Study Populations

We recruited subjects who underwent multidetector computed tomography (MDCT) coronary angiography between October 2013 and April 2016 at the Tokushima University Hospital, Tokushima, Japan or at the Tomishiro Central Hospital, Okinawa, Japan. The subjects underwent MDCT if they had symptoms suggestive of angina pectoris or asymptomatic coronary artery disease (CAD) in a moderate-to-high CAD risk category.[13] All participants provided written informed consent after they were advised regarding the radiation exposure-related risk and possible complications of iodine-containing contrast.[13]

The subjects were then divided into the following groups

Table 2. Simple Regression Analysis to Predict Paroxysmal or Persistent AF

Parameters	Paroxysmal AF (n=133)			Persistent AF (n=71)			All AF (n=204)		
	Estimate	95% CI	P value	Estimate	95% CI	P value	Estimate	95% CI	P value
Age (years)	0.020	0.000~0.040	0.140	0.010	−0.010~0.030	0.440	0.010	−0.010~0.030	0.130
Male sex (yes)	0.740	0.220~1.260	0.006	1.130	0.460~1.800	<0.001	0.860	0.380~1.340	<0.001
Anthropometry									
Body height (cm)	0.020	−0.010~0.050	0.190	0.040	0.010~0.070	0.014	0.030	0.010~0.050	0.039
BMI (kg/m^2)	0.030	−0.030~0.090	0.290	0.060	−0.010~0.130	0.056	0.050	−0.010~0.110	0.089
Blood measurements									
BNP (pg/mL)	0.010	0.010~0.010	0.019	0.020	0.010~0.030	<0.001	0.010	0.000~0.020	<0.001
Log BNP (pg/mL)	0.410	0.140~0.680	0.003	1.480	0.970~1.990	<0.001	0.650	0.380~0.920	<0.001
Comorbidities									
Smoking history	0.230	−0.290~0.750	0.390	0.370	−0.240~0.980	0.230	0.280	−0.200~0.760	0.250
Hypertension (yes)	−0.310	−0.850~0.230	0.260	−0.120	−0.770~0.530	0.730	−0.250	−0.750~0.250	0.340
T2DM (yes)	−0.120	−0.690~0.450	0.680	−0.130	−0.810~0.550	0.700	−0.120	−0.640~0.400	0.640
Dyslipidemia (yes)	−0.080	−0.620~0.460	0.760	−0.530	−1.150~0.090	0.090	−0.250	−0.740~0.240	0.330
BMI ≥25 kg/m^2, n (%)	0.290	−0.220~0.800	0.270	0.790	0.180~1.400	0.011	0.460	−0.010~0.930	0.054
EAT measurements									
EATV (mL)	0.010	0.000~0.020	<0.001	0.020	0.010~0.030	<0.001	0.010	0.000~0.020	<0.001
EATVI (mL/m^2)	0.020	0.010~0.030	0.003	0.020	0.010~0.030	0.001	0.020	0.010~0.030	<0.001
Echocardiography									
LAd (mm)	0.020	−0.020~0.060	0.380	0.110	0.050~0.170	<0.001	0.050	0.010~0.090	0.013
LAVI (mL/m^2)	−0.010	−0.070~0.050	0.640	0.060	−0.020~0.140	0.140	0.010	−0.050~0.070	0.750
LVDd (cm)	0.020	−0.030~0.070	0.430	0.010	−0.050~0.070	0.760	0.020	−0.020~0.060	0.490
IVS thickness (cm)	0.070	−0.070~0.210	0.330	0.090	−0.070~0.250	0.260	0.080	−0.050~0.210	0.220
LVMI (mL/m^2)	0.000	−0.010~0.010	0.490	0.000	−0.010~0.010	0.440	0.000	−0.010~0.010	0.400
LVEF (%)	0.050	0.010~0.090	0.008	−0.040	−0.080~0.000	0.047	0.010	−0.020~0.040	0.370
Septal E/e'	0.040	−0.020~0.100	0.240	0.090	0.020~0.160	0.013	0.060	0.000~0.120	0.038
Lateral E/e'	0.070	−0.030~0.170	0.200	0.070	−0.040~0.180	0.200	0.060	−0.030~0.150	0.150

Data are expressed as hazard ratio (95% confidence interval). Abbreviations as in Table 1.

according to their medical history: sinus rhythm (SR), PAF, or PeAF. According to the ACCF/AHA/HRS guideline,[14] an episode of AF was defined as an event lasting >30 s, PAF referred to patients with spontaneous termination of the arrhythmia within 7 days of its onset, and PeAF was patients with arrhythmia sustained beyond 7 days. Subjects with permanent AF were excluded. To eliminate strong confounding effects of coronary atherosclerosis on the EAT, we excluded patients with CAD. Among patients who had undergone coronary CT angiography and/or invasive coronary angiography, those who had lost >50% of the luminal diameter in at least 1 major epicardial coronary artery or branch were excluded. The other exclusion criteria included: iodine-based contrast allergy, renal failure (creatinine level >1.5 mg/mL), history of cardiomyopathy, valvular or congenital heart disease, uncontrolled hypertension, malignancy, connective tissue disease, and any acute or chronic inflammatory disease. Hypertension was defined as a systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or current use of antihypertensive medication. Diabetes mellitus was defined as a glycated hemoglobin (HbA_{1c}) concentration ≥6.5%, a fasting plasma glucose level >126 mg/L, or current use of antidiabetic medication. Dyslipidemia was defined as either a serum level of low-density lipoprotein cholesterol ≥3.62 mmol/L (140 mg/L), serum level of triglyceride (TG) ≥150 mg/dL (1.69 mmol/L), and serum level of high-density lipoprotein cholesterol <40 mg/dL (1.04 mmol/L) and/or the current use of antilipidemic medication.

All data were collected retrospectively. The protocol of this study was approved by the institutional review boards of the University of Tokushima Hospital and the Tomishiro Central Hospital.

Biochemical Measurements

The blood samples were drawn, stored in ice-chilled tubes with and without ethylenediaminetetraacetic acid, and immediately centrifuged. All samples were frozen at −80°C until assayed by technicians blinded to all information regarding the participants. The HbA_{1c} concentration was measured using high-performance liquid chromatography and B-type natriuretic peptide (BNP) by a chemiluminescent enzyme immunoassay.

Table 3. Multivariate Regression Analysis to Predict Paroxysmal, Persistent or All AF

PAF

	Model 1		Model 2		Model 3		Model 4		Model 5	
Corrected R^2	**0.045**		**0.073**		**0.096**		**0.065**		**0.095**	
P value	**0.003**		**0.006**		**0.001**		**0.002**		**0.000**	
Parameter	**Estimate**	**P value**	**Estimate**	**P value**	**Estimate**	**P value**	**Estimate**	**P value**	**Estimate**	**P value**
Age (years)	0.006	0.026	0.006	0.016	0.003	0.252	0.003	0.256	0.002	0.553
Male sex (yes)	0.205	0.002	0.205	0.002	0.199	0.002	0.199	0.002	0.198	0.002
BMI (kg/m^2)	0.012	0.086	0.015	0.045	0.007	0.344	0.007	0.379	0.008	0.280
Smoking history (yes)			0.065	0.321	0.061	0.344	0.061	0.345	0.046	0.477
Hypertension (yes)			−0.114	0.096	−0.126	0.064	−0.127	0.065	−0.126	0.060
T2DM (yes)			−0.067	0.360	−0.077	0.292	−0.077	0.293	−0.079	0.274
EATVI (mL/m^2)					0.003	0.015	0.003	0.017	0.003	0.010
LAd (mm)							0.000	0.934		
LVEF (%)									−0.012	0.005

PeAF

	Model 1		Model 2		Model 3		Model 4		Model 5	
Corrected R^2	**0.092**		**0.102**		**0.096**		**0.167**		**0.130**	
P value	**0.000**		**0.000**		**0.001**		**<0.0001**		**<0.0001**	
Parameters	**Estimate**	**P value**	**Estimate**	**P value**	**Estimate**	**P value**	**Estimate**	**P value**	**Estimate**	**P value**
Age (years)	0.010	0.0655	0.012	0.037	0.003	0.252	0.003	0.631	0.005	0.487
Male sex (yes)	0.571	0.000	0.613	<0.0001	0.199	0.002	0.551	0.000	0.547	0.000
BMI (kg/m^2)	0.042	0.007	0.045	0.004	0.007	0.344	0.013	0.445	0.029	0.088
Smoking history (yes)			0.276	0.056	0.061	0.344	0.247	0.077	0.234	0.101
Hypertension (yes)			−0.159	0.309	−0.126	0.064	−0.074	0.626	−0.109	0.481
T2DM (yes)			−0.071	0.658	−0.077	0.292	−0.126	0.416	−0.117	0.464
EATVI (mL/m^2)					0.003	0.015	0.005	0.130	0.007	0.031
LAd (mm)							0.039	0.001		
LVEF (%)									−0.016	0.076

All AF

	Model 1		Model 2		Model 3		Model 4		Model 5	
Corrected R^2	**0.062**		**0.066**		**0.085**		**0.087**		**0.086**	
P value	**<0.0001**		**0.000**		**<0.0001**		**<0.0001**		**<0.0001**	
Parameters	**Estimate**	**P value**	**Estimate**	**P value**	**Estimate**	**P value**	**Estimate**	**P value**	**Estimate**	**P value**
Age (years)	0.006	0.009	0.007	0.004	0.004	0.150	0.003	0.185	0.003	0.192
Male sex (yes)	0.228	<0.0001	0.223	<0.0001	0.215	0.000	0.211	0.000	0.219	<0.0001
BMI (kg/m^2)	0.014	0.019	0.017	0.008	0.010	0.142	0.007	0.306	0.011	0.120
Smoking history (yes)			0.064	0.236	0.058	0.280	0.062	0.248	0.056	0.295
Hypertension (yes)			−0.088	0.127	−0.094	0.100	−0.097	0.089	−0.097	0.088
T2DM (yes)			−0.066	0.283	−0.070	0.246	−0.072	0.238	−0.069	0.252
EATVI (mL/m^2)					0.003	0.007	0.003	0.014	0.003	0.007
LAd (mm)							0.006	0.214		
LVEF (%)									−0.004	0.217

Data are expressed as hazard ratio (95% confidence interval). Abbreviations as in Table 1.

MDCT Scan Protocol and Analysis of the EATV

MDCT scanning was performed as previously described.[15,16] Briefly, the coronary artery tree was segmented in accordance with the modified American Heart Association classification;[17] the coronary vessel and diameter were assessed using 2D multiplanar reconstruction and 2D thin slab maximum intensity projection images. The patients were suspected to have CAD when they had a plaque resulting in >50% luminal narrowing in the major coronary arteries. For the measurement of the EATV, the volume measurement software of Vincent was used. In a semi-automated process, the pericardium counter was first manually traced in each transaxial slice, followed by an automated step of processing all continuous voxels with a density range of −190 to −30 Hounsfield units within the pericardial sac for the calculation of the EATV. The upper border of the EATV measurements represented the lower surface of the left pulmonary artery origin, and the lower border represented the LV apex. The EAT area of each slice was then summed and multiplied by the slice thickness and number

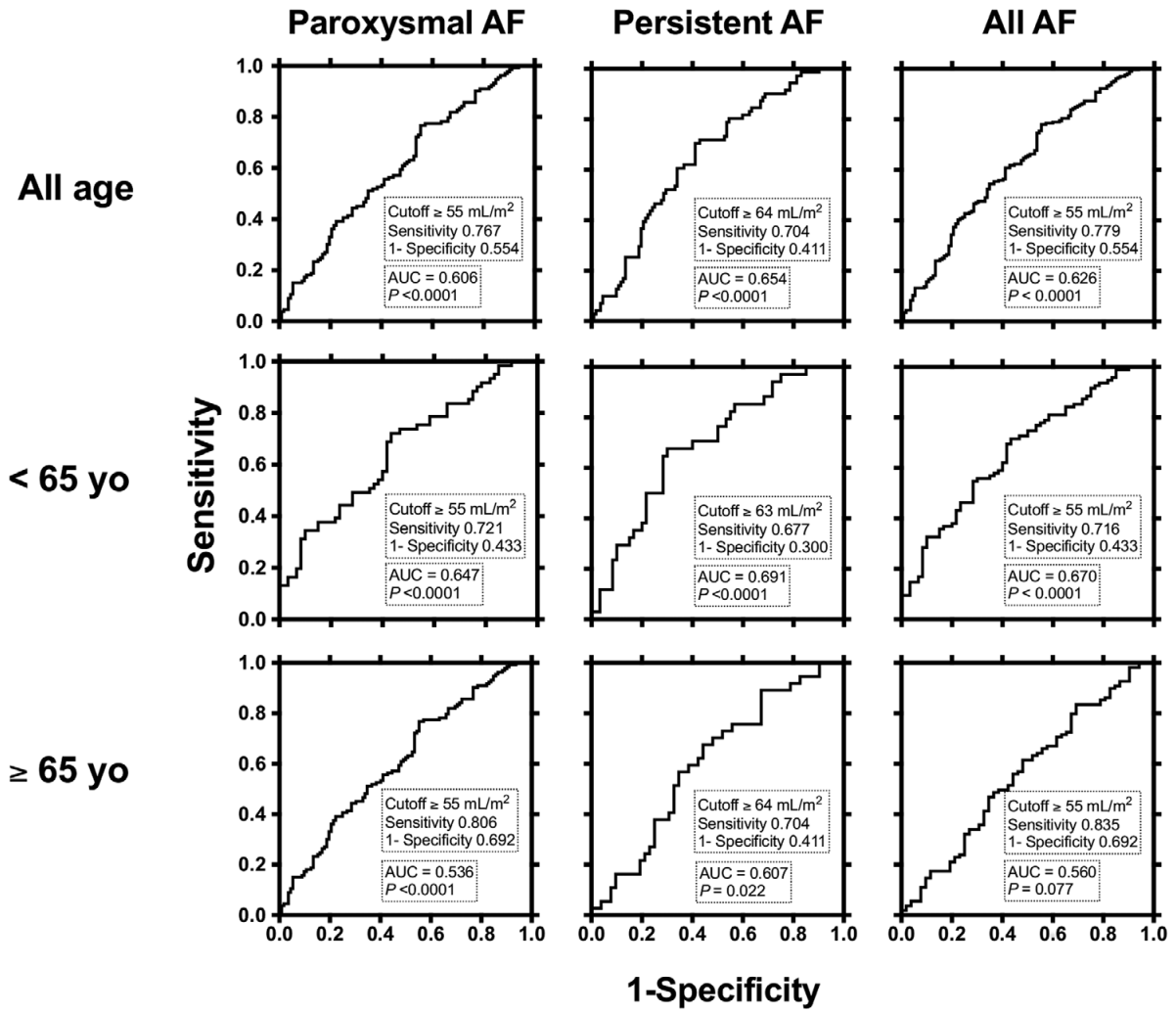

Figure 1. Receiver-operating characteristic (ROC) curves for predicting the prevalence of paroxysmal atrial fibrillation (AF), persistent AF, and both types of AF (All AF) in all ages, <65 years old (yo) and ≥65 yo. The cutoff values on the basis of the epicardial adipose tissue volume index were calculated to obtain the maximal area under the curve (AUC). The cutoff value and its sensitivity and 1-specificity for detecting AF are shown. The subjects included the following groups: sinus rhythm (n=112), paroxysmal AF (n=133), and persistent AF (n=71).

of slices to determine the total EATV. The EATV index (EATVI: mL/m^2) was defined as EATV (mL)/body surface area (BSA, m^2). In selected patients who had undergone cardiac CT at least twice at more than 1 year's interval, we evaluated the longitudinal changes in the EATVI.

Echocardiographic Measurements

Echocardiography was performed in a standard manner using commercially available ultrasound diagnostic machines. The recordings and measurements were performed in accordance with the guidelines issued by the American Society of Echocardiography.[18] Transmitral flow (TMF) velocity was recorded from the apical long-axis or 4-chamber view. The ratio of the peak early diastolic (E) and the peak atrial systolic (A) TMF velocities was calculated, if applicable. The deceleration time of the early TMF velocity was also measured. The mitral annular motion velocity pattern was recorded from the apical 4-chamber view with the sample volume located at the lateral or septal side of the mitral annulus using pulsed tissue Doppler echocardiography. The mean peak early diastolic mitral annular velocity (e') in the septal and lateral sides was measured, and the ratio of E to e' (E/e') was then calculated as a marker of LV filling pressure. In addition to these diastolic parameters, routine echocardiographic parameters were also measured and included the left atrial dimension (LAd), LV end-diastolic dimension (LVDd) and LV end-systolic dimension (LVDs) measured from the M-mode or 2D echocardiogram of the LV. The LV ejection fraction (LVEF) was measured and calculated from the apical 2- and 4-chamber views using a modified Simpson's method. LA volume, LV volume index (LAV/BSA), LV mass (LVM), and LVM index (LVMI:LVM/BSA) were calculated as reported previously.[18,19] Relative wall thickness was

calculated as twice the posterior wall thickness divided by LVDd.[18] All Doppler recordings were performed during an end-expiratory breath hold. The mean values of 3 consecutive cardiac cycles were used in the analysis. Measurement and interpretation of the echocardiography were performed locally at each institution.

Statistical Analysis

Continuous variables with a normal distribution are expressed as mean±standard deviation (SD) and those with an unequal variance as median and interquartile range (25–75th percentiles); categorical variables are expressed as numbers and frequencies. The group means for the continuous variables with normal distributions and the group median for non-normal distributions were compared using one-way analysis of variance and Kruskal-Wallis test, respectively, among the 3 groups. The two-tailed unpaired Student's t-test or Mann-Whitney U test was used for continuous variables with a normal distribution or skewed distribution for the comparison of 2 groups. Categorical variables were compared using Fischer's exact test. Univariate and multivariate regression models were used to identify the factors that had associations with the prevalence of PAF and PeAF. Associated factors with a significance level of $P<0.05$ in the univariate analysis were entered into the multivariate model. The optimal cutoff values of the EATVI for the prediction of PAF and PeAF development were identified using the ROC curve. Prediction score models for detecting the prevalence of PAF, PeAF, and both were produced by employing rational covariates in the multiple logistic regression analysis.[20] All statistical analyses were performed using JMP 13.2.0 (SAS Institute Inc. Cary, NC, USA) or R application.

Results

General Characteristics of the Patients With SR, PAF, and PeAF (Table 1)

Among the subjects in this study, 112 had SR, 133 had PAF, and 71 had PeAF. The mean age of all subjects was 63±12 years, and 207 (66%) were men. The patient age was comparable among the SR, PAF, and PeAF groups, and the male sex was prevalent in the PAF and PeAF groups. The height and BMI were higher, and BMI ≥25 kg/m^2 was prevalent in the PAF and PeAF groups. The BNP and log BNP levels were higher in the PAF and PeAF groups. The prevalence of smoking history, hypertension, type 2 diabetes mellitus (T2DM), and dyslipidemia was all comparable among the SR, PAF, and PeAF groups. The EATV and EATV index were higher in the PAF and PeAF groups. Regarding the echocardiographic parameters, the LAd and LAVI were larger, and the LVEF was lower in the PeAF group. The LVM was larger in the PAF and PeAF groups; however, the LVMI was comparable among the 3 groups. In the PAF and PeAF groups, the septal e' was slightly larger; however, the E-wave was much taller, resulting in a higher septal E/e'.

Simple and Multivariate Regression Analyses for Predicting the Prevalence of PAF, PeAF, and Both (Tables 2,3)

The univariate analysis revealed that the risk factors associated with PAF and PeAF were male sex, BNP and log BNP levels, EATV, and EATVI. The risk factors associated only with PeAF were body height, BMI ≥25 kg/m^2, LAd, and septal E/e'. The LVEF was associated positively with PAF and negatively with PeAF.

The multivariate analysis revealed that age, male sex, and BMI were associated with PAF and PeAF (Model 2). Even after adjusting for confounding factors, including male sex, BMI, smoking history, hypertension, and T2DM, the EATVI was strongly associated with PAF and PeAF (Model 3). When the LAd was included in the multivariate model, the EATVI was associated with PAF, but not with PeAF (model 4). When the LVEF was included, the EATVI was still associated with both PAF and PeAF (model 5).

In the ROC curve analysis for predicting the prevalence of PAF and PeAF based on the EATVI, the cutoff values for PAF and PeAF were 55 and 64 mL/m^2, respectively, in all age subjects (**Figure 1**). When stratified by age <65 and ≥65 years (**Figure 1**, **Tables S1**–**S3**), the EATVI was significantly associated with PAF and PeAF in age <65 years, but not in ≥65 years (**Table S3**) and the area under the curve (AUC) for EATVI was larger in <65-year-old subjects for PAF, PeAF and both types of AF (**Figure 1**).

Table 4. Prediction Score Model for Paroxysmal, Persistent or All AF

	Score
Age (years)	
<20	3
21–30	5
31–40	6
41–50	8
51–60	9
61–70	11
71–80	12
81–90	14
91–	15
Sex	
Female	0
Male	10
BMI (kg/m^2)	
<15	5
15≤BMI<20	6
20≤BMI<24	8
24≤BMI<28	9
>28	10
LAd (mm)	
<35	10
35≤LAd<40	11
40≤LAd<45	13
45≤LAd<50	14
>50	16
EATVI (mL/m^2)	
<50	8
50≤EATVI<100	15
100≤EATVI<150	23
150≤EATVI<200	30
200≤EATVI<250	38
>250	45
Total	96 points

Abbreviations as in Table 1.

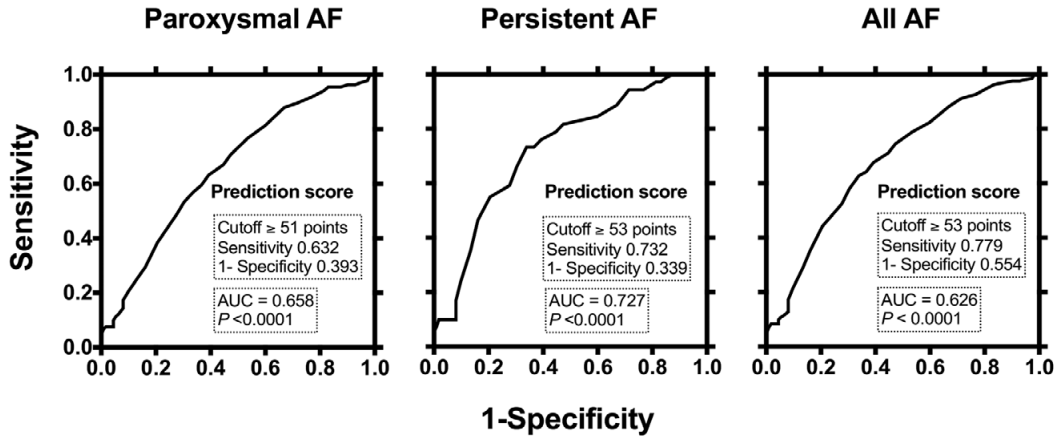

Figure 2. Receiver-operating characteristic (ROC) curves of predicting score models for the prevalence of paroxysmal atrial fibrillation (AF), persistent AF, and both types of AF (All AF). The area under the curve (AUC) of AF and the cutoff values (sensitivity, 1-specificity) and P values are shown. The subjects included the following groups: sinus rhythm (n=112), paroxysmal AF (n=133), and persistent AF (n=71).

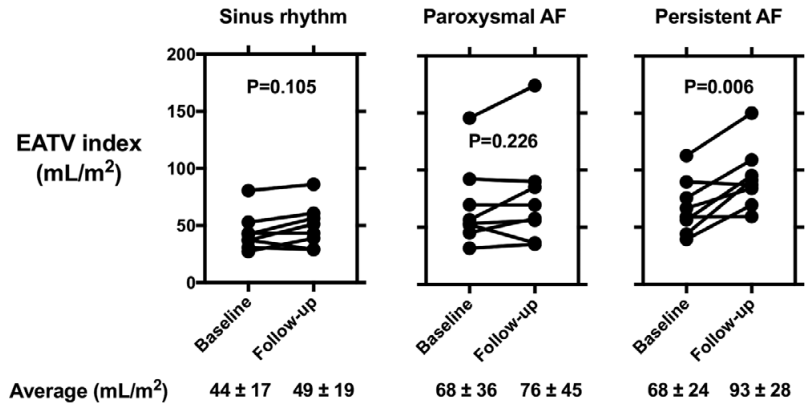

Figure 3. Longitudinal changes in epicardial adipose tissue volume (EATV) index in representative subjects with sinus rhythm (n=8), paroxysmal atrial fibrillation (AF) (n=8) and persistent AF (n=8). Average (±SD) observation periods (days) were 1,051±934, 1,065±461 and 1,212±1,285, respectively (P=0.933, one-way ANOVA). P values calculated by two-tailed paired t-test.

Prediction Score Model for Detecting the Prevalence of PAF, PeAF, and Both

We created a prediction score model for detecting the prevalence of PAF, PeAF, and both by using rational covariates in the multiple logistic regression analysis (Model 4, **Table 3**). For clinical utility of the prediction score, β-coefficients were multiplied 10 times and rounded to create integral numbers for categorical covariates. Finally, we adopted categorical covariates for age, sex, BMI, LAd and EATVI (**Table 4**). As shown in **Figure 2**, ROC curve analysis showed that the cutoff for total points of categorical covariates (prediction score) in PAF (51 points), PeAF (53 points), and both (53 points) correlated relatively well with the prevalence of AF.

Longitudinal Changes in EATVI in Subjects With SR, PAF and PeAF

Longitudinal changes in the EATVI in representative subjects with SR (n=8), PAF (n=8) and PeAF (n=8) are shown in **Figure 3**. Average (±SD) observation period (days) was 1,051±934, 1,065±461 and 1,212±1,285, respectively (P=0.933, one-way ANOVA). P values were calculated by two-tailed paired t-test. We found that the EATVI was almost comparable during a period of ~1,000 days in subjects with SR and PAF, but was significantly increased in subjects with PeAF during almost the same period. Baseline EATVI was comparable between PAF and PeAF (68 vs. 68 mL/m^2), but the longitudinal change was larger in the PeAF group.

Discussion

In the current Japanese participants without CAD, we observed 3 major findings. First, the EATVI was strongly associated with the prevalence of PAF and PeAF in the model adjusted for known AF risk factors, such as age, male sex, BMI, smoking history, hypertension, and T2DM (**Table 3**, Model 3). Second, the effect of the EATVI on the prevalence of PeAF, but not on that of PAF, was modified by the LAd, suggesting that extension of the LAd is related

to the EATV expansion in PeAF. Third, the cutoff value of the EATVI for the prevalence of PeAF and PAF was higher in the former than in the latter (64 vs. 55 mL/m^2, P<0.01). As such, it suggested that the EATVI is associated with the prevalence of PAF and PeAF, and its cutoff values predict PAF and PeAF development independently of other AF risk factors.

EATV and the Prevalence of PAF and PeAF

The EAT is structurally located next to the myocardium and the coronary arteries and can play a beneficial role in the non-obese state by serving as a local TG storage in metabolic stress and by releasing protective adipocytokines, supporting normal cardiovascular homeostasis.[3,21,22] However, the EAT can accumulate in the setting of metabolic derangement, such as obesity and T2DM, promoting vascular and myocardial dysfunction. The accumulation of the EAT is associated strongly with visceral fat adiposity, and it is thought that hypertrophied and dysfunctional EAT promotes cardiovascular injuries, such as CAD.[3,23,24] Recent studies support that EAT accumulation is also more closely associated with the presence and severity of AF than measures of abdominal and overall adiposity.[6–8]

Several studies have reported that the EATV is higher in patients with PeAF than in those with PAF.[9–11] Won et al demonstrated that the EATV increased stepwise according to the presence and severity of AF (no AF, PAF, PeAF, and permanent AF), suggesting a dose-response relationship of increasing epicardial fat along the continuum of AF. Similarly, the current study showed that both the EATV and EATVI increased stepwise by SR<PAF<PeAF and that the EATVI was associated with the prevalence of PAF and PeAF (Model 3) after adjusting for confounding AF factors, including male sex, BMI, smoking history, hypertension, and T2DM. By contrast, when the LAd was included in the multivariate model, the EATVI was not associated with PeAF, but with PAF.

Increased epicardial fat is associated with various cardiac structural changes that could affect the propensity for AF development.[6,8] Increased EATV is reported to be associated with increased LAd independent of other AF risk factors.[25] Infiltration of the EAT to the atrium may lead to electromechanical changes in the atrial tissue caused by local inflammation and resulting fibrosis, promoting the development of AF.[26] This suggests that the EAT may alter atrial conduction, promoting atrial electrical remodeling and thus favoring the development of AF.[6,27]

Al Chekakie et al reported that LA dilatation (LAd >42 mm), as well as the EATV, was an independent risk factor of PeAF, but not of PAF.[9] Inclusion of LA dilatation in the multivariate model might abolish the effect of the EATVI, because the LAd is associated more closely with PeAF than with PAF.[12,28] Septal E/e' was associated with PeAF, but not with PAF. LV diastolic dysfunction could be induced by expansion of the EATV;[28–30] this could coexist with LA burden and LA dilatation[12] more severely in PeAF.

Cutoff Value of the EATVI for Predicting the Prevalence of PAF and PeAF

Since we previously reported that compared with the EATV, the EATVI was a suitable marker for predicting a candidate for coronary bypass surgery,[15,31] and significant coronary stenosis in asymptomatic patients,[16] we have adopted the EATVI as a measure of the EATV. By using the ROC curve for predicting the prevalence of PAF and PeAF based on the EATVI, the cutoff values for PAF and PeAF were 55 and 64 mL/m^2, respectively (**Figure 1**). Chao et al reported that at a cutoff value of 6 mm for PAF and 6.9 mm for non-PAF, the EAT thickness measured on transthoracic echocardiography could help identify patients at risk of recurrence after AF ablations.[32] To our knowledge, no report has evaluated the cutoff value of the EATV for predicting the development of AF.[33] Shmilovich et al evaluated the threshold for the upper normal limit of the EATVI measured on non-contrast cardiac CT; the 95th-percentile definition of the upper normal limit of the EATVI was 68 mL/m^2 (equivalent to EATV of 125 mL), and this value can be an independent predictor (OR, 2.8; 95% confidence interval, 1.3–6.4, P=0.012) of major adverse cardiovascular events (MACEs) consisting of cardiovascular death, myocardial infarction, stroke, and percutaneous or surgical coronary artery revascularization.[34] Interestingly, the cutoff values of the EATVI in the study by Shmilovich et al[34] for MACEs and in the current study for PAF and PeAF are comparable. Future prospective studies are warranted to evaluate the prognostic value of these cutoff values for the onset of new AF under common conditions.

We produced a prediction score model for detecting the prevalence of PAF, PeAF, and both by using rational covariates. AUCs for detecting PAF, PeAF, and both were larger in this model (**Figure 2**) than with only the EATVI (**Figure 1**). Because the cutoff for the prediction score correlated relatively well with the prevalence of AF, it may be reasonable to test the utility of this prediction score in other study populations. Of importance, the baseline EATVI was comparable between PAF and PeAF, but the longitudinal change was larger in PeAF, suggesting that an increase in the EATVI is at least partly a consequence of PeAF existence. Therefore, the cause-and-effect relationship between any type of AF and EATV should be considered in future studies.

Study Limitations

First, the cross-sectional design of this study limits interpretations of causality. Second, the predominantly Japanese patient sample also limits the generalizability of our findings to other ethnicities. Third, we did not measure the waist circumference or waist-to-hip ratio; these measures may have added incremental information on the effects of local vs. systemic adiposity. Fourth, AF frequently develops in elderly populations, who are typically lean. Our study subjects were relatively young and obese and this may bias the study results. To minimize a biased interpretation, we stratified subjects to age <65 and ≥65 years and reanalyzed the relationship between the EATVI and AF; it was somewhat weaker in our elderly group, suggesting that the effect of the EATVI may be larger in relatively young populations. Finally, because of the relatively small subgroup sizes, the number of variables adjusted for in the binary logistic regression models was limited to avoid overfitting the models.

Conclusions

In the present Japanese participants without CAD, the EATVI was strongly associated with the prevalence of PAF and PeAF in the model adjusted for known AF risk factors. The effect of the EATVI on the prevalence of PAF,

but not on that of PeAF, was modified by the LAd, indicating that extension of the LAd is related to EATV expansion in PAF. It is suggested that the EATVI is associated with the prevalence of PAF and PeAF, and its cutoff values predict PAF and PeAF development independently of other AF risk factors.

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Declarations

Ethics Approval and Consent to Participate: The protocol of this study was approved by the institutional review boards of the Tomishiro Central Hospital and University of Tokushima Hospital.

Consent for Publication: Not applicable

Competing Interests: The authors declare that they have no competing interests.

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Authors' Contributions: K.O., M.M. and M. Shimabukuro designed the research, analyzed the data, and wrote the manuscript; M.M. and G.M. measured the epicardial adipose tissue volume; S. Yamaguchi and M. Shimabukuro provided statistical analysis; K.O., M.M., O.A., D.F. and S. Yagi provided patient management and collected the samples; Y.H., S.N., K.K. and H.Y. postulated echocardiographic measurements; T.I., S.T. and M.H. contributed to MDCT measurements; T.S., T.W., H.M. and M. Sata supervised the study; all authors discussed the data and reviewed the manuscript.

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Supplementary Files

Supplementary File 1

Table S1. General characteristics of patients either with age <65 or age ≥65 years

Table S2. Simple regression analysis to predict paroxysmal or persistent AF

Table S3. Multivariate regression analysis to predict paroxysmal, persistent or all AF

Please find supplementary file(s);
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