

Influence of Sex on the Association Between Epicardial Adipose Tissue and Left Atrial Transport Function in Patients With Atrial Fibrillation: A Multislice Computed Tomography Study

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Background—Epicardial adipose tissue (EAT) is known to play an important role in atrial fibrillation substrate remodeling; however, the influence of sex on the association between EAT and left atrial (LA) transport function has not been elucidated.

Methods and Results—Of the 514 patients who underwent an index atrial fibrillation ablation procedure, 123 postmenopausal women with no history of hormone replacement therapy and 123 men who were matched for age, body mass index, type of atrial fibrillation, and CHADS₂ score were enrolled. Before the procedure, LA volume, LA emptying fraction, and EAT volume were assessed using multislice computed tomography. Blood samples were obtained from a coronary sinus for analysis of serum adiponectin level before the ablation procedure. There were no differences in baseline demographics and laboratory findings between sexes. Compared with men, women had significantly less total EAT ($P<0.001$) and higher serum adiponectin levels ($P=0.022$) but higher proportions of periatrial EAT to total EAT volume (P/T EAT ratio, $P<0.001$), lower LA emptying fraction ($P=0.042$), and lower LA voltage ($P=0.034$). The ratio of periatrial to total EAT volume correlated significantly with LA emptying fraction and LA voltage in both sexes, whereas total EAT volume and serum adiponectin level did not. On multivariate analysis, increased LA volume and higher periatrial:total EAT volume ratio were independent predictors of decreased LA emptying fraction in both sexes.

Conclusions—Compared with matched men, postmenopausal women with atrial fibrillation had higher periatrial adiposity, which was independently correlated with decreased LA voltage and LA transport function. (*J Am Heart Assoc.* 2017;6:e006077. DOI: 10.1161/JAHA.117.006077.)

Key Words: atrial fibrillation • computed tomography • epicardial fat • left atrial function • sex differences

Women are known to be at higher risk than men for thromboembolism related to atrial fibrillation (AF).^{1–3} However, the mechanism behind the observed sex difference in ischemic stroke is still unclear. Prior studies show that underlying atrial fibrosis and subsequent atrial dysfunction may contribute to cerebrovascular events in AF patients.^{4–6} In addition, recent and increasing evidence suggests that epicardial adipose tissue (EAT) is highly associated with AF.^{7,8} Furthermore, EAT has been shown to induce local

inflammation and subsequent atrial structural remodeling.⁹ Consequently, it is possible to postulate that substrate remodeling of the left atrium associated with periatrial adiposity may be different between men and women with AF, even though they are exposed to the same clinical conditions. To test our hypothesis, we sought (1) to evaluate sex disparities in total amount of EAT and/or its regional distribution measured by multislice computed tomography (MSCT) and (2) to determine whether EAT and/or its regional

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Clinical Perspective

What Is New?

- Until now, there has been a lack of literature on sex disparity in the association between epicardial adipose tissue and left atrial function in patients with atrial fibrillation.
- Moreover, the regional distribution of epicardial adipose tissue depending on sex and the influence of distribution on left atrial remodeling have not been elucidated.
- Compared with well-matched men, postmenopausal women had a greater degree of periatrial adiposity, which might affect the decrease in left atrial bipolar voltage and transport function.

What Are the Clinical Implications?

- Although female sex is known to be an independent risk factor for atrial fibrillation–related ischemic stroke, the underlying mechanism has yet to be fully understood.
- Our data could provide an additional basis for explaining the higher risk of atrial fibrillation–related stroke in postmenopausal women than in men.

distribution are related to the functional and structural remodeling of the left atrium depending on sex.

Methods

Study Population and Protocol

From January 2012 to August 2015, patients who underwent AF ablation at Korea University Guro Hospital were prospectively recruited. Of the total 514 patients who underwent an initial catheter ablation for AF, the postmenopausal women and men who were matched for age, body mass index, type of AF, and CHADS₂ score (cardiac failure [1], hypertension [1], age >75 years [1], diabetes mellitus [1], stroke history [2]) were enrolled in the present study (each n=123). In all participants, left atrial volume (LAV), left atrial emptying fraction (LAEF), and EAT were assessed using preprocedural MSCT. Left atrial (LA) bipolar voltage mapping was conducted before AF ablation. In an attempt to minimize the possible confounding effects of sex hormones, postmenopausal women receiving hormone replacement therapy and premenopausal women were excluded. Other exclusion criteria included history of previous AF ablation or cardiac surgery; history of cardiomyopathy, valvular or congenital heart disease; an acute cardiovascular or cerebrovascular event within the preceding 6 months; uncontrolled hypertension; malignancy; connective tissue disease; or any acute or chronic inflammatory diseases. The study protocol was approved by

the institutional review board of Korea University Guro Hospital, and all patients provided written informed consent.

MSCT and Image Analysis

The images were acquired using a 64-channel computed tomography (CT) scanner (Brilliance 64; Philips Healthcare) just before AF ablation. Imaging was performed during a single inspiratory breath hold in the craniocaudal direction, in helical mode, with retrospective ECG gating. Intravenous iodinated contrast (80 mL, Ultravist 370 mg/mL; Schering) followed by a 40-mL mixture of normal saline and contrast medium (ratio of 7:3) were administered, both at a rate of 5 mL/s. To ensure adequate gating and to minimize motion artifacts, participants with a heart rate >80 beats/min received beta-blockers before imaging. Imaging was performed using the following parameters: 64×0.625-mm detector collimation; tube voltage, 120 kVp; gantry rotation time, 420 ms; tube current, 1000 mAs; and pitch, 0.2. Axial multiphase images were reconstructed (slice thickness, 0.8 mm; increment, 0.5 mm) using retrospective ECG gating. The obtained images were used to assess LA contractile function and EAT, as described previously.¹⁰ The methods used for image processing and analysis are described briefly.

LAEF assessment

Images were reconstructed at intervals of 10% of the cardiac cycle. Image analysis was performed on a workstation (Extended Brilliance Workspace version 3.5.4.1056; Phillips Medical Systems). The endocardial border of the left atrium was traced semiautomatically on each axial image slice. The LA appendage and pulmonary veins were carefully excluded at their junctions with the left atrium on all images. The voxels in each slice were summed to yield the 3-dimensional LAV. The LAV was measured at 10% increments of the R–R interval, and the maximal and minimal LAVs (shown as LAV_{max} and LAV_{min}, respectively, in the equation) were determined. The LAEF was calculated using the following formula: LAEF=100×(LAV_{max}–LAV_{min})/LAV_{max}.

EAT assessment

Image reconstruction for EAT measurement was performed at the 80% point of the R–R interval. EAT was defined as the adipose tissue between the visceral layer of the pericardium and the surface of the heart. The volumes of the total and periatrial EAT surrounding the left atrium were measured using semiautomatic segmentation and manual tracing (Figure 1). Fat voxels were identified using a threshold attenuation value of –195 to –45 Hounsfield units and a window center of –120 Hounsfield units. EAT was separated from pericardial fat by manually tracing a single region of interest

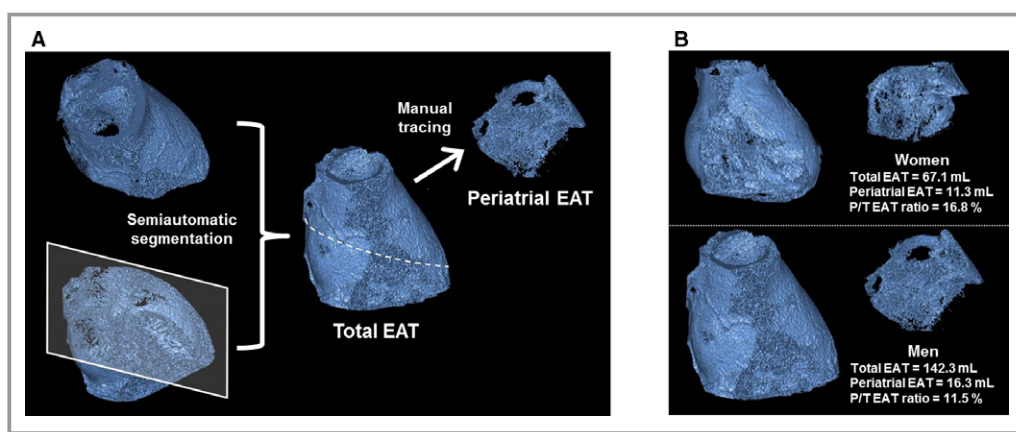


Figure 1. Total and periatrial EAT volume measurements on multislice computed tomography. A, Image analysis method for quantifying the total and periatrial EAT volumes. B, Representative examples of the measured total and periatrial EAT volumes in both sexes. EAT indicates epicardial adipose tissue; P/T EAT ratio, the proportion of periatrial to total EAT.

along the pericardium on each slice. We set the left main coronary artery as the top boundary and the apex as the lower boundary. The voxels in each slice were summed to determine the total and periatrial EAT.

All computed tomography parameters were analyzed by 2 independent investigators blinded to the clinical information of the patients. To determine the intra- and interobserver reproducibility of MSCT, 2 investigators repeated the LAV and EAT measurements at 2 different time points for 30 randomly selected participants. Maximal discordance of 5% in the estimation between 2 investigators was accepted. When higher discordance was observed, measurements were repeated. The intra- and interobserver correlations were 0.962 ($P < 0.001$) and 0.921 ($P < 0.001$), respectively.

Electroanatomic Voltage Mapping

The LA voltage map was created during sinus rhythm before AF ablation. If patients were in AF at the beginning of the procedure, an electrical direct-current cardioversion was performed. When ≥ 3 direct-current cardioversion attempts were required to restore sinus rhythm for voltage mapping, the corresponding voltage mapping data were excluded. A 3-dimensional reconstruction of the left atrium was created using an electroanatomic mapping system (NavX; St. Jude Medical Inc). A 3.5-mm tip catheter (Celsius; Biosense Webster) was used for bipolar voltage mapping. The system recorded the 12-lead ECG and bipolar electrogram filtered at 30 to 400 Hz from the mapping and reference catheters. Endocardial contact during point acquisition was validated by a stable contact signal for >2 beats, fluoroscopy, and the catheter icon on the NavX system.

To access LA voltage with an equal distribution, the left atrium was divided into 6 anatomical segments; anterior,

posterior, roof, inferior, lateral, and septal. At least 10 points of voltage were acquired from each segment, and the voltage values of all points were exported for analysis.

Blood Sampling and Analysis

A blood sample was obtained from a coronary sinus before AF ablation for analysis of high-sensitivity C-reactive protein, NT-proBNP (N-terminal probrain natriuretic peptide), and adiponectin levels. The blood was drawn into ice-chilled tubes containing EDTA and immediately centrifuged at $1026 \times g$ for 20 minutes. All samples were frozen at -80°C until assayed. The samples were assayed in batches and were processed by a technician blinded to all information about the participants. Adiponectin level was determined using ELISA and expressed in micrograms per milliliter.

Statistical Analysis

Continuous variables were initially tested for normal (gaussian) distribution by using the Kolmogoroff–Smirnov test. Normally distributed variables were expressed as mean $\pm$ SD, and the median (25th–75th interquartile range) was given for a nongaussian distribution. Categorical variables were presented as a number and percentage. In the present study, all analyses were stratified by sex. Statistical differences of continuous variables between male and female groups were evaluated using the Student t test or Mann–Whitney U test, as appropriate for the data distribution. Differences of categorical variables were tested for statistical significance using the χ^2 test. In each sex group, univariate and multivariate regression analyses were performed to identify independent parameters associated with LAEF. Multivariate linear regression analysis, including all variables with a P value < 0.05 in

the univariate analysis, was performed. Spearman rank correlations were used to assess the associations between LAEF and EAT profile (total EAT, periatrial EAT, periatrial:total EAT ratio [P/T EAT ratio], and serum adiponectin level) and between LA voltage and EAT profile. All statistical analyses were performed using SPSS statistical software, version 13.0 (IBM Corp), and the level of statistical significance was set at $P=0.05$ (2-sided).

Results

Baseline Characteristics

In total, 123 men and 123 women were enrolled in the present study. The baseline characteristics of the study participants are listed in Table 1. There were no significant differences in age, body mass index, type of AF, CHADS₂

score, medications, lipid profile, or any echocardiographic parameters between men and women. In comparing the laboratory parameters, only serum adiponectin level was higher in women than in men ($P=0.022$).

Comparison of LA Volume and Function and EAT Volume Between Sexes

MSCT data including LAV, LAEF, and EAT volume for each sex are summarized in Table 2. No difference in LAV was shown between sexes; however, LAEF was lower in women than in men, with statistical significance ($18.6\pm 10.0\%$ versus $21.4\pm 11.2\%$, respectively; $P=0.042$). Women had less total EAT than men (68.4 ± 26.5 versus 82.9 ± 30.8 mL, respectively; $P<0.001$), but the P/T EAT ratio, a marker of periatrial adiposity, was higher in women than in men ($22.3\pm 10.3\%$ versus $16.7\pm 6.1\%$, respectively; $P<0.001$).

Table 1. Baseline Characteristics of Study Participants

Variable	Men (n=123)	Women (n=123)	P Value
Age, y	64.4 $\pm$ 9.9	65.7 $\pm$ 9.5	0.289
BMI, kg/m ²	24.3 $\pm$ 2.5	24.3 $\pm$ 3.0	0.800
Persistent AF, %	56 (41.2)	49 (36.0)	0.455
Coronary artery disease, %	18 (14.6)	14 (11.4)	0.448
Heart failure, %	16 (13.0)	18 (14.6)	0.854
Hypertension, %	67 (49.3)	70 (51.5)	0.808
Diabetes mellitus, %	19 (14.0)	22 (16.2)	0.735
Previous stroke/TIA, %	11 (8.1)	12 (8.8)	1.000
CHADS ₂ score	1.3 $\pm$ 1.1	1.5 $\pm$ 1.2	0.712
Medications			
ACEI/ARB	51 (41.5)	55 (44.7)	0.607
Beta blocker	30 (24.4)	28 (22.8)	0.764
Statins	22 (17.9)	18 (14.6)	0.489
Echocardiography			
LVEF, %	65.5 $\pm$ 9.7	65.2 $\pm$ 10.6	0.803
LAV, mL	73.2 $\pm$ 25.3	77.0 $\pm$ 26.2	0.270
Diastolic dysfunction (1–4)	0.6 $\pm$ 0.8	0.8 $\pm$ 0.9	1.000
Laboratory findings			
Total cholesterol, mg/dL	172.6 $\pm$ 33.7	180.0 $\pm$ 38.9	0.159
Triglyceride, mg/dL	120.7 $\pm$ 48.0	117.1 $\pm$ 55.7	0.629
HDL cholesterol, mg/dL	48.8 $\pm$ 13.1	52.1 $\pm$ 13.3	0.080
LDL cholesterol, mg/dL	106.5 $\pm$ 30.7	111.9 $\pm$ 33.9	0.240
hs-CRP, mg/dL	1.6 $\pm$ 3.2	1.4 $\pm$ 2.2	0.583
NT-proBNP, pg/mL	127.7 (60.6–266.7)	125.4 (66.3–420.9)	0.523
Adiponectin, μ g/mL	11.5 $\pm$ 4.8	12.9 $\pm$ 4.5	0.022

Data are expressed as n (%), mean $\pm$ SD, or median (25th–75th percentile). ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; AF, atrial fibrillation; BMI, body mass index; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LAV, left atrial volume; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal probrain natriuretic peptide; TIA, transient ischemic attack.

Table 2. Left Atrial Function and Epicardial Adiposity Measured by Multislice Computed Tomography

Variable	Men (n=123)	Women (n=123)	P Value
LAV, mL	131.5±35.2	133.2±37.1	0.698
LAEF, %	21.4±11.2	18.6±10.0	0.042
EAT			
Total EAT, mL	82.9±30.8	68.4±26.5	<0.001
Periatrial EAT, mL	13.3±5.8	14.0±6.7	0.363
P/T EAT ratio, %	16.7±6.1	22.3±10.3	<0.001

Data are expressed as mean±SD. EAT indicates epicardial adipose tissue; LAEF, left atrial emptying fraction; LAV, left atrial volume; P/T EAT ratio, proportion of periatrial to total EAT.

Correlations Between LAEF and EAT Profiles or Serum Adiponectin Level

The relationships between LAEF and EAT profiles or serum adiponectin level for each sex are shown in Figure 2. In both sexes, LAEF was not associated with total EAT volume and serum adiponectin level. In contrast, it was significantly correlated with P/T EAT ratio (men: $r=-0.204$, $P=0.024$; women: $r=-0.214$, $P=0.018$). Periatrial EAT volume was significantly correlated with LAEF in women ($r=-0.347$, $P=0.023$), whereas it showed a tendency for a negative correlation with LAEF in men ($r=-0.162$, $P=0.083$).

Variables Affecting LAEF in Men and Women With AF

On univariate analysis, body mass index, NT-proBNP, left ventricular ejection fraction, LAV, and P/T EAT ratio were significantly associated with LAEF in men. In contrast, history of heart failure, high-sensitivity C-reactive protein, NT-proBNP, LAV, periatrial EAT volume, and P/T EAT ratio were significantly associated with LAEF in women (Table 3).

On multivariate analysis, LAV and P/T EAT ratio were independently associated with LAEF in both sexes. Although periatrial EAT volume ($P=0.030$) and NT-proBNP ($P=0.032$) were independently associated with LAEF in women, there were no associations in men (Table 3).

Relationship Between LA Voltage and P/T EAT Ratio in Men and Women With AF

The LA voltage mapping data were available for 106 patients: 49 men (39.8%) and 57 women (46.3%). A mean of 70.1 ± 8.0 points per patient was analyzed; there was no significant difference in the number of points analyzed between men and women (70.6 ± 7.8 versus 69.5 ± 8.4 points, respectively; $P=0.528$). The mean LA bipolar voltage amplitude was higher

in men than in women (2.54 ± 0.99 versus 2.12 ± 1.03 mV, respectively; $P=0.034$; Figure 3A). The relationships between bipolar voltage amplitude and P/T EAT ratio in both sexes are shown in Figure 3B. P/T EAT ratio had an inverse relationship with LA voltage in both men ($r=-0.285$, $P=0.042$) and women ($r=-0.269$, $P=0.034$).

Discussion

Main Findings

This study is the first to demonstrate that the regional distribution of EAT is closely related to the sex-related difference in LA transport function in patients with AF. The main findings of the present study were as follows: (1) LAEF was significantly lower in postmenopausal women than in matched men; (2) periatrial adiposity (P/T EAT ratio) was significantly higher in women, although men had greater total EAT volume and lower serum adiponectin levels; (3) the P/T EAT ratio showed an independent association with LAEF in both sexes; and (4) LA bipolar voltage was significantly lower in women than in men, and it showed a negative correlation with P/T EAT ratio in both sexes.

Potential Roles of EAT in Atrial Remodeling in AF

Previous studies have highlighted the important role of EAT in AF genesis and perpetuation,^{7,8,11} but the underlying mechanisms linking EAT to AF have not been fully elucidated. To date, in serial research, the biological mechanisms that relate EAT to AF have been described as follows: First, EAT is anatomically contiguous with the myocardium without a distinct barrier, resulting in paracrine effects through the release of inflammatory cytokines,¹² which promote inflammation and lead to structural and electrical remodeling.^{13,14} Second, adipose tissue can also infiltrate the atrial myocardium, and this may contribute to functional disorganization of the myocardium and, furthermore, to structural remodeling, forming an arrhythmogenic substrate.^{15–17} Third, EAT is known to contain progenitor cells in abundance,^{18,19} which enables us to speculate that EAT may be a source of myofibroblasts, contributing to the cellular remodeling of AF substrate. Fourth, a recent study demonstrated that rapid atrial pacing or AF itself can induce adipocyte-specific atrial gene expression, which may facilitate the development of AF substrate by fat infiltration of the atria.²⁰ Fifth, other possible mechanisms may involve oxidative stress, autonomic dysfunction via ganglionated plexi in EAT, and other pathways.²¹

A recent study revealed that the amount of EAT was associated with the dynamic function of the left atrium and LA appendage in AF patients.²² In the present study, although

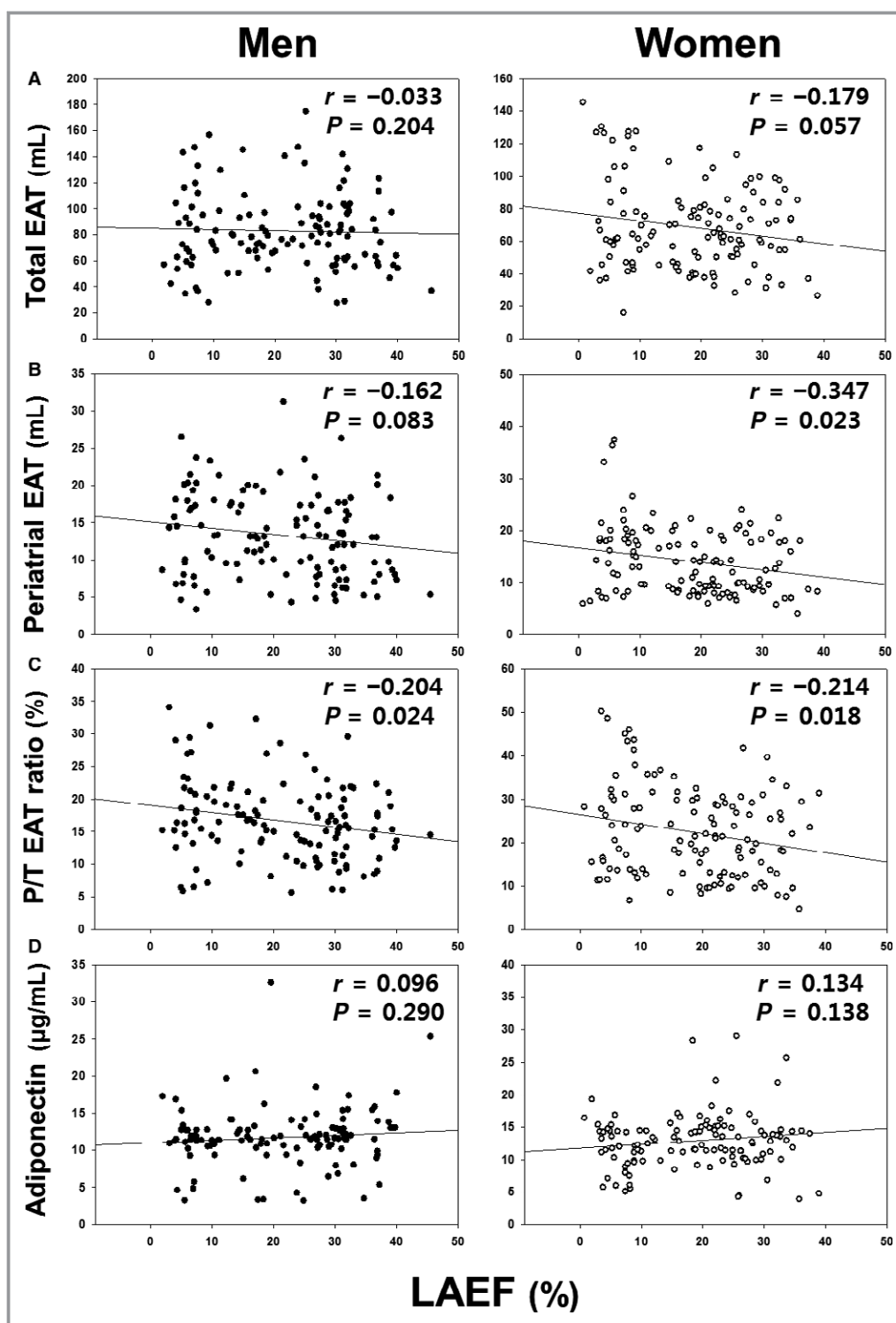


Figure 2. Linear correlations between LAEF and total EAT (A), periatral EAT (B), P/T EAT ratio (C), and serum adiponectin level (D) in men and women. EAT indicates epicardial adipose tissue; LAEF, left atrial emptying fraction; P/T EAT ratio, the proportion of periatral to total EAT.

total EAT volume was significantly greater and serum adiponectin level was significantly lower in men than in women, LA bipolar voltage and LAEF were significantly lower in women than in men. The most remarkable finding in our

study was that the total EAT volume and serum adiponectin levels did not exhibit any correlation with LAEF, whereas the P/T EAT ratio was independently associated with LAEF in both sexes. Furthermore, the P/T EAT ratio rather than periatral

Table 3. Univariate and Multivariate Analysis for Factors Affecting LAEF in Men and Women

	Men				Women			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	β	P Value	β	P Value	β	P Value	β	P Value
Age, y	−0.098	0.283			0.117	0.190		
BMI, kg/m ²	−0.229	0.011	−0.012	0.900	0.139	0.129		
Hypertension	−0.052	0.569			0.067	0.459		
Diabetes mellitus	−0.108	0.233			0.173	0.056		
Heart failure	−0.020	0.827			−0.204	0.023	−0.133	0.136
Previous stroke/TIA	0.030	0.743			−0.065	0.478		
hs-CRP, mg/dL	−0.076	0.440			−0.224	0.018	−0.060	0.426
NT-proBNP, pg/mL	−0.203	0.040	−0.093	0.314	−0.224	0.017	−0.274	0.032
Total cholesterol, mg/dL	0.118	0.253			−0.122	0.228		
Triglyceride, mg/dL	0.059	0.571			0.040	0.693		
HDL cholesterol, mg/dL	−0.092	0.377			−0.054	0.594		
LDL cholesterol, mg/dL	0.161	0.118			−0.103	0.308		
LVEF, %	0.314	0.001	0.073	0.428	0.122	0.199		
LAV on MSCT, mL	−0.269	0.003	−0.182	0.048	−0.180	0.046	−0.152	0.038
Total EAT, mL	−0.033	0.204			−0.179	0.057		
Periatrial EAT, mL	−0.162	0.083			−0.347	0.023	−0.189	0.030
P/T EAT ratio, %	−0.204	0.024	−0.204	0.027	−0.214	0.018	−0.274	0.002
Adiponectin, ng/mL	0.082	0.366			0.134	0.138		

BMI indicates body mass index; EAT, epicardial adipose tissue; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LAEF, left atrial emptying fraction; LAV, left atrial volume; LDL, low-density lipoprotein; MSCT, multislice computed tomography; NT-proBNP, N-terminal probrain natriuretic peptide; P/T EAT ratio, proportion of periatrial to total EAT; TIA, transient ischemic attack.

EAT volume itself was significantly associated with LA voltage in both sexes. These findings suggest that relatively abundant periatrial EAT, rather than the total amount of EAT, affects the functional and structural remodeling of the left atrium.

LA Transport Function and Bioactivity of EAT According to Sex in Patients With AF

In this study, the mean LAEF was lower in women than in men ($P=0.042$). This difference could be explained from a hemodynamic perspective. The changes in hemodynamics and structure of the left ventricle are well known in postmenopausal women. Compared with premenopausal women, postmenopausal women not only have higher peripheral resistance and less nocturnal decrease in both systolic and diastolic blood pressures but also have greater left ventricle wall thickness.²³ In addition, compared with men, women are more likely to present with diastolic heart failure with preserved ejection fraction.²⁴ Impaired relaxation of the left ventricle can affect further stiffening of the ventricle and result in reducing chamber compliance.²⁵ The resultant increase in left ventricular pressure is transmitted to the left

atrium, thereby inducing atrial strain and dysfunction. On multivariate analysis in this study, serum NT-proBNP level was independently associated with LAEF in women, not in men. It is possible, however, that these hemodynamic effects on LA transport function may be adjusted to a degree between men and women, as baseline echocardiographic parameters and serum NT-proBNP levels did not differ significantly between sexes. Consequently, it might be reasonable to assume that another mechanism could be involved in the sex disparity of LA transport function in AF patients.

Until now, there has been a lack of literature regarding sex disparity in the association between EAT and LA function in AF patients. Moreover, the regional distribution of EAT depending on sex and its influence on LA remodeling has not been elucidated. Generally, regional fat distribution has been shown to be dissimilar between men and women: Visceral fat obesity is dominant in men, whereas subcutaneous fat obesity is dominant in women.²⁶ Previous research from the Framingham Heart Study demonstrated that both intrathoracic and pericardial fat volumes were significantly larger in men than women; however, these fat volumes were associated with more adverse risk factor profiles in women.²⁷ In addition, the

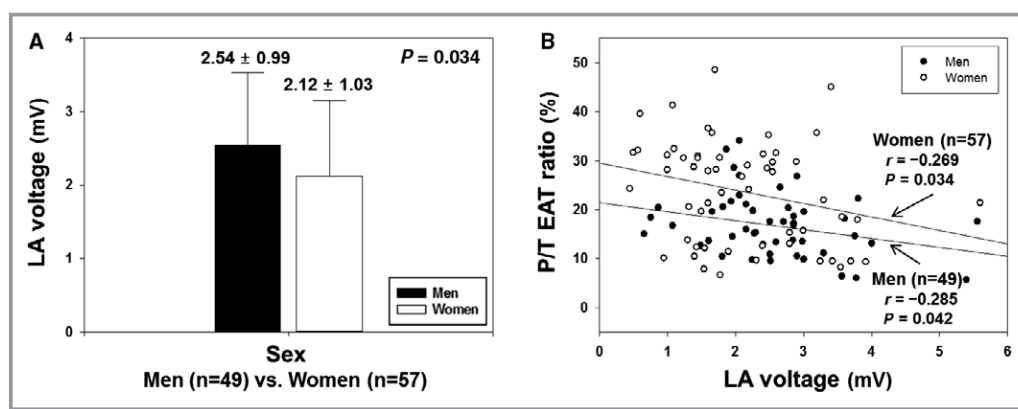


Figure 3. A, Comparison of the mean bipolar LA voltage amplitude between men and women. B, Relationship between LA voltage and P/T EAT ratio in men and women. EAT indicates epicardial adipose tissue; LA, left atrial; P/T EAT ratio, the proportion of periatrial to total EAT.

metabolic function of adipocytes was proven to be different according to their own locations.^{28,29}

Previous studies have shown that both the abundance and biological activity of EAT are diverse among individuals and during various clinical conditions.^{12,30,31} In patients with established coronary artery disease, for example, EAT was reported to secrete less adiponectin and fewer anti-inflammatory cytokines and more inflammatory cytokines such as interleukin 6 and tumor necrosis factor α ,^{12,32} which could provide a basis for the clinical findings of recent studies that show increased EAT volume was associated with the progression of coronary atherosclerosis,³³ mainly in men.²²

With regard to the association of EAT with LA voltage in patients with AF, the presence of overlying EAT was reported to be associated with lower bipolar voltage and electrogram fractionation as electrophysiologic substrates for AF.³⁴ In the present study, higher P/T EAT ratio (periatrial adiposity) rather than periatrial EAT volume itself showed a significant relationship with LAEF and LA voltage in both sexes. We can thus postulate (1) that the bioactivity of periatrial EAT may be determined by the degree of periatrial adiposity; (2) that a metabolically active periatrial EAT produces proinflammatory cytokines, which may contribute to atrial remodeling and lead to further atrial contractile dysfunction in AF patients; and (3) that the difference in the regional distribution of EAT may contribute to the sex disparity in the functional and structural remodeling of the left atrium.

Clinical Implications

Female sex has been known to be an independent risk factor for AF-related stroke. In a recent review of literature on this sex difference regarding stroke risk, several potential mechanisms were suggested.³⁵ These include sex-related differences in hemodynamics and cardiovascular remodeling and a potential increase in prothrombotic milieu, especially in

postmenopausal women. The present study demonstrated that higher P/T EAT ratio was significantly associated with decreased LA transport function and LA bipolar voltage in both sexes, independent of CHADS₂ score and LAV. Together with the increasing evidence of an association between LA dysfunction and stroke,^{5,6,22} our study might offer a basis for explaining the higher risk of AF-related stroke in postmenopausal women.

Study Limitations

This study has several limitations. First, we did not measure other components of body fat such as visceral fat of abdomen. Moreover, as a marker of bioactivity of EAT, we assessed only serum adiponectin level from the blood through a coronary sinus and not other inflammatory markers such as interleukin 6 or tumor necrosis factor α . These measurements might have added incremental information about the effects of local versus systemic adiposity. Previous studies, however, have demonstrated that decreased adiponectin expression in EAT is associated with enhanced expression of cytokine interleukin 6 and tumor necrosis factor α .³² In addition, the present study revealed that decreased serum adiponectin levels, as well as total EAT volume, were not associated with LAEF in either sex, suggesting that circulating adipocytokines may not be a useful parameter for predicting the degree of LA remodeling in AF patients. Second, the number of participants who underwent analysis of LA bipolar voltage mapping was relatively small; however, this did not negate the ability to assess the association between LA voltages and EAT profile by sex. Third, we could not conclusively determine whether local fatty accumulation directly contributed to LA substrate remodeling because we did not perform a quantitative analysis of regional periatrial adipose tissue overlying the low-LA voltage areas, nor did we perform substrate mapping such as rotors or complex fractionated atrial electrograms

during AF. The causal relationships between periatrial adiposity and AF substrate remain to be clarified. Fourth, we did not evaluate the impact of periatrial adiposity on ablation outcome because the present study was designed to be cross-sectional in nature. In addition, ablation protocols among enrolled patients were heterogeneous, which may have influenced procedure outcome. Finally, our results may not be generalizable to other racial groups because the population in the present study was predominantly Korean.

Conclusions

In comparing LAEF and EAT profiles assessed by MSCT between postmenopausal women and matched men who underwent AF ablation procedure, we found that periatrial adiposity (P/T EAT ratio) was independently associated with LAEF and LA bipolar voltage in both sexes. Periatrial adiposity was significantly greater in women and thus may have an influence on their decreased LAEF and LA voltage. Our results suggest that the differences in regional distribution of EAT may play an important role in the sex disparity of LA functional and structural remodeling.

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Disclosures

None.

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