Resistin as a Biomarker for the Prediction of Left Atrial Substrate and Recurrence in Patients with Drug-Refractory Atrial Fibrillation Undergoing Catheter Ablation

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Summary

Resistin is an adipocytokine that is abundantly secreted from lipid cells and is related to the inflammatory process and cardiometabolic diseases.10) Increased resistin content in the epicardial adipose tissue is related to the incidence of AF.10) Increased resistin level is associated with poor left atrial substrate, high epicardial fat volume, and elevated TNF-α level in patients with AF. Plasma resistin may predict the recurrence of atrial arrhythmia after ablation.

Key words: Inflammation, Epicardial fat

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice and has been shown to cause frequent hospitalizations, hemodynamic abnormalities, and thromboembolic events.11) Accumulating evidences indicate that inflammation is involved in the pathogenesis of AF. Inflammatory biomarkers and mediators, such as C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin (IL)-2, IL-6, and IL-8, have been reported to be increased in patients with AF.12) Contrarily, visceral fat, the adipose tissue surrounding the internal organs, has been demonstrated to correlate with cardiovascular events.13-15) The epicardial adipose tissue is also composed of visceral fat, which is deposited between the myocardium and the visceral pericardium. With the development of imaging modalities, echocardiography, multi-detector computed tomography (CT), and cardiac magnetic resonance imaging are all capable of measuring the epicardial adipose tissue. Due to the endocrine and paracrine properties of the secretion of pro-inflammatory and anti-inflammatory cytokines and chemokines, several studies suggested that the epicardial adipose tissue is related not only to coronary atherosclerosis but also to AF.6-8) Resistin is an adipocytokine that is abundantly secreted from the lipid cells and is related to the inflammatory process and cardiometabolic diseases.9) Clinical studies have indicated that an increased level of plasma resistin is related to the incidence of AF.9,10) Increased resistin content in the epicardial adipose tissue has been shown to...
be an independent predictor of advanced coronary atherosclerosis and previous myocardial infarction. Based on the aforementioned data, we hypothesized that resistin level is associated with epicardial fat volume and plays a significant role in inflammation, thereby affecting the clinical outcome in patients with AF undergoing catheter ablation.

Methods

Patient population: A total of 126 participants consisting of 18 healthy individuals (42 ± 7 years, 61.1% male) and 108 symptomatic and drug-refractory AF patients (56.9 ± 12.0 years, 76.8% male) who underwent catheter ablation were consecutively enrolled in this retrospective study between August 2014 and June 2016 at Taipei Veterans General Hospital (a tertiary center). In order to compare the plasma resistin levels between the healthy group and AF group, 18 patients in the healthy group and 54 in the AF group were matched in a 1:3 ratio based on age and gender. Paroxysmal and persistent AF were defined based on the 2017 Heart Rhythm Society Expert Consensus Statement. Subjects were classified as having hypertension if systolic blood pressure ≥ 140 mm Hg at baseline visit or if diastolic blood pressure ≥ 90 mm Hg or by a history of hypertension diagnosed by a physician. Subjects were classified as having hyperlipidemia if total cholesterol > 240 mg/dL or if triglyceride > 200 mg/dL or by a history of hyperlipidemia diagnosed by a physician. Subjects were classified as having diabetes if fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L), if 2-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during oral glucose tolerance test, or if Hb A1C ≥ 6.5% (48 mmol/mol) or by a history of diabetes diagnosed by a physician. Subjects were classified as having heart failure if having typical signs and symptoms or left ventricular ejection fraction less than 50% or by a history of heart failure diagnosed by a physician.

Catheter ablation of paroxysmal and persistent AF: The stepwise procedure of catheter ablation of paroxysmal and persistent AF was achieved, as described in our previous studies. In brief, for patients with paroxysmal AF, the patients received continuous circumferential lesions which created circles at the atrial side of bilateral PV antrum guided by either the EnSite Velocity system using an irrigated ablation catheter (CoolFlex, St. Jude Medical, Minnesota, USA) or the Carto 3 system using an irrigated ablation catheter (Thermocool, Biosense Webster, California, USA). Radiofrequency energy was set to 25-35 W and 40 seconds for each lesion with temperature not exceeding 40°C. To confirm successful PV isolation, we obtained the entrance and exit blocks of the PVs without any electrical activity inside the PV or dissociated PV activity during AF. Cavotricuspid isthmus ablation was performed using an 8-mm-tip EPT ablation catheter (Boston Scientific Corporation) with a maximum power of 70 W and temperature of 70°C. Bidirectional conduction block of linear ablation was confirmed after restoration to sinus rhythm.

For patients with persistent AF, if AF did not stop after PV isolation, an additional complex fractionated atrial electrogram (CFAE) ablation was performed sequentially based on the results of the CFAE maps. The CFAE ablation was confined to the maximal CFAEs with fractionation interval (FI) < 50 ms in the left and right atrium. The endpoint of the CFAE ablation was to obtain a prolongation of the cycle length, elimination of the CFAEs with FI > 120 ms, or the local fractionated potential (bipolar voltage < 0.05 mV). If the AF still did not stop after performing the above procedures, sinus rhythm was restored by external cardioversion.

After sinus rhythm restoration, the location of non-PV foci was identified by evaluating the activation sequence of the right high atrium, His bundle area, and coronary sinus (CS). A duodecapolar catheter (1-mm electrode length and 2-mm interelectrode spacing) was placed to the superior vena cava (SVC) and atrio caval junction area to detect SVC triggers. A deflectable halo catheter with a 10-mm paired spacing (Halo, Cordis-Biosense-Webster) was placed around the tricuspid annulus to map right atrial non-PV triggers. The time interval (< 0 ms) between the high RA and His bundle area during the sinus rhythm and ectopy can differentiate the site of ectopy as the SVC, upper crista terminalis, or PV. Simultaneous mapping of the SVC and right PV was performed to elucidate the true initiating foci. If the earliest activation site was in the interatrial septum, simultaneous mapping of the right and left septum was performed. To map non-PV trigger from the left atrium, the activation time interval between the proximal and distal pairs of the CS catheter during ectopy was evaluated. Ectopic beats from the ligation of Marshall were identified according to the electro-physiological characteristics described in our previous report.

In patients with NPV triggers, catheter ablation toward the earliest electrical activity or a local unipolar QS pattern of the ectopic beat preceding the onset of AF was performed. The endpoint of non-PV trigger ablation was disconnection between the SVC and right atrium and elimination of other non-PV ectopic beats with negative provocation of AF.

Laboratory investigations: Blood samples were drawn after 8 hours of fasting in the morning before performing ablation. Plasma biochemical measurements, including the assessment of fasting blood glucose, uric acid, creatinine, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), and TNF-α levels, were performed by standard laboratory procedures. Resistin levels were measured by enzyme-linked immunosorbent assay (ELISA) for human resistin (Human Resistin ELISA Kit PicoKine EK0581, Boster Biological Technology, Pleasanton, CA 94566, USA).

Measurement of epicardial fat volume: Epicardial fat volume was assessed for each enrolled patient by manually tracing the pericardial sac as the outer border on the contrast CT images obtained 1 day prior to ablation. Fat was defined as pixels within a window of −195 to −45 Hounsfield units (HU) with window center of −120 HU within the region of interest, and the volume was automatically calculated by...
Post-ablation follow-up: The situations of patients were tracked 2 weeks following the catheter ablation and then every 3 months thereafter at our cardiology clinic or by the referring physicians. Antiarrhythmic drugs were prescribed during the blanking period to prevent any recurrence of atrial arrhythmia (the blanking period was defined as < 3 months following the ablation). When the patients were experiencing symptoms suggestive of a tachycardia following the ablation, a 24-hour Holter monitoring or a cardiac event recording would be performed to define the cause of the clinical symptoms. A regular 24-hour Holter monitoring or cardiac event recording was performed every 3 months. The recurrence of atrial arrhythmia was defined as any recurrence of AF, atrial flutter, or atrial tachycardia lasting longer than 30 seconds and confirmed by an electrocardiogram 3 months following the ablation.

Statistical analysis: Parametric data were expressed as mean ± SD and analyzed applying unpaired t-test. The chi-squared test with Yates correction was used for categorical data. The association between resistin and the clinical variables was analyzed by linear regression. The receiver operating characteristic (ROC) curve was used to find the cut-off value of the resistin level in the prediction of recurrence following the catheter ablation. The cumulative risk of AF recurrence within each group was estimated using the Kaplan-Meier method. Univariate logistic regression was conducted to evaluate the relationship between the baseline characteristics and recurrent atrial arrhythmia following catheter ablation. The variables used in the multivariate analysis were those with P < 0.05 in the univariate logistic regression. All statistical analyses were conducted using SPSS 22.0 (IBM Corporation, Armonk, NY).

Results

We enrolled 108 patients with AF with a mean age of 56.9 ± 12.0 years, majority (76.8%) of whom are male and 22.2% had persistent AF. Eighteen healthy adults (42 ± 7 years, 61.1% male) were also enrolled to measure the plasma resistin level. In order to compare the plasma resistin levels between the healthy group and AF group, 54 patients in the AF group were matched to the healthy group in a 1:3 ratio based on age and gender. The mean plasma resistin level in the matched AF group (44 ± 8 years, 61.1% male) was higher than that in the healthy group (P = 0.012, Figure 2A). Transthoracic and transesophageal echocardiography revealed mean LA diameter of 38 ± 6 mm and mean peak LA appendage emptying velocity of 60 ± 22 cm/second. The mean epicardial fat volume derived from CT was 89.3 ± 48.1 mL. The demographic characteristics of the AF population are presented in Table I.

In patients undergoing AF ablation, the level of plasma resistin was associated with the level of plasma TNF-α, epicardial fat volume, and LA scar area (Table II and Figure 2B-D). There was no significant difference in the level of resistin in terms of age, gender, and other comorbidities, such as hypertension, diabetes mellitus (DM), and congestive heart failure. Figure 2E and F presents the LA voltage maps in patients with AF with different plasma resistin levels.

After the index procedure, 25 of 84 (29.7%) patients with paroxysmal AF and 11 of 24 (45.8%) patients with persistent AF had a recurrent atrial arrhythmia during a mean follow-up period of 17.7 ± 14 months. In the univariate analysis, hypertension, persistent AF, LA diameter, and plasma resistin level were related to recurrent atrial arrhythmia. Multivariate regression analysis revealed that persistent AF, LA diameter, and plasma resistin level remained as independent predictors for recurrence following the catheter ablation (Table III). According to the ROC curve, we found that a level of plasma resistin ≥ 777 (pg/mL) can predict recurrence following the catheter ablation with a sensitivity of 70% and specificity of 68%. The area under a curve (AUC) of resistin level in the prediction of recurrent atrial arrhythmia was 0.72 (Figure 3), which was better than that of the LA diameter (AUC = 0.627) in predicting recurrence.

Discussion

Main findings: The main findings of this study are as follows: (1) The plasma resistin level is higher in patients with AF than in the healthy group. (2) The plasma resistin level is associated with epicardial fat volume, plasma TNF-α level, and LA scar area in patients with AF. (3) Persistent AF, LA diameter, and plasma resistin level are the independent predictors for recurrent atrial arrhythmia following the catheter ablation. (4) A level of plasma resistin ≥ 777 (pg/mL) can predict recurrence of atrial arrhythmia following the catheter ablation.

Resistin and inflammation: In addition to TNF-α, IL-6, and leptin, several studies revealed that resistin is another crucial cytokine related to inflammation and AF.9

Figure 1. Identification of epicardial fat in CT images. Within the region of interest, fat (red color) was defined as pixels within a window of −195 to −45 HU with a window center of −120 HU. CT, computed tomography; HU, Hounsfield unit.
Resistin is a cytokine that induces low-grade inflammation by stimulating monocytes. Lee, et al. demonstrated that human resistin can directly bind to adenylyl cyclase-associated protein 1 (CAP1) in monocytes and upregulate cyclic AMP (cAMP) concentration, protein kinase A (PKA) activity, and NF-kB-related transcription of inflammatory cytokines. Silswal, et al. also found that the addition of recombinant human resistin protein to macrophages would result in enhanced secretion of TNF-α and IL-12, which is similar to the effects of lipopolysaccharide. In agreement with previous studies, our study demonstrated that resistin is associated with the TNF-α level in patients with AF. Resistin may act as a surrogate marker to represent the inflammation process in patients with AF.

**Resistin and epicardial fat:** Previous studies reported that resistin promotes insulin resistance and DM, hypertrophy of cardiac myocytes, and impaired cardiac con-
justment for BMI, CRP, and IL-6. Neither leptin nor adi-pose tissue might play a role in the modulation of inflam-matory cytokines, such as TNF-α, resulting in the forma-
tion of atrial arrhythmogenic substrate and AF recurrence (Figure 4). Our present study indicated that resistin can

Table I. Baseline Characteristics and Outcome of Catheter Ablation

| Variable                      | Mean ± SD  |
|-------------------------------|------------|
| Age (years)                   | 56.9 ± 12.0|
| Male n (%)                    | 83 (76.8%) |
| BMI (kg/m²)                   | 25.4 ± 3.4 |
| Diabetes mellitus n (%)       | 12 (11.1%) |
| CHF n (%)                     | 2 (1.9%)   |
| Hypertension n (%)            | 45 (41.7%) |
| Dyslipidemia n (%)            | 13 (12%)   |
| Persistent AF n (%)           | 24 (22.2%) |
| LA diameter (mm)              | 38.0 ± 6.3 |
| LVEF (%)                      | 58.4 ± 5.4 |
| Peak LA appendage emptying velocity (cm/second) | 60.0 ± 21.9 |
| Epicardial fat volume (mL)    | 89.3 ± 48.1|
| Plasma TNF-α (pg/mL)          | 2.0 ± 1.7  |
| Plasma resistin (pg/mL)       | 899.7 ± 531|
| Mean LA voltage (mV)          | 1.6 ± 0.7  |
| LA scar area (cm²)            | 3.25 ± 3.0 |
| Follow-up duration (months)   | 17.7 ± 14  |
| Recurrence of AF n (%)        | 36 (33.3%) |

AF indicates atrial fibrillation; CHF, congestive heart failure; LA, left atrial; LVEF, left ventricular ejection fraction; and TNF, tumor necrosis factor.

Table II. The Association Between Patient Characteristics and Plasma Resistin Level

| Coefficient | P value |
|-------------|---------|
| Age         | -0.081  | 0.375 |
| Male        | -0.115  | 0.219 |
| BMI         | -0.070  | 0.452 |
| Diabetes mellitus | -0.036  | 0.693 |
| CHF         | 0.058   | 0.536 |
| Hypertension | -0.009  | 0.918 |
| Dyslipidemia | -0.022  | 0.813 |
| Persistent AF | 0.002  | 0.982 |
| CHADS2 score | 0.030  | 0.327 |
| LA Diameter | -0.113  | 0.237 |
| LVEF        | 0.033   | 0.732 |
| Peak LA appendage emptying velocity | 0.070  | 0.490 |
| Epicardial fat volume | 0.261  | 0.036 |
| Plasma TNF-α | 0.847  | < 0.001 |
| LA scar area | 0.271  | 0.046 |

AF indicates atrial fibrillation; CHF, congestive heart failure; LA, left atrial; LVEF, left ventricular ejection fraction; and TNF, tumor necrosis factor.

Epicardial fat volume was significantly associated with AF recurrence following ablation.26,27) Epicardial fat has been shown to be associated with electrophysiological substrates for AF. Zghaib, et al.28) found that the presence of overlaying epicardial adipose tissue was associated with lower bipolar voltage and electrogram fractionation in patients with AF. In our previous study, epicardial adipose tissue surrounding the LA was associated with AF recurrence following ablation.26,27) Our previous study demonstrated that epicardial fat can provoke spontaneous activity and burst firing in the left atrium of rabbits.29) Chekakie, et al. studied 300 patients who underwent cardiac CT prior to AF ablation or for the evaluation of coronary artery disease.29) Patients with persistent AF have larger pericardial fat volumes compared with patients with paroxysmal AF and with patients in sinus rhythm. This association was independent of body mass index and other traditional risk factors of AF. Epicardial fat volume was significantly associated with AF duration and symptom burden. Moreover, it predicted AF recurrence following ablation.26,27)

Furthermore, resistin can also activate endothelial cells and promote smooth muscle cell proliferation.30,31) Ermakov, et al. reported that elevated resistin level was associated with an increased risk of AF even after the adjustment for BMI, CRP, and IL-6. Neither leptin nor adiponectin was associated with the incidence of AF.30) Rachwalik, et al. found that resistin content in the epicardial adipose tissue was higher in patients with previous myocardial infarction and was independent of other established risk factors, such as age and male gender.31) These findings suggested that the resistin content in the epicardial adipose tissue not only caused local inflammation but also further triggered pathogenesis of atherosclerosis and AF.

**Epicardial fat tissue and AF:** Accumulating evidences suggested that epicardial adipose tissue was metabolically active and responsible for the secretion of several cytokines and adipokines, such as matrix metalloproteinase-2, TNF-α, IL-6, and leptin.32,23) Literatures indicated that excessive adipose tissue within the pericardial sac may play a significant role in the development of atrial arrhythmia. Our previous study demonstrated that epicardial fat can provoke spontaneous activity and burst firing in the left atrium of rabbits.29) Chekakie, et al. studied 300 patients who underwent cardiac CT prior to AF ablation or for the evaluation of coronary artery disease.29) Patients with persistent AF have larger pericardial fat volumes compared with patients with paroxysmal AF and with patients in sinus rhythm. This association was independent of body mass index and other traditional risk factors of AF. Epicardial fat volume was significantly associated with AF duration and symptom burden. Moreover, it predicted AF recurrence following ablation.26,27)
Figure 3. A: ROC curve of the plasma level of resistin and the recurrence of atrial arrhythmia. B: The Kaplan-Meier curve of the recurrent atrial arrhythmia. The Kaplan-Meier curve revealed that patients with plasma resistin level < 777 pg/mL had lower rates of recurrent atrial arrhythmia following the catheter ablation of atrial fibrillation. ROC, receiver operating characteristic; AUC, area under a curve.

Figure 4. The role of resistin and epicardial adipose tissue in chronic inflammation and recurrent atrial arrhythmia.

Conclusion

The plasma resistin level is associated with plasma TNF-α, epicardial fat volume, and larger LA scar. High resistin level is an independent predictor for the recurrence of atrial arrhythmia following the catheter ablation of AF.

Disclosures

Conflicts of interest: None.

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