Association of left atrial epicardial adipose tissue with electrogram bipolar voltage and fractionation: Electrophysiologic substrates for atrial fibrillation

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BACKGROUND Epicardial adipose tissue (EAdT) is metabolically active and likely contributes to atrial fibrillation (AF) through the release of inflammatory cytokines into the myocardium or through its rich innervation with ganglionated plexi at the pulmonary vein ostia. The electrophysiologic mechanisms underlying the association between EAdT and AF remain unclear.

OBJECTIVE The purpose of this study was to investigate the association of EAdT with adjacent myocardial substrate.

METHODS Thirty consecutive patients who underwent cardiac computed tomography as well as electroanatomic mapping in sinus rhythm before an initial AF ablation procedure were studied. Semiautomatic segmentation of atrial EAdT was performed and registered anatomically to the voltage map.

RESULTS In multivariable regression analysis clustered by patient, age (−0.01 per year) and EAdT (−0.29) were associated with log bipolar voltage as well as low-voltage zones (<0.5 mV). Age (odds ratio [OR]: 1.02 per year), male gender (OR: 3.50), diabetes (OR: 2.91), hypertension (OR: 2.55), and EAdT (OR: 8.56) were associated with fractionated electrograms, and age (OR: 2.80), male gender (OR: 3.00), and EAdT (OR: 7.03) were associated with widened signals. Age (OR: 1.03 per year) and body mass index (OR: 1.06 per kg/m²) were associated with atrial fat.

CONCLUSION The presence of overlaying EAdT was associated with lower bipolar voltage and electrogram fractionation as electrophysiologic substrates for AF. EAdT was not a statistical mediator of the association between clinical variables and AF substrate. Body mass index was directly associated with the presence of EAdT in patients with AF.

KEYWORDS Arrhythmias; Atrial fibrillation; Epicardial adipose tissue; Computed tomography; Fibrosis; Bipolar voltage; Signal fractionation

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Introduction

Pulmonary vein (PV) isolation is the cornerstone of atrial fibrillation (AF) ablation procedures. This reflects the importance of PV triggers in the initiation of AF. Factors that are important in maintenance of AF include heterogeneous fibrosis, refractory periods, and conduction velocity.2,3 Epicardial adipose tissue (EAdT), located between the myocardium and the visceral layer of the pericardium, has also been associated with AF.4 EAdT is metabolically active and may promote arrhythmogenesis through the release of inflammatory cytokines as well as adipokines into adjacent myocardium.4,5 Additionally, EAdT is postulated to contribute to AF through its rich innervation with ganglionated plexi in the proximity of the PV ostia.6 Despite recent advances, the electrophysiologic mechanisms underlying the association between EAdT and AF remain unclear. Specifically, the association of EAdT with adjacent atrial myocardial substrate has not been studied. In the present study, we sought to (1) determine clinical predictors of myocardial substrates, namely, low-voltage zones defined as <0.5 mV, as well as fractionated...
or widened electrograms, and (2) examine EAdT as a potential mediator of the association between clinical factors such as obesity with myocardial substrates.

## Methods

### Patients

We performed a prospective cohort study of a subset of 30 consecutive patients from the ongoing Johns Hopkins Prospective AF Registry. Patients who underwent an initial radiofrequency ablation procedure for paroxysmal or persistent AF at Johns Hopkins Hospital from January to December 2014 and agreed to be included in the registry were screened. We selected patients who underwent preprocedural computed tomographic (CT) study but only included patients who were in sinus rhythm at the time of voltage mapping (n = 30). The study was approved by The Johns Hopkins Medicine Institutional Review Board, and all patients provided written informed consent.

### Multislice CT

Images were acquired using a commercially available 320-detector CT scanner (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan) up to 1 week before the procedure. Slice collimation was 320 × 0.5 mm, and tube voltage was 80, 100, or 120 kV, depending on body habitus. Tube amperage ranged from 320 to 580 mA, depending on body habitus and heart rate. Image acquisition was gated to 40% of the R-R interval during a breath-hold. Beta-blockers were used as needed to decrease the heart rate below 80 bpm. The contrast protocol includes a total volume of 60 mL (70 mL if body mass index [BMI] >30 kg/m²) of the nonionic low-osmolar iodinated contrast material iopamidol (Isovue 370, Bracco Diagnostics, Princeton, NJ) administered at a rate of 5–6 mL/s. First-pass images were used for segmentation and analysis.

### Image analysis

CT images were processed offline using CartoSeg (Biosense Webster, Diamond Bar, CA). Semiautomatic segmentation of the left atrium (LA) and PVs was performed. Total intrathoracic adipose tissue was identified from the bifurcation of the pulmonary artery to the diaphragm as voxel intensities between −250 and −30 Hounsfield units. Thereafter, EAdT was manually segmented by excluding portions of the intrathoracic fat located outside the pericardium. We considered EAdT as a binomial variable derived from its presence or absence within 3 pixels (0.625 × 3 = 1.875 mm) of each endocardial mapping point. LA volume was measured using Osirix (Pixmeo, Geneva, Switzerland) by manually contouring the LA.

### Electroanatomic mapping

Before ablation, voltage mapping was performed during sinus rhythm using an electroanatomic mapping (EAM) system (CARTO3, Biosense Webster) and a mapping catheter with a 3.5-mm distal tip and 2-mm interelectrode spacing (NaviStar, ThermoCool, or ThermoCool SmartTouch, Biosense Webster). Endocardial contact during point acquisition was validated by recording of a stable contact signal for >2 beats. No immediate postoperative complications were noted.

### Registration of EAdT and voltage maps

Using the CARTOMerge module, registration of the EAM and LA mesh was performed using 3–5 anatomic landmarks defined during the procedure followed by surface registration (Figure 1). Each mapping point’s 3-dimensional position coordinates and local electrogams were extracted, and the presence or absence of overlaying EAdT was noted for each site. EAM points recorded during ectopic beats displaying differing intracardiac activation sequences or P-wave morphologies on surface ECGs from those of sinus rhythm were excluded.
Signal fractionation and widening

As previously described by Saghy et al., sinus rhythm fractionation measurements were made manually for each electrogram. The number of deflections crossing the baseline for each signal was counted and its duration measured. In order to define the threshold for signal fractionation, the 95th percentile of electrogram deflections in our patients was determined, and 95% of bipolar electrograms were found to show < 6 deflections; therefore, electrograms with ≥ 6 deflections were defined as abnormally fragmented. The threshold for signal widening was defined in a similar manner, and 95% of our electrograms were found to have duration < 93 ms; therefore, electrograms with duration ≥ 93 ms were defined as abnormally widened.

Statistical analysis

Continuous variables are expressed as mean ± SD, and categorical data as number or percentage. Because of non-normal (right skewed) distribution of bipolar voltage measures, log transformation was performed to enable analysis in a linear framework. The association of log bipolar voltage as the dependent variable with clinical variables as well as EAdT as independent variables was examined using multilevel multivariable generalized estimating equation (GEE) linear regression models, clustered by patient. An identity link function was used, with an exchangeable working correlation structure. The GEE model approach used here recognizes the existence of within-subject data clustering via modeling within-subject correlations. Failure to account for data clustering and the between-patient variability in slopes and intercepts can result in incorrect inferences and overstatement of statistical significance. A logit link function was then used to look for nonlinear associations between the same independent variables and dichotomized low-voltage zones defined by voltage threshold < 0.5 mV. Nonparametric Wilcoxon rank-sum test was used to compare bipolar voltage between low-voltage zones with and without EAdT as well as normal-voltage zones (≥ 0.5 mV) with and without EAdT. Subsequently, the association of EAdT as the dependent variable with clinical variables as independent variables was examined using multilevel multivariable GEE logistic regression models, clustered by patient (link function logit, exchangeable working correlation structure). Statistical analyses were performed using STATA (version 12, Stata-Corp, College Station, TX).

Results

Patient characteristics

Thirty patients were enrolled in this study (16 men [53%], age 58.9 ± 2.2 years, 22 [73%] paroxysmal AF, 8 (27%) persistent AF). Mean CHA2DS2-VAs score was 1.7 ± 0.2 (median 2, interquartile range [IQR]: 1–3), mean BMI was 28.7 ± 1.0 kg/m², and mean LA volume was 112.1 ± 31.0 cm³. Patient characteristics are summarized in Table 1.

Electroanatomic mapping

A total of 4545 points were acquired on EAM of 30 patients. Of all points, 2187 were excluded because of catheter instability or ectopic beats during point acquisition; the remaining 2358 points (mean of 78.6 points-per-patient) were included for voltage analysis. Mean bipolar voltage was 1.76 mV (median 1.33, IQR [0.642; 2.46]), and mean unipolar voltage was 2.22 mV (median 1.75, IQR [1.017; 3.093]). A total of 427 points were found to have a bipolar voltage < 0.5 mV and were considered as low-voltage zones. Low-voltage zones were present in all 30 patients of the cohort.

Predictors of bipolar voltage

In the patient-clustered GEE model given in Table 2, age, BMI, hypertension, and persistent AF were all significantly and inversely associated with log bipolar voltage on univariable analyses. In addition, male gender was positively associated with log bipolar voltage. In the multivariable GEE model without EAdT, age (–0.02 per year; P = .02) was the only variable that remained independently associated with
log bipolar voltage. In the multivariable GEE model with EAdT, age (–0.01 per year; \( P = .04 \)) remained associated with log bipolar voltage, although the magnitude of its association was reduced. In the latter model, EAdT was also associated (–0.29; \( P < .001 \)) with log bipolar voltage.

Predictors of low-voltage zones

To examine a potential nonlinear association with voltage, the association of epicardial fat and clinical predictors with low-voltage zones was examined. In this multivariable GEE model, age (+0.03 per year; \( P = .05 \)) and EAdT (+0.45; \( P < .001 \)) were associated with low-voltage zones. The results are summarized in Table 3.

To further understand the association between bipolar voltage and EAdT, our EAM points were stratified into 4 areas: normal-voltage (\( \geq 0.5 \mathrm{mV} \)) zones without EAdT (area 1); low-voltage zones (\( < 0.5 \mathrm{mV} \)) without EAdT (area 2); normal-voltage zones with EAdT (area 3); and low-voltage zones with EAdT (area 4), as summarized in Online Supplemental Table 1. Median bipolar voltage was significantly higher in area 1 compared to area 3 (1.788 [1.086; 2.871] vs 1.398 [0.870; 2.546]; \( P < .0001 \)) and in area 2 compared to area 4 (0.303 [0.198; 0.396] vs 0.252 [0.150; 0.369]; \( P = .007 \)). Although voltage of the myocardium with overlaying EAdT was not always lower than 0.5 mV, it was still lower on average than that of myocardium without EAdT.

Predictors of signal fractionation and widening

In a patient-clustered GEE model, age (odds ratio [OR]: 1.02 per year; \( P = .021 \)), male gender (OR: 3.50; \( P < .0001 \)), diabetes mellitus (OR: 2.91; \( P = .012 \)), hypertension (OR: 2.55; \( P < .0001 \)), and presence of EAdT (OR: 8.56; \( P < .0001 \)) were all significantly and positively associated with fractionated electrograms on multivariable analyses.

In a similar manner, age (OR: 2.80 per year; \( P = .047 \)), male gender (OR: 3.00; \( P = .027 \)), and presence of EAdT (OR: 7.03; \( P < .0001 \)) were significantly and positively associated with widened electrograms.

To further explore the association between EAdT and electrogram fractionation, 4 strata were defined: no EAdT with no fractionation (area 1); no EAdT and fractionation (area 2); EAdT with no fractionation (area 3); and EAdT with fractionation (area 4). The average number of electrogram peaks between these areas was compared. The mean number of peaks was significantly different between areas 1 and 3 (3.32 ± 0.76 vs 3.88 ± 0.74; \( P < .0001 \)) and between areas 2 and 4 (6.35 ± 0.69 vs 7.05 ± 1.14; \( P = .001 \)). A similar analysis was conducted with signal widening. Areas without widening and without EAdT had a significantly shorter duration than did areas under EAdT without widening (\( P < .001 \)) (see Online Supplemental Tables 2 and 3).

Predictors of EAdT

A total of 680 points were found to have overlaying EAdT. The summary of EAM points colocalized to EAdT stratified by patient characteristics (age tertile, BMI, AF type, and history of hypertension) is given in Table 4. Patients who were in the second (54 ≤ age ≤ 64) and third tertiles of age (>64) had a significantly higher proportion of points with overlaying EAdT (31.85% and 37.92%) than did patients who were ≤54 years of age (20.36%; \( P < .05 \) for both). Patients with BMI >30 kg/m², those with hypertension, and those with nonparoxysmal AF had a significantly higher proportion of points with overlaying EAdT than did patients with BMI ≤30, those without hypertension, and those with a history of paroxysmal AF (\( P < .05 \)). In a multivariable GEE model, only BMI (OR: 1.06 per kg/m²; \( P = .01 \)) and age (OR: 1.03 per year; \( P = .002 \)) were associated with the presence of atrial EAdT.

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**Table 2** Univariable and multivariable associations of clinical factors and EAdT with log bipolar voltage

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariable</th>
<th>Multivariable without EAdT</th>
<th>Multivariable with EAdT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \beta )</td>
<td>( P ) value</td>
<td>( \beta )</td>
</tr>
<tr>
<td>Age (years)</td>
<td>–0.02</td>
<td>&lt;.001</td>
<td>–0.02</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.37</td>
<td>.006</td>
<td>0.13</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>–0.02</td>
<td>.048</td>
<td>–0.01</td>
</tr>
<tr>
<td>CHA2DS2-VASc score ≥2</td>
<td>–0.19</td>
<td>.12</td>
<td>0.20</td>
</tr>
<tr>
<td>Hypertension</td>
<td>–0.27</td>
<td>.03</td>
<td>–0.23</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>–0.14</td>
<td>.40</td>
<td>0.03</td>
</tr>
<tr>
<td>Persistent atrial fibrillation</td>
<td>–0.38</td>
<td>.02</td>
<td>–0.25</td>
</tr>
<tr>
<td>Left atrial volume</td>
<td>–0.01</td>
<td>.07</td>
<td>–0.01</td>
</tr>
<tr>
<td>EAdT</td>
<td>–0.31</td>
<td>&lt;.001</td>
<td>–0.29</td>
</tr>
</tbody>
</table>

EAdT = epicardial adipose tissue.

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**Table 3** Multivariable predictors of low-voltage zones (<0.5 mV)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.02</td>
<td>.05</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.47</td>
<td>.23</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>0.99</td>
<td>.761</td>
</tr>
<tr>
<td>CHA2DS2-VASc score ≥2</td>
<td>1.15</td>
<td>.845</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.06</td>
<td>.887</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.13</td>
<td>.772</td>
</tr>
<tr>
<td>Persistent atrial fibrillation</td>
<td>1.33</td>
<td>.571</td>
</tr>
<tr>
<td>Left atrial volume</td>
<td>1.01</td>
<td>.08</td>
</tr>
<tr>
<td>Epicardial adipose tissue</td>
<td><strong>1.60</strong></td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**Table 4** Patients who had paroxysmal AF (413) and no paroxysmal AF (408)

<table>
<thead>
<tr>
<th>History of hypertension</th>
<th>Paroxysmal AF</th>
<th>No paroxysmal AF</th>
<th>Odds ratio</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>413</td>
<td>408</td>
<td>1.33</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Yes</td>
<td>412</td>
<td>407</td>
<td>1.15</td>
<td>.887</td>
</tr>
</tbody>
</table>
Table 4 Proportion of electroanatomic mapping points colocalized to epicardial adipose tissue, stratified by tertiles of age, BMI, hypertension and AF type

<table>
<thead>
<tr>
<th>Variable</th>
<th>Percent frequency</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;54</td>
<td>20.36</td>
<td>.02*</td>
</tr>
<tr>
<td>[54; 64]</td>
<td>31.85</td>
<td>.002*</td>
</tr>
<tr>
<td>&gt; 64</td>
<td>37.92</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>24.72</td>
<td>.004</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>35.52</td>
<td>.03</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>25.71</td>
<td>.04</td>
</tr>
<tr>
<td>Yes</td>
<td>33.64</td>
<td>.03</td>
</tr>
<tr>
<td>AF type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAF</td>
<td>28.17</td>
<td></td>
</tr>
<tr>
<td>Non-PAF</td>
<td>36.11</td>
<td></td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; BMI = body mass index; PAF = paroxysmal atrial fibrillation.

*Comparisons made with age <54 years.

**Discussion**

The main finding of this study was that intracardiac bipolar voltage was inversely associated with age and the presence of overlaying EAdT. In addition, electrogram fractionation in sinus rhythm was positively associated with age, male gender, diabetes, hypertension, and EAdT. Electrogram widening was associated with age, male gender, and EAdT. BMI and age were associated with the presence of EAdT. However, EAdT was not a statistical mediator of the association of clinical variables with atrial scar. Therefore, it appears to associate with the AF electrophysiologic substrate through mechanisms independent of the clinical variables incorporated in our models.

**Predictors of AF substrate**

The prevalence of AF is known to increase with age. By generating an arrhythmic substrate, atrial remodeling likely mediates some of the association between age and arrhythmia burden. Atrial remodeling includes fibrosis, heterogeneity in conduction velocity, shortening of atrial refractoriness, and subsequent formation of local reentrant circuits and unidirectional block. A study conducted by Spach and Dolber showed that aging is associated with electrical uncoupling of the side-to-side connections between myofibrils leading to a decrease in the "effective" transverse conduction. Previous studies have also shown a significant decrease in atrial endocardial bipolar voltage with age. Furthermore, hypertension is strongly associated with AF incidence. By generating a higher afterload, hypertension predisposes to atrial enlargement, electromechanical remodeling, and a drop in atrial bipolar voltage. In a study conducted by Medi et al., hypertensive patients were found to have slower conduction velocity, regional conduction delays, lower bipolar voltage, and higher propensity to AF compared to nonhypertensive patients. Our study suggests another potentially important contributor to AF substrate within the atrium. The presence of adjacent EAdT appears to be associated with reduced bipolar voltage, electrogram fractionation, and widening. Importantly, the association between arrhythmogenic substrates and regions with low electrogram amplitude is well established. Histologically, low-voltage zones observed in the setting of AF are characterized by fibrosis. It is important to note, however, that other etiologies such as poor tissue coupling, reduced thickness of myocardium, nonuniformity of the myocardial tissue (secondary to fatty infiltration or inflammation), and discontinuous conduction also may lead to reduced bipolar voltage.

**EAdT and AF substrate**

The association of EAdT with cardiac arrhythmias has been clearly demonstrated in the literature. An analysis of the Framingham Heart cohort involving 3217 participants showed that epicardial fat volume was an independent predictor of AF risk after adjusting for other risk factors. These studies suggest that EAdT may play a role in the generation of a myocar- dial arrhythmogenic substrate leading to AF. Biochemical studies have demonstrated that EAdT produces proinflammatory cytokines (e.g., tumor necrosis factor-_, interleukin-1, interleukin-6, monocyte chemotactic-1) and growth factors (e.g., transforming growth factors, and matrix metalloproteinases) with paracrine activity on the myocardium. These molecules are thought to contribute to the structural remodeling that begets AF, namely, fibrosis. In fact, Ventecllef et al. showed that human EAdT induced marked fibrosis of rodent atrial myocardium and favored the differentiation of fibroblasts into myofibroblasts. However, few studies have examined the role of EAdT in atrial remodeling in the setting of AF. In a study by Lin et al., incubation of rabbit atrial myocytes with EAdT modulated the electrophysiologic properties of the cells leading to arrhythmias. Nashima et al. showed the close correlation of EAdT with high dominant frequency sites during AF. Because high dominant frequency sites indicate local synchronous high-frequency activations likely related to the center of a focal-firing rotor or local reentrant circuit, their study suggests that EAdT promotes AF perpetuation. In our study, EAdT had a negative effect on the underlying bipolar voltage in the setting of AF and was independently associated with the presence of low-voltage zones. One potential mechanism for the negative effect of EAdT on electrogram amplitude and fractionation is through fatty deposits in the neighboring myocardium. This hypothesis is based on a study conducted in sheep by Mahajan et al. showing that obesity was accompanied by adipose infiltration of contiguous LA muscle leading to reduced local endocardial voltage, conduction abnormalities, and increased propensity for AF. To the best of our knowledge, this is the first in vivo study of the association of EAdT with the underlying myocardial substrate in the setting of AF.
Predictors of EAdT

Our findings show that the presence of epicardial fat overlying the LA is significantly associated with BMI. In the face of a rising epidemic of obesity, studies have clearly established its close link with AF incidence. In fact, a 1 kg/m² increase in BMI was shown to increase AF risk by 5%–12%. 3,26,27 In a recent meta-analysis, obesity was shown to increase the risk of AF recurrence after an ablation procedure (by 13% for every 5 kg/m²). 26 As to the underlying pathophysiology this phenomenon, human studies were challenged by numerous confounders commonly found in obese patients, such as hypertension, diabetes mellitus, obstructive sleep apnea, coronary artery disease, and heart failure, which predispose to AF. In a sheep model, Abed et al 29 provided a causal relationship between obesity and LA changes, namely, structural and electrical remodeling (increased atrial size, fibrosis, fatty infiltration, conduction heterogeneity, and inducibility of arrhythmia). In our study, we accounted for several of the potential confounding factors by including the CHA2DS2-VASc score along with patients’ clinical covariates and found that BMI was significantly and directly associated with the presence of epicardial fat. Thus, our study provides the foundation for establishing the direct impact of obesity on atrial substrate and AF burden through EAdT deposition.

Clinical implications and future directions

The association between epicardial fat deposits secondary to obesity and atrial substrate provide a framework supporting the benefit of weight loss on AF reduction. The effect of weight loss on the amount of adipose tissue around the heart has been demonstrated in several studies, and several trials have also supported the benefit of weight management on AF burden. 30,31 Thus, a preventive strategy incorporating risk factor management should effectively reduce AF burden.

Study limitations

This study had a relatively a small population, restricted to patients undergoing LA voltage mapping as part of an AF ablation procedure. Future studies with larger cohorts as well as denser EAMs may refine and improve the generalizability of our results. In addition, our results might be affected by positional errors when registering EAMs to the LA mesh. However, the extent of error appears to be very low based on previous validation studies. 32 Finally, the use of a linear regression GEE model only ascertains an association and not a relationship of causality between our variables such as EAdT and bipolar voltage. This points to the importance of biochemical studies to demonstrate the mechanistic interaction between EAdT and atrial myocytes.

Conclusion

In the setting of AF, myocardial bipolar voltage on EAM of the atrium is negatively associated with age and the presence of overlying EAdT. Electrogram fractionation in sinus rhythm is positively associated with age, male gender, diabetes, hypertension, and EAdT. Electrogram widening is associated with age, male gender, and EAdT. BMI was directly associated with the presence of EAdT in patients with AF. However, EAdT was not a statistical mediator of the association between clinical variables and LA scar.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.hrthm.2016.08.030.

References


