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Plasma FABP4 levels are associated with left atrial fat volume in persistent atrial fibrillation and predict recurrence after catheter ablation

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ABSTRACT

Background: Imaging techniques have shown the association between left atrial adipose tissue (LAAT) volume and atrial fibrillation (AF) risk.
Purpose: To analyze 1) adipokines in peripheral and atrial plasma from patients undergoing AF ablation; 2) its association with LAAT volume measured by multislice CT and 3) its predictive value for AF recurrence.
Methods: Seventy consecutive patients undergoing AF catheter ablation were screened. Blood samples were extracted from the left atrium and peripheral vein before catheter ablation. Multiplex fluorimetric immunoassay, enzyme-linked immunoassay and Western blot techniques were used for analyzing some adipokines, fatty acid binding protein 4 (FABP4), and leptin and perilipin analysis, respectively. Patients were followed up with clinical visits until one year after ablation. Generalized additive regression (GAM) was used for determining the best indicator of LAAT volume. Logistic regression analysis determined the best predictor of AF recurrence after persistent AF catheter ablation.
Results: Our results showed 1) differences in the levels of FABP4 between peripheral and left atrial blood samples. 2) persistent AF patients had higher LAAT volume than those with paroxysmal AF (5.12 ± 2.76 vs. 3.82 ± 1.81 mL; $p < 0.036$). FABP4 was the best adipokine associated with LAAT in persistent AF ($p < 0.01$) 3) and predictive value for AF recurrence after catheter ablation (AUC-ROC 0.883 with 95% CI 0.739–1.028).
Conclusions: Plasma FABP4 levels, which were associated with LAAT volume in persistent AF, can be predictors of recurrence after catheter ablation. Whether persistent AF patients require more intensive management and monitoring according to FABP4 deserves further investigation.

1. Introduction

High resolution imaging techniques, computed tomography scan (CT) and magnetic resonance (MR), have improved the quantification of epicardial fat thickness or volume at different heart localizations ([1] atrial, [2] coronary and [3] ventricular). This is relevant at the time of LAAT thickness quantification because it has been shown to be a better predictor of AF burden than obesity [1,3]. Moreover, LAAT thickness can identify those patients whose complex fractionated atrial electrogram is maintained after pulmonary veins isolation [4]. Infiltrated fat on the left atrial tissue can bring on a structural disruption of atrial electrical propagation [5]. Additionally, epicardial adipose tissue (EAT), as a paracrine organ, can contribute to the structural remodeling and AF substrate [6]. Nevertheless, even though transcriptomic studies found differential expression levels of contractile and metabolic genes between peri-atrial and peri-coronary or peri-ventricular adipose tissue [7], at present there is not a specific plasma (peripheral and/or local) biomarker of LAAT. Some of the adipogenic markers are fatty acid binding protein 4 (FABP4) [8], leptin [9] and perilipin [10]. For instance, leptin might play an important role on AF because it can inhibit the

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intracellular calcium and contraction of cardiomyocytes [11]. Subsequently, contrary to fatty acid composition [12], adipokines produced by LAAT could be good indicators of the LAAT volume explaining the mechanisms underlying the relationship between epicardial fat and AF.

We aimed to analyze adipocytes biomarkers, adipokines, in peripheral and atrial plasma from patients undergoing AF ablation, and verify its association with LAAT volume measured by multislice CT and its predictive value for recurrence after AF ablation.

2. Material and methods

2.1. Subjects

This is a cross-sectional study of 70 consecutive patients with paroxysmal or persistent AF [13] referred to our institution for AF ablation. All of the patients signed informed consent. The exclusion criteria were age under 18 years, any active infectious condition, post-surgery AF and previous AF ablation. The study protocol follows the ethical guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Clinical Research of our region according to the Helsinki Declaration.

2.2. Ablation procedure and patient follow-up

A catheter was inserted into the inguinal vein and through the inferior vena cava and into the right atrium (RA). A sheath was inserted from the RA into the left atrium (LA) using the Brockenbrough procedure via a transseptal approach. Patients underwent pulmonary vein isolation (PVI) by contact force by guided, point-by-point radiofrequency ablation (SmartTouch, Biosense Inc.). The procedural endpoint was ipsilateral PVI assessed by a circular mapping catheter and challenged by adenosine. Ablation at the cavotricuspid isthmus was performed in patients with documented typical atrial flutter.

Patients were discharged the day after the ablation procedure, and oral anticoagulation (OA) was continued for at least three months. According to the general recommendation [13], in those patients with a CHA_2DS_2-VASc score ≥ 2, OA is continued lifelong. It is the standard of care in our institution to continue or restart previously ineffective Class 1C or 3 antiarrhythmic drug therapy (ADT) throughout the initial blanking period of three months. If the patient is free of atrial tachyarrhythmias at three months, as evidenced by symptom evaluation and 24 h of Holter recording, patients are encouraged to discontinue ADT. On the contrary, if AF relapsed, ADT is allowed. In case of recurrence of relapse despite ADT, and if AF sustained, patients were treated by electrical cardioversion (ECV). If the recurrence occurred outside the blanking period despite the use of ADT and/or ECV, patients were referred for a redo procedure in order to check pulmonary vein reconnection and rule out extrapulmonary vein triggers.

Study visits were performed at three, six and twelve months after ablation. Each visit comprised detailed history, physical examination with blood pressure measurement, and a 12-lead electrocardiogram (ECG). Holter monitoring was routinely performed at 3, 6 and 12 months.

2.3. FABP4, leptin and perilipin levels

Immediately after the transeptal puncture and previous to heparin administration, blood samples were obtained from the LA through the sheath. At the same time, a peripheral blood sample was obtained from an ante-cubital vein using an 18-G butterfly cannula with a two-syringe technique, discarding the first 5 mL of blood and using the second 5 mL for measures. Left atrial and peripheral blood samples were collected in EDTA-tubes.

After centrifuging at 1800 ×*g* for 10 min, plasma samples were stored at −80 °C until they were used. A Magnetic Luminex Assay Multiplex Kit (R&D Systems, MN, USA) was used. The manufacturer's instructions were followed in analyzing FABP4 and leptin plasma levels. Perilipin-1 was analyzed by Western blot. Albumin and immunoglobulins were depleted from plasma (20 μL) with a specific kit based on a mixture of Cibacron Blue Dye and Protein A agarose affinity resin (Thermo Fisher Scientific, MA, USA). Concentrated proteins with amicon ultracentrifugal columns (10×) (Sigma-Aldrich, MO, USA), after loading buffer addition, were separately by sodium dodecyl sulfate (SDS) acrylamide gel (12%) and transferred in a polyvinylidene difluoride (PVDF) membrane for 90 min at 300 mA. After being blocked with bovine serum albumin (3%) in Tris buffer saline with tween 20 (0.1%) for 1 h in agitation, perilipin-1 (Sigma-Aldrich) was incubated in a blocking solution at 1:1000 dilution overnight at 4 °C. Next, secondary horseradish peroxidase (1:2000) was incubated for 1 h and developed in radiography, after ECL substrate addition. The intensity of bands, represented by arbitrary units (a. u.) was corrected by the intensity of the non-specific band, quantifying by Quantity-One 1D analysis software (Bio-Rad Laboratories, CA, USA).

2.4. Left atrial adipose tissue volume (LAAT)

Before AF ablation, cardiac CT was performed using 64-slice MDCT scanner (LightSpeed GE 64-files, GE Healthcare, Milwaukee, WI) with collimation of 64 × 0.625 mm, gantry rotation time of 350 ms and temporal resolution of 175 ms. The imaging protocol was a contrast-enhanced prospectively ECG-gated cardiac CT, in the 75% of the R-R interval of the cardiac cycle, and during a deep inspiration breath hold.

We selected cardiac CT of a very high quality. Eleven patients whose LAAT was not well visualized due to motion artifacts or acquisition problems, were excluded from the analysis.

LAAT volume was quantified manually using the software program (MultiModality Tumor Tracking. Intellispace Portal v9. Philips Medical Systems, Best, the Netherlands). The anatomical limits used to define this periatrial fat mass were the ostium of the left upper pulmonary vein, the interatrial septum, the great cardiac vein, and the coronary sinus in the short axis and standard two and four chambers views were obtained (Fig. 1). Adipose tissue was defined by the Hounsfield Units between −190 and −45, as described previously [14]. LAAT was indexed by body surface area [15].

2.5. Statistical analysis

Numerical data were tested for normality using the Shapiro-Wilk test, and for homoskedasticity with the Levene's test, then summarized with mean, median, standard deviation (SD) and where appropriate, with interquartile range (IQR). The EAT volume in LA was indexed to body surface area.

The bivariable analysis was performed either with the Wilcoxon rank-sum test or with the Pearson's Chi-squared test where appropriate. The correlation was explored with scatterplots, and Kendall's tau with bootstrap 95% confidence intervals was calculated for each correlation. Agreement analysis for the correlations was examined with Bland-Altman (Tukey mean-difference) plots [16].

For multivariable analysis, a generalized additive model (GAM) was adjusted with the indexed LAAT volume as a dependent and continuous variable. Random effects were included in the final model to account for patient heterogeneity. Also, logistic regression was fitted with the type of AF (paroxysmal vs. persistent) as the dependent variable.

Multiple testing was addressed with false discovery ratio (FDR) control by Benjamini-Hochberg procedure [17]. All analyses were programmed in R (R Core Team, Vienna, Austria), using the packages ggplot [18], dplyr [19], BlandAltmanLeh and mgcv [20].

For multivariable analysis, sample size was calculated according to the method described by Peduzzi [21], which requires 50 patients for a multivariable model with up to five predictors and taking into account a 15% of patients with missing data.

For Wilcoxon rank-sum tests and generalized additive modeling, the LAAT indexed volume, and all biomarkers were transformed with natural logarithms in order to model left skewness.

Logistic regression and area under the curve-ROC were performed for analyzing the predictive value of FABP4 or LAAT volume for AF recurrence after one-year follow-up.

3. Results

3.1. Study population

The mean age of the study population was 57 ± 10.5, and 44 (75%) were male. Of the 59 patients, 29 (49%) had persistent AF. The mean body mass index (BMI) was 29.5 ± 5.75 kg/m^2, and the mean LAAT indexed volume was 3.97 ± 2.91 mL. Values for the different adipocytes markers are described in Table 1.

After classifying patients according to AF type (paroxysmal or persistent), we observed a younger population (55 ± 10 vs. 60 ± 8, $p < 0.05$) and higher male percentage (89% vs. 60%, $p < 0.01$) in the persistent group. However, we observed a similar percentage of active smokers, hypertensive or diabetic patients in both groups of patients. Although higher atrial fat volume was found in persistent AF patients, there were no differences regarding adipokines levels (FABP4, leptin or perilipin) as shown in Table 1. In the logistic regression analysis, the most important associated factor with persistent AF was the indexed LAAT volume (OR 1.37 95% CI 0.86–1.00, $p < 0.05$).

3.1.1. Adipocytes biomarkers in peripheral and atrial plasma

Higher FABP4 and leptin levels were detected in the peripheral vein than in left atrial blood samples ($p < 0.001$). However, perilipin levels did not differ between atrial and peripheral samples.

After analyzing the correlation between BMI and adipokines, we observed the highest association with peripheral FABP4 levels (0.27, 95% CI: 0.142–0.393) (Supplementary Table 1). When Bland-Altman analyses were performed, only perilipin (at both atrial and peripheral levels) was reliably correlated without any identifiable patterns.

3.1.2. Association between adipocytes biomarkers and LAAT volume

LAAT indexed volume was found to be a predictor of persistent AF in age, gender, and BMI-independent manner. The model can correctly discriminate 76% of cases at risk of persistent AF (AUC-ROC: 0.76. 95% CI: 0.63–0.88). After testing for non-linearity of the risk predicted by

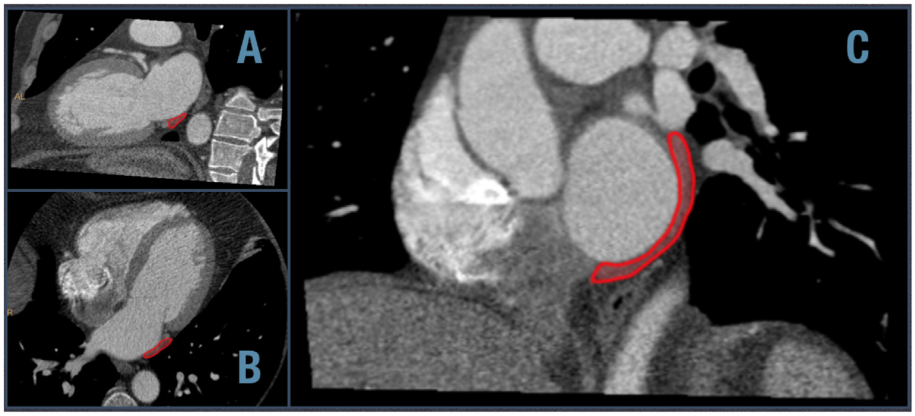

Fig. 1. Representative figure of posterior left periatrial fat quantification from the cardiac planes 2C, 4C and EC.

LAAT volume, it was not statistically significant. This suggests that the risk of persistent AF may increase linearly as the LAAT volume increases.

After exploring the correlations between LAAT volume and adipocytes biomarkers, we observed a weak correlation with perilipin or atrial FABP4 levels (0.14, 95% CI 0.023–0.257) (Supplementary Table 2A). However, after differentiating paroxysmal from persistent AF (Supplementary Table 2B, C), FABP4 was found to have the highest association with LAAT volume in persistent (0.36, 95% CI 0.209–0.425) but not in paroxysmal AF.

In Bland-Altman analyses, the corresponding plots showed heavily heteroskedastic (e.g., funnel-like) patterns. All of the correlations with LAAT volume were corrected after natural-logarithmic transformation of the data.

When the analysis was performed with GAM, both FABP4 and leptin levels in left atrial blood predicted the LAAT volume, in age- and BMI-independent manner. After gender adjustment, leptin was no longer significant (*p*-value 0.26). Thus, peripheral and left atrial FABP4 levels were the most associated with LAAT volume in persistent AF (Table 2), but not in paroxysmal AF. The differences in deviance as observed in atrial (24%) versus peripheral (25.09%) predictive models ($p = 0.054$) were not significant. This indicates that adipokines levels taken from the peripheral blood may be as good indicators of LAAT volume as those taken from the left atrium. After fitting FABP4 with flexible penalized splines in the final model, the LAAT volume showed a linear increase with FABP4 levels.

3.1.3. FABP4 and LAAT volume as a risk predictor of AF recurrence after PVI

After classifying patients as paroxysmal or persistent AF, the main differences between patients with or without recurrence after one-year of follow-up were FABP4 levels and LAAT volume (Table 3). Regression logistic analysis determined that atrial and peripheral FABP4 or LAAT volume were risk predictors of AF recurrence. Therefore, atrial FABP4 was able to correctly discriminate the 74% of cases at risk of AF recurrence (AUC-ROC: 0.744. 95% CI: 0.58–0.91), for peripheral FABP4 the discrimination was 70% (AUC-ROC: 0.707. 95% CI: 0.54–0.871) and for LAAT volume the discrimination was 71%. After splitting population according to the AF type, it was observed that in persistent AF, atrial and peripheral FABP4 levels were the best predictors of recurrence, discriminating 88% and 85% of the patients who developed AF one year after catheter ablation (AUC-ROC: 0.883. 95% CI: 0.739–1.028 and 0.850. 95% CI: 0.694–1.000 respectively) (Supplementary Fig. 1).

4. Discussion

Several studies had shown the relationship between atrial fat thickness assessed by imaging techniques and AF. However, this is the first study in which a new plasma indicator, namely the LAAT volume, is evaluated in patients with AF (at local and peripheral level) with its corresponding prognostic value for AF recurrence after PVI. After testing several adipokines, plasma FABP4 was the best indicator of LAAT

Table 1
Characteristics of included patients according paroxysmal or persistent AF.

Variable	Paroxysmal ($n = 30$)	Persistent ($n = 29$)	*p*-Value
Age (mean ± SD)	60 ± 8	55 ± 10	**0.021**[*]
Gender (male), *n* (%)	18 (60%)	26 (89%)	**0.009**[**]
Active smokers, *n* (%)	7 (23%)	6 (21%)	0.807
Type 2 diabetes mellitus, *n* (%)	4 (13%)	3 (10%)	0.723
Arterial hypertension, *n* (%)	14 (47%)	13 (45%)	0.887
BMI kg/m^2 (mean ± SD)	29.62 ± 3.96	30.49 ± 4.43	0.425
Body surface area (mean ± SD)	1.92 ± 0.17	2.00 ± 0.18	0.074
Obstructive sleep apnea syndrome, *n* (%)	0 (0%)	3 (10%)	0.071
FABP4 ng/mL - atrial (median ± IQR)	16.33 [11−22]	12.82 [9–20]	0.200
FABP4 ng/mL - peripheral (median ± IQR)	19.76 [12–25]	17.03 [10−22]	0.458
Leptin ng/mL - atrial (median ± IQR)	11.73 [6–20]	8.3 [5–14]	0.246
Leptin ng/mL - peripheral (median ± IQR)	13.84 [8–24]	11.26 [7–16]	0.203
Perilipin a.u. - atrial (mean ± SD)	1.20 ± 0.41	1.20 ± 0.32	0.998
Perilipin a.u. - peripheral (mean ± SD)	1.22 ± 0.35	1.06 ± 0.28	0.192
Left atrial fat volume mL - indexed (mean ± SD)	3.82 ± 1.81	5.12 ± 2.76	**0.036**[*]
Left atrial volume mL - indexed (mean ± SD)	59.43 ± 17.76	65.84 ± 16.37	0.155
Statines intake, *n* (%)	12 (40%)	8(28%)	0.314

IQR: interquartile range.
[*] $p < 0.05$.
[**] $p < 0.01$.

Table 2
Generalized additive model (GAM) analysis in persistent AF. Dependent variable: left atrial fat volume.

	Exp (beta)	Standard error	*p* value
Atrial variables			
(Intercept)	0.56	1.91	0.384
Age	1	1.00	0.600
Gender	1.21	1.33	0.520
BMI	1	1.02	0.933
Log FABP4, atrial (ng/mL)	1.77	1.21	**0.008**[**]
Log leptin, atrial (ng/mL)	0.77	1.16	0.096
Peripheral variables			
(Intercept)	1.39	2.82	0.757
Age	1	1.01	0.791
Gender - male	1.06	1.59	0.902
BMI (kg/m^2)	1.02	1.04	0.627
Log FABP4, peripheral (ng/ml)	1.81	1.26	**0.020**[*]
Log leptin, peripheral (ng/ml)	0.68	1.27	0.127

[*] $p < 0.05$.
[**] $p < 0.01$.

Table 3
Logistic regression. AF recurrence as dependent variable.

Variables	Odds ratio	95% confidence interval	*p*-Value
Paroxysmal			
Gender - male	0.46	0.01; 17.08	0.675
BMI	0.39	0.13; 1.16	0.090
Atrial fat volume - indexed	2.87	0.81; 10.2	0.103
FABP4 - atrial	1.05	0.90; 1.32	0.350
Persistent			
Gender - male	52.8	0.001; 2,048,391	0.462
BMI	0.47	0.20; 1.11	0.088
Atrial fat volume - indexed	1.36	0.74; 2.52	0.325
FABP4 - atrial	1.62	1.03; 2.54	**0.036***

* $p < 0.05$.

volume in persistent but not in paroxysmal AF. Importantly, both atrial and peripheral FABP4 levels were able to discriminate those patients with persistent AF at a higher risk of recurrence after catheter ablation.

4.1. LAAT and AF

Several investigators have described the association between indexed LAAT corrected by body surface area, and AF severity [22–24]. In another study, pericardial fat volume was significantly larger in patients with paroxysmal AF than in those with sinus rhythm. However, in both situations, the pericardial fat is also lower than in persistent AF. While pericardial fat volume is a predictor of AF recurrence after ablation in patients with permanent AF in a BMI-independent manner, it lacks prognostic value in patients with paroxysmal AF [24] undergoing PVI. In line with those findings, we found highest differences in indexed LAAT volume between paroxysmal and persistent AF than BMI, which supported the concept of "dose-response relationship" of increasing epicardial fat along the continuum of paroxysmal-AF-persistent-AF/long-lasting-persistent-AF, which highlights the possible arrhythmogenicity of this adipose tissue depot.

The association between EAT and AF seems compelling. However, at present there is no biochemical association between EAT and AF. In the experimental setting, AF was associated with significant changes in atrial gene expression consistent with the induction of an adipocyte-related expression profile. However, there is sparse information in this regard among humans.

4.2. Biochemical markers

We sought to find an adipokine as an indicator of LAAT volume in patients with AF before catheter ablation. This procedure allows us to obtain samples nor only for the peripheral blood but also directly from the LA, which is important in order to differentiate local or systemic activity.

We tested perilipin, [10], FABP4 [25] and leptin [9] because they are adipogenic markers and they were associated with cardiomyocytes contractility dysfunction. Perilipin is the lipid droplet coat protein, which is intracellular but can be released into circulation after metabolic stress [26]. Although the determination of this protein at peripheral blood level is difficult, we analyzed it in all patients. However, we were only able to identify this protein in the plasma from 28 patients. Despite the small size of samples, there was a substantial correlation between left atrial perilipin levels and indexed LAAT volume. However, the main limitation was its undetectable levels in some patients.

Another adipokine, mainly produced by adipocytes, with a fatty acids transporter role, is FABP4 [27]. Its high EAT levels were described in metabolic syndrome [28] and can be easily detected in plasma. Our results showed that left atrium FABP4 levels were more associated with LAAT volume than peripheral levels. After splitting the population on the basis of AF type, we found a clear association of FABP4, atrial and peripheral, with LAAT volume in persistent, but not in paroxysmal AF. The differential behavior of FABP4 regarding gender [29], age [30] and BMI [31] and their relevance in lipid metabolism, suggested the inclusion of these variables in a generalized additive model for predicting LAAT volume. These results conclusively showed that both atrial and peripheral FABP4 levels were good indicators of LAAT volume in persistent AF. This might suggest an association between adipocytes enlargement and FABP4 expression levels [32]. In consequence, this protein might upregulate inflammatory cytokines and macrophages infiltration into epicardial fat [33] also contributing to high atrial FABP4 levels. Therefore, enlarged epicardial fat and macrophages might justify the association between atrial plasma FABP4 levels and LAAT volume in persistent AF patients who showed a thicker enclosed atrial fat than paroxysmal AF patients. Therefore, epicardial fat, through FAPB4, can exert a paracrine effect over atrial cardiomyocytes contraction, as it was previously described in rat cardiomyocytes [25] and perpetuate AF. Thus, high plasma FABP4 levels were even stronger predictors of AF recurrence, than LAAT volume. After measuring left atrial dimensions by echocardiography or CT (good correlation between them $p \le 0.001$) we observed that FABP4 levels were also better predictors of AF recurrence after catheter ablation, than left atrial dilation (data not shown).

Leptin [34] is also an adipokine, but we did not find its correlation with indexed LAAT volume. However, we cannot discard its role in AF since circulating leptin can reduce the intracellular calcium and their levels are associated with epicardial fat volume in patients with cardiovascular disease [35,36].

4.3. Clinical implications and future directions

Our findings suggest a new plasma quantitative indicator of LAAT in persistent AF which has been associated with AF severity. It could be of interest not only as a marker of severity before planning invasive strategies but also from the medical point of view. Observational and randomized studies suggest that aggressive management of measured weight and other risk factors results in marked improvements in AF burden and symptom severity [37]. These benefits seem to occur in conjunction with significant reductions in epicardial fat volume [38].

As a hypothesis, patients with high LAAT or some markers as the one described herein (FAPB4), might help in identifying persistent AF patients who will benefit from closer monitoring, and also those patients who would benefit by more intensive management. For instance, long treatments with olmesartan [39] or atorvastatin [40], which can reduce the FABP4 expression levels induced by oxidized-LDL, could be of benefit in patients with persistent AF (whose epicardial fat is more relevant for the arrhythmogenicity standpoint). However, further studies are needed since FABP4 levels were similar between persistent AF patients who were or were not taking statins and their values were more predictors for AF recurrence than statins intake (data not shown). Ideally, future targeting of these pathways, for example, adipokines, may lead to identifying personalized therapies for prevention and treatment of AF.

4.4. Limitations of the study

This is a study with low sample size. Thus, it may be underpowered to detect smaller associations, which may be detected with larger sample size.

The lack of association for perilipin could be caused by a lack of statistical power due to the presence of missing data.

Perilipin is a cytosolic protein that coats lipid droplets in adipocytes. Its low levels in plasma make its detection difficult, and plasmatic proteins had to be concentrated after albumin and immunoglobulins depletion. This method might cause a higher interassay variability. Moreover, Western blot is a semiquantitative method that determines relative levels.

This study found the association between FABP4 levels and LAAT volume, independently from BMI. However, we did not get the body fat percentage by Dual-energy X-ray absorptiometry (DEXA). Thus, we cannot rule out the possibility that FABP4 levels from our patients are associated with both LAAT and total body fat volumes.

5. Conclusion

Our results show that atrial or peripheral blood FABP4 levels can be good indicators of LAAT in patients with persistent AF being able to discriminate the risk of AF recurrence after catheter ablation.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.04.031.

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Disclosures

None.

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