Epicardial adipose tissue, pulmonary veins anatomy, and the P-wave/PR interval ratio in young patients with atrial fibrillation

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BACKGROUND Atrial fibrillation (AF) is uncommon in the youngest population. Epicardial adipose tissue (EAT) volume has been proposed as an independent AF risk factor.

OBJECTIVE The aim of this retrospective study was to evaluate the impact of the EAT, the anatomy of the pulmonary veins (PVs), and electrocardiogram (ECG) features in these young patients with AF.

METHODS Sixty-two patients divided in 2 groups, one with history of paroxysmal AF treated with ablation and the other, a control group, all younger than 30 years of age, were included. Computed tomography scans were performed in both groups to estimate the PVs anatomy and EAT volume. Twelve-lead ECGs were performed in all patients. Patients underwent follow-up in our outpatient clinic (35.9 ± 18.3 months).

RESULTS In the AF group, the EAT volume around the left atrium was 22.25 ± 9.3 cm^3 compared with 12.61 ± 3.37 cm^3, showing a statistically significance difference ($P = .003$). Family history resulted to be another significant risk factor ($P = .009$). During follow-up, 67.7% of the patients treated were still free of events. The anatomy and morphology of the right-sided PVs seemed to play a more consistent role in the patients with AF recurrences ($P = .04$). The P/PR ratio, a new ECG index, seemed predict AF recurrences after ablation ($P = .03$).

CONCLUSION The abundance of EAT seems related to the risk of developing AF in young patients. The recurrence of AF is about 33% and does not seem related to the EAT volume, but rather to the anatomy of the PVs. A higher P/PR ratio might suggest recurrences.

KEYWORDS Atrial fibrillation; Epicardial adipose tissue; Computed tomography; Cryoballoon ablation; Young patients; ECG AF predictor index

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. Hypertension, heart failure, coronary artery disease, diabetes mellitus, sleep apnea, and aging are some of various clinical conditions associated with a high risk of developing AF.[1,2] Obesity was reported to be independently associated with a high risk of developing AF.[3,4] The cardiac adipose tissue is composed of the pericardial fat located outside the visceral pericardium and the epicardial adipose tissue (EAT) situated between the visceral pericardium and the epicardium.[5] In adult patients it has been observed, using computed tomography (CT), that the volume of EAT predicted AF risk independently of other measures of adiposity.[6,7]

AF is relatively uncommon in the young population (younger than 40 years of age), particularly when not associated with other electrophysiological substrates (accessory pathways, focal atrial tachycardia, channelopathies) or congenital/acquired structural heart diseases. However, information focusing on these young patients with AF, their risk factors, the EAT role on the pathogenesis of the arrhythmia, the influence of the anatomy of the pulmonary veins (PVs) and the possible outcome of catheter ablation are still limited.

The aim of this retrospective single-center study was to evaluate the impact of the EAT, the anatomy of the PVs, and ECG characteristics in this population of young patients with paroxysmal AF.

Materials and Methods

This study was reviewed and approved by our Institutional Ethical Board (Verona and Rovigo Ethical Committee). All the procedures reported were performed in accordance with

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KEY FINDINGS

- Atrial fibrillation (AF) is the most common arrhythmia in the population but is relatively rare in young people.
- Epicardial adipose tissue has been associated with a high risk of AF after adjusting for traditional risk factors in common elderly patients.
- Our study assesses for the first time that epicardial adipose tissue, alongside family history, seems to be one of the most import risk factors for developing AF in otherwise normal and healthy young patients.
- Genetic background, still not completely unveiled, might be determinant on the developing of EAT, its volume, distribution around the heart and therefore AF in these young patients.
- The P/PR ECG ratio seems to be a new potential predictor index of AF recurrences.

relevant guidelines and regulations. Informed consents were obtained by all the patients involved in this research.

Patients

We performed a retrospective review on 2 groups of patients admitted in our center since 2017. Group 1 comprised patients admitted for elective PVs isolation due to paroxysmal and symptomatic AF, and were younger than 30 years of age. Thirty-one patients had this characteristic at the time of the procedure and were included. A thoracic CT scan was performed in sinus rhythm, as per hospital protocol, before cryoballoon (CB) AF ablation. Group 2, the control group, comprised 31 patients who were age-, sex-, and general medical characteristics–matched control individuals, with no history of AF, who underwent a thoracic CT scan during their admission for other medical reasons (mainly an exclusion diagnosis of pulmonary embolism and congenital heart disease). We investigated the family history on both groups, in particular the history of AF in family members (first and second degree), considering positive those who experienced AF before their 50s. Digital 12-lead ECGs were recorded (Cardiovit AT-180; Schiller, Baar, Switzerland) in all patients in the supine position and during spontaneous breathing, and for the AF patients, while being off from antiarrhythmic drugs (flecainide and/or beta-blockers) for at least 5 days before admission for the CB AF ablation procedure. Parameters, such as P-wave durations (from the beginning of the P-wave deflection to the end at the isoelectric line) and PR intervals (from the beginning of the P-wave deflection to the beginning of the first deflection of the QRS), both in lead II, were digitally calculated using calipers of the ECG software, by 2 expert electrophysiologists (A.M. and K.T.).

Computed tomography acquisitions

The CT data acquisition was performed using a third-generation dual-source CT scanner (Somatom Force; Siemens Healthineers, Forchheim, Germany) for all patients and up to 1 week before the procedure for patients of group 1, when in sinus rhythm, using a dedicated cardiac scan protocol. As already described and suggested by Marwan and colleagues[8] in their work about quantification of EAT, slice collimation was 2 × 192 × 0.6 mm and tube voltage was 80, 100, or 120 kV, depending on body habitus. Tube current ranged from 320 to 580 mA, depending on body habitus. 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 beats/min. The contrast protocol includes a total volume of 60 mL of the nonionic, low-osmolar iodinated contrast material iopamidol (Isovue 370; Bracco Diagnostics, Princeton, NJ) administered at a rate of 5 to 6 mL/s. First-pass images were used for segmentation and analysis.[8]

Image analysis

For both groups, CT images were processed offline using OsiriX-Md software Version 12.5.1 (Pixmeo Sarl, Bernex, Switzerland). The contour of the pericardial sac was semi-automatically traced and adjusted by the reader, if necessary. The EAT volume was automatically calculated by including all contiguous 3-dimensional voxels with CT attenuations between the specified upper threshold of –30 Hounsfield units (HU) and the lower threshold of –190 HU.[8] Total EAT was identified from the bifurcation of the pulmonary artery to the diaphragm. Thereafter, the EAT surrounding the left atrium (LA) was calculated by manually contouring the LA, from the pulmonary artery bifurcation and the coronary sinus groove and applying the same voxel intensities (–190 and –30 HU), as shown in Figure 1. EAT volumes around the LA and the whole heart were indexed by the body surface area (BSA). Semi-automatic segmentation of LA and PVs was performed. We decided to measure the LA and LA appendage (LAA) volumes at end-diastole, indicating the maximal volume, still using CT scans. LA and LAA volumes were indexed by the BSA. Using CT scan coronal plane views, the PVs anatomy was classified accordingly to Marom and colleagues'[9] classification and PVs ostium diameters were calculated on the cranial-to-caudal axis, at the edges between the LA walls and the veins origin, adjusted by the readers accordingly to the vein orientations and angulations. The imaging analysis was carried out by 2 cardiologists (K.T. and S.B.) with expertise on cardiac imaging. The left ventricular ejection fractions were obtained by standard echocardiography.

Ablation procedure

Each patient of group 1 underwent a 3-wires electrophysiological study, at baseline and after isoproterenol infusion, with 2 quadripolar catheters, 1 in the right ventricle, 1 on the His position, and a decapolar in the coronary sinus, via

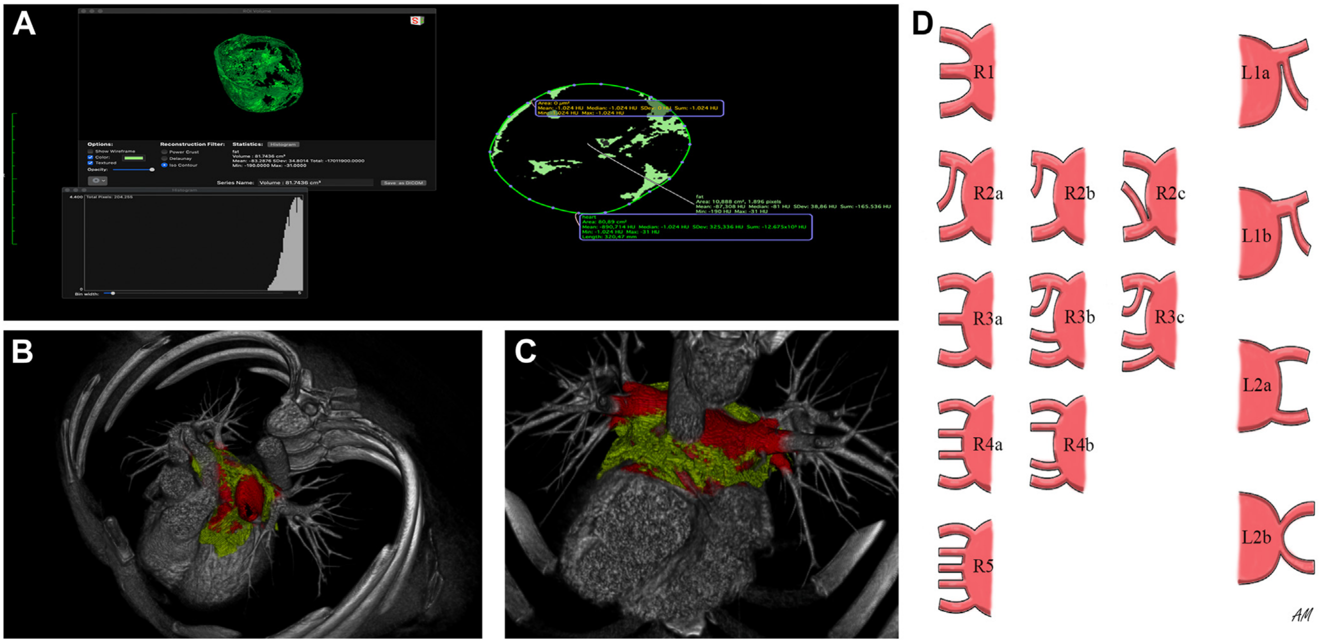

Figure 1 Computed tomography evaluation of epicardial adipose tissue and Marom and colleagues'[9] pulmonary veins classification. **A:** After encountering the pericardial sac and applying the density requested (–190 to – 30 Hounsfield units) epicardial adipose tissue is highlighted (left), volume calculated automatically (right), and 3-dimensional reconstruction allowed after segmentation of the left atrium and pulmonary veins (**B:** cranial left oblique view; **C:** inferior view). **D:** Marom and colleagues' pulmonary veins classification.

the modified Seldinger technique and ultrasound-guided right femoral vein accesses, in order to rule out any other substrates (accessory pathways, nodal re-entrant tachycardia, atrial flutter, and/or focal tachycardia). If the electrophysiological study did not show any particular substrate, CB ablation was performed under general anaesthesia. Details have been described previously.[10]

In brief, a single transseptal puncture was performed under fluoroscopy and transesophageal echocardiography guidance. The activated clotting time was maintained between 300 and 350 seconds. The sheath was then exchanged for the 12F steerable transseptal sheath (FlexCath, CryoCath; Medtronic Inc, Minneapolis, MN) over a stiff guidewire (0.032 inch, 180 cm; Rossen J-tip; Cook Medical, Bloomington, IN). The 28-mm CB (Arctic Front Advance; Medtronic) and the inner circular catheter (Achieve mapping catheter; Medtronic Inc) were used in all patients for PV isolation (PVI). After guiding the balloon toward the respective PV ostia, adequate occlusion was confirmed with 50% diluted contrast through the CB catheter's central lumen. PV potentials were monitored using the Achieve catheter. If a clear time to PVI effect was observed within the first 60 seconds (either a temperature of minus 40 °C or a clear PVI isolation by the Achieve catheter), the number of therapies was reduced to 1 lasting 180 seconds, otherwise a second CB application was delivered up to 240 seconds (for a maximum for each vein of 480 seconds and lower temperature accepted of minus 60 °C). For all cases, CB ablation was performed in the following order: left superior, left inferior, right superior, and ultimately, the right inferior PVs. No further targets of ablation were considered (the posterior wall, roof, mitral annulus, or right atrium).

All patients (N = 31 of 31) were discharged on flecainide and oral anticoagulation (new direct oral anticoagulants: 29 of 31 were on apixaban, 2 of 31 on edoxaban) for 3 months, covering the blanking period, and all of them underwent follow-up (mean 35.9 ± 18.3 months) in our outpatient clinic, 3 months after ablation and every 3 to 6 months thereafter, evaluated by 24-hour Holter monitor, standard 12-lead ECG, and because they were very symptomatic when in AF, using telephone calls 1 month after every 24-hour ECG Holter monitor. Patients were also asked to contact our outpatient clinic in case of any symptoms resembling AF. No longer ECG monitoring, with implantable loop recorders or other external monitor devices, was used due to patients' preferences (usually related to their job/study/sport activities).

Statistical analysis

Continuous variables are expressed as mean ± SD and categorical data as number and percentage. Differences between the 2 groups were compared on demographic, clinical, and anatomical characteristics and outcomes using 2-sample unequal-variance Student's *t* test for continuous variables. The chi-square test or Fisher's exact test was used for categorical variables. Correlation analyses between EAT and clinical characteristics were performed. The variables were shown by Pearson's and/or Spearman's correlation coefficients. Univariable and multivariable Cox proportional hazards models were developed to determine independent predictors of arrhythmia recurrence. The hazard ratio (HR) and 95% confidence interval (CI) are reported from the proportional hazards models. A P value $<.05$ was

Table 1 Baseline characteristics in patients with atrial fibrillation and those with normal sinus rhythm

Variable	AF (n = 31)	No AF (n = 31)	*P* Value
Age, y	27.9 ± 2.1	26.8 ± 3.2	.34*
Male	28 (90.3)	28 (90.3)	.99*
Body mass index, kg/m^2	24.30 ± 2.31	24.10 ± 2.48	.88*
Height, cm	179.5 ± 8.7	180.6 ± 8.1	.74*
P-wave, ms	100 ± 10.9	89.3 ± 15.4	.09*
PR interval, ms	169.1 ± 20.7	147.5 ± 20.3	.037*
P/PR, %	59.7 ± 7.8	60.8 ± 8.7	.77*
First-degree relative with AF history	23 (74.2)	6 (19.3)	.009†
Hypertension	9 (2.9)	8 (2.5)	.74†
Smoking habit	4 (12.3)	6 (19.3)	.43†
Alcohol (more than 2 units/day as per WHO)	5 (16.1)	4 (12.3)	.78†
Total cholesterol, mg/dL	168.9 ± 12.9	165.9 ± 23.1	.84*
High-density lipoprotein, mg/dL	58.93 ± 12.5	61.48 ± 14.3	.76*
Low-density lipoprotein, mg/dL	94.7 ± 18.6	93.2 ± 20.5	.90*
Triglycerides, mg/dL	72.25 ± 35.4	80.41 ± 35.4	.85*

Values are mean ± SD or n (%).
AF = atrial fibrillation; WHO = World Health Organization.
*Student's *t* test.
†Chi-square/Fisher exact test.

considered statistically significant. Statistical power based on our number of patients was higher than 90% (0.9536 using G*Power Software version 3.1.9.4; https://gpower.software.informer.com/3.1/). Statistical analyses were performed using Microsoft Excel (version 2202; Microsoft Corporation, Redmond, WA).

Results

Sixty-two patients were enrolled in this study. Age, sex, and body mass index (BMI) were similar in patients with AF and control individuals. Patient characteristics are summarized in Table 1.

Twenty-eight (90.3%) of the 31 patients with AF were male. Eleven (35%) were overweight (BMI >25 kg/m^2), but none were obese (BMI 24.30 ± 2.31 kg/m^2). There were also no statistically significant differences between the AF patients and control individuals regarding height (179.5 ± 8.7 cm vs 180.6 ± 8.1 cm; *P* = .74), hypertension (9 of 31 vs 8 of 31; *P* = .74), smoking habit (4 of 31 vs 6 of 31; *P* = .43), and alcohol intake (more than 2 units per day: 5 of 31 vs 4 of 31; *P* = .78). Total cholesterol levels as well as high- and low-density lipoprotein values, triglycerides, thyroid function (normal in both groups), and other blood test markers did not differ significantly either, as shown in Table 1. When considering electrocardiographic characteristics, in particular the P-wave duration, PR interval, and P/PR ratio, as indexes of intra-atrial impulse propagation or delay, there was a statistically significant difference between the 2 groups only for the PR interval (169.1 ± 20.7 ms vs 147.5 ± 20.3 ms; *P* = .037). No long QT–like or Brugada-like ECG patterns were described, as well as no PV ectopic beats on ECG or 24-hour monitoring. The presence of a first-degree relative (meaning a parent or a sibling) with a diagnosis of AF before 50 years of age was relevant (23 of 31 vs 6 of 31; *P* = .009).

Table 2 Anatomical characteristics in patients with AF and those in sinus rhythm

Variable	AF (n = 31)	No AF (n = 31)	*P* Value
Right-sided PV anatomy			.16*
The more common R2a morphology	19 (61.3)	24 (77.4)	
Other variants	12 (38.7) (4-R3a; 2-R3b; 3-R2c; 3-R2b)	7 (22.6) (3-R3a; 2-R3b; 2-R2c)	
Left-sided PV anatomy			.43*
The more common L2b morphology	18 (58.1)	21 (67.7)	
Common ostium	13 (41.9)	10 (32.3)	
Diameter of left upper PV, mm	18.5 ± 2.1	16.9 ± 3.4	.33†
Diameter of common ostium, mm	22.7 ± 1.9	22.2 ± 1.9	.76†
Diameter of left lower PV, mm	18.3 ± 1.9	16.8 ± 2.1	.18†
Diameter of right upper PV, mm	18.4 ± 3.3	17.8 ± 1.4	.60†
Diameter of right lower PV, mm	17.85 ± 2.6	17.1 ± 2.9	.55†
Total EAT, cm^3	63.61 ± 43.6	42.15 ± 17.1	.12†
Total EAT index, cm^3/m^2	31.44 ± 20.5	21.39 ± 17.4	.13†
EAT around LA, cm^3	22.25 ± 9.3	12.61 ± 3.87	.003†
EAT around LA index, cm^3/m^2	11.06 ± 4.0	6.35 ± 3.7	.0015†
EAT percentage around LA vs total volume	45.23 ± 20.4	31.81 ± 9.51	.04†
LA volume index, mL/m^2	40.01 ± 16.01	33.19 ± 10.15	.23†
LAA volume index, mL/m^2	3.57 ± 1.53	3.51 ± 1.75	.92†
Ejection fraction, %	56.7 ± 10.4	56.9 ± 9.3	.89†

Values are mean ± SD or n (%).
AF = atrial fibrillation; BMI = body mass index; EAT = epicardial adipose tissue; LA = left atrium; LAA = left atrial appendage; PV = pulmonary vein.
*Chi-square/Fisher exact test.
†Student's *t* test.

Table 2 summarizes the anatomical characteristics in patients with AF and those in sinus rhythm. We analyzed the anatomy of the right and left PVs as per Marom and colleagues'[9] classification. There were no significant differences in the 2 groups. No differences were found on the diameters of the PVs. The mean volume of the total EAT around the heart in the AF patients was 63.61 ± 43.6 cm^3 (31.44 ± 20.5 cm^3/m^2 indexed by BSA), and it was not significantly different compared with a mean volume of 42.15 ± 17.1 cm^3 (21.39 ± 17.4 cm^3/m^2 indexed by BSA) in the control group (*P* = .12 for absolute values and *P* = .13 for indexed values). Nevertheless, the mean EAT volume around the LA, as well as the fraction of it in relation to the total EAT volume, was significantly higher in the AF patients compared with the control individuals (22.25 ± 9.3 cm^3vs 12.61 ± 3.8 cm^3; *P* = .003; and 45.24 ± 20.4% vs 31.81 ± 9.5%; *P* = .04, respectively). Even more statistically relevant was the difference when considering the volume of EAT around the LA indexed by BSA (11.06 ± 4.0 cm^3/m^2 vs 6.35 ± 3.7 cm^3/m^2; *P* = .0015). The LA and LAA volume indexes, as well as the left ventricular ejection fractions, did not show any significant differences.

Using Pearson's correlation, we also found a strong relation between the EAT around the whole heart and the EAT around the LA in the AF patients (R^2 = 0.88, *P* < .0001), which was less strong in the control group (R^2 = 0.68, *P* = .0008) (Figure 2A and 2B). When looking at the relationship between the BMI and EAT around the LA, there was still a good correlation in the AF patients, although less strong (R^2 = 0.34, *P* = .05), which was neutral in the control group (R^2 = 0.0006, *P* = .98) (Figure 2C and 2D). Interestingly, albeit not statistically significant, there was a weak positive correlation between triglycerides and the EAT volume around the LA in the AF patients (R^2 = 0.33, *P* = .06) and a weak negative correlation with the low-density lipoprotein values (R^2 = 0.051, *P* = .48) (Figure 2D–2F).

Analyzing the AF patients, all of them treated with CB ablation, we created 2 subgroups, patients who experienced recurrence of AF and those free of arrhythmia during the follow-up, summarized in Table 3. During this period of more than 3 years (as mean), 10 (32.3%) of the 31 patients had AF recurrence, while the others (67.7%) remained free from arrhythmia. Five patients had the first recurrence just after 3 months, 4 at 6 months, and the last one at 12 months post-ablation. Patients with recurrence were usually slightly younger (26.9 ± 3.1 years of age vs 27.6 ± 2.4 years of age; *P* = .15) and significantly less tall (173.2 ± 8.8 cm vs 183.8 ± 5.6 cm; *P* = .03). Looking at the ECG, the PR interval and P-wave duration were not relevant, but the P/PR ratio appeared significant (65.3 ± 2.7% vs 56.5 ± 8.1%; *P* = .03). The EAT around the whole heart and around the LA showed no differences between the 2 groups, similar to the LA and LAA volume. In multivariate analysis, when looking at the PVs anatomy, those who experienced AF recurrence were the patients usually with right PVs variants (*P* = .04). No differences were found for the left PVs morphology or for the diameters of both PVs sides.

Family history and an EAT superior than 15 cm^3 around the LA resulted significant risk factors for AF in this young population (for family history HR 4; 95% CI 1.2–7; *P* = .009; EAT >15 cm^3 HR 3; 95% CI 1.3–6.9; *P* = .029) (Figure 3A). On the other hand, only the right PVs morphology, in terms of the presence of variants, seemed a risk factor of recurrence in the patients treated with CB ablation (HR 3.6; 95% CI 1.12–6.4; *P* = .044) (Figure 3B).

Discussion

In the last few years, different studies have shown EAT's possible pathophysiological role on some of the mechanisms behind AF. Epicardial fat is involved in lipid and energy homeostasis. It is a source of free fatty acids for myocardial energetic metabolism and may protect the heart against their toxic levels. This might explain our findings, consistent with another study,[11] showing a positive, albeit weak, correlation between the level of triglycerides and the EAT volume and a negative correlation with the level of low-density lipoprotein, even though both were not statistically significant, likely because of the relatively small number of patients. Adipose tissue also produces several bioactive molecules, including infilammatory mediators and adipocytokines. A paracrine effect on the neighboring atrial myocardium could be a potential mechanism by which the EAT contributes to the arrhythmogenic substrate. Recently, Ernault and colleagues[12] showed that EAT facilitates re-entrant arrhythmias, inducing myocardial remodeling. They demonstrated a decreased expression of the potassium channel subunit KCNJ2 and therefore a reduced inward rectifier K^+ current, resulting in a depolarized resting membrane of the cardiomyocytes. In addition, EAT decreased expression of connexin 43. Therefore, by slowing the atrial myocardium conduction, depolarizing the resting potential, altering the electrical cell-to-cell coupling, and finally facilitating re-entrant circuits, EAT plays an important role on developing AF substrates.[12,13] The electrophysiological effect of EAT in older AF patients was also well demonstrated using voltage-electroanatomical mapping. The presence of EAT was associated with lower bipolar voltage and electrogram fractionation.[14]

Our study corroborates the important role of EAT, and in particular that surrounding the LA, on developing AF, not only among the older patients suffering from AF, but also for the first time among the youngest, without any other substrates. Whereas the BMI had a good correlation with the EAT volume in the AF young patients, in those in sinus rhythm the correlation was neutral, suggesting a potential role of other variables, likely genetic or epigenetic, on the developing and distribution of EAT around the heart and the LA, still not properly assessed in literature. Probably the same could be stated looking at the correlation between the total amount of EAT around the heart and the one just around the LA. In our AF population, this correlation was significantly strong, while in the control group it tended to be less significant, suggesting a different distribution of the EAT in patients in sinus rhythm. To further support this finding, the percentage of EAT around the LA was higher

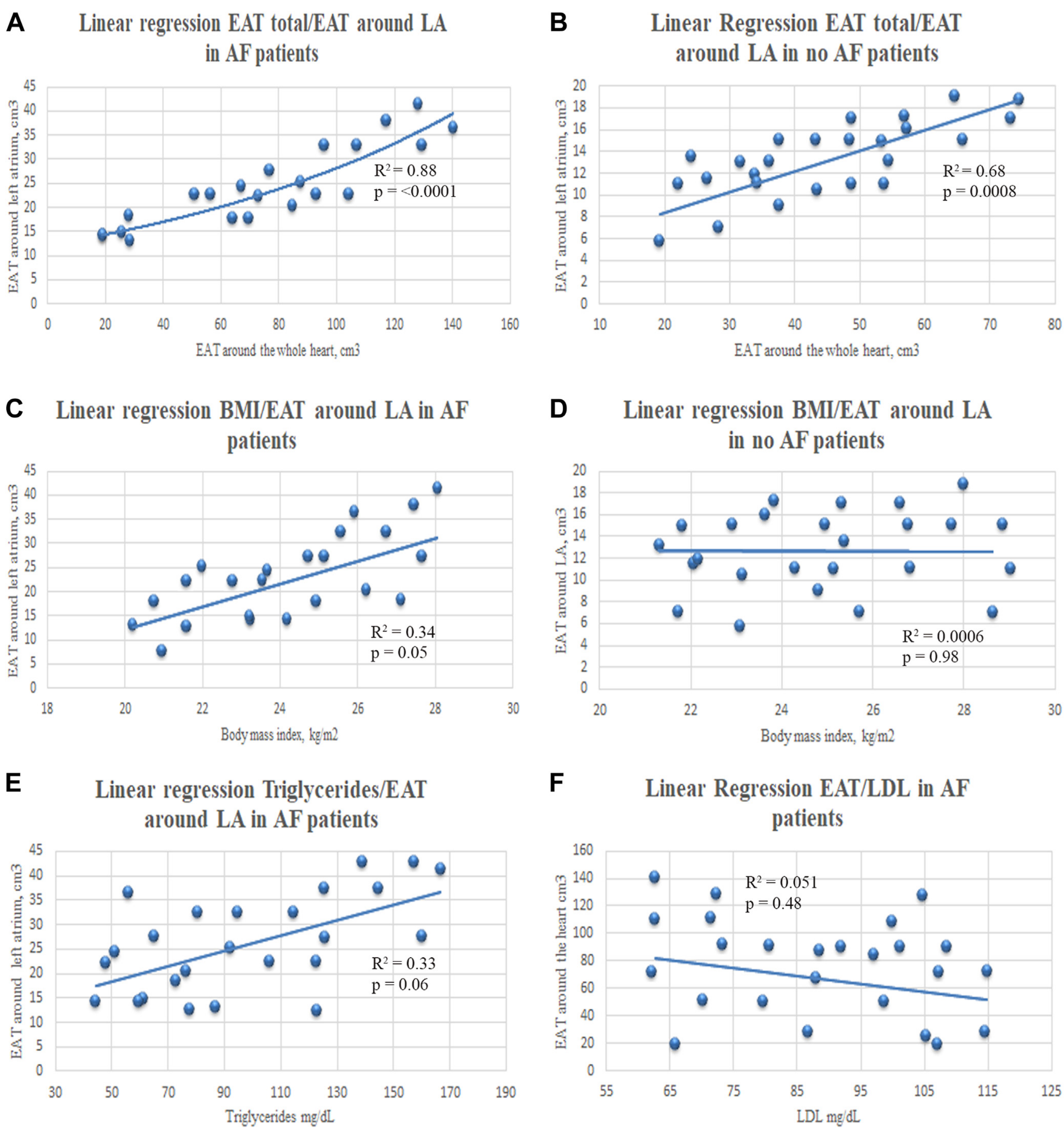

Figure 2 Pearson's correlations with epicardial adipose tissue (EAT). **A:** A strong correlation between the total amount of EAT and the volume around the left atrium (LA) in patients with atrial fibrillation (AF), which is maintained in patients with no AF even if less strong **(B)**. **C and D:** The correlation between EAT and body mass index (BMI), positive for AF patients, neutral/absent in patients with no AF. **E:** A positive, albeit weak and no statistically significant correlation between the LA-EAT volume and the triglycerides level in AF patients. **F:** A weak, negative correlation between EAT and low-density lipoprotein (LDL) cholesterol levels in AF patients.

in the AF group compared with the control group. Furthermore, it was demonstrated how EAT tends to overlie the major anatomical ganglionated plexi areas and complex fractionated atrial electrogram sites associated with AF.[15] CB ablation could affect these areas and may explain the long-term efficacy of the ablation, as shown also in our patients. The recurrence rate on our young population is consistent with other studies, around 30% to 35%. Recently, El Assaad and colleagues[16] published their study on 241 children and young adults. AF recurred in 39% during almost 2.5 years of follow-up. They also demonstrated well how family history could play a pivotal role in this group of young patients with AF. Patients with a first-degree family member, usually one of the parents, less often a sibling, having a

Table 3 Characteristics in patients treated with AF ablation with and without recurrence

Variable	Recurrence of AF: No	Recurrence of AF: Yes	P Value
Patients	21 (67.7)	10 (32.3)	
Age, y	27.6 ± 2.4	26.9 ± 3.1	.15*
BMI, kg/m^2	23.7± 1.2	25.4 ± 3.5	.42*
Height, cm	183.8 ± 5.6	173.2 ± 8.8	.03*
P-wave, ms	95.7 ± 8.4	107 ± 11.9	.08*
PR interval, ms	171.4 ± 21.7	165 ± 21.2	.64*
P/PR, %	56.5 ± 8.1	65.3 ± 2.7	.03*
First-degree relative with AF history	15/21 (71.4)	7/10 (70)	.89†
Total EAT index, cm^3/m^2	29.5 ± 12.6	34.1 ± 11.4	.76*
EAT around LA index, cm^3/m^2)	10.61 ± 3.8	11.8 ± 4.8	.65*
LA volume index, mL/m^2	47.4 ± 19.1	33.3 ± 7.5	.20*
LAA volume index, mL/m^2	3.86 ± 1.69	3.83 ± 2.1	.97*
Right-sided PVs anatomy			.04†
The more common R2a morphology	16/21 (76.2)	3/10 (30.0)	
Other variants	5/21 (23.8) (2-R3a; 3-R2b)	7/10 (70.0) (2-R3a; 2-R3b; 3-R2c)	
Left-sided PV anatomy			.88†
The more common L2b morphology	12 (57.2)	6 (60.0)	
Common ostium	9 (42.8)	4 (40.0)	
Left superior PV diameter, mm	20.4 ± 6.8	18.3 ± 3.2	.27*
Left inferior PV diameter, mm	19.1 ± 2.3	17.1 ± 1	.19*
Right superior PV diameter, mm	19.1 ± 2.5	17.1 ± 4.8	.38*
Right inferior PV diameter, mm	19.2 ± 2.4	15.8 ± 2.4	.13*

Values are mean ± SD or n (%).

AF = atrial fibrillation; BMI = body mass index; EAT = epicardial adipose tissue; LA = left atrium; LAA = left atrial appendage; PV = pulmonary vein.

*Student's *t* test.

†Chi-square/Fisher exact test.

history of AF before 50 years of age, were more likely to have AF and recurrences. We arrived at the same conclusion analyzing the AF patients and the control group. As described by El Assaad and colleagues, the incidence of recurrences was similar whether no treatment or a daily medication strategy was followed. We decided to stop antiarrhythmic drugs (flecainide) after 3 months, in order to cover only the blanking period. For all 62 patients, we took into consideration not only the P-wave duration and PR interval, but also, at the best of our knowledge for the first time, the P/PR ratio, to have more parameters of intra-atrial propagation, possibly suggestive of an underlying atrial myopathy.[17] For the AF group patients, the ECG data were collected before AF ablation, when off of any medications (beta-blocker and/or flecainide) for at least 5 days. The PR interval was longer in the AF patients compared with the control individuals, but when studying the group with AF recurrences, neither the P-wave duration nor the PR interval showed significant differences in the 2 groups. Nevertheless, a higher ratio between the P-wave and the PR interval (a longer P-wave in a normal/shorter PR) was significant, suggesting another possible parameter of atrial signal propagation or delay and likely of atrial myopathy, which when relevant, can contribute to possible recurrences. Interestingly, opposite to what we would expect,[18] the patients who had recurrences were usually less tall. The reason of that remains unclear.

Finally, looking at the anatomical variant of the PVs, among the patients with AF, we found a higher number of less common anatomy than in the control group, albeit not significant. Whereas looking at the group with recurrences and those free from arrhythmia, an uncommon right-sided PV anatomy seemed to increase the risk of new episodes of AF. This might be likely related to the procedure strategy itself, being very difficult sometimes with the CB to achieve proper PV isolation on the right side, particularly if there is a small intermediate branch or an ostium with an accentuated angle. No differences were found in terms of PV diameter in the 2 groups.

Study limitations

The single-center, retrospective nature of the study might result in selection bias of some data, especially for the control group. The relatively small number of patients and control individuals analyzed may have reduced the statistical significance of some results. Lack of long-term ambulatory monitoring, with possible underestimation of AF recurrences, is another limitation. Additional studies with a higher number of patients would be needed in order to corroborate these results and evaluate the outcome of the ablation possibly using other sources of energy and different mapping systems.

Conclusion

To the best of our knowledge, this is the first study in which the EAT volume, PVs anatomy, and some ECG features and indexes have been addressed in young patients with AF. Arrhythmia seems to be more common in male patients. The abundance of EAT around the LA seems to be related to the risks of developing AF in the contest of a heart with normal structure. Family history plays a pivotal role. The recurrence of AF is about 35% and does not seem related to the EAT volume, but rather to the anatomy of the PVs, in particular of the right-sided PVs and to some grade of atrial myopathy, probably related to the paracrine effect of the EAT. The P/PR ECG ratio seems to be a new potential predictor index of AF recurrences.

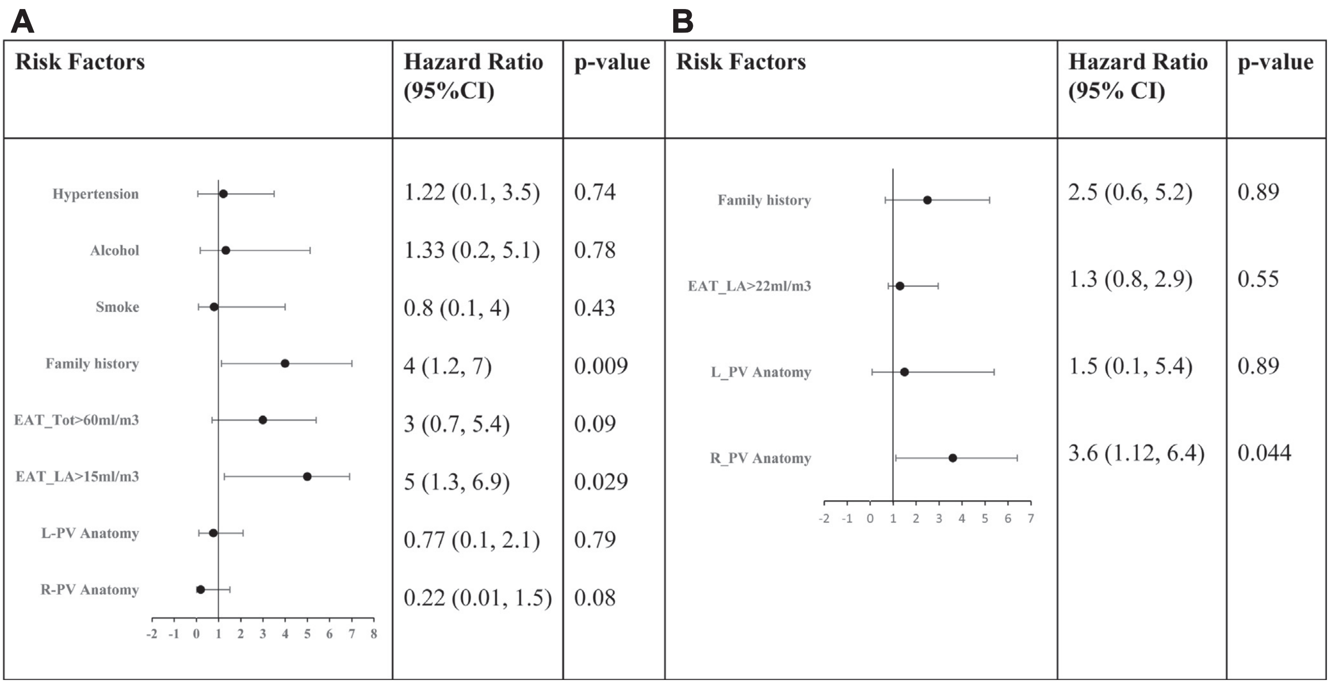

Figure 3 Forest plots from univariable and multivariable Cox proportional hazards model analysis. **A:** Analysis in all the young patients with atrial fibrillation (AF); family history and epicardial adipose tissue (EAT) volume around the left atrium (LA) higher than 15 cm^3 seem to be the 2 most significant risk factors for developing AF. **B:** Among the population with AF recurrence after ablation, the right-sided pulmonary vein (R-PV) anatomy appeared to be the strongest risk factor for recurrences. CI = confidence interval; L-PV = left-sided pulmonary vein.

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Ethics Statement: This study was reviewed and approved by our Institutional Ethical Board (Verona and Rovigo Ethical Committee). All the procedures reported were performed in accordance with relevant guidelines and regulations.

Data Availability: The data used and analyzed during this study are available from the corresponding author on reasonable request.

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