Multi-modality imaging in ischemic heart disease, arrhythmia and cardiac-mechanics

El Mahdiui, M.

Posterior left atrial adipose tissue attenuation assessed by computed tomography and recurrence of atrial fibrillation after catheter ablation

El Mahdiui M, Simon J, Smit JM, Kuneman JH, van Rosendael AR, Steyerberg EW, van der Geest RJ, Száraz L, Herczeg S, Szegedi N, Gellér L, Delgado V, Merkely B, Bax JJ, Maurovich-Horvat P.

Circ Arrhythm Electrophysiol. 2021 Apr;14(4):e009135.

ABSTRACT

Atrial fibrillation (AF) recurrence following catheter ablation remains high. Recent studies have shown a relation between epicardial adipose tissue (EAT) and AF. EAT secretes several pro- and anti-inflammatory adipokines that directly interact with the adjacent myocardium. The aim of the current study was to evaluate whether posterior left atrial (LA) adipose tissue attenuation, as marker of inflammation, is related to AF recurrences after catheter ablation. Consecutive patients with symptomatic AF referred for first AF catheter ablation who underwent CT were included. The total EAT and posterior LA adipose tissue were manually traced and adipose tissue was automatically recognized as tissue with Hounsfield units (HU) between -195 and -45. The attenuation value of the posterior LA adipose tissue was assessed and the population divided according to the mean HU value (-96.4 HU). In total, 460 patients (66% male, age 61 ± 10 years) were included in the analysis. After a median follow-up of 18 months (IQR 6-32), 168 (37%) patients had AF recurrence. Patients with higher attenuation (≥-96.4 HU) of the posterior LA adipose tissue showed higher AF recurrence rates compared to patients with lower attenuation (<-96.4 HU) (log-rank test p=0.046). Univariate analysis showed an association between AF recurrence and higher posterior LA adipose tissue attenuation (≥-96.4 HU) (p<0.05). On multivariable analysis posterior LA adipose tissue attenuation (HR 1.26; 95% CI 0.90-1.76; p=0.181) remained a promising predictor of AF recurrence following catheter ablation. In conclusion, posterior LA adipose tissue attenuation is a promising predictor of AF recurrence in patients who undergo catheter ablation. Higher adipose tissue attenuation might signal increased local inflammation and serve as an imaging biomarker of increased risk of AF recurrence.

INTRODUCTION

Atrial fibrillation (AF) remains the most prevalent arrhythmic disease worldwide and is associated with increased morbidity and mortality. Currently it is projected that AF prevalence will continue to rise, which is partially explained by increasing prevalence of obesity worldwide. Body mass index (BMI) is related to new-onset AF and patients with weight loss have reduced AF burden, symptom severity and less AF recurrences following AF catheter ablation.[1,2] However, AF recurrence rates are high following AF catheter ablation and adequate patient selection is crucial.[3] Recently, the relation between epicardial adipose tissue (EAT) surrounding the myocardium and AF has been reported.[4,5] EAT is a unique energy depot and is composed of adipocytes, stromovascular cells, immune cells, ganglia and interconnecting nerves.[6] There is no fascial layer separating the EAT and the myocardium which allows for direct paracrine and vasocrine effects on the myocardium.[6] This is important since EAT secretes both pro- and anti-inflammatory adipokines and direct effect on the myocardium has been demonstrated.[4] Computed tomography (CT) attenuation values for adipose tissue range between -195 and -45 Hounsfield units (HU).[7] Inflammation shifts the attenuation of the adipose tissue from a more lipid phase, closer to -195 HU, towards a more aqueous phase, closer to -45 HU. Attenuation of EAT on CT as a marker of inflammation has been linked to culprit coronary lesions in acute coronary syndrome[8] and cardiac mortality[9]. One study suggested a correlation between AF recurrence after AF catheter ablation and higher EAT attenuation, i.e. closer to -45 HU, obtained from one slice on a four-chamber view.[10] Volumetric assessment of EAT however may further increase accuracy since variability exists in EAT thickness at different myocardial regions.[11] Furthermore, recent studies have demonstrated that adipose tissue posterior to the left atrium (LA) had the strongest relationship with AF.[12,13] Whether the posterior LA adipose tissue mass and/or attenuation are related to AF recurrence following AF catheter ablation is evaluated in the current study.

METHODS

Patient population

The data that support the findings of this study are available upon reasonable request to the corresponding author. Consecutive patients with symptomatic AF who underwent preprocedural CT imaging for a first AF catheter ablation between January 2014 and June 2018 at the Heart and Vascular Center of the Semmelweis University Hungary, were included. CT was performed for evaluation of LA anatomical characteristics and location of pulmonary veins. Patients with uninterpretable CT images or who did not undergo a catheter ablation procedure after CT were excluded. Patients were followed at the outpatient clinic and a three month blanking period was implemented for AF recurrence following catheter ablation. Outpatient clinical visits were scheduled at 3, 6 and 12 months and at least yearly thereafter or when patients experienced symptoms. Follow-up visits included clinical assessment, 12-lead ECG and 24h Holter monitoring. Recurrence was prospectively recorded in the electronical medical records and defined as documented AF or atrial tachycardia episode lasting for more than 30seconds. Echocardiographic data, including left ventricular ejection fraction (LVEF) and E/A-ratio were collected from the echocardiographic database. Demographic and clinical data were collected from the electronic medical records. For retrospective analysis of clinically acquired data, the institutional review board waived the need of written patient informed consent. All data used for this study were acquired for clinical purposes and handled anonymously.

CT acquisition

Patients were scanned using a 256-slice CT scanner (Brilliance iCT 256, Phillips Healthcare, Best, The Netherlands) with 270msec rotation-time, 128 x 0.625mm collimation and tube voltage of 100-120kV. Patients were pretreated with beta-blockers if the heart rate exceeded 65 beats per minutes. Four-phasic injection protocol with 85-95ml of iodinated contrast agent was used (Iomeron 400, Bracco Ltd; Milan, Italy) at a rate of 4.5-5.5ml/s. CT was acquired using prospective ECG-gating covering 75 to 81% of the RR-interval. The CT datasets were reconstructed with 0.8mm slice thickness and 0.4mm increment with hybrid iterative reconstruction technique (iDose5, Philips Healthcare, Best, The Netherlands)

CT image and LA adipose tissue analysis

LA adipose tissue measurements were performed using MASS software (Leiden University Medical Centre, Leiden, the Netherlands) as described previously.[14] In short, a cross-sectional view of the LA was obtained from the mitral annulus to the LA roof from reconstructed two-and four-chamber views with a slice thickness of 2mm. The LA adipose tissue located posterior of the LA was manually traced from the base of the LA until the mitral annulus. Adipose tissue was automatically recognized by the software as tissue with HU between -195 and -45 and the mean HU of the adipose tissue was calculated (Figure S1 in Data Supplement). LA volume was calculated on CT images using IntelliSpace Portal (Philips Healthcare, Best, The Netherlands).

Catheter ablation procedure

The indications for performed AF ablation procedures were in accordance with the current guidelines.[15] Paroxysmal AF was defined as self-terminating AF, while persistent AF was defined as AF lasting longer than 7 days.[15] Intravenous fentanyl, midazolam, and propofol were used in all cases for conscious sedation. Femoral venous access was used for all procedures. Transseptal puncture was performed under fluoroscopy positioning and pressure monitoring. Intracardiac echocardiography was used for visualization of the interatrial septum in case of difficulty in performing safe transseptal puncture. An electroanatomical mapping system (CARTO, Biosense Webster, Inc., Diamond Bar, CA, USA or ENSITE, St. Jude Medical, Inc., MN, USA), and left atrial fast anatomical map was merged with the cardiac CT images to guide ablation. Temperature controlled ablation was performed with an irrigated 4mm tip catheter, with an standard target power delivery of 25-35W in the majority of cases. Pulmonary vein isolation was the goal of each initial procedure.

Statistical analysis

Categorical variables are presented as frequencies and percentages. Continuous variables are presented as mean ± standard deviation (SD) if normally distributed and median and interquartile range (IQR) if not normally distributed. Categorical variables were compared using the $\chi 2$ test. Continuous variables were compared using the Student's *t*-test if normally distributed and the Mann-Whitney *U*-test if not normally distributed. The relation of BMI with total EAT, posterior LA adipose tissue mass and attenuation was investigated using Pearson correlation. Recurrent

AF incidence rates were calculated from the end of the blanking period. Kaplan-Meier analysis was performed for cumulative AF recurrence. The study population was divided into two groups according to the mean posterior LA adipose tissue attenuation (-96.4 HU) and compared with a log-rank test. We performed a multivariable Cox proportional-hazards analyses and adjusted posterior LA adipose tissue mass and attenuation for age[16], sex[3], type of AF[3], BMI[2], antiarrhythmic drugs[17], LVEF[18], E/A-ratio[18] and LA volume[19]. Any missing values among these variables were statistically imputed. Four observers independently performed all measurements and were blinded to patient outcome data. Ten patients were randomly selected for inter-observer agreement and analyzed using inter-class correlation coefficient. A p-value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 23.0 (SPSS, Armonk, NY, USA).

RESULTS

Patient characteristics

A total of 460 patients (66% male, age 61 ± 10 years) were included in the analysis. Clinical characteristics are shown in Table 1. There were 168 (37%) patients that developed AF recurrence after catheter ablation during a median follow-up period of 18 months (IQR 6-32). Patients with AF recurrence after catheter ablation were older (62 ± 10 vs 60 ± 10 years; p=0.038), more often females (42 vs 30%, p=0.012) and had more often persistent AF (33 vs 18%, p<0.001).

Table 1. Patient characteristics

	Total patients (n=460)	With recurrence (n=168)	No recurrence (n=292)	p-value
Clinical variables				
Age (years)	61±10	62±10	60±10	0.038
Male, n(%)	302 (66)	98 (58)	204 (70)	0.012
BMI (kg/m^2)	29±5	29±5	29±4	0.285
Persistent AF, n(%)	106 (23)	54 (32)	52 (18)	<0.001
Hypertension, n(%)	330 (72)	125 (74)	205 (70)	0.335
Diabetes mellitus, n(%)	70 (15)	22 (13)	48 (16)	0.336
Hyperlipidemia, n(%)	116 (25)	43 (26)	73 (25)	0.887

Table 1. Continued.

	Total patients (n=460)	With recurrence (n=168)	No recurrence (n=292)	p-value
Smoking, n(%)	130 (28)	59 (35)	71 (24)	0.054
Prior myocardial infarction, n(%)	14 (3)	6 (4)	8 (3)	0.689
Medication				
Antiarrhythmic drugs	252 (55)	98 (58)	154 (53)	0.347
β-blocker	147 (32)	53 (32)	94 (32)	0.702
Calcium antagonist	70 (15)	23 (14)	47 (16)	0.393
ACE-I/ARB	144 (31)	51 (30)	93 (32)	0.551
Diuretics	91 (20)	34 (20)	57 (20)	0.996
Statins	164 (36)	64 (38)	100 (34)	0.583
Aspirin	52 (11)	18 (11)	34 (12)	0.660
Coumarins	193 (42)	79 (47)	114 (39)	0.095
DOAC's	153 (33)	55 (33)	98 (34)	0.857
Laboratory findings				
eGFR ml/min/1.73 m2	82 (60-90)	83 (60-90)	80 (60-90)	0.779

Values are mean ± standard deviation if normally distributed and median (interquartile range) if not normally distributed.
ACE-I: angiotensin-converting enzyme inhibitor, AF: atrial fibrillation, ARB: angiotensin receptor blocker, BMI: body mass index, DOAC's: directly acting oral anticoagulants, eGFR: estimated glomerular filtration rate.

Imaging variables

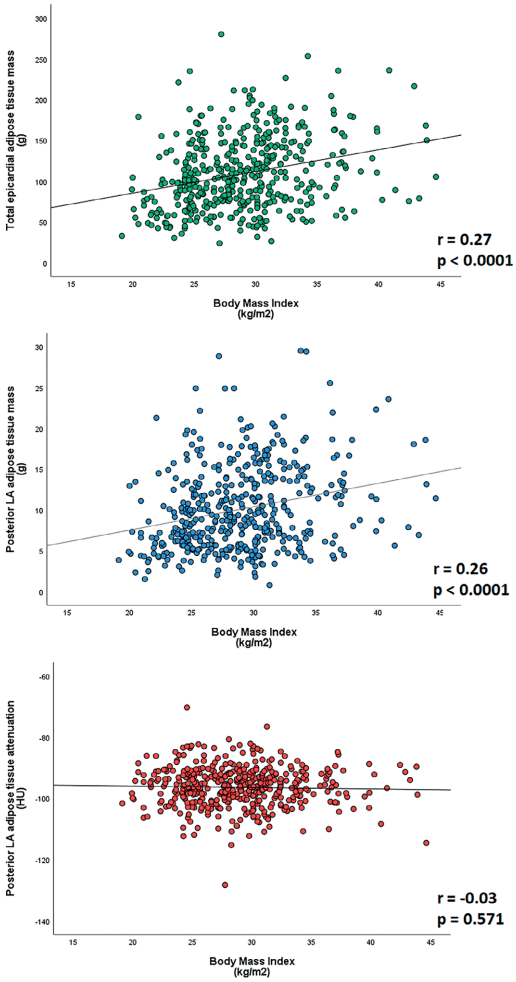
Imaging variables of the total population, patients with and without AF recurrence are shown in Table 2. Patients with AF recurrence had significantly more often LVEF dysfunction (6 vs 2%, P=0.031), larger LA volumes (108 ± 32ml vs 97 ± 24ml, p<0.001) and more often higher attenuation (≥-96.4 HU) of the posterior LA adipose tissue (60 vs 50%, p=0.041). The sensitivity and specificity for the mean posterior LA adipose tissue was 60% and 50%, respectively. There was a weak but significant correlation between BMI and total EAT (r=0.27, p<0.0001) and between BMI and posterior LA adipose tissue mass (r=0.26, p<0.0001). No significant correlation was found for BMI and posterior LA adipose tissue attenuation (r=0.03, p=0.571) (Figure 1).

Table 2. Imaging variables of the total population and stratified according to recurrence

	Total patients (n=460)	With recurrence (n=168)	No recurrence (n=292)	p-value
Echocardiographic variables				
LVEF<50%, n(%)	16 (4)	10 (6)	6 (2)	0.031
E/A-ratio	1.2±0.4	1.2±0.4	1.2±0.4	0.557
CT variables				
LA volume (ml)	101±28	108±32	97±24	<0.001
Posterior LA adipose tissue mass (g)	10.1±5.1	10.0±5.0	10.1±5.1	0.923
Total epicardial adipose tissue mass (g)	109±44	111±43	108±45	0.488
Posterior LA adipose tissue attenuation (HU)	-96.4±7.9	-95.6±6.2	-96.8±8.7	0.098
Posterior LA adipose tissue attenuation ≥ -96.4 HU, n(%)	245 (53)	100 (60)	145 (50)	0.041

Values are mean ± standard deviation if normally distributed and median (interquartile range) if not normally distributed.
CT: computed tomography, HU: Hounsfield units, LA: left atrial, LVEF: left ventricular ejection fraction,

Figure 1. Correlations between BMI, total EAT, posterior LA adipose tissue mass and attenuation.



The relation between BMI and total EAT, BMI and posterior LA adipose tissue mass and attenuation.
BMI: body mass index, g: gram, HU: Hounsfield units, LA: left atrium.

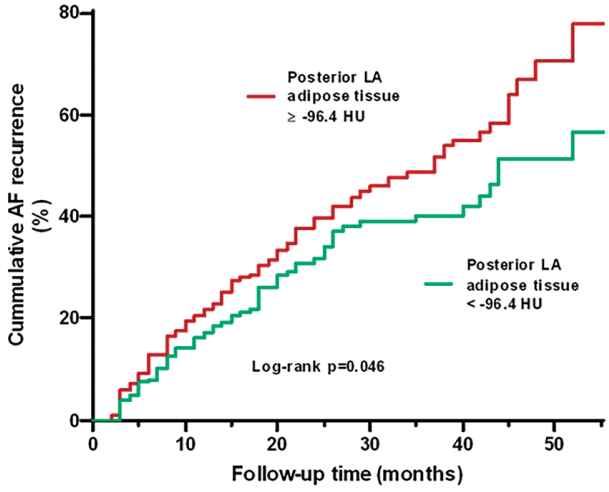
Posterior LA adipose tissue attenuation and AF recurrence

Patients with higher posterior LA adipose tissue attenuation (≥-96.4 HU) had more cumulative recurrence rates of AF than patients with lower posterior LA adipose tissue attenuation (<-96.4 HU) by Kaplan-Meier analysis (log-rank test p=0.046; Figure 2). Table 3 summarizes the Cox regression analysis of the posterior LA

adipose tissue mass and attenuation for AF recurrence following catheter ablation. After correcting for known associates of AF recurrence posterior LA adipose tissue attenuation (HR 1.26; 95% CI 0.90-1.76; p=0.181) remained a promising predictor of AF recurrence following catheter ablation.

The inter-class correlation coefficient for inter-observer variability for posterior LA adipose tissue mass was 0.995 (95% CI 0.988-0.999; p<0.001) and for LA adipose tissue attenuation 0.990 (95% CI 0.971-0.997; p<0.001).

Figure 2. Kaplan-Meier curve for atrial fibrillation recurrence following catheter ablation according to posterior LA adipose tissue attenuation.



AF: atrial fibrillation, HU: Hounsfield units, LA: left atrial

Table 3. Uni- and multivariable Cox regression analysis for atrial fibrillation recurrence following catheter ablation.

	Univariable Hazard ratio (95% CI)	p-value	Multivariable Hazard ratio (95% CI)	p-value
Posterior LA adipose tissue mass (per one unit increase)	1.00 (0.97-1.03)	0.970	1.01 (0.97-1.04)	0.759
Posterior LA adipose tissue attenuation ≥ -96.4 HU(yes/no)	1.37 (1.00-1.86)	0.047	1.26 (0.90-1.76)	0.181

* Adjusted for age, sex, AF type, body mass index, use of antiarrhythmic drugs, left ventricular ejection fraction <50%, E/A-ratio and left atrial volume.
CI = confidence interval, HU = Hounsfield units, LA = left atrial

DISCUSSION

The current study demonstrated that patients with higher posterior LA adipose tissue attenuation had significantly more often AF recurrences following AF catheter ablation. After correction for several known risk factors for AF recurrences following catheter ablation, higher posterior LA adipose tissue attenuation remained a promising predictor of AF recurrence.

EAT and AF

Recently, obesity has been recognized as an important, and modifiable risk factor for AF development.[1,2] Although BMI has been used as a marker of general adiposity, it incorporates both subcutaneous and visceral adipose tissue, despite both structures being distinct.[20] Of note, higher levels of proinflammatory adipokines are secreted by visceral adipose tissue as compared to subcutaneous adipose tissue, and visceral adipose tissue has been associated with a greater risk for cardiovascular diseases.[6,8,9,20] EAT, the adipose tissue within the visceral layer of the pericardium, has demonstrated to be an important source of adipokines.[6] Total EAT is a stronger predictor for the presence of AF as compared to BMI.[5] More specifically, the relation between peri-atrial EAT and AF was examined in a population of 618 patients in sinus rhythm or with AF. Although, peri-atrial EAT thickness was higher in patients with AF compared to those in sinus rhythm, posterior LA adipose tissue thickness had the strongest correlation with the occurrence of AF of all LA adipose tissue pads.[13] Moreover, Batal et al. reported that only posterior LA adipose tissue thickness was significantly associated with AF burden.[12] Subsequently, Rosendael and colleagues quantified the posterior LA adipose tissue and found that each gram increase in posterior LA adipose tissue mass was associated with an increase of 32% in the risk of AF.[14] While some studies also demonstrated a relation between peri-atrial EAT assessed on CT and late AF recurrence after ablation,[21-23] others could not confirm this relation.[24,25] This discrepancy could be explained by methodological differences in assessment of peri-atrial EAT. Likewise, in the current study we could not demonstrate an association indicating that the quantity of posterior LA adipose tissue might not be an important measure for predicting AF recurrence. Another explanation could be related to the large posterior LA adipose tissue mass (mean 10.1 gram) found in our population. The higher BMI in the current population, compared to populations in previous studies, suggest higher adiposity and higher peri-atrial EAT in the current population. It may be that the posterior

LA adipose tissue mass has reached the maximum mass in both the recurrence and no-recurrence groups. This is further supported by the higher total EAT in the current population compared to previous studies.[21,25]

Inflammation and AF

Histological examination of atrial tissue in patients with AF has shown evidence of inflammation.[26] Various clinical studies have also reported a relation between inflammation and AF.[27,28] Specifically, systemic inflammatory biomarkers are increased in AF patients while anti-inflammatory therapy decreases the AF risk.[27-29] However, systemic inflammatory biomarkers might not represent inflammatory activity at the tissue level.[30] The close proximity of EAT to the LA, the ability of EAT to produce inflammatory adipokines and its association with AF makes EAT an attractive target for measuring inflammation in AF patients. Mazurek et al. quantified the inflammatory activity of EAT, visceral thoracic adipose tissue and subcutaneous adipose tissue using ^{18}F-fluorodeoxyglucose positron emission tomography in 21 patients with AF and 21 controls.[31] Inflammatory activity of EAT in AF patients was significantly higher compared to controls. Moreover, inflammatory activity of EAT was higher compared to subcutaneous adipose tissue and even thoracic visceral adipose tissue in AF patients.[31] Ciuffo et al. demonstrated in 143 patients that increased attenuation (as a marker of inflammation) of peri-atrial adipose tissue measured from a single slice four-chamber view on CT was a predictor of AF recurrence after catheter ablation.[10] However, in the same study attenuation of the peri-atrial adipose tissue measured from the two-chamber view was not associated with AF recurrence, highlighting the variability of the EAT at different myocardial regions and the importance of volumetric quantification of EAT.[11] The results from the current study demonstrate similar findings, using volumetric quantification in a larger patient population: more inflamed peri-atrial adipose tissue is associated with AF recurrence after catheter ablation. Several explanations for this relation could be considered. A more inflamed atrial wall might impede adequate lesion transmurality during ablation through the formation of edema.[32] Another explanation might be the formation of atrial fibrosis through localized inflammatory processes induced by EAT.[30] Atrial fibrosis might enable the formation of intra-atrial re-entry circuits and the presence of atrial fibrosis reduces catheter ablation success.[33] While we observed similar posterior LA adipose tissue mass between those patients that experienced AF recurrence and those patients that did not, patients with AF recurrence had larger LA volumes. Increasing LA

volumes leads to more enhanced stretching of the LA wall allowing for a larger contact area between the EAT and the LA wall. As the inflammatory adipokines of EAT directly exert their action on the LA wall through paracrine effects,[6] in addition to the attenuation of the posterior LA adipose tissue, the contact area between the EAT and the LA wall might also be an important factor in AF recurrences.

Assessment of the posterior LA adipose tissue attenuation on CT is a novel and easily accessible tissue specific biomarker of inflammation prior to AF catheter ablation. Moreover, attenuation of peri-vascular EAT assessed from CT could be a marker to track response to anti-inflammatory therapy.[34] In addition, several studies have demonstrated that anti-inflammatory therapy reduces the risk for AF.[28,29] Assessment of posterior LA adipose tissue attenuation may potentially guide/personalize the use of anti-inflammatory therapy to reduce AF recurrences.

Study limitations

This was a single center study with a retrospective design. Patients with inadequate CT quality were excluded, which may have introduced selection bias. Moreover, the attenuation values reported in this study may be limited to this specific CT scanner and should be validated with other CT scanners. The optimal cut-off values found in this study population should be confirmed in future studies including larger populations and using different CT scanners. Such validation is important to further assess the role of posterior LA adipose tissue attenuation before clinical implementation. Since AF recurrences were defined as documented episodes and we did not solely rely on reported complaints, some patients with recurrences might have been missed.

CONCLUSIONS

Posterior LA adipose tissue attenuation is a promising novel and tissue specific biomarker of AF recurrence. Higher attenuation of the posterior LA adipose tissue might signal local inflammation and serve as an imaging biomarker of increased risk of AF recurrence.

REFERENCES

1. Wang TJ, Parise H, Levy D, D'Agostino RB, Sr., Wolf PA, Vasan RS, et al. Obesity and the risk of new-onset atrial fibrillation. JAMA 2004;292:2471-2477.
2. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. J Am Coll Cardiol 2014;64:2222-2231.
3. Sultan A, Luker J, Andresen D, Kuck KH, Hoffmann E, Brachmann J, et al. Predictors of Atrial Fibrillation Recurrence after Catheter Ablation: Data from the German Ablation Registry. Sci Rep 2017;7:16678.
4. Sacks HS, Fain JN. Human epicardial adipose tissue: a review. Am Heart J 2007;153:907-917.
5. Thanassoulis G, Massaro JM, O'Donnell CJ, Hoffmann U, Levy D, Ellinor PT, et al. Pericardial fat is associated with prevalent atrial fibrillation: the Framingham Heart Study. Circ Arrhythm Electrophysiol 2010;3:345-350.
6. Iacobellis G. Local and systemic effects of the multifaceted epicardial adipose tissue depot. Nat Rev Endocrinol 2015;11:363-371.
7. Maurovich-Horvat P, Massaro J, Fox CS, Moselewski F, O'Donnell CJ, Hoffmann U. Comparison of anthropometric, area- and volume-based assessment of abdominal subcutaneous and visceral adipose tissue volumes using multi-detector computed tomography. Int J Obes (Lond) 2007;31:500-506.
8. Goeller M, Achenbach S, Cadet S, Kwan AC, Commandeur F, Slomka PJ, et al. Pericoronary Adipose Tissue Computed Tomography Attenuation and High-Risk Plaque Characteristics in Acute Coronary Syndrome Compared With Stable Coronary Artery Disease. JAMA Cardiol 2018;3:858-863.
9. Oikonomou EK, Marwan M, Desai MY, Mancio J, Alashi A, Hutt Centeno E, et al. Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP CT study): a post-hoc analysis of prospective outcome data. Lancet 2018;392:929-939.
10. Ciuffo L, Nguyen H, Marques MD, Aronis KN, Sivasambu B, de Vasconcelos HD, et al. Periatrial Fat Quality Predicts Atrial Fibrillation Ablation Outcome. Circ Cardiovasc Imaging 2019;12:e008764.
11. Lemola K, Sneider M, Desjardins B, Case I, Han J, Good E, et al. Computed tomographic analysis of the anatomy of the left atrium and the esophagus: implications for left atrial catheter ablation. Circulation 2004;110:3655-3660.
12. Batal O, Schoenhagen P, Shao M, Ayyad AE, Van Wagoner DR, Halliburton SS, et al. Left atrial epicardial adiposity and atrial fibrillation. Circ Arrhythm Electrophysiol 2010;3:230-236.
13. Yorgun H, Canpolat U, Aytemir K, Hazirolan T, Sahiner L, Kaya EB, et al. Association of epicardial and peri-atrial adiposity with the presence and severity of non-valvular atrial fibrillation. Int J Cardiovasc Imaging 2015;31:649-657.
14. van Rosendael AR, Dimitriu-Leen AC, van Rosendael PJ, Leung M, Smit JM, Saraste A, et al. Association Between Posterior Left Atrial Adipose Tissue Mass and Atrial Fibrillation. Circ Arrhythm Electrophysiol 2017;10.
15. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace 2016;18:1609-1678.

16. Bunch TJ, May HT, Bair TL, Jacobs V, Crandall BG, Cutler M, et al. The Impact of Age on 5-Year Outcomes After Atrial Fibrillation Catheter Ablation. J Cardiovasc Electrophysiol 2016;27:141-146.

17. Duytschaever M, Demolder A, Phlips T, Sarkozy A, El Haddad M, Taghji P, et al. PulmOnary vein isolation With vs. without continued antiarrhythmic Drug trEatment in subjects with Recurrent Atrial Fibrillation (POWDER AF): results from a multicentre randomized trial. Eur Heart J 2018;39:1429-1437.

18. Cha Y-M, Wokhlu A, Asirvatham SJ, Shen W-K, Friedman PA, Munger TM, et al. Success of Ablation for Atrial Fibrillation in Isolated Left Ventricular Diastolic Dysfunction. Circ Arrhythm Electrophysiol 2011;4:724-732.

19. Njoku A, Kannabhiran M, Arora R, Reddy P, Gopinathannair R, Lakkireddy D, et al. Left atrial volume predicts atrial fibrillation recurrence after radiofrequency ablation: a meta-analysis. *EP* Europace 2017;20:33-42.

20. Oikonomou EK, Antoniades C. The role of adipose tissue in cardiovascular health and disease. Nat Rev Cardiol 2019;16:83-99.

21. Nagashima K, Okumura Y, Watanabe I, Nakai T, Ohkubo K, Kofune T, et al. Association between epicardial adipose tissue volumes on 3-dimensional reconstructed CT images and recurrence of atrial fibrillation after catheter ablation. Circ J 2011;75:2559-2565.

22. Tsao HM, Hu WC, Wu MH, Tai CT, Lin YJ, Chang SL, et al. Quantitative analysis of quantity and distribution of epicardial adipose tissue surrounding the left atrium in patients with atrial fibrillation and effect of recurrence after ablation. Am J Cardiol 2011;107:1498-1503.

23. Kocyigit D, Gurses KM, Yalcin MU, Turk G, Evranos B, Yorgun H, et al. Periatrial epicardial adipose tissue thickness is an independent predictor of atrial fibrillation recurrence after cryoballoon-based pulmonary vein isolation. J Cardiovasc Comput Tomogr 2015;9:295-302.

24. Vroomen M, Olsthoorn JR, Maesen B, L'Espoir V, La Meir M, Das M, et al. Quantification of epicardial adipose tissue in patients undergoing hybrid ablation for atrial fibrillation. Eur J Cardiothorac Surg 2019;56:79-86.

25. Masuda M, Mizuno H, Enchi Y, Minamiguchi H, Konishi S, Ohtani T, et al. Abundant epicardial adipose tissue surrounding the left atrium predicts early rather than late recurrence of atrial fibrillation after catheter ablation. J Interv Card Electrophysiol 2015;44:31-37.

26. Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. Circulation 1997;96:1180-1184.

27. Chung MK, Martin DO, Sprecher D, Wazni O, Kanderian A, Carnes CA, et al. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. Circulation 2001;104:2886-2891.

28. Peña JM, MacFadyen J, Glynn RJ, Ridker PM. High-sensitivity C-reactive protein, statin therapy, and risks of atrial fibrillation: an exploratory analysis of the JUPITER trial. Eur Heart J 2012;33:531-537.

29. Halonen J, Halonen P, Järvinen O, Taskinen P, Auvinen T, Tarkka M, et al. Corticosteroids for the prevention of atrial fibrillation after cardiac surgery: a randomized controlled trial. JAMA 2007;297:1562-1567.

30. Abe I, Teshima Y, Kondo H, Kaku H, Kira S, Ikebe Y, et al. Association of fibrotic remodeling and cytokines/chemokines content in epicardial adipose tissue with atrial myocardial fibrosis in patients with atrial fibrillation. Heart rhythm 2018;15:1717-1727.

31. Mazurek T, Kiliszek M, Kobylecka M, Skubisz-Gluchowska J, Kochman J, Filipiak K, et al. Relation of proinflammatory activity of epicardial adipose tissue to the occurrence of atrial fibrillation. Am J Cardiol 2014;113:1505-1508.

32. Taclas JE, Nezafat R, Wylie JV, Josephson ME, Hsing J, Manning WJ, et al. Relationship between intended sites of RF ablation and post-procedural scar in AF patients, using late gadolinium enhancement cardiovascular magnetic resonance. Heart rhythm 2010;7:489-496.

33. Verma A, Wazni OM, Marrouche NF, Martin DO, Kilicaslan F, Minor S, et al. Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: an independent predictor of procedural failure. J Am Coll Cardiol 2005;45:285-292.

34. Elnabawi YA, Oikonomou EK, Dey AK, Mancio J, Rodante JA, Aksentijevich M, et al. Association of Biologic Therapy With Coronary Inflammation in Patients With Psoriasis as Assessed by Perivascular Fat Attenuation Index. JAMA Cardiol 2019;4:885-891.