



## Editorial

## Fat chance for POAF? Pericardial adipose tissue and the arrhythmogenic substrate for postoperative atrial fibrillation



Atrial fibrillation (AF) is the most common arrhythmia affecting more than 43 million people globally [1]. In addition, post-operative AF (POAF) is a common complication of cardiac and non-cardiac surgery, associated with prolonged hospitalization and increased risk of future adverse events, including AF recurrence [2]. Despite the substantial progress in the understanding of the mechanisms underlying different forms of AF [3], currently available therapies have limited efficacy and there are many obstacles in the translation of basic science findings to the clinical management of AF [4,5]. Thus, there is a clear unmet need for novel anti-AF therapeutics.

Pericardial adipose tissue is increasingly recognized as a potential contributor to AF pathogenesis [6]. It constitutes a specialized depot of visceral fat comprising paracardial adipose tissue, which includes the total amount of fat on the external surface of the parietal pericardium, and epicardial adipose tissue (EAT), which is located between the myocardium and visceral pericardium. Accumulating epidemiological evidence [7] suggests a significant correlation between the size of pericardial adipose tissue, mainly EAT, and the development of POAF (Table 1). Pericardial fat volume, assessed by computed tomography (CT), strongly predicts the risk of POAF independent of other clinical factors [8]. Similarly, CT-derived left atrial (LA) EAT volume predicts the occurrence of POAF [9], whereas total-EAT was not an independent predictor of POAF risk in another study using similar cardiac fat imaging techniques [10]. Kogo et al. [11] demonstrated that CT scan-derived LA/total-EAT ratio may also predict the development of POAF. In two other studies [12,13], employing transthoracic echocardiography (TTE) to assess total-EAT, a cut-off for total-EAT of 7.05–7.20 mm was found to predict POAF. Together, these studies clearly show that both imaging approaches (TTE and CT) can be used to demonstrate the relationship between cardiac fat and POAF, although modality-specific cut-offs values and standardized imaging criteria for cardiac fat assessment are clearly warranted.

The exact underlying heart disease predisposing to POAF could also influence the predictive value of EAT. In one study [12], in which a substratification of patients with and without valvular heart disease (VHD) was performed, showed that the incidence of POAF is much higher in patients with VHD (41%) compared to those without VHD (30%). Interestingly, while total-EAT was independently associated with POAF in the control group without VHD, this association was absent in the VHD group. These data suggest that proper clinical matching of patient groups is essential to unmask the potential link between EAT size and POAF risk.

In the present issue of the journal the potential relationship between EAT size and POAF risk was addressed in 83 patients undergoing cardiac surgery [14], of which more than 50% developed POAF. Advanced age and LA volume index were independent predictors of POAF, consistent with previous findings [2], whereas the amount of LA-EAT was not significantly associated with POAF occurrence. The authors rightfully stressed that the lack of significant association between EAT size and POAF risk in their study does not indicate that the content of EAT of patients with and without POAF did not differ. EAT from POAF patients might still contain adipocytes with increased inflammatory signaling, altered metabolism, along with a stronger fibro-fatty infiltration of the atrial myocardium. Indeed, the activity of the atrial NACHT, LRR, and PYD Domains-containing Protein 3 (NLRP3) inflammasome is higher in patients prone to POAF [15] and increases with body mass elevation in patients and in obese mice as compared to respective controls [16]. Although the upstream mechanisms of NLRP3 inflammasome triggering in obesity are unknown, saturated fatty acids such as palmitate, which is highly abundant in EAT [17], could serve as upstream triggers. Since the NLRP3 inflammasome has also been shown to be regulated by adipokines [18], mechanistic studies addressing the impact of pericardial fat-secreted adipokines on NLRP3-inflammasome-dependent arrhythmogenesis are clearly warranted.

Novel techniques assessing *in vivo* the metabolic and inflammatory potential and other properties of EAT are clearly required to delineate the putative role of EAT in cardiac arrhythmogenesis. For instance, volumetric EAT assessment could be combined with the detection of sympathetic activity by metaiodobenzylguanidine scintigraphy, or with the assessment of inflammation and/or metabolic activity by fluorodeoxyglucose-positron emission tomography/CT, along with an assessment of classical indices of AF risk. Although such a panel of co-factors might help to better predict (PO)AF risk and the response to anti-arrhythmic approaches, the lack of validated or indexed threshold EAT volumes for a greater AF risk remains a major limitation of contemporary EAT quantification methods. High resolution 3D imaging methods such as the Dixon technique are constantly evolving for improved depiction of the heart and the surrounding fat, with lower intra- and inter-user variability [19]. Importantly, these innovative approaches can quantify not just EAT volume, but also its density, providing complementary information on the changing geometry over time [20]. *Ex vivo* magnetic resonance imaging for 3D quantification of the different LA components, including fibro-fatty infiltrates, in combination with histology [21], could also provide useful insights about

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**Table 1**  
Available studies assessing the relationship between postoperative atrial fibrillation and size of epicardial adipose tissue.

Reference	Study group	Technique	Cardiac fat part	Correlation between cardiac fat part in POAF vs Ctl
van der Heijden et al. the Netherlands 2022 [14]	POAF (n = 43, age 64 ± 9, 77% men, BMI 27 ± 3.7) Ctl (n = 40, age 61 ± 11, 75% men, BMI 27 ± 3.8)	CT	LA-EAT (volume)	- POAF vs Ctl: 0.68 [0.51–1.04] vs 0.67 [0.41–0.97] ml, P = 0.43 - LA-EAT not independently associated with POAF
Ozbek et al. [10] Turkey 2018	POAF (n = 35, age 69 ± 8.3, 66% men, BMI 29 ± 5.8) Ctl (n = 114, age 62 ± 9.1, 80% men, BMI 28 ± 3.9)	CT	Total-EAT (volume)	- POAF vs Ctl: 136 ± 47 vs 119 ± 43 cm <sup>3</sup> , P = 0.046 - Total-EAT not independently associated with POAF
Guntruk et al. [12] Turkey 2020	POAF (n = 45, age 66 ± 5.4, 52% men, BMI 27 ± 1.9) Ctl (n = 80, age 65 ± 7.1, 50% men, BMI 27 ± 2.3)	TTE	Total-EAT (thickness)	- POAF vs Ctl: 7.3 ± 0.6 vs 6.4 ± 0.4 mm, P < 0.01 - Total-EAT (OR 4.47, 95% CI 3.07–5.87) independently associated with POAF - Cut-off for total-EAT to predict POAF was 7.05 mm (67% sensitivity, 61% specificity)
Wang et al. [13] China 2019	VHD-POAF (n = 20, age 62 ± 6.8, 50% men, BMI 22 ± 4.2) VHD-Ctl (n = 29, age 56 ± 11, 45% men, BMI 22 ± 5.7) Non-VHD-POAF (n = 12, age 60 ± 5.2, 58% men, BMI 22 ± 2.7) Non-VHD-Ctl (n = 28, age 56 ± 10, 54% men, BMI 21 ± 2.8)	TTE	Total-EAT (thickness)	- VHD-POAF vs VHD-Ctl: 7.6 ± 0.7 vs 7.1 ± 1.1 mm, P = NS - Non-VHD-POAF vs non-VHD-Ctl: 7.6 ± 1.0 vs 6.1 ± 0.9 mm, P < 0.05 - Total-EAT (OR 2.52, 95% CI 1.06–6.00) independently associated with POAF - Cut-off for total-EAT to predict POAF was: ≥7.2 mm (sensitivity 69%, specificity 79%) (overall) ≥6.5 mm (sensitivity 100%, specificity 59%) (VHD) ≥7.1 mm (sensitivity 67%, specificity 89%) (Non-VHD)

**Table 1 (continued)**

Reference	Study group	Technique	Cardiac fat part	Correlation between cardiac fat part in POAF vs Ctl
Kogo et al. [11] Japan 2019	POAF (n = 21, age 73 [71–79], 62% men, BMI 22 [19–25]) Ctl (n = 56, age 70 [65–75], 61% men, BMI 23 [21–25])		Total-EAT (volume) LA-EAT (volume)	- POAF vs Ctl: 196 [108–248] vs 157 [100–232] cm <sup>3</sup> , P = 0.71 (total-EAT), 58 [33–79] vs 38 [22–65] cm <sup>3</sup> , P = 0.12 (LA-EAT), 0.30 [0.26–0.36] vs 0.23 [0.20–0.30], P = 0.02 (LA/total-EAT ratio) - LA/total-EAT ratio (OR 107, 95% CI 1.06–10750.4) independently associated with POAF
Opolski et al. [9] Poland 2015	POAF (n = 24, age 67 ± 8, 76% men, BMI 30 ± 4.8) Ctl (n = 78, age 63 ± 11, 76% men, BMI 27 ± 3.9)	CT	LA-EAT (volume)	- POAF vs Ctl: 5.6 ± 3.0 vs 4 ± 2.5 ml, P < 0.01 - LA-EAT (OR 1.21, 95% CI 1.01–1.44) independently associated with POAF - Cut-off value of LA-EAT to predict POAF was 3.4 ml (sensitivity: 83%, specificity: 53%)
Drossos et al. [8] Greece 2014	POAF (n = 28, age 66 ± 8, 79% men, BMI 29 ± 4.6) Ctl (n = 55, age 64 ± 9, 80% men, BMI 30 ± 4.5)	CT	Total-pericardial adipose tissue (volume)	- POAF vs Ctl: 195 ± 80 vs 126 ± 47 ml, P < 0.01 - Total-pericardial adipose tissue (OR 1.018, 95% CI: 1.009–1.027) independently associated with POAF

Abbreviations: BMI, body mass index; CI, coincidence interval; CT, computed tomography; Ctl, control; LA-EAT, left atrial epicardial adipose tissue; OR, odd ratio; POAF, postoperative atrial fibrillation; total-EAT, total epicardial adipose tissue; TTE, transthoracic echocardiography; VHD, valvular heart disease.

the role of EAT in cardiac pathology. There are also possibilities to monitor coronary inflammation by integrating *ex vivo* CT angiography to monitor coronary inflammation by integrating *ex vivo* CT angiography for 3D assessment of perivascular adipose tissue with *in vivo* CT-scan data [22]. Moreover, the authors developed the CT Fat Attenuation Index as an imaging metric to describe lipid content and adipocyte size and to detect and monitor tissue inflammation [22], along with an innovative artificial intelligence tool that incorporates the radiomic and transcriptomic profiles of pericoronary EAT. The value of this combined approach to predict EAT inflammation, fibrosis, and vascularization could be validated in a prospective clinical trial [23].

Finally, maps of fat tissue and computed fat fractions could be integrated with other patient-specific parameters such as LA morphology and dimensions, elasticity and strain, levels of circulating biomarkers and culprit adipokines, along with transcriptome, proteome and secretome data of the individual biopsy material. Innovative machine learning methods may facilitate the comprehensive mapping of changes predictive of AF development and the substrate response to intervention, potentially enabling personalized risk prediction and identification

of innovative treatment options. Such a holistic approach is already being applied in the Influence of EPICardial adipose tissue in HEART diseases (EPICHEART) study [24], which aims to establish a protocol for the study of EAT-driven coronary atherosclerosis. Similar approaches may help to establish the precise role of cardiac EAT for atrial arrhythmogenesis.

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### Declaration of Competing Interest

M.G. has nothing to disclose. D.D. is member of the Scientific Advisory Boards of Omeicos Therapeutics GmbH and Acesion Pharma.

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Monika Gawaiko

*Institute of Pharmacology, West German Heart and Vascular Center,  
University Duisburg-Essen, Germany*  
1<sup>st</sup> Department of Cardiology, Medical University of Warsaw, Warsaw,  
Poland

Dobromir Dobrev\*

*Institute of Pharmacology, West German Heart and Vascular Center,  
University Duisburg-Essen, Germany*  
*Department of Medicine and Research Center, Montreal Heart Institute and  
Université de Montréal, Montréal, Canada*  
*Department of Molecular Physiology & Biophysics, Baylor College of  
Medicine, Houston, USA*

\* Corresponding author at: Hufelandstrasse 55, 45122-Essen, Germany.  
E-mail address: [dobromir.dobrev@uk-essen.de](mailto:dobromir.dobrev@uk-essen.de) (D. Dobrev).