EDITORIAL COMMENTARY

The role of adiposity in atrial fibrillation pathogenesis – An area of growing scientific and clinical interest

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Obesity is a well-recognized independent and modifiable risk factor for a range of cardiovascular diseases, including atrial fibrillation (AF).[1] Epidemiological studies demonstrate that a rise in body mass index is paralleled by an increased risk of AF.[2] A major breakthrough in our understanding of obesity is the appreciation of the difference between adipose tissue depots and their associated risk: visceral adipose tissue appears to be better correlated with the cardiovascular risk compared to subcutaneous adipose tissue.[3]

The roles of overall body obesity and visceral fat and their relative contributions to the pathophysiology of AF are not fully elucidated. Left atrial (LA) enlargement is associated with obesity and correlates with AF risk.[4] Moreover, epicardial adipose tissue (EAT), a type of visceral fat, has also been associated with AF.[5,6] Epicardial fat is a metabolically active, beige adipose tissue that plays the role of a local energy supply and functions as an endocrine organ that secretes a number of adipokines. These metabolically active molecules can freely diffuse into the adjacent myocardium and may be associated with myocardial inflammation, which leads to myocardial fibrosis.[7] This paracrine effect is facilitated by the fact that EAT and the neighboring myocardium share a common microcirculation and are not separated by any fascial boundaries.[8] In addition, direct EAT infiltration into the myocardium is postulated as another potential mechanism of AF pathogenesis.[9] EAT also harbors a large number of ganglionated plexi (part of the autonomic nervous system), which also play a significant role in AF pathogenesis.[10]

Noninvasive assessment and quantification of EAT can be achieved by echocardiographic measurement of its thickness on the free wall of the right ventricle, where it is usually more prominent.[11] This does not allow for accurate volumetric EAT estimates compared to more advanced noninvasive imaging methods such as cardiac magnetic resonance imaging and computed tomography (CT). Abe and colleagues[12] recently demonstrated that fibrotic remodeling in EAT around the left atrium is associated with LA myocardial fibrosis as a main substrate for AF. On the other hand, Antonopoulos and colleagues[13] recently described a method that enables reliable tracking of inflammation in the human coronaries by characterizing changes in the perivascular adipose tissue CT attenuation. Based on a similar concept, Ishii and colleagues,[14] in this issue of *Heart Rhythm O*^{2}, tested the hypothesis that determining the percent change (%change) in EAT fat attenuation using CT images noninvasively predicts LA fibrotic remodeling.

The investigators studied the EAT of the LA appendage obtained from 76 patients with AF undergoing cardiovascular surgery. Histologically, the authors demonstrated that the adipocyte diameter was smaller, atrial tissue fibrosis was more severe, and macrophage/myofibroblast infiltration was more abundant in marginal (M) EAT compared to central (C) EAT. A positive correlation was also demonstrated between fibrotic remodeling of EAT and the C/M diameter ratio ($r = 0.73$, $P < .01$). The authors also noted, through CT imaging, a positive correlation between %change in EAT fat attenuation and EAT fibrosis ($r = 0.47$, $P < .01$). Finally, EAT fibrosis, C/M diameter ratio, and %change in EAT fat attenuation were shown to be greater in patients with persistent AF as compared to those with paroxysmal AF. The authors are congratulated on performing this rigorous study describing a noninvasive novel imaging technique to localize EAT fibrosis and correlating it with underlying LA appendage tissue fibrosis. Three important limitations are worth mentioning: (1) the lack of a control group without AF, (2) the small number of patients included in the microarray analysis, and (3) the retrospective use of CT images, which lead a to slightly reduced accuracy of the % change in EAT fat attenuation calculation.

At present these findings are limited to the context of AF patients undergoing cardiovascular surgery. Whether this surgical population is representative of the larger AF population is unproven. As our understanding of the correlation between AF and EAT continues to improve with a growing number of studies examining this relationship, one aspect of this correlation that remains rather underevaluated is the difference between EAT sub-depots. Distinct gene expression profiles were demonstrated by Gaborit and colleagues[15] in periatrial, pericoronary, and periventricular EAT sub-depots,

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demonstrating that periatrial fat uniquely expresses genes implicated in oxidative phosphorylation, muscular contraction, and calcium signaling, lending support to the notion that periatrial EAT was better correlated with AF than other EAT sub-depots. Differences within the periatrial EAT itself have also not been well characterized yet. In a recent study by Nalliah and colleagues,[16] the right atrial appendage was surgically excised from 19 consecutive patients undergoing coronary artery bypass grafting, and researchers demonstrated that local EAT accumulation affects myocardial electrophysiology by direct infiltration and tissue myocyte disruption, local fibrosis, and gap junction remodeling. Therefore, whether LA appendage EAT, which was studied by Ishii and colleagues, carries similar characteristics to other periatrial EAT is still to be elucidated.

Ishii and colleagues have successfully identified a method to localize LA fibrosis noninvasively through periatrial EAT fat attenuation change on CT imaging. This sets the stage for future studies that leverage this novel finding. One direction may be to guide a substrate modification strategy in AF (persistent AF in particular) ablation. Other directions for future investigation include therapies targeting EAT using specific drugs (antidiabetics and lipid-lowering drugs) and weight loss strategies to demonstrate a positive impact on LA remodeling.

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Authorship

All authors attest they meet the current ICMJE criteria for authorship.

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