SCIENTIFIC EDITORIAL

Is epicardial adipose tissue an epiphenomenon or a new player in the pathophysiology of atrial fibrillation?

Tissu gras épicardique : épiphénomène ou nouvel acteur de la physiopathologie de la fibrillation auriculaire?

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Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and one of the leading cardiovascular causes of hospitalization [1,2]. Various clinical conditions are associated with a high risk of developing AF, including hypertension, heart failure, coronary artery disease, diabetes mellitus, and sleep apnoea [3]. The aging of the population is another major cause of the growing prevalence of AF. Recently, obesity was reported to be independently associated with a high risk of developing AF [4–8]. This was confirmed in an experimental animal model of weight gain [9,10].

One explanation for the epidemiology of AF is that the arrhythmia is favoured by structural and functional alterations of the atrial myocardium, which can be caused by a multitude of pathogenic factors operating at different times during the natural course of the arrhythmia. This atrial remodelling is characterized by profound alterations in the structural and functional properties of the atrial myocardium responsible for the shortening of atrial refractoriness, formation of re-entry circuits and local conduction block patterns [11,12]. The histological remodelling of the atrial myocardium is central to the

Abbreviations: AF, atrial fibrillation; EAT, epicardial adipose tissue; IL, interleukin; LA, left atrial; MMP, matrix metalloproteinase; TNF, tumour necrosis factor.

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Evidence for a relationship between epicardial fat and AF

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 [21]. Of note, the term "pericardial fat" has been used in studies evaluating the relationship with AF, with some studies defining epicardial fat as pericardial fat (i.e. inside the pericardial sac) [22,23], while others define pericardial fat as the sum of both epicardial and pericardial adipose tissue [24]. In a study involving 2317 participants of the Framingham Heart Study Offspring and Third Generation Cohorts, it has been observed using computed tomography that the volume of pericardial fat (adipose tissue within the pericardial sac) predicted AF risk independent of other measures of adiposity [23]. In another study using computed tomography in 169 patients, the posterior left atrial (LA) fat thickness (comprising that between the oesophagus, the main pulmonary artery and descending thoracic aorta) was associated with AF burden, independent of LA area and body mass index [25]. In addition, pericardial fat volume is associated with a high risk of AF after adjusting for traditional risk factors and LA dilation [22]. Similar results were obtained by studying pericardial fat via cardiac magnetic resonance imaging [24]. Peri-atrial fat volume, but not body mass index, is associated with elevated risk of AF, indicating that EAT volume may be more predictive of the presence and severity of AF than the traditional or body surface area measurements. Finally, several studies have reported that pericardial fat volume is associated with AF recurrence after radiofrequency ablation [24,26]. In the same line, dominant frequency sites could be associated with epicardial fat locations [27].

Paracrine effects of epicardial fat on the atrial myocardium

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 toxic levels of fatty acids [21,28–30]. Adipose tissue also produces a number of bioactive molecules, including inflammatory mediators and adipocytokines [31–33]. During ischaemic cardiopathy, EAT expresses inflammatory cytokines, such as tumour necrosis factor (TNF)-α and interleukin (IL)-6, and chemokines such as monocyte chemotactic-1 [34]. EAT is in direct contact with the adjacent myocardium, allowing paracrine interactions between the two tissues (cytokines secreted by EAT can accumulate in the pericardial fluid) [35]. Reduced expression of antiatherogenic adiponectins has been reported in EAT from patients with coronary artery disease, whereas conditioned media from the same patients induced atherogenic changes [36].

One explanation for the relationship between EAT abundance and the severity of the arrhythmia could be that EAT-secreted adipokines contribute to the remodelling of the atrial myocardium. This has been shown for fibrosis. Indeed, the secretome of human epicardial fat, but not subcutaneous adipose tissue, induces marked fibrosis of the atrial myocardium and stimulates the transformation of fibroblasts into myofibroblasts, the source of extracellular matrix components [37]. Among the cytokines found in abundance in the EAT secretome, activin A (a member of the transforming growth factor-β superfamily) and matrix metalloproteinases (MMPs) are strong candidates for the fibrotic effect of the EAT secretome. MMPs regulate extracellular matrix homeostasis, including the various collagen fibres and basement membrane components, whereas several MMPs are up-regulated during AF, notably MMP2 and MMP7 [17]. A profibrotic effect of activin A has already been described for liver fibrosis [38–40]. Anti-activin A antibody neutralized the profibrotic effects of the human EAT secretome on the atrial myocardium [37]. Activin A also has a negative inotropic effect on isolated guinea pig cardiac myocytes, which could contribute to its effects on the atrial myocardium [41].

Both activin A and MMP8 are enhanced in patients with heart failure, and activin A is abundantly expressed in the EAT of obese patients with type 2 diabetes [42]. Both heart failure and diabetes are well-established risk factors for AF suggesting a role of EAT in these clinical settings. Inflammation is recognized as the mechanism underlying the development of the AF substrate, for instance in the context of pericarditis, myocarditis or cardiac surgery. Circulating inflammatory factors are associated with the incidence and prevalence of AF [43], including C-reactive protein, IL-6, IL-8, IL-1β and TNF-α. All of these inflammatory factors are produced and secreted by EAT in abundance, notably during ischaemic cardiopathy, obesity or diabetes. Finally, epicardial fat tissue could be an important source of reactive oxygen species, for instance in the context of ischaemic disease or post-operative AF [44].

Conclusion

EAT appears to be a new "player" in the formation of the AF substrate. A paracrine effect on the neighbouring atrial myocardium could be a potential mechanism by which a fat depot contributes to the formation of the arrhythmogenic substrate. Other processes such as fibrofatty infiltration or oxidative stress could also operate in this crosstalk between adipose tissue and myocardium [12,15]. This new field of research should lead to the identification of a new therapeutic target and biomarkers of AF.
Disclosure of interest

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