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SPOTLIGHT REVIEW

Cardiac adipose tissue and atrial fibrillation: the perils of adiposity

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Abstract The amount of adipose tissue that accumulates around the atria is associated with the risk, persistence, and severity of atrial fibrillation (AF). A strong body of clinical and experimental evidence indicates that this relationship is not an epiphenomenon but is the result of complex crosstalk between the adipose tissue and the neighbouring atrial myocardium. For instance, epicardial adipose tissue is a major source of adipokines, inflammatory cytokines, or reactive oxidative species, which can contribute to the fibrotic remodelling of the atrial myocardium. Fibro-fatty infiltrations of the subepicardium could also contribute to the functional disorganization of the atrial myocardium. The observation that obesity is associated with distinct structural and functional remodelling of the atria has opened new perspectives of treating AF substrate with aggressive risk factor management. Advances in cardiac imaging should lead to an improved ability to visualize myocardial fat depositions and to localize AF substrates.

Keywords Atrial fibrillation • Adipose tissue • Atrial fibrosis • Adipokines

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1. Introduction

The heart contains fat tissue well visible at its surface. For instance, at the atrial level, fat tissue predominates in the atrioventricular grooves, in the posterior wall, and at the crest of appendages. This cardiac or pericardial adipose tissue is composed of paracardial fat located outside the visceral pericardium and epicardial fat (EAT) situated between the visceral pericardium and the epicardium. Only EAT is in direct contact with the adjacent myocardium without any barrier that could limit paracrine crosstalk between the two tissues, which is also facilitated by a dense vasavasorum network.[1] The two fat layers, which evolve from brown adipose tissue, have distinct embryological origin and biological properties without evidence for crosstalk between them.[1] For instance, EAT is a source of free fatty acids; it expresses the uncoupling protein-1 (UCP-1), a mitochondrial inner membrane protein, that characterizes brown-type adipose tissue.[2] The biochemical properties of EAT suggest a role in energy supply and protection against hypothermia of the myocardium. Of note, UCP-1 is more expressed in ventricular than in atrial EAT.[3] EAT also produces a number of cytokines and adipocytokines that mediate its effect on neighbouring visceral tissues.[4]

Both the abundance and biological activities of cardiac adipose tissue vary between individuals and during various clinical conditions.[5–10] For instance, in patients suffering from coronary artery disease, EAT secretes less anti-atherogenic adiponectins and anti-inflammatory cytokines and more tumour necrosis factor (TNF)-α or interleukin (IL)-6 and chemokines such as monocyte chemotactic protein-1 (MCP-1).[11,12] EAT could contribute to insulin resistance of the myocardium by secreting adipocyte-derived TNF-α that inhibits insulin receptor signalling and increases the release of non-esterified fatty acids (*Table 1*).[11,13]

These considerations, together with the growing evidence of an association between pericardial fat and atrial fibrillation (AF), open new perspectives of research on the pathogenesis of this arrhythmia. In this article, we will review the clinical and experimental evidence linking cardiac adipose tissue and AF and discuss our current knowledge on the underlying mechanisms and potential translational and clinical applications of this interaction.

2. Clinical evidence of a relationship between cardiac fat and AF

Several observational studies based on cardiac imaging have demonstrated a close association between pericardial fat and the occurrence of AF. Of note, most of these studies quantify both paracardial fat and EAT, without distinction between the two adipose tissues. In the Framingham Heart cohort involving 3217 participants, pericardial fat volume quantified by computed tomography (CT) is an independent predictor of AF even after adjusting for other AF risk factors and global

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Table 1 Factors secreted by epicardial adipose tissue

Category	Factors	Clinical history	References
Metabolic activity	Free fatty acids; UCP-1	Coronary artery disease; diabetes, metabolic syndrome	3,4
Angiogenic factors	Angiotenin, endostatin, VEGF, thrombospondin-2, angiopoietin	Coronary artery disease	14,15
Growth and remodelling factors	Activin A; follistatin	Heart failure, diabetes	14,15
	TGF-1, -2, -3; MMP-1, -2, -3, -8, -9, -13	Heart failure	14
Adipocytokines	Adiponectin; leptin	Coronary artery disease	7,12,16–18
	Resistin, visfatin, omentin	Obesity	8,9,19
	Fatty acid-binding proteins (FABP4)	Obesity metabolic syndrome	20
Inflammatory cytokines chemokines	Interleukin-6, -1β; Il-6 and Il-7-soluble receptor, PAI-1, TNF-α, monocyte chemotactic protein-1, chemokine ligands, adrenomedullin, phospholipase A2	Coronary artery disease	7,10,11,15,21–26

VEGF, vascular endothelial growth factor; MMPs, matrix metalloproteinases; TNF, tumor necrosis factor; PAI-1, plasminogen activator inhibitor-1.

measures of adiposity such as body mass index (BMI) [OR per SD of fat volume: 1.28; 95% confidence interval (CI): 1.03–1.58; $P = 0.03$].[27] This observation was further confirmed in other studies using other imaging modalities including cardiac magnetic resonance imaging (MRI).[28,29] The abundance of cardiac adipose tissue is an independent predictor of lone AF,[30] as well as AF associated with structural heart diseases including hypertrophic cardiomyopathy or coronary artery disease and post-operative AF after coronary bypass (CAD).[31–33]

There is also a close relationship between the extent of pericardial adipose tissue or EAT determined by various imaging modalities and the persistence of AF.[28,34,35] Thus, pericardial fat volume was significantly associated with AF chronicity and AF symptom burden.[29] The relationship between volume of EAT and AF persistence was observed independently of other AF risk factors or BMI.[36]

Several studies suggested that EAT quantification could predict AF recurrence after catheter ablation or electrical cardioversion.[29,34,37,38] Nagashima *et al.*[38] found that total and left atrial (LA)-EAT volumes measured by CT were independent predictors of AF recurrence after catheter ablation. Other parameters characterizing cardiac adipose tissue extent as total and LA pericardial fat volumes measured by MRI or EAT thickness characterized by echocardiography also predicted catheter ablation outcome independently of LA size and BMI.[29,34] More recently, Kocyigit *et al.*[39] observed that only LA (but not ventricular)-EAT thickness determined by CT was predictive of AF recurrence after pulmonary vein isolation. However, other studies found a correlation only with early AF recurrence[40] or in patients with persistent AF.[41]

Taken together, these clinical studies suggest a predominant association between EAT abundance and long-standing persistent form of AF or risk of recurrence of arrhythmia after cardioversion of the ablation procedure. This consideration points to an association between EAT and the progression of the substrate of AF; this point will be discussed in the rest of this review article.

3. AF and fat, not just an epiphenomenon

What are the pathophysiological processes linking cardiac adipose tissue and AF? This is the major question raised by clinical studies described earlier.

The general view is that AF results from the conjunction of a substrate, a trigger, and the activation of the nervous system.[42] Subsequently, cardiac adipose tissue might contribute mainly to the formation of the substrate, as detailed in the rest of this review. However, both the abundance of fat tissue in the posterior wall wrapping pulmonary veins (a source of triggers)[43] and the dense sympathetic and parasympathetic innervation of cardiac adipose tissue[44] point to a possible role of cardiac adipose tissue in the triggering and the autonomic tone modulation of arrhythmia. This is suggested by the observation of a link between EAT thickness and cardiac autonomic function such as heart rate variability and heart rate turbulences.[32,45] One explanation could be the rich innervation of the fat tissue of the posterior wall.[44] This point will not be discussed further here, because of the lack of evidence, but it is clearly an exciting new area of research.

Again, initial clinical studies provide evidence that cardiac adipose tissue could be a determinant of the progression of the substrate of AF. For instance, LA size, which reflects global LA remodelling, correlates with the abundance of paracardial fat.[34,36,46,47] The comparison of extension and localization of high-dominant frequency (DF) and complex fractionated atrial electrograms (CFAEs) suggest a close relationship between EAT and the electrical substrate of AF. Nagashima *et al.*[35] observed that sites of EAT accumulation correlate with high DF sites. Moreover, EAT accumulates mainly at the antra of pulmonary veins and within anterior wall, roof, floor, and mitral isthmus, which are frequent targets for AF catheter ablation. There is also an association between total pericardial fat volume and CFAE area.[30]

3.1. Fibrosis, one possible link between fat tissue and AF substrate

The substrate of AF is characterized by short refractory periods, electrical heterogeneity, and local conduction block that favour the formation of rotors and breakthrough of the electrical impulse.[48–50] Alterations of both functional and structural properties of the atrial myocardium cause electrical remodelling of the atria.[51,52] Fibrosis is central to this process by contributing to local conduction blocks and disorganization of the conduction electrical wave.[53]

Epicardial adipose tissue could contribute to the fibrosis of neighbouring atrial myocardium by secreting profibrotic factors including inflammatory cytokines, growth factors, or matrix metalloproteinases (MMPs).[13,14,54] This hypothesis could be tested *ex vivo*. When the secretome of EAT, interventricular, and atrioventricular grooves obtained during coronary bypass surgery of patients in sinus rhythm is applied on an atrium, it induces a massive myocardial fibrosis within a few days, which is associated with the transformation of fibroblasts into myofibroblasts. As the secretome obtained from subcutaneous adipose tissue of same patients has no effect on the atrial myocardium, the profibrotic effect could be specific to EAT,[14] reflecting probably the distinct nature of the two adipose tissues.[1,54]

Among the adipokines secreted by EAT, activin A is a good candidate to account for the fibrotic effect of its secretome on atrial myocardium. This member[38] of TGF-β superfamily is expressed in various tissues and has multiple effects including fibrosis as observed for the liver.[55] Indeed, activin A induces the fibrosis of the atrial myocardium, whereas anti-activin A antibody neutralizes the profibrotic effects of EAT secretome.[14] The abundance of activin A in the EAT secretome varies between patients, higher levels being observed during heart failure[14] and in obese patients with type 2 diabetes,[54] two clinical settings that are associated with a high risk of AF.[56,57]

Not only the abundance but also the localization of fibrosis is crucial for its arrhythmogenicity. It has been shown that wave-breaks and rotors predominate in the subepicardium of the atrial wall as the consequence of an electrical dissociation between epicardial layers and the endocardial bundle network, favouring disturbances in electrical conduction. This electrical dissociation is favoured by the distinct orientation of myocardial layers located between the epicardium and the endocardium and is worsened by the fibrosis, which accumulates in the subepicardium.[48] Fatty infiltration of the subepicardium is a common observation of atrial histology in humans, without a relationship between the abundance of fatty infiltrates and AF. Interestingly, the fatty infiltrate can become fibrotic and even replaced by dense fibro-fatty infiltration; an immune response mediated by CD8+ T lymphocytes could be involved in the replacement of adipose tissue by fibrosis. Both in human and in goat models, persistent AF is an independent predictor of fibrotic remodelling of subepicardial adipose tissue, a process that might contribute to epi/endocardium dissociation.[58] Of note, similar fibro-fatty infiltration of the subepicardium has been observed in the ventricle during arrhythmogenic right ventricular cardiomyopathy[59] and ischaemic cardiomyopathy.[60]

3.2. Not only fibrosis could contribute to the relationship between cardiac adipose tissue and AF

The epicardial adipose tissue secretes a number of inflammatory cytokines that have been shown to be associated with a high incidence of AF or a poor outcome after ablation including IL-6, -8, -1β, and TNF-α.[11,23,61] In addition, monocytes attracted into fat tissue by MCP-1 produced by expanded adipocytes can also secrete inflammatory cytokines.[11] Therefore, cardiac adipose tissue is probably an important source of inflammatory cytokines, which can diffuse easily into the neighbouring myocardium but also accumulate in the pericardial fluid.[62] Several mechanisms have been proposed to explain the role of inflammation in initiation and perpetuation of AF.[63] In mice, TNF-α through the transforming growth factor-β1 (TGF-β1) signalling pathway activates myofibroblasts, increases the secretion of MMPs, and alters the gap junction channel, connexin-40, expression.[64]

EAT tissue is also an important source of reactive oxygen species as the result of its high oxidative stress activity and thus could be involved in the progression of the AF substrate, for instance, in the context of ischaemic cardiomyopathy or post-operative AF.[65,66]

There is clear evidence that abnormalities of calcium homeostasis of atrial myocytes play a crucial role in the pathophysiology of paroxysmal[67] and persistent[68] AF, not only through their involvement in the alterations of electrical properties but also on the structural remodelling of the atria.[69] In this line, several adipokines secreted by EAT can regulate the calcium homeostasis of cardiac myocytes including TNF-α or activin A as reported for the latter in the high fat feeding guinea pig model during diabetes[15] (*Figure 1*).

4. The paradigm of obesity

Large prospective clinical studies have well established that obesity is an independent risk factor of AF. For instance, every unit increase in BMI raises AF risk by 4%.[70–73] In addition, strict weight management programme for patients with AF reduces symptom burden and severity and reduces the use of anti-arrhythmics more efficiently than just optimal management of risk factors alone.[74–76]

Left ventricular dysfunction, hypertension, sleep apnoea, and autonomic dysfunction, which are risk factors for AF, are often observed in obese patients and thus could explain the association between the two clinical entities.[77] However, a direct impact of obesity on the atria is also likely. This is suggested by the observation that obesity is characterized by distinct deformation of the LA, resulting in an 'oval-shaped' morphology and dilated LA, which can contribute to AF susceptibility in obese individuals.[78] Low-grade inflammation, increased activity of renin–angiotensin–aldosterone system, and high plasma levels of endothelin and TGF-β1 can contribute to the progression of the substrate of AF in obese patients.[79]

Experimental studies have clearly demonstrated a direct and specific impact of obesity on the atria and on progression of AF substrate.[76,80,81] In sheep, obesity is associated with changes in atrial size, conduction, histology, and expression of fibrotic mediators that are associated with spontaneous and more persistent AF.[80] After more than 1 year of high-fat diet, sheep developed a massive obesity together with a typical AF substrate including LA dilation, conduction abnormalities, fractioned electrocardiograms, and a high vulnerability to AF. In addition to a diffuse interstitial fibrosis of the atrial myocardium due to local secretion of TGF-β1 by EAT, a massive fatty infiltration of the posterior wall of the LA at the junction of the pulmonary veins was observed in obese sheep. These myocardial areas infiltrated by dense adipose tissues are characterized by low and heterogeneous voltages recorded using endocardial mapping, which could contribute to the electrical remodelling of the atria of obese sheep.[81]

Mechanisms underlying the accumulation of adipose tissue (both epicardial and subepicardial) are still largely unknown. Interesting, rapid atrial pacing in the pig induces the expression of several adipocyte-related genes (*RETN*, *IGF1*, *HK2*, *PYGM*, *LOX*, and *NR4A3*) that can regulate adipose tissue accumulation and which are also upregulated in the atrial myocardium of patients with persistent AF in humans.[82] This observation suggests a crosstalk between adipocyte precursors, fat tissue, and myocardium.[16] During various myocardial stresses such as rapid beating or haemodynamic overload of the atria, this crosstalk might

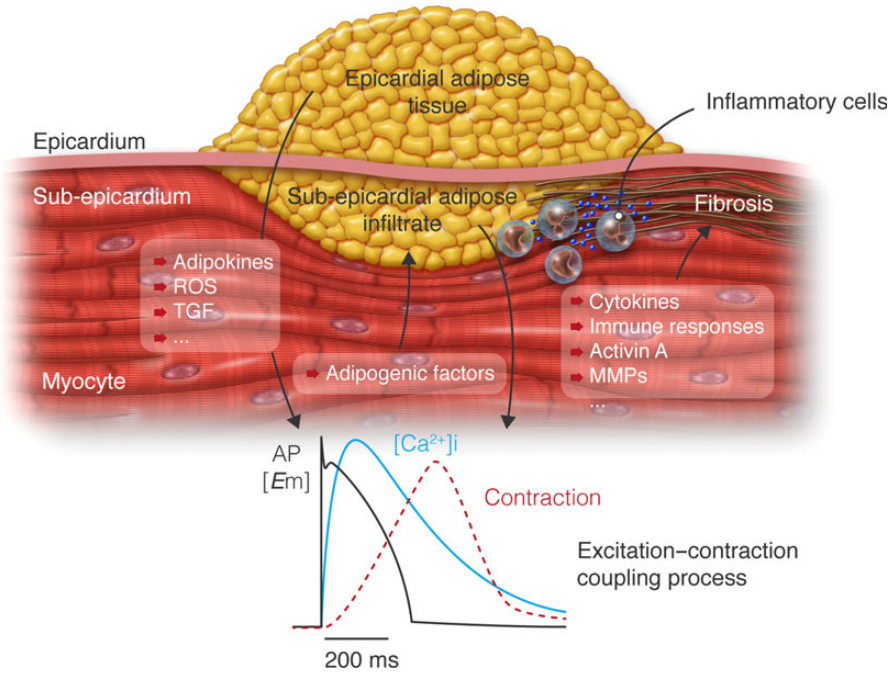

Figure 1 Scheme of the various potential signalling pathways by which the adipose tissue that accumulates at the epicardium and subepicardium of the atrial myocardium can contribute to the progression of the substrate of AF.

contribute to fat accumulation with a good face—energy supply—and a bad face—inflammation and fibrosis.

5. Translation in clinical practice: new imaging of the substrate of AF

The impact in clinical practice of the current knowledge on the interactions between cardiac adipose tissue and AF will depend largely on the advances in cardiac imaging and improved ability to visualize myocardial tissue components.

Although ultrasound can identify areas of pericardial fat, this technique is impaired by the incomplete visualization of cardiac and pericardiac structures and the absence of specific adipose tissue characterization. Although data from pericardial fat measured with echo are interesting and hypothesis-generating,[34] we should be cautious about the reproducibility and significance of one-dimensional (1D) local manual measurement of thickness to account for global EAT.

CT has the advantage of a full coverage of the chest, good native fat to myocardium contrast not requiring contrast injection, high spatial resolution and has largely been used to quantify EAT thickness, area, and volume. However, characterizing inflammation within EAT by quantification of myocardial density after contrast injection largely remains a challenge under investigation. As it is also a reference technique for non-invasive coronary artery atherosclerotic plaque imaging, increasing data show a relation between EAT volume measured in CT and both calcified and non-calcified atherosclerosis,[83] adverse cardiovascular events,[83] and also AF.[84] Some major issues remain; in particular, there is a wide range of 2D and 3D methods mostly based on manual segmentation and confusion remains regarding anatomical terminology and definition of EAT. The study of a large group of patients from the Framingham cohort shows a relationship of the Framingham study showed a relationship between EAT, not mediastinal fat with coronary calcification independent of cardiovascular risk factors[85] and also with prevalent AF.[27] Contrary to adipose tissue, fibrosis is hardly directly identifiable using CT, making the study of EAT a potential surrogate of fibrosis assessment by depicting transition tissue containing a mix of fat and fibrosis as the two processes have been shown to be related.[59]

MRI is a non-invasive technique established as a gold standard for cardiac volumes, mass, and ejection fraction measurements but can also uniquely quantitatively assess dense replacement fibrosis or interstitial fibrosis as well as fat or water content within the myocardium and around the heart. If the latter has been extensively reported in ventricular myocardium, the atrial wall, owing to its thinness, has been less studied and presents critical technical challenges. In particular, as the spatial resolution used in MRI for most studies is close to only two-fold the thickness of the atrial wall (1 vs. 2 mm), partial volume effect remains a drawback in most techniques aimed at differentiating fibrosis from fat or sane myocardium including blood vessels. The intrinsic strength of the MRI is the ability to separate fat from water from their magnetic properties. It is possible to generate specific parametric images of both components in the imaging domain using the Dixon technique, based on in- and out-of-phase images applied to the heart. Most MRIs are based on physical properties of tissues characterized by T1 and T2 relaxation times. Semi-quantitative T2-weighted or quantitative T2-mapping are sensitive to water content, and oedema will be depicted as a signal increase within the myocardium. Semi-quantitative T1-weighted or quantitative T1-mapping are also sensitive to water content, and fibrosis associated with an increase in extracellular matrix will be seen as a signal increase within the myocardium before contrast injection and a decrease at a steady state after contrast. Extracellular

volume can then be computed from pre- and post-contrast myocardial T1 images normalized for T1 values inside the cavity and the haematocrit. T1-based approaches remain indirect measures of fibrosis as collagen-specific imaging *in vivo* remains under investigation. However, as mentioned earlier, these techniques have been mainly applied to the left ventricle as spatial resolution remains a major problem for them to be reliable *in vivo* in humans on the atrial wall. Several issues will have to be solved before tissue characterization techniques can be used for the atria. However, MRI is already optimal for the comprehensive evaluation of regional deformation (strain) and deformation velocity (strain rate) in the three spatial dimensions (radial, circumferential, and longitudinal). Functional anomalies identified by imaging may be associated with tissue-level anomalies before they can be reliably assessed with imaging and precede global atrial dysfunction, dilatation, and extensive fibrosis. These approaches have been already validated for the LA[86] and were applied to a sample of a wide population study (MESA) with good results, demonstrating the acceptable 'real world' feasibility of the technique.[87]

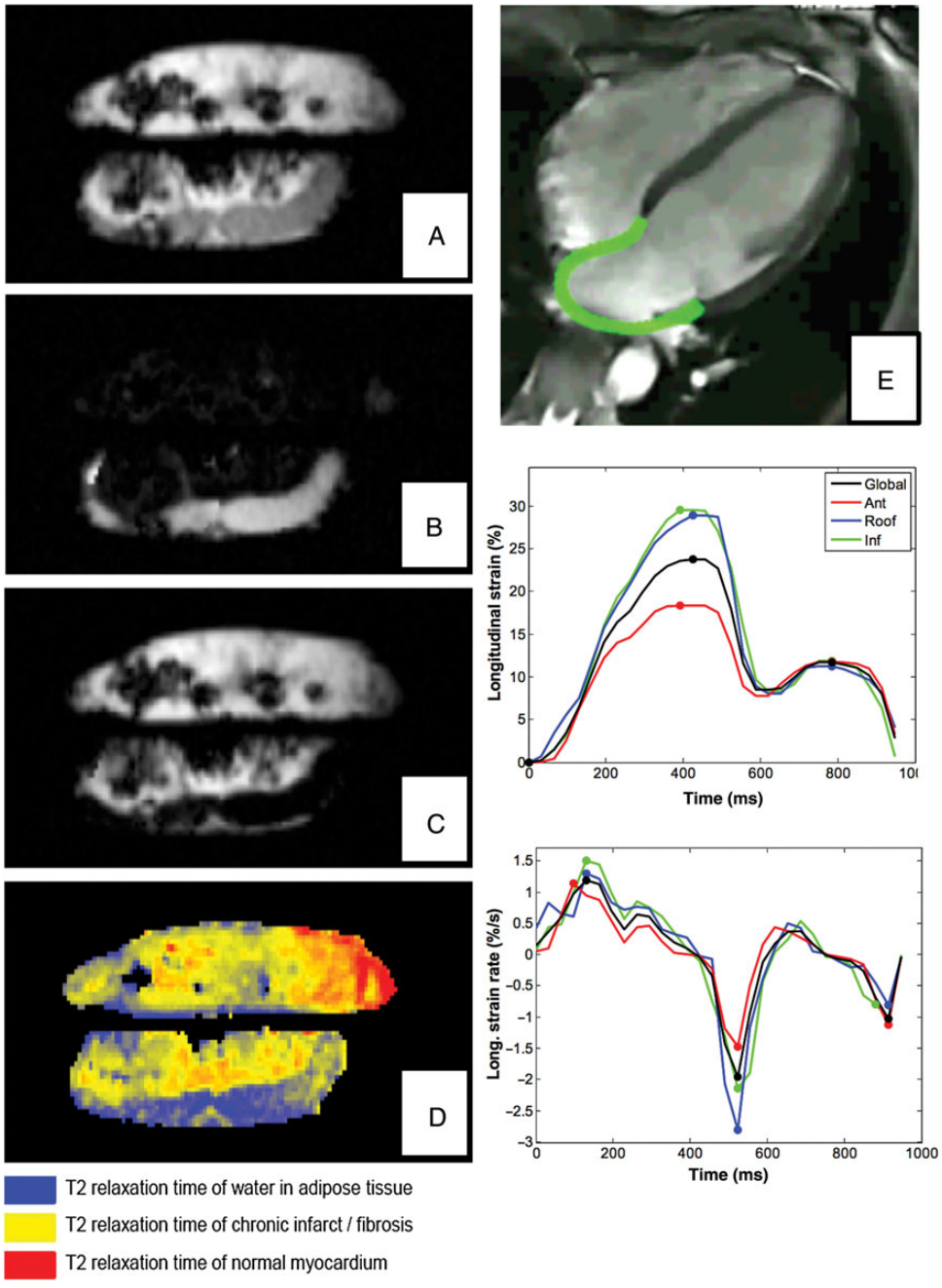

Figure 2 *Ex vivo* high-resolution MRIs of two human LA tissues. (*A*) Image acquired with GRE sequence with the echo time TE at which water and fat signals are in phase. (*B*) Fat image obtained using the Dixon method. (*C*) Water image obtained using the method. (*D*) Map of T2 transverse relaxation time values reveals a fibrotic region in the fatty tissue. (*E*) LA strain measurement using MRI feature tracking and resulting longitudinal strain and strain rate curves.

Coming innovations in imaging will be to generate precise and reliable 3D measurements of EAT in different modalities, to characterize adipose tissue in terms of extracellular matrix, vascularization, and perhaps fibrosis, and to combine this information with 3D functional analysis of wall deformation and atrial flow to define new imaging biomarkers of atrial remodelling and dysfunction (*Figure 2*).

6. Conclusion

It seems now well established that cardiac adipose tissue is a partner of the pathogenesis of AF. Its precise role in the development of the substrate and triggers of AF is still incompletely understood, but is likely to be multiple and complex, depending on the clinical context associated with AF. Given the effect of ageing, metabolic disorders, or systemic disease on its biological properties, the role of fat in the development and prognostic of AF might be particularly important during diabetes, ischaemic cardiomyopathy, in obese patients or during ageing. An important direct translational impact of the discovery of the relationship between cardiac adipose tissue and AF could be the development of new biomarkers and new imaging methodologies to improve the detection and localization of the substrate of AF.

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