INTRODUCTION

Atrial fibrillation (AF) is the most frequent cardiac arrhythmia in clinical practice. AF is often associated with profound functional and structural alterations of the atrial myocardium that compose its substrate. Recently, a relationship between the thickness of epicardial adipose tissue (EAT) and the incidence and severity of AF has been reported (1). Adipose tissue is a biologically active organ regulating the metabolism of neighboring organs. It is also a major source of cytokines. In the heart, EAT is contiguous with the myocardium without fascia boundaries resulting in paracrine effects through the release of adipokines (1, 2).

The infiltration of adipocytes into the atrial myocardium could also disorganize the depolarization wave front favoring micro re-entry circuits and local conduction block (2).

The terms epicardial fat, paracardial and pericardial fat, have been used interchangeably through-out the literature, despite differences in location and function. They are often collectively referred to as cardiac ectopic fat or cardiac adipose tissue (3).

In recent years, a number of studies that were able to accurately quantify cardiac ectopic fat using modern imaging

techniques were published almost simultaneously. These described similar associations between fat layers surrounding the heart and the presence and chronicity of AF and, taken together, have provided suggestive evidence supporting a relationship between the two entities (3).

AIM OF THE WORK

The aim of this work is to study the prevalence of thickened epicardial fat, measured by trans-thoracic echo-cardiography, in Egyptian patients with AF.

Chapter (1)

EPICARDIAL FAT (EF)

Epicardial, Paracardial and Pericardial Fat

The terms epicardial fat, paracardial and pericardial fat, have been used interchangeably throughout the literature, despite differences in location and function. They are often collectively referred to as cardiac ectopic fat or cardiac adipose tissue (3). Pericardial fat consists of two layers: the visceral, epicardial fat layer and the parietal, paracardial fat layer. Epicardial fat is adipose tissue layer situated between the myocardium and visceral pericardium. Paracardial fat is the adipose tissue layer located external to the parietal pericardium (figure 1). Given the different embryological origins and vascular supply of these two fat depots, there is reason to suspect they may have distinct biochemical properties. However, there is a lack of standardized nomenclature and most reports haven't individually studied each depot in relation to metabolic parameters and outcomes and collectively referred to as epicardial fat (3).

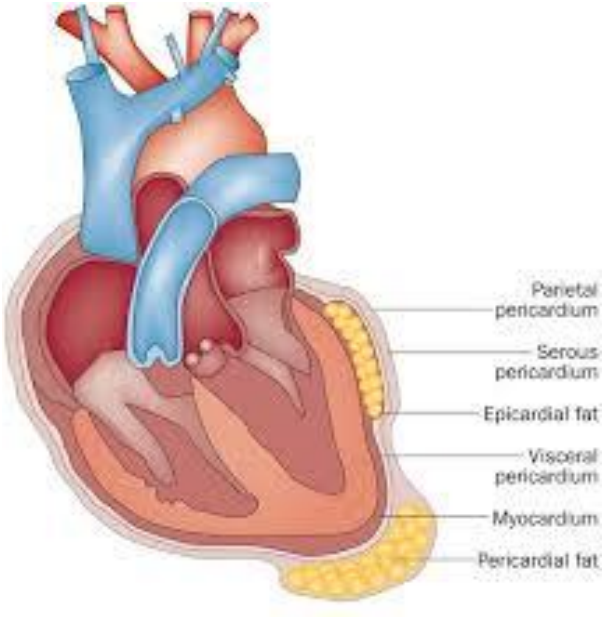

Fig. (1): Epicardial and pericardial fat.(3)

The thickness of the epicardial adipose tissue on the right ventricle varies between 1.9 and 15.7 mm. No significant difference in epicardial adipose tissue between men and women was found (4).

Biochemically epicardial and pericardial fat are different. In humans, the evidences that the epicardial adipose tissue is an active endocrine organ are robust (5, 6), whereas the role of pericardial fat as source of adipokines is still partially unknown. Echocardiographically, epicardial and pericardial fat thickness are different (2). For the anatomical and biomolecular features reported above, It was first proposed to measure the epicardial fat rather than the pericardial fat thickness.

Epicardial fat is identified as the echo free space between the outer wall of the myocardium and the visceral layer of pericardium (figure 2), measured from parasternal long axis view (figure 3). Pericardial fat thickness can be identified as the hypoechoic space anterior to the epicardial fat and parietal pericardium and it does not significantly change size during the cardiac cycle (2). Clinically epicardial and pericardial fat are different. The role of echocardiographic epicardial fat in predicting AF was demonstrated (3). Pericardial fat has not yet shown all these features. The article by Kluge WF. may definitively open new avenues on the role of pericardial fat (1).

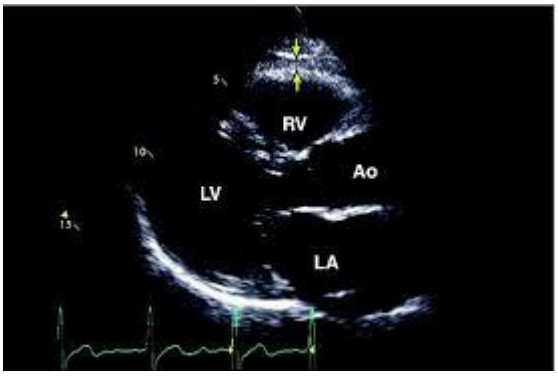

Fig. (2): Epicardial fat by transthoracic ECHO appears as an echo free space between the outer wall of the myocardium and the visceral layer of pericardium.(2)

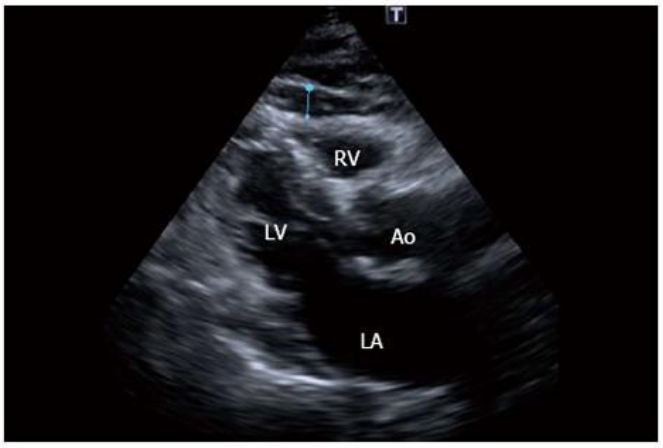

Fig. (3): Measuring epicardial fat from parasternal long axis view.(3)

Echocardiography can provide only a linear measurement of epicardial fat and may be not accurate as CT. However echocardiographic assessment of epicardial visceral fat would certainly be less expensive than CT and as echocardiography is routinely performed in high-risk cardiac patients, this objective non invasive measure may be readily available at no extra cost (5, 6).

For all these reasons, the need to distinguish between epicardial and pericardial fat was compelling. If a body of evidences is suggesting that epicardial fat could play an active role as cardiometabolic risk factor, diagnostic tool and therapeutic target, further studies will be necessary to strengthen the role of pericardial fat (5).

Several EAT-expressed adipokines are known to be involved in the formation of the AF substrate. This includes inflammatory cytokines, growth factor, or matrix metalloproteinases (MMPs) (7, 8). Therefore, one explanation for the relationship between EAT abundance and the severity of the arrhythmia could be that EAT-secreted adipokines contribute to structural remodelling of the atrial myocardium, such as fibrosis. This hypothesis was tested directly using an *ex vivo* model of rat atrial organoculture, which permitted the study of the effects of human adipose tissue secretomes on the myocardium independently of co-morbidity factors. For this study, EAT was obtained from the inter-ventricular and atrio-ventricular grooves of patients undergoing cardiac surgery for coronary bypass or aortic valve replacement. Conditioned medium from human EAT induced marked fibrosis of the atrial myocardium as illustrated in figure (4) In addition, the EAT-conditioned media favoured the transformation of fibroblasts into myofibroblasts, which then produce extracellular matrix components (9, 10, 11).

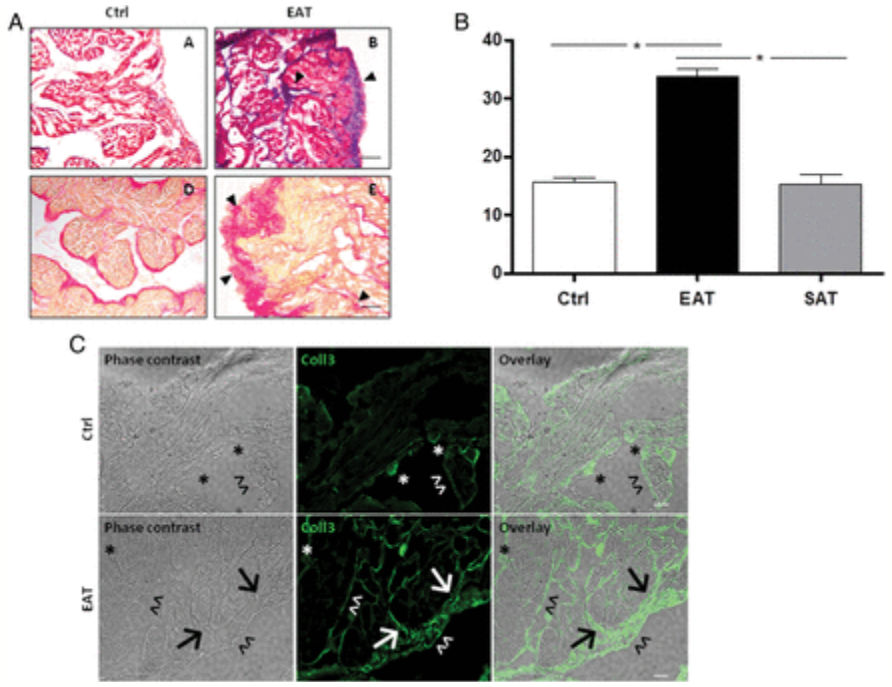

Fig. (4): Atrial fibrosis induced by the secretome of human EAT. (*A*) Picrosirius red staining of an isolated rat atria maintained in organoculture condition and incubated with the secretome of human EAT during 3 days. A marked epicardial and interstitial fibrosis is observed with EAT-conditioned media. (*B*) Quantification and comparison of the fibrosis between control, EAT, and SAT (SAT obtained from the same group of patients)-conditioned media (*$P < 0.001$). (*C*) Distribution of fibroblasts and collagen fibres in rat atrial explants treated with EAT-conditioned medium. Arrow heads indicate perimyocyte (or peritrabecula) and epicardial collagen fibres, and stars point fibroblast cell bodies.(10)

Adipokines involved in the formation of the AF:

Among the cytokines found in abundance in the EAT secretome, activin A and MMPs are excellent candidates for causing the fibrotic effect of EAT secretome on the atrial myocardium.

Activin A is a member of the TGF-β superfamily. First recognized as an inducer of follicle-stimulating hormone release, activin A is a multi functional cytokine expressed in various tissue types. A pro-fibrotic effect of activin A has already been described for liver fibrosis (12, 13). The supplementation of culture media with recombinant human activin A reproduced the atrial myocardial fibrosis observed with EAT secretome. Moreover, anti-activin A antibody neutralized the pro-fibrotic effects induced by the EAT secretome. Both EAT-conditioned medium and activin A induced the expression of TGF-β1 and -β2 in the atria, which could indirectly contribute to the pro-fibrotic effect of activin A. (11). Activin A-induced cardiac effects other than fibrosis have also been described. For instance, this cytokine has anti-hypertrophic and -apoptotic properties on the myocardium when it is exposed to ischaemia/reperfusion and pressure overload injuries (14, 15). Activin A causes a negative inotropic effect on isolated guinea pig cardiac myocytes, suggesting a direct effect of this cytokine on the excitation–contraction coupling process (16).

MMPs are key regulators of extracellular matrix homeostasis, including the various collagen fibres and basement membrane components. During AF, it has been demonstrated that up-regulated activity of several MMPs, notably MMP2 and 7,

contributes to the accumulation of interstitial fibrosis (17). MMP8, which is abundantly expressed in EAT, is known to be involved in the formation of atherosclerosis plaques (18, 19), whereas little is known of its role during myocardial fibrosis (20).

The observation that EAT secretes adipokines that can induce fibrosis of the atrial myocardium raises the following question; Under which clinical circumstances would the biological activity of cardiac fat tissue contribute to AF substrate formation? Is this effect only related to EAT abundance? Or are there specific clinical conditions associated with increased EAT biological activity? Venteclef *et al.* found that the level of both activin A and MMP8 is enhanced in patients with heart failure. Moreover, Greulich *et al.* (21) report that activin A is more abundantly expressed in the EAT of obese patients with Type 2 diabetes than in the other study patients. Heart failure and diabetes are well-established risk factors for AF, highlighting the role of EAT biological activity in these epidemiologic relationships. Of note, it has been reported that higher EAT thickness could be associated with higher biological activity (inflammatory cytokines) (22).

Inflammation is an important determinant of the pathogenesis of AF. For instance, pericarditis, myocarditis, or cardiac surgery, all conditions that are characterized by some

degree of myocardial inflammation, are associated with a high risk of AF.

In addition, the C-reactive protein, a marker of systemic inflammation, is greater than two folds higher in patients with none post-operative AF; a higher level was found in the subgroup of patients with chronic compared with those with paroxysmal AF. IL-6, -8, 1b (interleukins 6, 8, 1b), or TNF-α (tumour necrosis factor alpha) are other circulating inflammatory factors independently associated with the incidence and prevalence of AF (23).

All these inflammatory factors are produced and secreted by EAT in abundance, notably during ischaemic cardiopathy, obesity, or diabetes. In EAT, not only adipocytes, but monocytes also can be a source of inflammatory cytokines when they are attracted by MCP-1 secreted by expanded adipocytes (24), as described in obese mice (25, 26).

Epicardial fat is characterized by a higher oxidative stress activity when compared with SAT (27). For instance, in patients suffering ischaemic cardiopathy, EAT contains more reactive oxygen species (ROS) whereas the activity of catalase is reduced compared to SAT, catalase is an antioxidant enzyme that protect cells against ROSH_2O_2. (27).

In addition to be produced by the myocardium (28), epicardial fat tissue might be an important source of ROS, for instance, in the context of ischaemic disease or post-operative AF. Clearly, more translational clinical studies using human EAT explants are needed to establish the precise scheme of the relationships between the biological activity of EAT and the remodelling of the myocardial tissue.

Chapter (2)

ATRIAL FIBRILLATION (AF)

Atrial fibrillation (AF or A-fib) is an abnormal heart rhythm characterized by rapid and irregular beating (29). Often it starts as brief periods of abnormal beating which become longer and possibly constant over time (30). Most episodes have no symptoms (31). Occasionally there may be heart palpitations, fainting, shortness of breath, or chest pain (32). The disease increases the risk of heart failure, dementia, and stroke (31).

Atrial fibrillation is the most common abnormal heart rhythm (31). In Europe and North America, as of 2014, it affects about 2% to 3% of the population (30). This is an increase from 0.4 to 1% of the population around 2005 (30).

In the developing world about 0.6% of males and 0.4% of females are affected. The percentage of people with AF increases with age with 0.14% under 50 years old, 4% between 60 and 70 years old, and 14% over 80 years old being affected (30).

A-fib resulted in 112, 000 deaths in 2013, up from 29, 000 in 1990 (34). The first known report of an irregular pulse

was by John Baptist Senac in 1749. This was first documented by ECG in 1909 by Thomas Lewis (31).

Signs and symptoms:

AF is usually accompanied by symptoms related to a rapid heart rate. Rapid and irregular heart rates may be perceived as palpitations or exercise intolerance and occasionally may produce anginal chest pain (if the high heart rate causes ischemia). Other possible symptoms include congestive symptoms such as shortness of breath or swelling. The arrhythmia is sometimes only identified with the onset of a stroke or a transient ischemic attack (TIA). It is not uncommon for a patient to first become aware of AF from a routine physical examination or ECG, as it often does not cause symptoms (35).

Since most cases of AF are secondary to other medical problems, the presence of chest pain or angina, signs and symptoms of hyperthyroidism (an over active thyroid gland) such as weight loss and diarrhea, and symptoms suggestive of lung disease can indicate an underlying cause. A history of stroke or TIA, as well as high blood pressure, diabetes, heart failure, or rheumatic fever may indicate whether someone with AF is at a higher risk of complications (35). The risk of a blood clot forming in the left atrium, breaking off, and then traveling in