Epicardial fat in patients with chronic obstructive pulmonary disease as a marker of high cardiovascular risk

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Abstract
Chronic obstructive pulmonary disease (COPD) and cardiovascular diseases (CVD) are commonly interconnected, and this coincidence negatively influences patients' mortality and morbidity. On the basis of the current available data originating mainly from cardiovascular studies epicardial fat (EF) has been proposed as a marker of cardiovascular risk. This review is focused on a potential role of epicardial fat as a new biomarker for risk stratification of COPD patients. Epicardial fat may present an important link between chronic obstructive pulmonary disease and cardiovascular diseases, mainly coronary artery disease.

Key words: epicardial fat, COPD, risk stratification


Introduction
Chronic obstructive pulmonary disease (COPD) and cardiovascular diseases (CVD) are commonly interconnected, and this coincidence negatively influences patients' mortality and morbidity. In clinical practice it is usually hard to stratify COPD patients according to their cardiovascular risk, and nowadays we are looking for new biomarkers. Epicardial fat (EF) has been proposed as a marker of cardiovascular risk, and these days there are available data mainly from cardiovascular studies. Recently, as well as the relationship between COPD and EF has been studied. This review shows measurement methods of EF, pathophysiology, and data regarding EF in patients with COPD.

Definitions

Epicardial fat
Epicardial fat is the visceral thoracic fat deposition located between the myocardium and the visceral pericardium (Fig. 1) [1]. Epicardial fat is highly metabolically active — it produces many cytokines, which, for example, play a role in atherosclerosis progression [2]. Due to its activity, it should be distinguished from paracardial fat (adipose tissue located external to the parietal pericardium) and pericardial fat (paracardial fat with all the adipose tissue located internal to the parietal pericardium) [3]. In fact, the term pericardial fat is often used to describe all the adipose tissue located in the pericardial sac [4].
EF is usually found in atrioventricular and interventricular grooves extending to the apex of the heart, specifically between the myocardium and visceral pericardium [5, 6].

**Epicardial fat measurement**

For the measurement of epicardial fat, a few modalities could be used. The ‘gold standard’ is generally considered cardiac magnetic resonance (Fig. 2) [3]. This method offers excellent spatial resolution and is the only imaging modality in which volumetric quantification of epicardial fat has been validated ex vivo [7, 8]. The advantages are obvious — no radiation or iodinated contrast exposure. On the other hand, this method presents with many disadvantages amongst which are its high costs, time requirements and lower availability in some centres.

The chest computed tomography (CT) scan is an alternative that can be used for the measurement of epicardial fat (Fig. 3). This method was used widely in previous studies, especially because a chest CT was performed due to other indications like pulmonary embolism, calcium score measurement, emphysema quantification, etc. It offers high spatial resolution and attenuation value ranges can be defined to allow for either manual or semi-automatic quantification of adipose tissue [9, 10]. Advantages are a good resolution, excellent reproducibility and the possibility of volumetric quantification. The disadvantage is the exposure to both ionizing radiation and iodine-containing contrast.

The third option is echocardiography, which is the most accessible and affordable imaging modality (Fig. 4). It is important to notice that 2D echocardiography does not offer measurement of the amount of epicardial fat like volumetric measurement during cardiac magnetic resonance or computed tomography imaging. This is possible only using 3D echocardiography, though this method is not widely available and it is time-consuming. Instead of the measurement of epicardial fat volume, epicardial fat thickness is used. EF is identified as a hypoechoic space anteriorly to the right ventricle wall, and its thickness is measured between the epicardial surface and pericardium identified by the sliding between these two layers [11]. This is measured over the free wall of the right ventricle in diastole.
Adiponectin has antidiabetic, antiatherogenic, antioxidative and anti-inflammatory properties [22]. This adipokine also inhibits the production of tumour necrosis factor alpha (TNF-α) and other inflammatory pathways in adipocytes and macrophages, producing an anti-inflammatory effect [23]. Also, EF produces a high amount of adrenomedullin, which is a potent vasodilator peptide [24]. It has also been proposed that adrenomedullin has antioxidant properties antagonising oxidative stress induced by angiotensin II [25].

EF is also a producer of pro-inflammatory adipokines like interleukin 1 (IL-1), interleukin 8 (IL-8), interleukin 6 (IL-6) and TNF-α [26, 27]. IL-6 is considered to be one of the key adipokines involved in atherosclerotic plaque development [28] as well as in insulin resistance [29]. TNF-α is another important adipokine produced by epicardial fat adipocytes. Its serum level is elevated in obese individuals where it actually worsens insulin resistance. TNF-α is also a potent vasoconstrictor [30]. It decreases adiponectin production and stimulates the production of other pro-inflammatory adipokines [31].

**Epicardial fat and cardiovascular diseases**

Epicardial fat physiology

Epicardial fat originates from the splanchnopleuric mesoderm [15], in contrast to paracardial fat, which is derived from the primitive thoracic mesenchyme [16]. Epicardial fat is directly perfused by the coronary arteries and thus it has a direct paracrine effect on the myocardium [17]. Its functions include lipid storage for myocardial energy, thermoregulation and the protection of autonomic ganglia and nervous tissue [4]. There have also been discussions regarding further potential functions such as its effect on local distribution and regulation of vascular flow [16]; its role as an immune barrier in the protection of the myocardium and coronary arteries from inflammatory and pathogenic substances [18] as well as the mechanical protection of the coronary arteries.

EF is a highly metabolically active organ and a major source of anti-inflammatory and proinflammatory adipokines [19, 20].

Of the anti-inflammatory adipokines, the most important are adiponectin, adrenomedullin and omentin [21]. Adiponectin has antidiabetic, antiatherogenic, antioxidative and anti-inflammatory properties [22]. This adipokine also inhibits the production of tumour necrosis factor alpha (TNF-α) and other inflammatory pathways in adipocytes and macrophages, producing an anti-inflammatory effect [23]. Also, EF produces a high amount of adrenomedullin, which is a potent vasodilator peptide [24]. It has also been proposed that adrenomedullin has antioxidant properties antagonising oxidative stress induced by angiotensin II [25].

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**Epicardial fat and cardiovascular diseases**

There are many studies available on epicardial fat in patients with CVD. Higher amounts of EF were found to be related to the presence of coronary syndromes and weakening of atheromatous plaques [32, 33]. There is also data showing that individuals with a higher amount of EF have a more severe coronary plaques, indicating that the thickness of epicardial fat plays a key role in the progression of coronary atherosclerotic disease [34]. EF thickening is thus considered a risk factor of coronary plaque formation and their vulnerability [35]. An independent association between pericardial fat and cardiovascular risk factors, coronary calcification and the presence of carotid artery disease has also been demonstrated [11]. Further researches on atrial fibrillation (AF) and epicardial fat provide interesting data. Numerous studies support the association of epicardial fat with the presence of AF [36]. Data from the Framingham Heart Study suggests that EF volume is independently associated with prevalent AF [37]. Many pathophysiological mechanisms are discussed as possible causes. EF is a known source of reactive oxygen species [38], which may, according to some authors, play a role in the genesis of AF [4]. Autonomic dysfunction may also contribute, as the autonomic nervous system is thought, to play a crucial role in the initiation and
maintenance of AF [39]. Ganglionated plexi are located in the epicardial fat and their dysfunction could lead to AF development as well [40].

**Epicardial fat and chronic obstructive pulmonary disease**

In the field of COPD and EF, only a few studies have been performed. Zagaceta et al. [1] enrolled 171 stable COPD patients (mostly stage I and II according to GOLD 2009 guidelines) and 70 controls (ex-smokers) in whom the amount of EF was measured using CT imaging. Multivariate analysis exploring the association of EF volume and COPD diagnosis, after adjusting for the Charlson Comorbidity Index, showed that the presence of COPD was a statistical predictor of EF volume (β coefficient 28.86; 95% CI: 7.6–51.1; p = 0.008). Moreover, EF was independently associated with modifiable CVD risk factors like smoking history, BMI and decreased exercise capacity. As was shown in a previous study [41], a higher EF volume predicts higher CVD risk in community-based adults without a history of CVD. This could represent a strong link between COPD and CVD risk. There is also increasing evidence that adipose tissue is a significant contributor to the systemic inflammation load in COPD [42, 43]. Visceral fat plays a main role where adipose tissue dysfunction, including enhanced adipose tissue inflammation, was described and could contribute to the low-grade inflammation, which has been described in patients with COPD. For example, excessive visceral fat mass was positively associated with all-cause and cardiovascular disease mortalities as well as with a higher serum level of IL-6 [43]. It is unclear whether pulmonary impairment or poor lifestyle predispose to excessive visceral fat accumulation.

In another study, Kiraz et al. [44] enrolled a sample of 157 COPD patients and 45 controls where the epicardial fat thickness was measured using echocardiography. EF thickness was higher in the COPD patients in comparison with the controls (p < 0.05). In the same study, an inverse correlation between the BODE index and EF thickness was found. Similarly, the study by Demir et al. [45] found higher EF thickness in those with COPD in comparison to healthy subjects (p < 0.001). However, the study by Kaplan et al. [12] paradoxically found EF thickness to be lower in patients with COPD and systolic dysfunction of the right ventricle.

The important aspect and possible future direction of research is the relationship between EF volume and different COPD phenotypes, as COPD is a highly heterogeneous disease, and the same cardiovascular risk cannot be presumed for all phenotypes. Furthermore, data regarding the possible effect of bronchodilator treatment in the reduction of cardiovascular disease risk is missing.

**Conclusion**

Epicardial fat may present an important link between chronic obstructive pulmonary disease and cardiovascular diseases, mainly coronary artery disease. Currently, the data available tends to support the hypothesis of a higher volume of EF in COPD patients with a possibly subsequent higher level of systemic inflammation. Measurement of EF thickness could present a novel approach to CVD risk stratification in patients with COPD. However, more robust data is needed.

**Conflict of interest**

The authors declare no conflict of interest.

**References:**


