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Epicardial Adipose Tissue and Right Ventricular Function in Type 2 Diabetes Mellitus

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Abstract

Type 2 diabetes mellitus (T2DM) is one of the most common chronic metabolic diseases and has come to be considered as an important cardiovascular risk factor. Myocardial dysfunction has already presented in diabetes mellitus patients even in the absence of coronary artery disease, hypertensive, and valvular heart disease. This is known as diabetic cardiomyopathy which was first confirmed in 1972. The existing literatures about the effect of diabetes on myocardial function mainly focus on left ventricular. Due to the complex geometric shape of the right ventricular (RV), it is difficult and challenging in clinical practice to early and accurately assess RV function. And studies on RV function in T2DM patients are relatively rare. Cardiovascular complications were the leading cause of death in T2DM patients. Currently, about the pathogenesis of cardiovascular complications in T2DM patients has not been fully elucidated. EAT is an emerging cardiovascular risk factor which is located between the myocardium and the visceral pericardium. Large body of evidences indicate that EAT in excess is associated with cardiovascular dysfunction in a variety of disease states. However, the association between EAT and RV function in patients with T2DM remains uncertain.

Keywords: Epicardial adipose tissue, right ventricular function, type 2 diabetes mellitus.

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1. Introduction

Diabetes mellitus represents a critical health care problem with a worldwide escalation mostly related to ageing population, socio-economic development, unhealthy diet regimes, and sedentary lifestyle. Its global estimated prevalence was 9.3% in 2019 and is projected to cover a quarter of the global population in 2030, and more than half in 2045 [1]. As a result, a substantial disease burden is expected, mainly due to CV complications that represent the leading cause of death among diabetic people, although the morbidity of the other chronic complications of diabetes overall has a high prevalence and a huge impact on National Health Systems [2]. The adipose tissue surrounding the heart involves two types of depots, the pericardial adipose tissue (PAT) and the EAT, even if the nomenclature is confusing, as some researchers use the terms paracardial or intrathoracic or mediastinal for pericardial fat, and the term pericardial fat to indicate the combination of paracardial fat with EAT [3]. PAT rests on the external surface of the pericardial fibrous layer, consists of adipocytes originating from the primitive thoracic mesenchyme, and is vascularized by non-coronary arteries.

Otherwise, EAT is located under visceral pericardium in anatomical continuity with myocardium and is embriologically derived, as mesenteric and omental fat, from brown adipose tissue (BAT) of splanchnic mesoderm. Importantly, EAT is supplied by branches of coronary arteries with a shared microcirculation that facilitates a direct crosstalk with the myocardium [3]. Based on these features, only EAT may be considered to be a true heart-specific visceral fat. In healthy individuals, EAT accounts for ~20% of total heart weight and is heterogeneously distributed on an area exceeding 80% of the cardiac total surface. It mainly occupies atrioventricular and interventricular grooves and surrounds the right coronary artery and left anterior descending coronary artery, and to a lesser extent covers atria, free wall of right ventricle, and apex [4]. Microscopically, EAT is mainly composed of white adipocytes specialized in energy storage, with a higher cellularity than subcutaneous and other visceral fat depots, with a prevalence of preadipocytes over mature adipocytes [4].

1.1. Functional properties

EAT may contribute to heart physiology by mechanical, metabolic, thermogenic, and paracrine/vasocrine mechanisms. Due to its spatial distribution, EAT exerts mechanical protection of coronary arteries from excessive distortion and compression during contraction of neighboring myocardium. Compared with subcutaneous adipose tissue (SAT), human EAT is richer in saturated fatty acids (FAs)

and poorer in unsaturated ones [5]. This different composition may account for its greater capacity of mobilization, deposition, and synthesis of FAs than all body fat and other visceral adipose depots. Thanks to this remarkable flexibility of FA turnover, EAT can play important physiological role of metabolic sensor for heart, which greatly depends on FA oxidation as primary fuel. To that end, EAT provides FAs directly to myocardium at times of high energy demand and implements local triacylglycerol storage as request decreases [6]. High rates of lipogenesis displayed by EAT act as scavenger for excess FAs in systemic circulation to protect against their myocardial lipotoxicity responsible of functional deterioration and possible lethal arrhythmias [7]. Animal and human data indicate that EAT is phenotypically brown during early stages of life. Despite whitening with age, it retains in adulthood biological property to combust proinflammatory FAs, showing molecular features and a gene profile of beige adipocytes, a new class of adipocytes that display properties of brown adipocytes, but located within WAT depots [7].

In a study on fat samples taken at open heart surgery, expression of uncoupling protein-1 (UCP-1), inner mitochondrial membrane protein that is a specific marker for and a mediator of nonshivering thermogenesis in brown adipocytes, 5-fold higher in epicardial than substernal fat and basically undetectable in SAT [8]. Chronic exposure to cold promotes activation of epicardial fat peroxisome proliferator-activated receptor γ (PPAR-γ) coactivator 1-α (PGC 1-α), a key mediator of the white-to-beige adipocyte transformation. These BAT-like features of EAT could defend myocardium against hypothermia or unfavorable hemodynamic conditions, such ischemia or hypoxia. However, there is no direct evidence of heat production, and a role in regulation of myocardial and/or vascular redox state has suggested [5]. EAT is an extremely active endocrine organ producing adipocytokines, not only ones involved in thermogenesis and regulation of lipid and glucose metabolism, but even those capable of both pro-inflammatory and anti-inflammatory response (interleukin (IL)-1b, interleukin (IL) 6 and interleukin (IL) 6 soluble receptor, tumor necrosis factor-α (TNF), adiponectin). Through shared microcirculation, these bioactive molecules may locally modulate structure and function of adjacent myocardium in a paracrine fashion [9].

There is even evidence for a microcirculatory connection between EAT and the coronary wall, by which cytokines may be released from epicardial tissue directly into vasa vasorum and transported downstream into the arterial wall by mean of a vasocrine-signaling mechanism. Thus, an interrelation of pericoronary fat with vasomotor function is mediated by the release of specific vasoactive factors such as leptin and adiponectin among others [10]. EAT has a unique transcriptome enriched in genes involved in coagulation, endothelial function, phospholipase activity, apoptosis, and immune signaling, and a secretome that may be influenced by environmental, epigenetic, and genetic factors. Under physiological conditions, EAT secretes the adiponectin, an adipocyte-derived adaptive adipokine that nourishes the myocardium contributing to FAs combustion, and exerts a series of protective actions against hypertrophy stimuli for cardiomyocytes and against inflammation and fibrosis of myocardium and coronary arteries [11]. Other anti-inflammation adipokines may be secreted by a normal EAT such as adrenomedullin, C1q/TNF-related proteins, omentin, and secreted frizzled-related protein 5.

Additionally, EAT is a major source of mesenchymal stem cells that, transiting through the shared microcirculation, can provide the regeneration and repair of injured myocardium. As opposed to these protective actions, detrimental roles for heart are attributed to epicardial fat [12]. An imbalanced proinflammatory secretome promoting the EAT synthesis of leptin, TNF-α, IL-1b and IL-6, may disrupt myocardial function. These results have been found in a small population of patients with CAD and the local inflammatory burden was independent of other clinical variables and of the plasma concentrations of circulating cytokines. Moreover, in the epicardial fat of a sub-group of patients, the authors observed an up-regulation of almost 800 inflammatory and immune response genes [13]. Similarly, a high-FA feeding of the heart by EAT may lead to intramyocardial fat accumulation causing functional derangements. This is what can happen when an enlarged and biologically transformed EAT coats the heart, thus losing its physiological protective role, and acquiring lipotoxic effects throughout an excess FFa release, which leads to abnormal lipid deposition and fatty infiltration in the myocardium [13].

1.2. Epicardial adipose tissue in diabetes

An expansion of EAT is associated with insulin resistance and visceral fat accumulation, the core defects of metabolic syndrome and two fundamental elements of T2DM that frequently precede its diagnosis by a long-lasting period. It has been calculated that EAT thickness is almost double in individuals with metabolic syndrome compared to controls, with a significant correlation with each component of syndrome [14]. In non-diabetic people, impaired fasting glucose, or obesity-related reduction of insulin sensitivity, as assessed by euglycemic hyperinsulinemic clamp and other markers of insulin resistance, associated with increased epicardial fat. Various studies indicate that an enlarged EAT mass in T2DM is associated with obesity and metabolic syndrome and its components [15]. In T1DM, a study describes a higher epicardial fat independently of obesity. Instead, in a pilot study in T1DM patients from the DCCT/EDIC (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications), epicardial accumulation of adipose tissue was strongly associated with elements of metabolic syndrome such as higher body mass index (BMI) and waist-to-hip ratio, and elevated triglycerides [16].

A meta-analysis including 13 relevant studies for 1102 diabetic patients and 813 healthy subjects, suggests that the amount of EAT is significantly higher in individuals with diabetes than healthy controls, irrespective of T1DM or T2DM, BMI and EAT measurement techniques. Importantly, EAT adiposity is associated with alterations of myocardial function in T2DM people and may be a predictor of diastolic dysfunction in new diagnosed patients [17]. Already two decades ago, EAT identified as a source of inflammatory mediators in high-risk cardiac patients. In a bioptical study comparing SAT and EAT among subjects with or without diabetes, adipocyte size in EAT was significantly larger in diabetic than non-diabetic subjects, and both SAT and EAT featured in diabetic group by a predominantly inflammatory profile [18]. Recent genetic investigations evidence that the EAT transcriptome of T2DM subjects is highly enriched in immune genes like Pentraxin 3 and endothelial lipase G compared to SAT from the same individuals. An altered

secretory profile associated with increased volume of EAT is confirmed in a population of T2DM patients with CAD [18]. EFT can be measured by echocardiography, cardiac magnetic resonance imaging, and computed tomography (CT). Recent studies have confirmed EFT associated with obesity, fasting blood glucose levels, insulin resistance, and adiponectin in patients with T2DM, and an increase in EFT observed in patients with T1DM and T2DM [19].

2. Right Ventricular Function

2.1. Anatomy

The shape of the right ventricle (RV) has been compared to that of a bagpipe and consists of an inflow and an outflow compartment. The RV and the left ventricle [5] are closely linked together. The interventricular septum connects the two ventricles. They share the same pericardial space and have mutual epicardial fibers [20]. The RV generates the same stroke volume as the LV but due to low resistance in the pulmonary vasculature it requires only one quarter of the stroke work. This explains the thin right ventricular wall as compared to the left ventricular myocardium. When pulmonary pressures rise and/or right ventricular volume overload occurs, the RV reacts with hypertrophy, dilatation, and increased contractility [20].

2.2. Right ventricular function

The main role of the RV is to sustain an effective cardiac output. Stroke volume of the RV is predominantly generated by longitudinal shortening rather than by reduction of the cavity diameter (radial function) as is the case in the LV. Due to complex anatomy of the RV, echocardiographic evaluation of RV function is often difficult [21]. Visual examination is the most commonly used method to quantify right ventricular function (RVF). There are many pitfalls that can lead to overestimation or underestimation of function. If used as a single parameter, visual examination proved to be an inaccurate method for evaluation of RVF; therefore, the guidelines suggest using at least one other parameter to quantify RVF. Several echocardiographic RVF parameters have been established and validated. Each of the parameters has significant limitations and pitfalls [21].

2.3. Two-dimensional analysis of RV function

The complex nature of RV contour makes it difficult to re-construct RV shape mentally utilizing even multiple 2D imaging planes. In addition, incorporation of these scanning planes still falls short of a complete 3D geometry, therefore echocardiographers have been using surrogate parameters to describe RV function [22]. Among these, the most frequently reported 2DE measurements for RV function are tricuspid annular plane systolic excursion (TAPSE) and RV fractional area change (FAC) by the apical 4-chamber view. TAPSE is defined as the distance traveled between end-diastole and end-systole at lateral corner of the tricuspid annulus. TAPSE has validated to correlate strongly with RVEF measured by radionuclide angiography, with low observer variabilities [22]. In addition, it has also been validated against RVEF by biplane Simpson method and RV FAC. In a large series of 900 cases, including 150 normal subjects, a cutoff value >17 mm of TAPSE is defined as normal and the guideline recommends the use of <16 mm of TAPSE as abnormal. Of note, TAPSE is angle dependent, and measurement can be affected by sliding motion of the heart within the chest cavity. TAPSE is also load dependent, and TAPSE is increased in the presence of severe TR while in the presence of mildly reduced RV systolic function, TAPSE may appear to be within normal range [23]. TAPSE is a one-dimensional measurement which does not always reflect global RV function.

However, it is an easily obtained surrogate marker for routine practice [23]. FAC is area difference between RV end-diastolic and end-systolic areas measured through ideally RV-focused apical view. Border should be traced carefully to exclude the heavy trabeculations inside the right ventricle. FAC has validated with cardiac magnetic resonance (CMR) and shown to be an independent predictor for sudden death, mortality after pulmonary embolism, heart failure, stroke, and myocardial infarction [24]. An FAC <35% is considered abnormal by guideline. FAC has advantage of being a quickly and easily obtainable parameter like TAPSE and is one of recommended methods alongside TAPSE. However, since FAC is 2D measurement, its disadvantage is that it does not represent global RV function or actual RVEF [25]. 2D RV volume quantification has used with area-length methods and disk summation methods. Area-length method, based on assumption of modified pyramidal or ellipsoid models for RV geometry approximation, underestimate CMR-derived RV volume and is inferior compared to 3DE derived volume [25]. Disk summation method, primarily adopted for calculating RV "body" volume, therefore underestimates true RV volume since RV inflow and outflow parts not included during quantification. Pooled studies of these 2DE methods derived RVEF has lower reference value of 44% with 95% confidence interval (CI) 38–50%. However, calculation of 2D RVEF is currently not recommended by the American Society of Echocardiography [22].

2.4. Right ventricular function in diabetes

The Right ventricular (RV) function plays a significant role in the overall myocardial contractility. Nevertheless, most of the previous studies regarding diabetes-induced changes in myocardial dysfunction were dedicated to the LV at the cost of ignoring the role of the right heart chambers. However, assessment of RV function remains difficult, because of complex geometry, non-uniform contraction and partly retro-sternal position of the RV as recently validated, strain/strain rate imaging, comprehensive approach providing extensive information about regional myocardial function, may be applicable to the RV [26]. Diabetic cardiomyopathy is characterized by the occurrence of ventricular dysfunction independent of coronary artery disease and hypertension4. The proposed metabolic impairments contributing to diabetic cardiomyopathy include deposition of advanced glycation end products, atherosclerosis, subclinical microinfarctions, mitochondrial dysfunction, and lipotoxicity. These impairments not only lead to left ventricle [5] impairment but also might inevitably hamper right ventricle (RV) function because of the systematic nature of these impairments [27]. RV function is known to have diagnostic and prognostic values in multiple cardiovascular diseases and pulmonary disorders. The association between RV dysfunction with aggravation of myocardial function and prognosis in distinct cardiac diseases has been confirmed. The favorable effect of healthy diet and physical activity on RV mechanics indicates that RV myocardial abnormalities are probably modifiable through adequate interventional strategies. Most previous studies on

myocardial dysfunction in diabetes have paid more attention to LV [27].

2.5. Two-dimensional speckle-tracking echocardiography analysis

Three consecutive cardiac cycles images of apical four chamber of RV were acquired during an end-expiratory breath-hold and were transferred to the Echo PAC software (Echo PAC Version: 201, GE Vingmed Ultrasound) for offline STE analysis. The endocardial border of the RV was traced manually in the end-systolic frame at the point in the cardiac cycle in which the endocardial border was the clearest. Then the software would generate a region of interest automatically and adjusted the region of interest to make the myocardial included well [28]. If it was not feasible to track 1 or more segments, the case was excluded. The RV free wall was automatically divided into three segments: basal, mid, and apical. RV peak systolic longitudinal strain (RV LS) and strain rate (RV LSR-S), RV peak early diastolic longitudinal strain rate (RV LSR-E), and RV peak late diastolic longitudinal strain rate (RV LSR-A) were calculated as the mean of the values of the three segments of RV free wall. Due to RV LS is a negative value, we took its absolute value for a simpler interpretation [28].

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