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Review

Proinflammatory phenotype of cardiac visceral fat in heart failure with preserved ejection fraction in the elderly

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Nearly half of all patients with heart failure (HF) symptoms have HF with preserved ejection fraction (HFpEF) and the prevalence of this pathologic condition is rising being aging one of the most important risk factors. HFpEF is a very challenging syndrome vulnerable and frail affecting, in the most of cases, patients, with high health care costs due to high number of hospitalizations and medical cares.

More and more evidence are accumulating on the role of inflammation in the pathogenesis of HFpEF. The presence of multiple comorbidities in HFpEF may significantly contribute to a systemic pro-inflammatory state which negatively affects the myocardium.

Obesity promotes systemic inflammation and exacerbates the inflammatory burden imposed by many chronic extracardiac comorbidities. Importantly, the chronic systemic inflammation related to obesity is associated to a significant increase of the amount of epicardial adipose tissue (EAT), the cardiac visceral fat. The increase of EAT volume is associated to a pro-inflammatory state of this fat depot. Several observations support the hypothesis that the inflammation of EAT can act in a paracrine and vasocrine manner to influence the structure and function of the heart, thus contributing to the pathohenesis of HFpEF. Given the recognized role of EAT in the pathophysiology of HFpEF, it should be desirable to identify specific therapies targeting the cardiac visceral fat and able to modulate its pro-inflammatory profile and the negative effect of the inflammatory burden on the neighboring myocardium.

Key words: Epicardial adipose tissue, Heart failure, Elderly

INTRODUCTION

In the elders, heart failure (HF) shows clinical features that are substantially different to those observed in the adult population. In fact, in patients over 75 years, this syndrome predominantly affects women with isolated systolic hypertension, normal left ventricular ejection fraction, and several extracardiac comorbidities. In this regard, since 2000, Rich et al. identified the main characteristics of HF in the elderly population and paved the way for the nosographic identification of a new cardiovascular syndrome, to date known as heart failure with preserved ejection fraction (HFpEF) [1]. Nearly half of all patients with HF symptoms have HFpEF and the prevalence of this pathologic condition is rising being aging one of the most important risk factors. The clinical outcomes of HFpEF are similar to those with HFrEF. In fact, 30-day to 1-year mortality post hospital discharge is similar between HFpEF and HFrEF and patients with either HF syndrome show similar functional limitations and poor quality of life [2-10]. On the other hand, morbidity and cause of death are quite different between the two syndromes, being HFpEF predominantly associated with extracardiac comorbidities and deaths of non cardiac causes. The peculiarities of HFpEF imply many challenges for the researchers and the clinicians for several reasons: the population affected by HFpEF

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is very heterogeneous and its inclusion in clinical trials is particularly difficult, especially for the oldest-old; mechanistic hypothesis are still lacking due to limited access to biopsies from human heart tissues and the difficulties in obtaining adequate experimental models; the pathophysiological mechanisms accounting for this syndrome are often multifactorial, thus explaining why there is no evidence based therapy, to date, showing efficacy on the hard outcomes, such as morbidity and mortality [11-15].

Overall, HFpEF is a very challenging syndrome, affecting, in the most of cases, patients vulnerable and frail, with high health care costs due to high number of hospitalizations and medical cares. This review aims to report recent advances in the knowledge of the pathophysiology of HFpEF that can help for a better understanding of the mechanisms potentially involved in the onset and progression of such devastating cardiovascular disease.

EXTRACARDIAC COMORBIDITIES, SYSTEMIC INFLAMMATION AND HFPEF

More and more evidence are accumulating on the role of inflammation in the pathogenesis of HFpEF. Results from left ventricular (LV) endomyocardial biopsy [16] and analyses of inflammatory cell markers [17] indicate increased oxidative stress and depressed NO-signaling resulting in inflammation. Importantly, the presence of multiple comorbidities in HFpEF may significantly contribute to a systemic pro-inflammatory state which negatively affects the myocardium.

Chronic kidney disease (CKD) occurs in one third of HFpEF patients and is associated with poor prognosis [7 18 19]. Albuminuria, occurring in almost 30% of HFpEF patients, leads to activation of the RAAS system, and systemic inflammation. It has been hypothesized a bidirectional continuum between renal dysfunction and HFpEF. CKD may lead by itself to myocardial inflammation, fibrosis, and resultant HFpEF. On the other hand, HFpEF may cause renal dysfunction by triggering RAAS pathway activation and venous congestion. In this regard, there are several pathways that may link renal and cardiac disease such as transient receptor potential channel-6, a Gq-receptor and ROS activated nonselective cation channel that plays an important role in proteinuria and glomerular dysfunction [20] but that can also induce cardiac hypertrophy [21] and fibrosis [22].

Chronic inflammation is obviously associated to chronic obstructive pulmonary disease (COPD), which is a crucial determinant of HFpEF mortality [23]. Furthermore, sleep disordered breathing, often associated to COPD and HF, lead to systemic inflammation, other than adrenergic and oxidative activation [24].

Iron deficiency and anemia also contribute to immune responses, systemic inflammation and oxidative stress in HFpEF [25].

Diabetes mellitus (DM) is a common comorbidity in HFpEF and has a significant negative impact on prognosis. Insulin resistance in diabetes mellitus increases free fatty acid utilization by cardiomyocytes, thus leading to mitochondrial dysfunction, production of toxic lipid intermediates, and increased reactive oxygen species [26]. Increased visceral fat, frequently seen in the DM population, also results in the release of proinflammatory cytokines. Hyperglycemia-induced advanced glycation end-products impair microvascular function and decrease nitric oxide availability [26].

Sarcopenia is another common condition in HFpEF. Frail patients with HFpEF are frequently affected by sarcopenia, which is a major component of the pathophysiology of frailty [27]. Sarcopenia, given the impairment of limb and respiratory skeletal muscles leading to further functional decline, may contribute to cardiovascular remodelling and dysfunction and to the development of HFpEF through systemic inflammation and different metabolic and endocrine abnormalities [28].

The incidence of new-onset depression is high in HF (5.7-7.9%). The pathophysiology underlying the adverse effect of depression in HF patients has not been delineated. Potential factors linking depression with HF include activation of inflammatory cascades, dysregulation of neurohormonal axes, arrhythmias, and behavioural effects [29].

All these comorbidities induce a systemic proinflammatory state with elevated plasma levels of interleukin (IL)-6, tumor necrosis factor (TNF)-a, soluble ST2 (sST2), and pentraxin 3 [30]. Coronary microvascular endothelial cells reactively produce reactive oxygen species, vascular cell adhesion molecule (VCAM), and E-selectin. Production of ROS leads to formation of peroxynitrite and reduction of nitric oxide bioavailability with consequent lower soluble guanylate cyclase (sGC) activity in cardiomyocytes. Lower sGC activity decreases cyclic guanosine monophosphate concentration and protein kinase G (PKG) activity. This represents a prohypertrophic stimuli inducing cardiomyocyte hypertrophy. Endothelial expression of VCAM and E-selectin is associated to monocytes migration into the subendothelium which release transforming growth factor, thus stimulating conversion of fibroblasts to myofibroblasts, with consequent deposition of collagen in the interstitial space.

EPICARDIAL ADIPOSE TISSUE MEDIATES DELETERIOUS EFFECTS OF OBESITY AND INFLAMMATION ON THE MYOCARDIUM IN HFPEF

Obesity promotes systemic inflammation [31 32] and exacerbates the inflammatory burden imposed by many chronic extracardiac comorbidities. Importantly, the chronic systemic inflammation related to obesity is accompanied by a significant increase of epicardial adipose tissue (EAT) mass [33]. It is known that inflammation may lead to adipogenesis. This represents an adaptive mechanism preventing the deposition of proinflammatory fatty acids in cells [34]. Interestingly, EAT is more sensitive to lipogenesis than other types of visceral adipose tissue [35]. In fact, it contains plastic mesenchymal cells that are the source of progenitor cardiomyocytes during fetal development but, in adulthood, differentiate into adipocytes [36]). Systemic inflammation affects the biology of EAT [37-39], promoting its transition toward a proinflammatory phenotype [40]. Several observations support the hypothesis that the inflammation of EAT can act in a paracrine manner to influence the structure and function of neighboring tissues [41 42]. Furthermore, the release of proinflammatory adipocytokines from EAT into the general circulation may contribute to the systemic inflammatory state; systemic inflammation, in turn, can promote the accumulation of EAT, which induces local and systemic inflammation and end-organ dysfunction, thus creating a bidirectional continuum [43-48].

Therefore, obesity, such as other extracardiac comorbidities, promotes changes in the physiological characteristics of EAT which starts to produce and secrete proinflammatory factors. Of these, leptin, tumor necrosis factor-a, interleukin 1-β, interleukin-6, and resistin promote the infiltration of macrophages, destroy microvascular systems, and activate profibrotic pathways [49-52]. As regard to leptin, it is known that obesity is characterized by high circulating levels of aldosterone, secreted by adipocytes or directly released from the adrenal gland in response to leptin [53]. This is also exacerbated by a loss of the antialdosterone action of natriuretic peptides given the increased neprilysin activity in obesity. Visceral adiposity also leads to increased signaling through the leptin receptor, which causes sodium retention by a direct action on the renal tubules. EAT-derived leptin promotes cardiac inflammation, microcirculatory abnormalities, and fibrosis. The resulting interaction of aldosterone and leptin promotes plasma volume expansion and regional and systemic inflammation and fibrosis.

Another important mechanism by which EAT may exert an unfavourable activity for the myocardium and causes cardiac damage depends on the migration of EAT derived mesenchymal stem cells to the neighboring myocardium and differentiation of these cells into fibroblasts [54-56].

There are several experimental and clinical studies indicating a relationship between EAT volume and inflammatory profile and the degree of cardiac inflammation [43 50 57 58]. It is widely recognized that EAT, especially the periatrial fat, may represent an inflammatory substrate acting as a trigger for the development of atrial arrhythmias [59-64]. Interestingly, increased volume and proinflammatory abnormalities of EAT are close to myocardial areas of myocardium characterized by marked electrophysiological derangement [65 66]. In obese individuals, increased EAT volume is significantly associated with an impaired myocardial microcirculation, abnormalities of cardiac diastolic properties and increased vascular stiffness, and left atrial dilatation [67-70]. In these patients, structural and functional abnormalities of EAT often precedes clinical presentation of HFpEF [71-74]. Another important evidence supporting the role of EAT as transducer of inflammatory signals derives from the observation of the structural abnormalities of cardiac visceral fat in patients affected by chronic systemic inflammatory disorders. In this regard, patients with rheumatoid arthritis, human immunodeficiency, virus infection, psoriasis, show increased EAT mass that is also associated to alterations of cardiac microcirculation, myocardial fibrosis, and cardiac diastolic abnormalities, that are all typical of HFpEF [75-79]. This may explain the significant higher risk of developing HF in these clinical settings.

If it is true that extracardiac comorbidities contribute to the pathogenesis of HFpEF, it is also evident that EAT may play a role, through the release of proinflammatory adipocytokines, in exacerbating the dysfunction of visceral organs, other than the heart. In fact, increased EAT volume is associated to inflammation and fibrosis in the kidneys, lungs, liver, and brain, whose dysfunction participates to the clinical features of HFpEF [80-82].

EAT AND CARDIAC SYMPATHETIC DENERVATION IN HF

Cardiac sympathetic nervous system (SNS) hyperactivity is associated to HF [1-6] and represents a compensatory mechanism to the loss of cardiac contractility aiming at increasing myocardial inotropism to preserve cardiac output. However, in the long term, this mechanism is associated to unfavourable cardiac remodeling and increased mortality [83-88]. In the failing heart, a defect of neuronal norepinephrine reuptake caused by post-transcriptional downregulation of the cardiac norepinephrine transporter [89-93] leads to an increase

in norepinephrine concentration in the sympathetic synapses. This is responsible for impaired myocardial β-adrenergic receptor system and functional and anatomic sympathetic denervation of the heart [94 95].

Although SNS hyperactivity in HF is mainly mediated by norepinephrine-releasing neurons and by circulating norepinephrine and epinephrine, other mechanisms may contribute to sympathetic derangement. For example, the adipose tissue, particularly the visceral fat depots, may stimulate central SNS activity through dysregulated adipokines production and secretion [96 97]. In addition, experimental studies have recently demonstrated that adipocytes produce and secrete both norepinephrine and epinephrine [98], thus indicating that the sympathetic fibers within adipose tissue are not the only source of catecholamines. In a recent study, Parisi et al have demonstrated, in HF patients, that EAT represents an important source of norepinephrine, whose levels are 2-fold higher than those found in plasma [99]. Because of the EAT proximity to the myocardium, the increase in catecholamine content in this tissue could result in a negative feedback on cardiac sympathetic nerves, which are associated with the ventricular myocardium, thus inducing a functional and anatomic denervation of the heart. Therefore, in the context of a widespread SNS hyperactivity in HF, EAT seems to play an additive role in generating the final net effect of cardiac sympathetic denervation. In this study, the EAT thickness, assessed by echocardiography, was an independent predictor of 123I-MIBG planar and SPECT scintigraphic parameters (indexes of cardiac sympathetic innervation) and provided additional predictive information on cardiac adrenergic nerve activity respect to important demographic, clinical, and left ventricular function parameters. Therefore, assessing EAT thickness in patients with HF may provide surrogate information on the status of cardiac adrenergic derangement that is strongly correlated with worse prognosis in HF.

In another study, Parisi et al. also explored the relationship between the presence of sleep disordered breathing and EAT thickness in patients with HF [100]. They found a significant correlation between the EAT increase and the presence and the severity of sleep apneas and a significant increase of circulating norepinephrine in patients with central sleep apnea (CSAs). These data confirm the results of previous study exploring SNS activation in HF patients with prevalent obstructive or central sleep apneas (CSAs). According to results of Parisi et al, all these studies indicate that CSAs are associated with a greater SNS activation [101-103]).

Overall these evidence indicate EAT as a possible contributor to SNS activation in HF, thus reinforcing the negative activity of cardiac visceral fat in the pathogenesis and progression of HF.

EAT AS A POTENTIAL THERAPEUTIC TARGET IN HF

Given the recognized role of EAT in the pathophysiology of HFpEF, it should be desirable to identify specific therapies targeting the cardiac visceral fat and able to modulate its pro-inflammatory profile and the negative effect of the inflammatory burden on the neighboring myocardium. The discovery of new drugs for HFpEF is dramatically needed since the lack, to date, of evidence based therapy able to ameliorate the outcomes of this syndrome. In this rewiew, we report the results of recent studies focusing on this topic.

Statins have been shown to reduce both EAT accumulation and inflammatory status in HF patients [104 105]. In a recent study, Parisi et al. [106-108] explored, in a population of elderly patients with calcific aortic stenosis, a clinical model of HFpEF, whether statin therapy might affect EAT accumulation and inflammatory profile. Major findings of this study was that statin therapy was significantly associated to a reduced EAT thickness. Furthermore, the association between statin therapy and reduction of EAT accumulation was paralleled by an attenuation of EAT inflammatory profile. Finally, in vitro studies conducted on the EAT secretomes, obtained from patients with aortic stenosis, indicated that statin had a direct and selective anti-inflammatory effect on EAT.

These evidence may explain why statins, independently from their antihyperlipidemic effect, reduce the development of ventricular diastolic abnormalities, myocardial microcirculatory alterations, and cardiac fibrosis [109-111]. Furthermore, the use of statins in patients with HFpEF is associated with a reduced risk of death in several observational studies [112 113].

Patients with type 2 diabetes show a marked increase in the amount of EAT and a high incidence of HFpEF has been reported in this population [114]. Importantly, many antidiabetic drugs cause weight gain, thus inducing a further increase of adipogenesis and of EAT. In this regard, insulin increases the volume of EAT [39 73]; this may explain, at least in part, why its use is associated with an increased risk of heart failure [115]. Sulfonylureas promote the insulin activity on adipocytes and enhance the secretion of proinflammatory adipokines [116-118]. Thiazolidinediones reduce EAT volume and inflammation and the secretion of proinflammatory adipocytokines [119-122].

Newer antihyperglycemic medications, such as glucagon-like peptide 1 receptor antagonists are typically associated with weight loss and may reduce the accumulation of EAT [123], although they do not revert its pro-inflammatory phenotype [124 125]. This may explain why these drugs do not affect the HF outcome in clinical trials [126 127]. Although other antidiabetic drugs, such as dipeptidyl peptidase-4 inhibitors are able to reduce

the volume of EAT [128], they may exacerbate its inflammatory state and lead to cardiac fibrosis [129-131]. This finding explains why dipeptidyl peptidase-4 inhibitors negatively affect cardiac remodeling and increase the risk of HF in patients with type 2 diabetes [132].

It has been recently demonstrated that sodium-glucose cotransporter 2 inhibitors not only reduce the amount of EAT, but also ameliorate its inflammation and its secretion of pro-atherosclerotic and pro-fibrotic cytokines [133 134]. This may explain why these drugs reduce myocardial fibrosis and improve ventricular diastolic properties [135-137] and reduce the risk of several HF outcomes in observational studies and randomized controlled trials [138-141].

Given the ability of mineralocorticoid receptor antagonists, such as eplerenone to revert inflammation in visceral adipose tissue of obese individuals [142], further studies are desiderable to confirm this effect also in EAT. Preliminary data on these drugs indicate a favourable activity to reduce cardiovascular events in patients with HFpEF [143].

Recent encouraging evidence indicate a positive activity of neprilysin inhibition in HFpEF [144]. This drug could counteract the breakdown of natriuretic peptides that is known to be accelerated in HFpEF.

Finally, the prominent role of inflammation in HFpEF represents an important motivation for the current research to explore the efficacy of drugs targeting circulating and local inflammatory mediators. The results of the recent CANTOS trial have demonstrated that inhibition of Interleukin 1β has potent effect on cardiovascular morbidity and mortality in patients with previous myocardial infarction [145]. Future studies are needed the potential role of immune therapy also in HFpEF.

CONCLUSIONS

Accumulating evidence strongly support the role of structural and functional changes of EAT in the pathogenesis of HFpEF. Many inflammatory factors produced by cardiac visceral fat may penetrate the myocardium and coronary vessels in a paracrine and vasocrine manner and express their toxicity in the neighboring tissue. This promotes profound cardiac alterations such as fibrosis, alterations of left ventricular filling, derangement of electrophysiological properties, and sympathetic denervation that are all crucial factors for the development of HFpEF. Although it is widely recognized the multifactorial nature of HFpEF, EAT represents an intriguing target for future therapeutic strategies since its tight interconnection with the heart and its prominent role in enhance local and systemic inflammation. The epidemiological explosion of HFpEF and the lack of efficacious therapy strengthen the need to explore novel mechanisms and innovative therapeutic approaches to face the dramatic increase of cardiovascular deaths that are expected in the next decades.

Conflict of interest

The Authors declare to have no conflict of interest.

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