Characterization of the inflammatory-metabolic phenotype of heart failure with a preserved ejection fraction: a hypothesis to explain influence of sex on the evolution and potential treatment of the disease

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Accumulating evidence points to the existence of an inflammatory-metabolic phenotype of heart failure with a preserved ejection fraction (HFpEF), which is characterized by biomarkers of inflammation, an expanded epicardial adipose tissue mass, microvascular endothelial dysfunction, normal-to-mildly increased left ventricular volumes and systolic blood pressures, and possibly, altered activity of adipocyte-associated inflammatory mediators. A broad range of adipogenic metabolic and systemic inflammatory disorders – e.g. obesity, diabetes and metabolic syndrome as well as rheumatoid arthritis and psoriasis – can cause this phenotype, independent of the presence of large vessel coronary artery disease. Interestingly, when compared with men, women are both at greater risk of and may suffer greater cardiac consequences from these systemic inflammatory and metabolic disorders. Women show disproportionate increases in left ventricular filling pressures following increases in central blood volume and have greater arterial stiffness than men. Additionally, they are particularly predisposed to epicardial and intramyocardial fat expansion and imbalances in adipocyte-associated proinflammatory mediators. The hormonal interrelationships seen in inflammatory-metabolic phenotype may explain why mineralocorticoid receptor antagonists and neprilysin inhibitors may be more effective in women than in men with HFpEF. Recognition of the inflammatory-metabolic phenotype may improve an understanding of the pathogenesis of HFpEF and enhance the ability to design clinical trials of interventions in this heterogeneous syndrome.

Keywords
Heart failure with preserved ejection fraction • Systemic inflammation • Obesity • Diabetes
• Aldosterone • Neprilysin

Introduction

The most common cardiovascular disorder in the general population results from an inflammatory response to an ectopic accumulation of dysfunctional lipids. Hypercholesterolaemia is a major risk factor for coronary artery disease, but it is the inflammatory response to oxidized lipoproteins that leads to the formation of and undermines the stability of the atherosclerotic plaque. However, inflammation in atherosclerosis may not solely be a response to lipids that are imbibed from the bloodstream. Many systemic inflammatory diseases (e.g. rheumatoid arthritis and psoriasis) are characterized by accelerated coronary atherosclerosis

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and a heightened risk of coronary ischaemic events. In these disorders, the coronary vessels are the target of a systemic inflammatory response whose trigger resides outside of the cardiovascular system. Some have proposed that systemic inflammation induces transformational changes in epicardial adipose tissue; the resulting pockets of inflammation are transmitted to the immediately adjacent coronary vessels to cause occlusive lesions.

Like the coronary arteries, the myocardium can be a target of a systemic inflammatory disorder that is initiated in non-cardiac tissues. These diseases can adversely affect the coronary microvasculature directly. Additionally, these disorders are often accompanied by the accumulation and dysfunction of epicardial adipose tissue and intramyocardial lipids, which are poised to focus the effects of the systemic disorder onto the underlying cardiac tissues. The epicardial release of proinflammatory mediators can cause microcirculatory dysfunction and fibrosis of the adjacent muscle. When this process affects the atria, the resulting electroanatomical remodelling may lead to atrial fibrillation. When the process adjoins the left ventricle, it may impair the chamber's distensibility and increase diastolic stiffness and left ventricular (LV) filling pressures. This phenotype is designated herein as 'inflammatory-metabolic heart failure with a preserved ejection fraction' (HFpEF).

The myocardial inflammatory process in these patients often compromises systolic function, but in general, the LV ejection fraction is not severely depressed; typically, it is >40%. However, many patients with a LV ejection fraction of 40–50% do not have meaningful evidence of inflammation; instead, they have features of heart failure and a reduced ejection fraction (HFrEF), with evidence of cardiomyocyte injury and stretch. These latter patients often respond favorably to drugs that produce important benefits in those with marked systolic dysfunction (i.e. LV ejection fraction <35–40%). Therefore, the diagnosis of 'inflammatory-metabolic HFpEF' is not based on the measurement of LV ejection fraction, but instead, it is primarily determined by evidence of systemic and adipose tissue inflammation, microvascular endothelial dysfunction, and myocardial fibrosis.

Previous work on the influence of visceral fat and the actions of hormonal mediators has focused on HFpEF in obese people. By contrast, this paper characterizes the pathophysiologic abnormalities that may lead to a distinctive form of HFpEF that is seen in a broad range of systemic inflammatory and metabolic disorders, potentially explaining why this HFpEF phenotype is predominantly a disease of women.

Characterization of the heart failure phenotype in patients with a systemic inflammatory or adipogenic metabolic disorder

A diverse range of disorders can cause heart failure with a LV ejection fraction in the normal range. Some patients have surgically correctable lesions (e.g. valvular disease), and others have hypervolaemic or high-output states (e.g. obesity, cirrhosis and shunts). Still others may have hypertrophic or an infiltrative cardiomyopathy. The most common infiltrative disease leading to a clinical picture that may mimic HFpEF is amyloidosis, which affects up to 15% of elderly people with heart failure, primarily men. However, the majority of patients with HFpEF in clinical practice have a phenotype that is closely linked to systemic and adipose tissue inflammation, and is primarily seen in women.

Pathophysiological distinctions between inflammatory-metabolic heart failure with a preserved ejection fraction and hypertrophic or infiltrative cardiomyopathy

When first recognized, HFpEF was regarded as a form of hypertrophic cardiomyopathy, a disorder that is characterized by excessive thickening of the LV walls and small LV volumes. The hypertrophic process may encroach into LV cavity, impeding the capacity of the left ventricle to accommodate blood. These patients have depressed stroke volumes and low blood pressures and may deteriorate clinically when plasma volumes are reduced by diuretics. The LV end-diastolic pressure–volume relation is shifted upwards and to the left, so that cardiac filling pressures are elevated, even though cardiac filling is inadequate.

Many of these features are also present in patients with wild-type transthyretin amyloid cardiomyopathy. These individuals are generally men who have low-to-normal systolic blood pressures, a reduced LV cavity size, striking thickening of the ventricular walls, and disportionately increased levels of natriuretic peptides. The LV end-diastolic pressure–volume relation is also shifted upwards and to the left as in hypertrophic cardiomyopathy, but in contrast with the latter, patients with cardiac amyloidosis often have right ventricular involvement as a result of amyloid infiltration.

In contrast, the HFpEF phenotype that accompanies a broad range of systemic inflammatory or metabolic diseases is primarily seen in older women with comorbidities, which may reflect the effects of the inflammatory or metabolic process on various end-organ functions. The LV walls are often not thickened or only mildly so, and ventricular volumes (when indexed for body surface area and sex) are normal or modestly enlarged, and not decreased. This HFpEF phenotype is frequently accompanied by sodium retention and possibly by a decrease in systemic venous capacitance, both of which can lead to an increase in central blood volume. However, the ventricles cannot accommodate the expansion and redistribution of blood volume because cardiac distensibility is impaired, most likely related to coronary microvascular dysfunction and myocardial fibrosis and/or pericardial restraint. Inflammation-related phosphorylation of titin may also enhance myocardial stiffness. The LV end-diastolic pressure–volume relationship is not necessarily shifted in these patients as it is in infiltrative cardiomyopathies;
Inflammatory-metabolic HFpEF and influence of sex

Table 1 Contrasting features of cardiac amyloidosis and inflammatory-metabolic heart failure with a preserved ejection fraction

| Demographic features | Wild-type transthyretin amyloid cardiomyopathy | Inflammatory-metabolic heart failure with a preserved ejection fraction |
|----------------------|-----------------------------------------------|---------------------------------------------------------------------|
| Older adults, men > women | LV filling pressures are increased | Middle-aged to elderly, women > men |
| Heart failure, typically with increased right-sided pressures | LV systolic function | Heart failure, often with increased right-sided pressures |
| LV end-diastolic volumes (indexed for age and gender) | Left atrial enlargement | Characteristically present |
| LV systolic function | LV diastolic filling abnormalities | Modestly increased (or taking antihypertensive drugs) |
| Ejection fraction typically >40% | LV wall thickness | LV systolic function |
| Typically present | Markedly increased (especially in men) | LV systolic function typically >40% |
| Cardiac troponin | LV end-diastolic volumes (indexed for age and gender) | Ejection fraction typically >40% |
| LV diastolic filling abnormalities | LV wall thickness | Typically (but not invariably) present |
| LV systolic function | Clinical presentation | LV diastolic filling abnormalities |
| LV end-diastolic volumes (indexed for age and gender) | LV systolic function | LV diastolic filling abnormalities |
| LV wall thickness | LV diastolic filling abnormalities | LV diastolic filling abnormalities |

LV, left ventricular.

Table 2 Principal clinical and pathophysiological characteristics of inflammatory-metabolic heart failure with a preserved ejection fraction

- Exertional dyspnoea due to heart failure with a left ventricular ejection fraction that is generally >40%
- Primarily a disease of women
- Generally accompanied by a chronic systemic inflammatory or metabolic disorder that is characterized by a derangement of adipose tissue biology (e.g. obesity, diabetes, metabolic syndrome, non-alcoholic fatty liver disease, rheumatoid arthritis, psoriasis)
- Increased biomarkers reflecting systemic inflammation or insulin resistance (e.g. C-reactive protein)
- Mildly increased systolic blood pressure or taking medications for the treatment of hypertension
- Echocardiography reveals normal to modestly increased left ventricular volumes (indexed for gender and body surface area), generally with diastolic filling abnormalities, but without marked septal thickening
- Magnetic resonance imaging demonstrates increased epicardial adipose tissue volume, with variable degrees of fibrosis
- Coronary microvascular dysfunction, ideally measured by reduced coronary flow reserve during adenosine-induced hyperaemia, but approximated by provocative testing during non-invasive imaging
- Renal dysfunction (typically, an estimated glomerular filtration rate of 50–80 mL/min/1.73 m²), with evidence of increased perirenal fat or renal microvascular disease related to systemic inflammation
- Potentially impaired systemic venous capacitance (often with plasma volume expansion) leading to an increase in central blood volume
- Potential reduction in adverse heart failure-related outcomes with mineralocorticoid receptor antagonists and nephrilysin inhibitors

Influence of sex on the mechanisms of inflammatory-metabolic heart failure with a preserved ejection fraction

The pathways that drive inflammatory-metabolic HFpEF are particularly common in women. Women are prone to the systemic metabolic and autoimmune disorders that cause adipose tissue inflammation, and they show a heightened systemic inflammatory response to the accumulation of body fat. Women are particularly likely to develop myocardial steatosis in response to metabolic derangements, and when compared with men, they are more susceptible to developing coronary microvascular dysfunction and...
Systemic inflammatory and metabolic disorders that lead to cardiac inflammation, diastolic filling abnormalities and heart failure

Many chronic systemic inflammatory and metabolic disorders are accompanied by an increased risk of heart failure, particularly HFrEF (Table 3), and this risk is independent of the development of macrovascular coronary heart disease. As noted earlier, most of these systemic disorders are more prevalent in women.

Systemic inflammatory disorders leading to heart failure with a preserved ejection fraction

Rheumatoid arthritis and systemic lupus erythematosus can lead to myocardial inflammation, coronary microcirculatory abnormalities, diastolic dysfunction, LA enlargement, and heart failure, particularly HFrEF; these abnormalities parallel the degree of clinical inflammation and are not explained by traditional cardiovascular risk factors or ischaemic heart disease. Patients with psoriasis also exhibit coronary microvascular dysfunction, abnormalities of LA structure and LV filling that are typical of HFrEF, and have an adverse prognosis.

Metabolic and hormonal derangements leading to heart failure with a preserved ejection fraction

In addition to systemic inflammation, numerous metabolic disorders that are accompanied by the expansion and inflammation of visceral adipose tissue have been linked to the development of HFrEF (Table 3). Obesity is predictably accompanied by diastolic filling abnormalities, microvascular dysfunction, and cardiac fibrosis. An elevated body mass (especially visceral adiposity) presages a dramatic increase in the risk of heart failure (especially HFrEF) and independent of any association with ischaemic cardiac injury. Additionally, there is a strong mechanistic relationship between diabetes and heart failure; hyperglycaemia and insulin resistance are often accompanied by cardiac inflammation, coronary microvascular disease, myocardial fibrosis, and diastolic dysfunction, which may collectively culminate in HFrEF. Other disorders that are characterized by visceral adiposity and insulin resistance – e.g. the metabolic syndrome and non-alcoholic fatty liver disease – are also strongly associated with coronary microcirculatory dysfunction, ventricular fibrosis, abnormalities of diastolic filling, and an increased risk of heart failure. Finally, patients with hyperaldosteronism, hypercortisolism and primary hyperaldosteronism manifest cardiac fibrosis, abnormalities of LV filling and an increased risk of heart failure, which may be ameliorated by treatment of the underlying hormonal derangement. Each of these metabolic disorders is characterized by the expansion and inflammation of adipose tissue depots.

The kidneys as a secondary target of inflammation

These systemic disorders may not only adversely affect the heart, but also the kidneys. The most common causes of inflammatory-metabolic HFrEF – diabetes and obesity – are important causes of chronic kidney disease. Additionally, other diseases that are linked to HFrEF (e.g. rheumatoid arthritis, psoriasis and non-alcoholic steatohepatitis) increase the risk of chronic kidney disease, in proportion to the severity of the inflammatory derangement. Chronic kidney disease is often accompanied by systemic inflammation, whose severity predicts the development of diastolic dysfunction and heart failure, including HFrEF. Proinflammatory mediators that have been linked to HFrEF have been associated with a progressive decline in glomerular function. Furthermore, the renal response to adipose tissue expansion and

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Inflammation can trigger changes in tubuloglomerular feedback that promote glomerular hyperfiltration and its adverse effects on renal function.86,87

**Obesity as a link between systemic inflammation and metabolic disorders**

Obesity provides an important link between systemic inflammation and metabolic disorders, and thus, is a major determinant of HFpEF, whether the primary mechanism is identified as inflammatory or metabolic.10 Visceral adiposity amplifies the systemic inflammatory response even if its origins reside in non-adipocyte organs. As a result, concomitant obesity substantially increases the incidence and clinical severity of many inflammation-related disorders.

Obesity predicts adverse clinical outcomes and treatment responses in rheumatoid arthritis, systemic lupus erythematosus and psoriasis,98–90 worsens functional capacity in systemic sclerosis,91 increases the prevalence and worsens the severity of asthma,92 has deleterious effects in inflammatory bowel disease and multiple sclerosis,93,94 and contributes to the progression of diabetes, non-alcoholic steatohepatitis and chronic kidney disease.95–97 By acting as a broad accelerant of systemic inflammation, obesity potentiates the likelihood of heart failure (particularly HFpEF) in patients who are already prone to its development.

The predisposition to heart failure is particularly enhanced by an action of obesity to promote sodium reabsorption across multiple sites along the renal tubular epithelium.10 Obese patients with HFpEF have plasma volume expansion that is directly proportional to body mass,7 and additionally, obesity may limit systemic venous capacitance.98 The resulting expansion of central blood volume is poorly tolerated when LV distensibility is impaired.7

**Influence of sex on cardiac and vascular dysfunction leading to heart failure with a preserved ejection fraction**

Women are not only at greater risk of the systemic inflammatory and metabolic disorders that are linked to HFpEF, but sex also influences the cardiovascular response to stresses that predispose to HFpEF.99 As compared with men with HFpEF, women have more symptoms and disability,100,101 but have more favourable long-term outcomes.99 When compared with men, women (especially elderly women) exhibit greater impairment of LV diastolic reserve and show greater increases in pulmonary venous pressures with volume loading,102 possibly because systemic venous capacitance is limited in women.103 Furthermore, women show greater degrees of arterial stiffness, more impaired ventricular–vascular coupling, and more striking LV concentric remodelling with pressure overload than men.104–106 Importantly, in the absence of HFpEF, LV volumes are smaller in women than in men (even when accounting for body surface area),106–108 and thus, women are more reliant on a higher ejection fraction to maintain stroke volume and cardiac output,109 an effect that may be exaggerated by aging.110 In patients with established HFpEF, women show greater increases in pulmonary wedge pressure and abnormalities of diastolic filling at a given workload and manifest a greater LV wall thickness than men.107,108

Interestingly, the two most common harbingers of inflammatory–metabolic HFpEF – obesity and diabetes – have greater cardiac effects in women than men. Obesity causes greater structural changes in the hearts of women.39,32 Central obesity exacerbates age-related ventricular-arterial stiffening in women, but not in men.111 Both adiposity and diabetes are important determinants of LV mass and wall thickness in women, but not in men,112,113 especially as they grow older. Similarly, obesity and other inflammatory states have a greater influence to increase LA size in women than in men,114,115 particularly with aging.116 Visceral adiposity is accompanied by coronary microvascular dysfunction in women, but not in men.30 Obesity and diabetes accelerates the evolution of diastolic filling abnormalities during longitudinal follow-up more in women than men,117 and diabetes exacerbates exercise-induced diastolic abnormalities more in women than men.118 As a result – in obesity, diabetes and the metabolic syndrome – as compared with men, women show increased LV wall thickness and filling pressures by echocardiography and an enhanced risk of HFpEF.119–124

**Deleterious biological transformation of epicardial adipose tissue in systemic inflammatory and metabolic disorders**

Deleterious biological transformation of epicardial adipose tissue in systemic inflammatory and metabolic disorders

Why do systemic inflammatory and adipogenic metabolic disorders target the heart? These diseases may lead to HFpEF through their common action to cause endothelial dysfunction of the coronary microvasculature.3 Furthermore, each of these disorders also causes adipose tissue inflammation, which (if it involves the epicardial fat mass or intramyocardial lipids) may amplify and focus the systemic process onto the myocardium,4 thus potentiating cardiac inflammation and coronary microcirculatory dysfunction, thereby impairing the distensibility of the left ventricle.

**Adaptive and maladaptive roles of epicardial adipose tissue in nurturing and injuring underlying cardiovascular structures**

The epicardium shares an unobstructed microcirculation with the underlying muscle, given the absence of a fascial plane between the two structures. Embryonically, it is a major source of mesenchymal stem cells for cardiac regeneration, and healthy epicardial fat has the biological properties of brown adipose tissue, which combats proinflammatory fatty acids and secretes adipokines (e.g. adiponectin) that nourish the myocardium. However, under the influence of certain systemic inflammatory or metabolic disorders, mesenchymal cells in the epicardium are transformed into adipocytes, which develop features of white adipose tissue.4,10 When overfilled with lipids, these adipocytes are prone to lipolysis, and the release of fatty acids triggers macrophage infiltration125 and
the secretion of proinflammatory cytokines (leptin, tumour necrosis factor-α, interleukin-6, interleukin-1β and resistin). The intimacy of its interface with the myocardium allows these biological derangements to be transmitted to the neighbouring muscle. Proinflammatory cytokines synthesized in epicardial fat depots are ideally positioned to adversely influence the structure and function of the underlying tissues, i.e. the epicardium focuses the inflammation initiated in other organs onto the heart. Accordingly, in the presence or absence of HFrEF, the volume of epicardial adipose tissue is associated with the severity of coronary microvascular dysfunction, myocardial fibrosis and LV hypertrophy. Lipids may also accumulate to an excess degree within the myocardium itself and be accompanied by adverse structural changes.

Expansion of epicardial adipose tissue in patients with chronic systemic inflammatory and metabolic disorders and in patients with heart failure and a preserved ejection fraction

In light of the potential importance of epicardial adipose tissue expansion in the pathogenesis of HFrEF, it is noteworthy that each of the systemic inflammatory or adipogenic metabolic disorders that have been linked to HFrEF has been shown to be associated with an increase in epicardial fat volume (Table 3).

Specifically, rheumatoid arthritis, systemic lupus erythematosus and systemic sclerosis are accompanied by an increase in epicardial fat volume that is proportional to the duration and severity of the underlying disease and is paralleled by changes in diastolic filling parameters. Epicardial adiposity is also seen in psoriasis, inflammatory bowel disease, and chronic pulmonary inflammation. Similarly, in obesity, epicardial adipose tissue volume is increased in relation to the degree of microvascular dysfunction, cardiac fibrosis, and ventricular hypertrophy and to adverse changes in diastolic filling, LA dimensions and global longitudinal strain. Diabetes is accompanied by epicardial adipose expansion and inflammation, when diabetes and obesity coexist, each contributes to the volume of epicardial fat. Epicardial adiposity is strongly associated with insulin resistance and changes in ventricular structure and function. The metabolic syndrome and non-alcoholic fatty liver disease are associated with increases in epicardial fat that are accompanied by proportional degrees of diastolic dysfunction and microvascular injury. Other hormonal derangements that have been linked to HFrEF (primary hyperaldosteronism, Cushings syndrome and hypothyroidism) exhibit increases in epicardial fat volume that parallel the severity of the underlying disorder.

The systemic inflammatory or metabolic disorders that are linked to HFrEF are associated with epicardial adipose tissue expansion before the onset of heart failure, and thus, epicardial fat volume is increased in patients with established HFrEF — a feature that may distinguish HFrEF from HFrEF. [One report suggesting a decrease in epicardial fat volume in HFrEF evaluated obese patients who had an inexplicably low prevalence of atrial fibrillation and likely had a hypovolaemic (rather than an inflammatory) state.] In patients with HFrEF, epicardial adipose tissue expansion has been associated with greater degrees of LA and LV dysfunction and a higher prevalence of atrial fibrillation. Spread of the systemic inflammatory process to the kidneys may explain why epicardial fat is increased in chronic kidney disease. Epicardial adipose tissue mass predicts the progressive decline in glomerular function and the onset of albuminuria in diabetic nephropathy. Epicardial adiposity is associated with chronic kidney disease even in the absence of diabetes.

Influence of sex on epicardial adipose tissue in inflammatory-metabolic heart failure with a preserved ejection fraction

Given the potential importance of epicardial adipose tissue inflammation in mediating the structural and functional changes in the myocardium in HFrEF, it is noteworthy that epicardial fat volume appears to be particularly increased in women, particularly as they age and become postmenopausal. Epicardial fat is likely to be accompanied by evidence of systemic inflammation, increases in systolic blood pressure, coronary microcirculatory abnormalities and abnormalities of diastolic filling in women, but not in men. Intramyocardial fat accumulation in HFrEF is also particularly characteristic of women.

Challenges in assessing the role of epicardial adipose tissue derangements in inflammatory-metabolic heart failure with a preserved ejection fraction

Notwithstanding these observations, deciphering the role of epicardial adipose tissue inflammation in the pathogenesis of HFrEF is difficult. Imaging can quantify the volume of epicardial fat, but it cannot assess its biological activity, and thus, cannot determine if it is nutritive or proinflammatory. Furthermore, the increase in circulating proinflammatory adipocytokines in epicardial adiposity may reflect their release from non-cardiac visceral fat depots, which often increase in parallel with an expansion of epicardial adipose tissue. As in the case of epicardial fat, abdominal fat is closely associated with LV dysfunction.

Nevertheless, epicardial fat depots (as well as intramyocardial lipids) are unique in their exceptionally close proximity to the myocardium, and fat expansion adjacent to cardiomyocytes may be particularly linked to cardiac derangements. Furthermore, the premise that an expanded epicardial fat mass is biologically abnormal is supported by the analyses of tissue obtained during surgery and by the finding of an elevated transcardiac gradient for proinflammatory adipocytokines in states of epicardial adiposity. Yet, the intimacy of epicardial fat and the myocardium can be bidirectional; conceivably, epicardial adipose tissue expansion may reflect the extension of inflammation originating in the heart to the epicardium. If so, then increases in epicardial fat would represent a biomarker rather than a cause of cardiac dysfunction.
Role of aldosterone, natriuretic peptides and leptin in the genesis of adipose tissue inflammation and the development of heart failure with a preserved ejection fraction

Why does a broad range of systemic inflammatory and metabolic disorders lead to epicardial adipose tissue expansion? Systemic and adipose tissue inflammation has been linked to abnormalities in several hormonal mediators (i.e., aldosterone, leptin and natriuretic peptides) that may contribute to the development of epicardial adiposity. Previous work has focused on their contribution in the genesis of heart failure in obesity, whereas this paper focuses on their role in the epicardial adipose tissue expansion and in mediating the inflammatory processes seen in the myriad of systemic disorders that are linked to HFpEF.

Aldosterone promotes epicardial adipose tissue expansion and its adverse effects on the myocardium. Mineralocorticoid receptor signalling is required for the differentiation of adipocytes and their transition to a proinflammatory state, promoting epicardial adipogenesis and the secretion of proinflammatory cytokines. Elevated tissue activity of aldosterone causes coronary microvascular dysfunction and fibrosis, and the infusion of aldosterone contributes to the evolution of experimental HFpEF. Circulating levels of aldosterone are increased in parallel with abnormalities of LV geometry, although interestingly, hyperaldosteronism has not been noted in patients with established HFpEF. Supporting the hypothesis that aldosterone (if released by epicardial adipocytes) acts primarily in a paracrine manner.

In contrast to the actions of aldosterone, natriuretic peptides have direct effects to limit adipogenesis and restrain the proinflammatory transformation of adipose tissue; natriuretic peptides are capable of reversing epicardial fat to its healthy state, thereby enhancing its nutritive functions. By doing so, natriuretic peptide signalling opposes the actions of aldosterone to promote the expansion and inflammation of adipose tissue; circulating levels of natriuretic peptides are inversely related to epicardial as well as visceral fat mass. However, dysfunctional adipocytes accelerate the clearance of natriuretic peptides and secrete neprilysin (which degrades natriuretic peptides), thus promoting a positive feedback loop that stimulates adipogenesis. Attenuation of the actions of natriuretic peptides also leads to coronary microvascular dysfunction and cardiac fibrosis, the resulting limitation of ventricular stretch further weakens the stimulus to natriuretic peptide synthesis. Interestingly, circulating neprilysin levels have been reported to be increased in HFpEF in some studies (but not others); nevertheless, patients with HFpEF have accelerated breakdown of natriuretic peptides. In any case, neprilysin inhibition attenuates atrial distension and ventricular wall stress in patients with HFpEF with obesity, and these benefits are particularly notable in those who have type 2 diabetes.

The expansion and biological transformation of epicardial adipose tissue promotes its synthesis of proinflammatory adipocytokines, including leptin, tumour necrosis factor-α, interleukin-1β and interleukin-6. These mediators are released locally (promoting cardiac inflammation) and systemically (potentially contributing to renal dysfunction). Among the candidate adipocytokines, leptin is most likely to cause sodium retention and be linked to systemic inflammatory and adipogenic metabolic disorders. Circulating levels of leptin are closely associated with those of aldosterone in population studies. Leptin stimulates aldosterone secretion from the adrenal cortex and promotes its proinflammatory actions; in return, aldosterone can increase the synthesis of leptin. In a counterregulatory manner, natriuretic peptides inhibit the synthesis of both leptin and aldosterone; circulating levels of leptin and natriuretic peptides are inversely related. Circulating leptin levels are correlated with epicardial fat mass and are increased in patients with HFpEF.

Role of aldosterone, leptin and natriuretic peptides in the pathogenesis of systemic inflammatory and adipogenic metabolic disorders

If derangements in aldosterone, natriuretic peptides and leptin contribute to the expansion of epicardial adipose tissue, it is not surprising that imbalances in these hormonal systems are seen in the systemic inflammatory and metabolic disorders linked to HFpEF. In fact, these adipocyte-associated mediators appear to play a central role in promoting and modulating the inflammatory process itself.

Aldosterone stimulates proinflammatory pathways in a broad range of cell types, and mineralocorticoid receptor antagonist attenuates inflammasome activity and blocks the production of proinflammatory cytokines in adipocytes and macrophages. Rheumatoid arthritis is characterized by increased levels of aldosterone in blood and inflamed tissues, and spironolactone has been proposed as an anti-inflammatory treatment for the disorder. The activity of aldosterone is increased in ulcerative colitis, multiple sclerosis, and pulmonary inflammation. Finally, adipocytes are an important source of aldosterone, and obesity is characterized by hyperaldosteronism; increased levels of aldosterone precede the development of the metabolic syndrome and predict the development of diabetes. Spironolactone ameliorates insulin resistance; and aldosterone contributes to the microvascular complications of diabetes. Leptin also plays a central role in immune responses and inflammation. The adipokine stimulates the proliferation of monocytes and their production of proinflammatory cytokines, and...
it fuels the activation of T cells. Levels of leptin in blood and synovial fluid are increased in rheumatoid arthritis in proportion to the disease activity, and leptin drives autocrine responses in systemic lupus erythematosus. Increased leptin is a marker of disease activity in chronic pulmonary disorders, inflammatory bowel disease and multiple sclerosis. Additionally, leptin is increased in proportion to body mass and insulin resistance in obesity and diabetes. Increased leptin levels are seen in hypercortisolism and primary aldosteronism and are reduced by treatment.

Endogenous natriuretic peptides also play an important role in the pathogenesis of systemic inflammatory and adipogenic metabolic disorders, but in a manner opposite to that of aldosterone and leptin. Natriuretic peptides inhibit pathways involved in inflammation and attenuate the production of proinflammatory cytokines by macrophages and adipocytes. Importantly, circulating levels of natriuretic peptides are decreased in obesity, diabetes, metabolic syndrome and non-alcoholic fatty liver disease, particularly in women; in addition, these disorders are accompanied by impaired responsiveness to the actions of natriuretic peptides in adipose tissue, blood vessels and the kidney. The impairment of natriuretic peptide signalling may be related to an increase in nephrilysin that is seen in states of visceral adiposity; enhanced nephrilysin activity has been implicated in the end-organ injury seen in diabetes. Furthermore, the activity of nephrilysin is increased at sites of disease activity in rheumatoid arthritis and systemic sclerosis, where it may negate the counterbalancing anti-inflammatory actions of locally active natriuretic peptides. The loss of the adaptive action of biologically active natriuretic peptides should not be confused with reports that circulating levels of N-terminal pro B-type natriuretic peptide (BNP) (an inactive prohormone) are increased in many systemic inflammatory disorders, where they primarily represent a biomarker of cardiac dysfunction.

Sex and the neurohormonal response to adipose tissue inflammation

Given the potential role of adipocyte-associated inflammatory mediators in the development of HfPef, it is noteworthy that sex influences their synthesis and their interactions. When compared with men, women have higher levels of leptin and aldosterone. These relationships may be related to greater visceral adiposity in women, but women also show higher levels of and are more sensitive to the effects of agonists of the secretion of aldosterone. Furthermore, women manifest a heightened leptin response to inflammation and visceral adiposity. Leptin activates the sympathetic nervous system and increases blood pressure; interestingly, women show greater sympathetic response to leptin than men, and leptin is correlated with blood pressure in women, but not in men. Conversely, although women have higher levels of natriuretic peptides than men when healthy, they have lower levels if they are obese, and these are further reduced when they become postmenopausal. Interestingly, natriuretic peptides are particularly decreased in visceral adiposity, and the lower levels of natriuretic peptides in women are still apparent in patients with heart failure. When compared with men, women with HfPef have lower levels of the biologically active BNP – but not the inactive prohormone, N-terminal proBNP – consistent with increased adiposity-related nephrilysin-mediated breakdown of the former, but not the latter.

Thus, systemic inflammatory and metabolic disorders are characterized by an increase in proinflammatory mediators (aldosterone and leptin) and decrease in the counterbalancing effects of natriuretic peptides. The net result may be to transform the biology of the visceral (and particularly epicardial) adipocytes, thus focusing the systemic inflammatory process onto the myocardium and leading to HfPef. These interactions are particularly prominent in women.

Potential therapeutic strategies for inflammatory-metabolic heart failure with a preserved ejection fraction

Patients with the inflammatory-metabolic phenotype of HfPef may respond to the treatment of the underlying systemic disorder. Observational studies have noted favourable effects on the course of heart failure following bariatric surgery for obesity; on the risk of death in patients with HfPef who were prescribed statins for dyslipidaemia or diabetes; and on the risk of heart failure hospitalization with the use of methotrexate in rheumatoid arthritis, but these benefits have not been evaluated in randomized controlled trials. Interestingly, the effect of statins on the course of HfPef is independent of any benefits on coronary heart disease, a pattern that differs from that seen when statins are prescribed to patients with HFrEF.

If increases in aldosterone and leptin along with decreases in natriuretic peptide signalling contribute to the development of inflammatory-metabolic HfPef, then interventions that ameliorate these abnormalities might be expected to have favourable effects, and such benefits (if present) may be particularly notable in women.

Mineralocorticoid receptor antagonists

The findings of randomized controlled trials suggest that inhibition of the action of aldosterone may have benefits in HfPef. Spironolactone improved LV filling dynamics and improved exercise tolerance in patients with HfPef in some studies, but not in others. In the TOPCAT trial, when the analyses were restricted to the regions where sites recruited patients with HfPef and where patients received their study medication, mineralocorticoid receptor antagonism appeared to reduce the risk of cardiovascular death and hospitalization for heart failure.

The proportion of patients with the inflammatory-metabolic form of HfPef in the TOPCAT trial is not known. However, patients with a higher body mass index were more likely to respond to spironolactone; a differential response might have been more readily distinguished if visceral adiposity had been assessed directly. This possibility is supported by analyses indicating that
patients were more likely to benefit from spironolactone if they had circulating natriuretic peptides that were lower than the median value; decreased levels likely identified patients with obesity- or inflammation-related HFpEF. Interestingly, low levels of natriuretic peptides also identified patients with HFpEF most likely to respond in the I-PRESERVE trial, which evaluated an inhibitor of aldosterone synthesis. Furthermore, in TOPCAT, women (who are prone to inflammatory-metabolic HFpEF) responded more favourably than men on certain outcome measures. Spironolactone reduced the risk of death by 34% in women, with no apparent benefit in men (interaction P = 0.02), although there was no treatment-by-sex interaction for the effect on hospitalizations for heart failure.

### Inhibitors of neprilysin

Neprilysin inhibition increases levels of natriuretic peptides, potentially explaining its ability to ameliorate cardiac and renal injury, inflammation and fibrosis in states of sodium overload or diabetes. In patients with HFpEF most of whom were obese, neprilysin inhibition reduced myocardial injury, biomarkers of LV filling pressures and LA size, and the effect was particularly notable in patients with diabetes.

In a large-scale double-blind randomized trial (PARAGON-HF), neprilysin inhibition produced a modest decrease in the number of hospitalizations for heart failure. As in TOPCAT, the trial enrolled both patients with inflammatory-metabolic HFpEF as well as other diseases that mimic HFpEF. Interestingly, the trial reported a sex-by-treatment interaction, which suggested a greater benefit of neprilysin inhibition in women. When compared with valsartan, sacubitril/valsartan reduced the likelihood of cardiovascular death and total hospitalizations for heart failure by 27% in women, but treatment did not influence this risk in men (interaction P < 0.006). Importantly, the treatment-by-sex interaction was independent of the influence of ejection fraction on the effects of neprilysin inhibition seen in the trial. Ongoing analyses are determining if this finding may be related to a favourable effect of neprilysin inhibition on the inflammatory-metabolic phenotype of HFpEF, particularly among women, or conversely, if the enrolment of patients with cardiac amyloidosis may have attenuated the benefit of neprilysin inhibition in men.

### Sodium–glucose co-transporter 2 inhibitors

In both experimental and clinical studies, sodium–glucose co-transporter 2 (SGLT2) inhibitors reduce adipose tissue inflammation and epicardial fat mass; inhibit coronary microvascular
dysfunction and myocardial fibrosis; and improve LV diastolic filling, thus ameliorating the evolution of HFP EF. In addition, these drugs inhibit sodium reabsorption in the proximal renal tubule, the site where metabolic disorders may act to cause sodium retention. As a result of these effects, SGLT2 inhibitors may function as physiological antagonists of leptin. These salutary actions may explain why SGLT2 inhibitors reduce the risk of heart failure hospitalizations in patients with type 2 diabetes; these trials noted a decrease in new-onset HFP EF as well as a reduction in heart failure events in patients with established HFP EF.

Summary and conclusions

A broad range of chronic systemic inflammatory and adipogenic metabolic and hormonal disorders increase the risk of HFP EF. These diseases may cause HFP EF by virtue of their common action to promote global microvascular endothelial dysfunction and adipose tissue inflammation, particularly among epicardial adipocytes. The activation of aldosterone, leptin and natriuretin that is seen in systemic inflammatory and metabolic disorders may mediate the accumulation and dysfunction of epicardial (and other forms of visceral) fat. The transmission of inflammation related to the accumulation of epicardial adipose tissue or intramyocardial lipids to the adjacent cardiac tissues may cause microvascular dysfunction, cardiac fibrosis and impaired LV distensibility – the features of inflammatory-metabolic HFP EF.

Importantly, the inflammatory-metabolic phenotype of HFP EF is primarily seen in women. When compared with men, women are at greater risk of the systemic inflammatory and metabolic disorders that are linked to HFP EF; and women experience exaggerated cardiovascular responses to the haemodynamic and inflammatory stresses that predispose to HFP EF. Epicardial fat volume is particularly increased in women, and such expansion is more likely to be accompanied by systemic inflammation, coronary microcirculatory abnormalities and abnormalities of LV diastolic filling in women than in men. Furthermore, when compared with men, women have higher levels and exhibit exaggerated responses to leptin and aldosterone and show greater relative deficiency of natriuretic peptides. Accordingly, systemic inflammation and metabolic disorders linked to adipose tissue inflammation are more likely to have adverse cardiovascular effects in women than men (Table 4).

If adipose tissue inflammation drives the pathogenesis of HFP EF in systemic inflammatory and adipogenic metabolic disorders, then interventions directed at reducing the influence of aldosterone or potentiating the actions of natriuretic peptides might have favourable effects in those with inflammatory-metabolic HFP EF. This hypothesis may explain sex differences in outcomes observed in trials of mineralocorticoid receptor antagonism and natriuretin inhibition in HFP EF.

Conflict of interest: M.P. has recently consulted for Abbvie, Actavis, Akcea, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiorentis, Daiichi-Sankyo, Gilead, Johnson & Johnson, Novo Nordisk, Pfizer, Relypsa, Sanofi, Synthetic Biologies and Theravance. None of these relationships are related to this work or to the topic of this manuscript. C.S.L. is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, and Vifor Pharma; has served as consultant or on the Advisory Board/Steering Committee/Executive Committee for Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, Vifor Pharma, Novartis, Amgen, Merck, Janssen Research & Development LLC, Menarini, Boehringer Ingelheim, Novo Nordisk, Abbott Diagnostics, Corvia, Stealth BioTherapeutics, JanaCare, Biofournirs, Darma, Applied Therapeutics, MyoKardia, WebMD Global LLC, Radcliffe Group Ltd and Corpus. None of these relationships are related to this work or to the topic of this manuscript. L.H.L. reports personal fees from Abbott, AstraZeneca, Bayer, Medscape, Merck, Mundipharma, Novartis, Pharmacosmos, Relypsa, Sanofi and Vifor-Fresenius and grants from AstraZeneca, Boehringer Ingelheim, Boston Scientific, Mundipharma, Novartis, Relypsa and Vifor-Frenenius. None of these relationships are related to this work or to the topic of this manuscript. M.S.M. receives grant support from NIH R01HL139671–01, R21AG058348 and K24AG036778. He has had consulting income from Pfizer, GSK, Eldos, Prothena, Akcea and Alnylam, and institution received clinical trial funding from Pfizer, Prothena, Eldos and Alnylam. None of these relationships are related to this work or to the topic of this manuscript. B.A.B. has received grant support from the NIH/NHLBI (RO1 HL128526 and U10 HL110262), Medtronic, Tenax, GlaxoSmithKline, Mesoblast, AstraZeneca, Novartis, Corvia.

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