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REVIEW

Metabolic inflammation in heart failure with preserved ejection fraction

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Abstract

One in 10 persons in the world aged 40 years and older will develop the syndrome of HFpEF (heart failure with preserved ejection fraction), the most common form of chronic cardiovascular disease for which no effective therapies are currently available. Metabolic disturbance and inflammatory burden contribute importantly to HFpEF pathogenesis. The interplay within these two biological processes is complex; indeed, it is now becoming clear that the notion of metabolic inflammation—metainflammation—must be considered central to HFpEF pathophysiology. Inflammation and metabolism interact over the course of syndrome progression, and likely impact HFpEF treatment and prevention. Here, we discuss evidence in support of a causal, mechanistic role of metainflammation in shaping HFpEF, proposing a framework in which metabolic comorbidities profoundly impact cardiac metabolism and inflammatory pathways in the syndrome.

Keywords HFpEF • Inflammation • Obesity • Immunity • Metabolism

Introduction

The human race is facing the unprecedented challenge of two major epidemics: obesity and heart failure (HF). The World Health Organization reports that in 2016 more than 1.9 billion adults worldwide were overweight and, of these, over 650 million were obese (13% of the world's adult population).[1] Similarly, despite the smaller scale, HF is a burgeoning global public health issue affecting more than 26 million people worldwide. It is pivotal to recognize that these conditions—obesity/metabolic syndrome/diabetes and HF—are epidemiologically and pathophysiological intertwined, culminating in an unprecedented burden on quality of life and global healthcare expenditures. As HF with preserved ejection fraction (HFpEF)—said to be the single greatest unmet need in cardiovascular medicine—is uniquely linked to these burgeoning comorbidities, focus on HFpEF is of paramount importance.

Indeed, the majority of HFpEF individuals are overweight or obese, and increased adiposity is associated with a worsening of functional parameters in HFpEF.[2,3] Although obesity also increases the risk of coronary artery disease, which can impair systolic function leading to HF with reduced ejection fraction (HFrEF), obese individuals are at markedly increased risk of HFpEF independent of ischaemic cardiac injury.[4,5] Despite their close relationship, mechanisms underlying obesity-induced alterations in HFpEF are poorly understood.

Over the last 10 years, a causal link between adiposity and alterations in cellular and molecular mediators of inflammation has been recognized. This metabolism-induced inflammation has been termed 'metainflammation' to describe the chronic low-grade inflammatory response in obesity, diabetes, and other metabolic diseases.[6] Metainflammation in the context of metabolic syndrome occurs in several tissues, including the heart. One of the hallmarks of metabolic alterations in cardiovascular diseases is toxic accumulation of lipids (i.e. lipotoxicity). Among several potential mechanisms of lipotoxicity-induced cardiac dysfunction, it is now established that immunometabolic pathways are greatly modulated by lipids and linked to lipotoxicity.

Here, we discuss existing evidence suggesting that HFpEF can be framed as an obesity-associated disease in which metabolic disturbance, inflammation, and impaired cardiac function are intertwined.

Clinical evidence of HFpEF as a cardiometabolic syndrome

HFpEF is a syndrome of epidemic proportions, accounting for at least 50% of HF hospital admissions with rapidly increasing incidence and prevalence, especially among the elderly.[7] Defining HFpEF is challenging. Canonical clinical presentations of HF signs and symptoms, together

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with heterogeneity in the use of diagnostic tools and criteria, as well as the lack of proven-effective treatments, makes HFpEF a complex entity.[8]

HFpEF cannot be viewed as a single disease.[9] Based on epidemiological, clinical, and laboratory findings, multiple phenotypes of HFpEF can be identified.[10] Patients with HFpEF comprise elderly women with hypertension and stiff arteries as well as obese/diabetic men with abnormal metabolism and liver and kidney dysfunction.[11] Cardiac structural abnormalities are also variably present among the different phenogroups, including left atrial enlargement and various types of left ventricular remodelling and hypertrophy (LVH).[12–15] Epidemiological studies have shown concentric, as opposed to eccentric, LVH as a common feature in patients with HFpEF[16,17] (*Figure 1*). Importantly, these differences in clinical and pathophysiological phenotypes drive diverse prognoses and differential responses to therapy.[11,18]

A distinct feature of HFpEF is the presence of multiple comorbidities, in aggregate shaping the complexity of the syndrome. Together with hypertension and ageing,[19,20] a main risk factor for HFpEF is obesity.[21] Increased body mass index (BMI) has been associated with increased risk of incident HF.[21] In particular, it has been reported than 80% of HFpEF patients in the USA are overweight or obese,[2] with an average BMI exceeding 35 kg/m^2.[3] Obese patients with HFpEF present with worse New York Heart Association class, more severe parameters of adverse cardiac remodelling, increased plasma volume, and decreased exercise capacity compared to non-obese HFpEF patients.[3,22]

It is now becoming clear that adipose tissue is likely involved in HFpEF pathophysiology through multiple mechanisms beyond the simple impact of greater mechanical load with increased body weight.[5] In fact, obesity might amplify its deleterious effects both indirectly, promoting other comorbidities, such as insulin resistance and hypertension but also directly, given the fact that adipose tissue is highly metabolically active and capable of releasing regulatory factors—adipokines—involved in promoting a systemic pro-inflammatory state. Thus, the impact of obesity on HFpEF pathophysiology encompasses haemodynamic, neurohumoral, and inflammatory mechanisms (*Figure 1*).

Comorbidity-driven systemic inflammation in HFpEF

Accumulating evidence has emerged on the role of a systemic pro-inflammatory state, predominantly induced by obesity and metabolic stress,[10] as a major determinant of HFpEF pathophysiology. For example, it has been proposed that microvascular endothelial inflammation impairs endothelial nitric oxide (NO) production, triggering cardiomyocyte dysfunction.[23,24] We and others have demonstrated increased burden of inflammation-dependent oxidative and nitrosative stress in HFpEF.[25,26] Additionally, recruitment of inflammatory cells has been recognized in endomyocardial biopsies from HFpEF patients.[27] Taken together, these findings position HFpEF as a manifestation of a chronic cardiovascular inflammatory disorder. Intriguingly, the extent to which elements of innate and adaptive immunity participate in the metainflammatory pathophysiology of HFpEF is unknown.

The world's population is ageing. The global population aged 60 years or over reached nearly 1 billion in 2017, and the number of elderly is expected to double by 2050.[28] Based on this, the number of individuals with HF—HFpEF in particular—is expected to rise steadily over the next 20 years.[7,29] Whereas HFpEF is epidemiologically linked to ageing, mechanisms whereby senescence contributes to HFpEF pathophysiology are largely unknown. As mentioned, similar to obesity, metabolic syndrome, and diabetes, ageing is characterized by chronic, low-grade, sterile inflammation—a condition that has been termed 'inflammaging'.[30–33] Intriguingly, metainflammatory events may precede and contribute to inflammaging and *vice versa*, sharing in common a number of signalling pathways and molecular effectors, fuelling both metainflammation and inflammaging as drivers of cardiometabolic disease.[34] Metabolic regulation of ageing is complex and involves the repurposing of metabolic pathways towards energy provision for maintenance and reparative processes.[35] Nutrient availability impacts longevity meaningfully. Whereas caloric restriction seems to be protective, over-nutrition might accelerate ageing. Interestingly, in both extreme states of nutrient imbalance (malnutrition and over-nutrition) inflammation flourishes.[32]

In light of this, one fundamental question arises: what is the evidence in support of the notion that comorbidities, and obesity, in particular, act as an upstream source of circulating cytokines inducing a systemic pro-inflammatory state in HFpEF?

As proof-of-concept, one study reported that the comorbidity burden in HFpEF correlates with elevations in circulating levels of C-reactive protein (CRP).[36] Reports of elevated circulating inflammatory biomarkers in HFpEF are not limited to CRP but also include soluble interleukin-1 (IL-1) receptor-like 1, growth differentiation factor 15 (GDF15), soluble ST2, and pentraxin-3.[37–41] Elevations in these inflammatory markers are of greater magnitude in HFpEF than in HFrEF,[37,40,41] or than in other acute and decompensated conditions.[42] High levels of tumour necrosis factor alpha (TNFα) are also predictive of incident risk of HFpEF.[43] Importantly, increases in inflammatory markers are independently associated with asymptomatic diastolic dysfunction in patients with metabolic syndrome 'at risk' for HFpEF. Interestingly, this correlation is stronger in hypertensive patients with metabolic syndrome than in those with hypertension alone.[44]

Consistent with these data, an elegant network analysis was conducted to infer the most prevalent pathophysiological pathways involved in HFpEF and HFrEF based on circulating biomarker profiles. Analysis of protein–protein interactions has shown that HFpEF biomarkers are specifically related to biological mechanisms of inflammation and extracellular matrix reorganization.[45] In addition, indirect evidence for HFpEF as a systemic inflammatory disease is suggested by the presence of extracardiac inflammatory manifestations in the syndrome.[10,46]

Collectively, a growing body of evidence points to a causal role of a comorbidity-driven, systemic pro-inflammatory state in HFpEF. Given the role of inflammation, signals arising from adipose tissue metabolism and from intermediary cardiac metabolism may mutually drive immune responses in obese HFpEF.

Impact of metabolic derangements on immunity

Metabolic alterations are frequently coupled with immune dysregulation. In fact, metabolic processes regulate immune cell responses and *vice versa*. This bidirectional crosstalk is emerging as a critical component of the pathogenesis of cardiometabolic diseases, such as HFpEF (***Figure 2***).

Immunometabolism—the interplay between immunological and metabolic processes—is a growing field of investigation, with extensive implications for cardiovascular disease.[47,48] The impact of obesity on HF entails a number of signals and stimuli at the interface of innate and adaptive immunity. Whereas mechanisms of cardiac metabolic reprogramming in response to chronic, systemic, low-grade inflammation in obesity

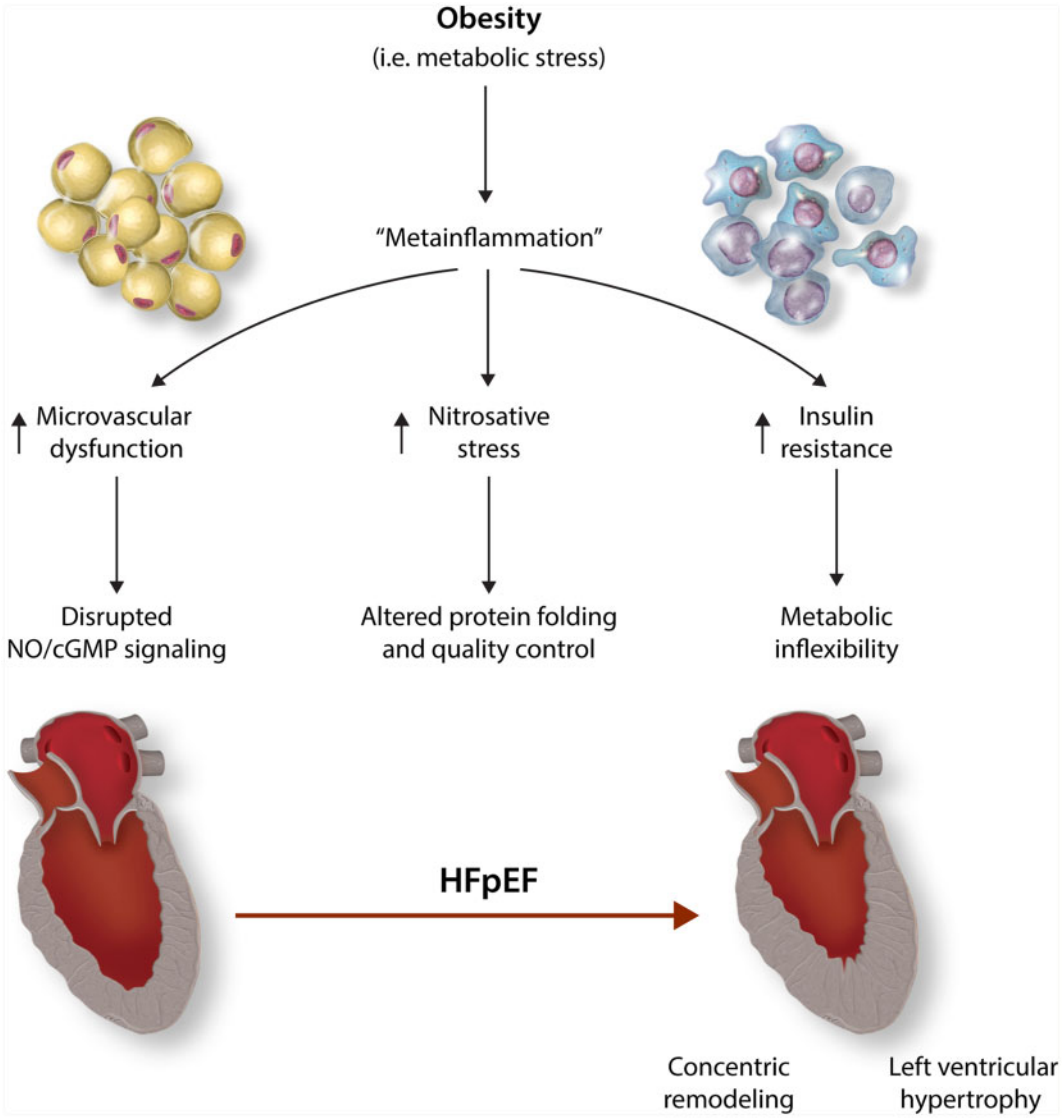

Figure 1 Metabolism and Immunity Coupling in HFpEF. Metainflammation is a chronic low-grade systemic state of inflammation associated with obesity. Systemic inflammation has been recognized as a cause of HFpEF through: (i) microvascular dysfunction and downregulation of NO/cGMP signalling; (ii) nitrosative stress and protein quality control impairment, altering the dynamic state of cardiomyocyte molecular constituents. In addition, nutrient overload in obesity has immune and metabolic consequences on insulin sensitivity. Insulin resistance limits cardiac metabolic flexibility and hampers energy provision (iii).

have been explored only partially, immunophenotypic changes occurring in obesity have been investigated in greater depth.

In obesity, adipose tissue expansion leads to secretion of chemokines, thereby initiating macrophage recruitment.[49,50] It is known that signals from this microenvironment direct macrophage polarization, and that M1-polarized macrophages display a pronounced pro-inflammatory phenotype. An increased ratio of infiltrating M1 to M2 macrophages is a hallmark of adipose tissue inflammation in obesity.[51] In this setting, the increased prevalence of the M1 macrophage subset is responsible for the release of cytokines, producing a systemic pro-inflammatory state. In HFpEF, local inflammation and macrophage infiltration of epicardial adipose tissue (EAT) have been proposed as a potential mechanism contributing to cardiac dysfunction. Despite the fact that experimental evidence of EAT inflammation in HFpEF remains lacking, the notion of a local metainflammatory insult as a contributor to HFpEF pathogenesis merits investigation.[52,53]

The contribution of inflammatory cells to some elements of HFpEF pathophysiology (e.g. diastolic dysfunction) has been explored in animal models and in human subjects.[54] A recent study has reported a causal role of cardiac macrophage expansion and IL-10 production in myocardial fibrosis and diastolic dysfunction in a mouse model of hypertensive HFpEF.[55] Despite the lack of metabolic stress in this model, it is clear that immune cells contribute to key pathophysiological features of HFpEF. Similarly, others have provided evidence of both classical and alternative macrophage activation by analysing serum from hypertensive HFpEF patients.[56]

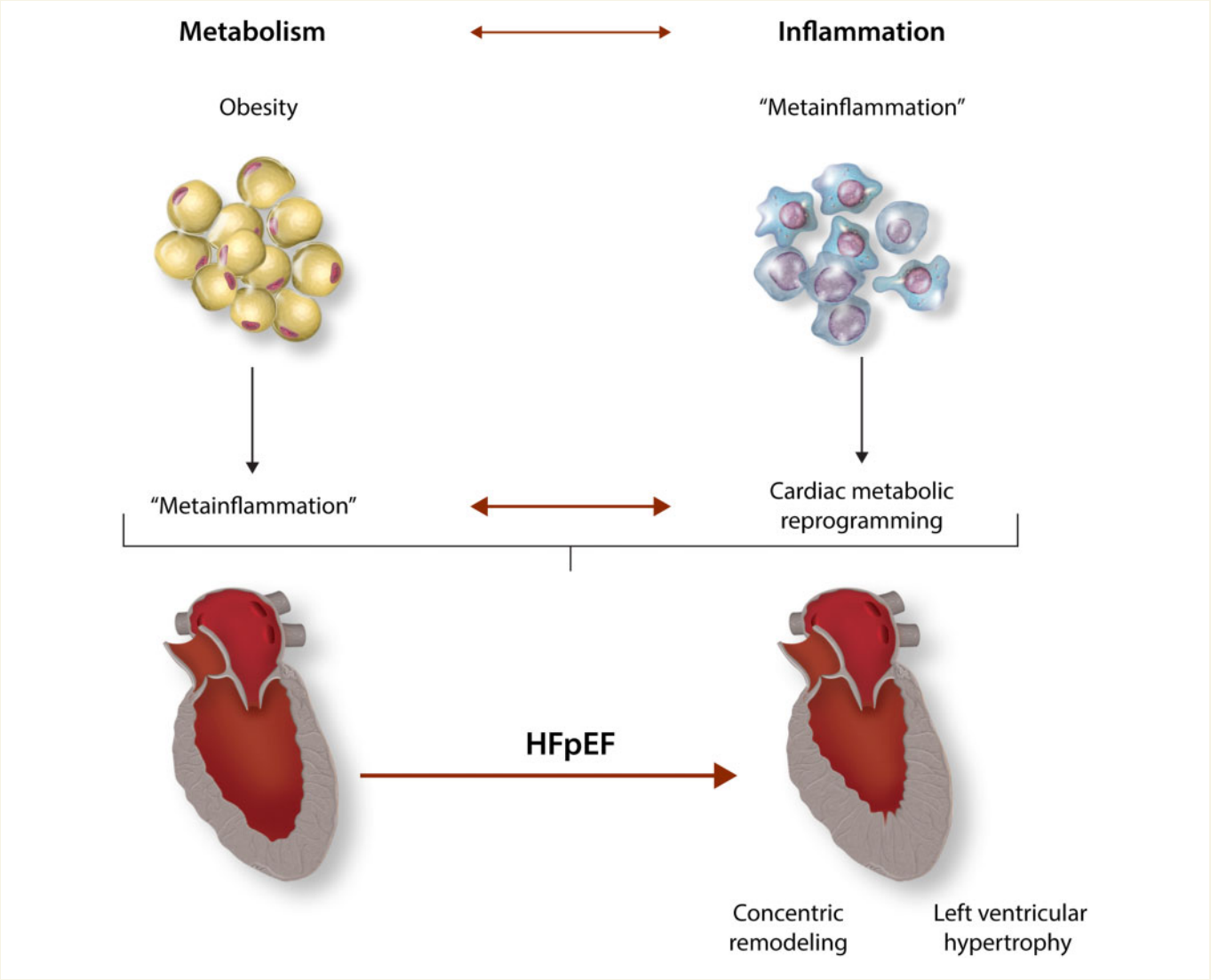

Figure 2 Overview of HFpEF pathophysiology: metabolic inflammation moves centre stage. Metabolic dysregulation is coupled with immune dysregulation. Systemic disruption of metabolic homoeostasis in obesity elicits a chronic low-grade inflammatory response (i.e. metainflammation). In the heart, cytokines and other inflammatory mediators modulate cardiac metabolism. Downstream, these alterations contribute to structural and functional remodelling in HFpEF.

Metabolic alterations can provoke changes in macrophage functional status. Metabolic reprogramming is a key driver of macrophage polarization in cardiac injury and in the presence of hypertension and obesity.[53] In particular, endoplasmic reticulum (ER) stress has been implicated in macrophage activation under conditions of metabolic inflammation.[57] Consistent with this, protein quality control is an emerging research focus in HFpEF pathophysiology. Accumulation of misfolded proteins has been uncovered recently in clinical HFpEF by evaluating the presence of wild-type transthyretin amyloidosis in elderly patients.[58] Accumulation of unfolded proteins is the leading cause of ER stress, a process highly interconnected with inflammatory pathways.[59,60] We and others have shown that in obesity and HFpEF, metabolic inflammation is linked to ER dysfunction through inducible nitric oxide synthase (iNOS)-dependent S-nitrosylation of inositol-requiring enzyme 1 alpha (IRE1α), one of the main arms of unfolded protein response signalling cascade.[26,61] Additional studies are required to explore the role of other protein quality control-related pathways in HFpEF, as well as the specific contribution of distinct immune cell populations in metainflammatory mechanisms. Notably, despite the research efforts to date, identification of the predominant cell types (e.g. cardiomyocytes vs. immune cells) responsible for the metabolic alterations observed in HFpEF hearts remains limited. In other words, the extent to which changes in cardiac metabolism and intracellular signalling pathways observed in HFpEF reflect primary changes in inflammatory cell density, composition, and metabolic state as opposed to changes in cardiomyocyte metabolism, is unclear. This knowledge gap reflects the difficulties of dealing with a complex and heterogeneous syndrome, such as HFpEF, for which multiple, complementary research approaches are required. Based on this reality, a call for more integrated clinical and experimental approaches, inclusive of the broad spectrum of HFpEF comorbidities and their metabolic and inflammatory correlates, has been highlighted as a relevant research priority in the field.[62]

Metabolic intermediates regulating inflammatory pathways

Adaptations of metabolic state greatly impact numerous fundamental cellular regulatory functions. Recognition of signalling properties of metabolic intermediates and their interaction with gene expression pathways is a groundbreaking advance in many areas of biology.[63] In immune cells, the dynamics of intermediary metabolism are crucial for a cell's ability to divide, differentiate, and activate properly.[64]

Metabolic cycles have evolved to ensure optimal use of cellular resources, taking advantage of a multitude of interconnections with other cellular functions.[65] Central to macrophage expansion and polarization in HFpEF, intermediates of the tricarboxylic acid cycle (TCA) can dictate changes in the expression of genes involved in inflammatory pathways.[66,67] In addition to its fundamental role in energy provision, the TCA cycle is a specific immunometabolic hub in macrophages.[68] Increased macrophage exposure to extracellular glucose, as well as to pro-inflammatory fatty acids (FA), activates nuclear factor-κB (NF-κB) and promotes M1 polarization.[53] A distinct metabolic signature of M1-macrophages is upregulated glycolysis, similar to what is universally known as the 'Warburg effect', with suppression of mitochondrial oxidative phosphorylation and, as consequence, the rewiring of metabolic flux through the TCA cycle, leading to accumulation of succinate. Succinate accumulation participates in M1 macrophage polarization, promoting hypoxia inducible factor-1α stabilization and increasing IL-1β production.[69]

Additional metabolic intermediates of the TCA cycle participate in the regulation of gene expression in immune cells through epigenetic mechanisms. Fumarate and α-ketoglutarate regulate the activity of enzymes required for epigenetic modifications, known as α-ketoglutarate-dependent dioxygenases.[70,71] In particular, α-ketoglutarate is a cofactor for Jumonji-C-domain-containing histone demethylases, a histone demethylase, and the ten-eleven translocation family of 5-methylcytosine hydroxylases, involved in DNA demethylation. Increased levels of α-ketoglutarate exert anti-inflammatory effects in macrophages. Conversely, low α-ketoglutarate/succinate ratios promote inflammation.[70] Consistently, fumarate, a competitive inhibitor of α-ketoglutarate-dependent dioxygenases, promotes epigenetic modifications leading to increased TNFα and interleukin-6 (IL-6) production.[71]

Other examples of TCA cycle-derived metabolic intermediates regulating inflammatory gene expression include the synthesis of itaconate from *cis*-aconitate.[72,73] Itaconate levels in macrophages are regulated by iNOS-derived NO.[74] This fact supports a model in which NO production by iNOS regulates the production of a metabolite critically involved in regulating metabolic remodelling and cytokine production. Metabolic reprogramming in classically activated macrophages also involves rewiring of metabolic flux towards the aspartate-arginosuccinate shunt, a series of reactions connecting the TCA cycle to the urea cycle and NO production.[73]

Among the many TCA cycle intermediates active in the regulation of immune cell function, citrate links several biological processes, playing an important role in the metabolic reprogramming of inflammation.[75] Inflammatory events upregulate citrate mitochondrial carrier SLC25a1 which exports citrate to the cytosol.[76] There, citrate is converted to acetyl-coA by the ATP-citrate lyase. Increased cytosolic acetyl-CoA serves as a cofactor of MEC17 acetyltransferase, leading to tubulin acetylation and increased production of IL-10.[77]Acetyl-CoA can also be carboxylated to malonyl-CoA and then used for FA biosynthesis, contributing to the production of lipid rafts, prostaglandins, and other inflammatory molecules.[78] In addition, accumulation of malonyl-CoA can promote protein malonylation, a lysine-based post-translational modification that has been shown to facilitate TNFα translation.[79,80]

Whereas all these mechanisms are involved in the metainflammatory reprogramming of macrophages, the impact of metabolic changes in macrophages or other immune cells on cardiac function in HFpEF remains unknown. In aggregate, the totality of evidence supports the role of intermediate metabolites as critical immunomodulating molecules providing potential mechanistic insights into metainflammatory events occurring in HFpEF and other cardiometabolic diseases.

Impact of immunity on cardiac energy metabolism

A distinct feature of cardiac biology and an integral part of myocardial adaptation is metabolic flexibility, i.e. the ability to transition among different energy substrates depending on specific physiological and pathological conditions, substrate availability, and hormonal milieu. The heart can select the most suitable source of energy substrate depending on extant conditions, shifting from one prevailing class of substrate to another, and is therefore often portrayed as an 'omnivore' due to this energetic flexibility.[81] Under aerobic conditions, FA are the main fuel for the heart, and mitochondrial β-oxidation provides 60–90% of the acetyl-CoA required for cardiac contraction and relaxation.[82] Metabolic flexibility occurs in response to changes in oxygen and substrate supply or in response to changes in workload.[83] For example, under hypoxic conditions, the heart mainly oxidizes carbohydrates. Reliance of the heart on glucose is an energetically favourable adaptation, as documented *in vivo*.[84] These adaptations are primed by high cardiac ATP demand: with a relatively low ATP content (5 μmol/g wet wt) and a high rate of ATP hydrolysis (~ 0.5 μmol·g wet wt^{-1}·s^{-1} at rest), under normal conditions, the complete turnover of the myocardial ATP pool occurs approximately every 10 s[85,86] and accelerates in proportion to increases in cardiac workload.[87]

Tight coupling of cardiac metabolism, energy provision, and contractile function is epitomized by the notion of the failing heart as an 'engine out of fuel'.[88] Nevertheless, the link between energy transfer and cardiac contraction becomes less clear in dysregulated metabolic states, such as diabetes and obesity: under these conditions, even in the absence of overt blood flow alterations, hence despite the uninterrupted supply of energy substrates, the heart is not starved but fails 'in the midst of plenty', and its characteristic metabolic flexibility is impaired.[89]

Mitochondrial metabolism is governed by calcium (Ca^{2+}).[90] Specifically, Ca^{2+} concentrations in the mitochondrial matrix ([Ca^{2+}]m) regulate mitochondrial ATP production.[90] Despite the large body of evidence in HFrEF suggesting that [Ca^{2+}]m and, as a consequence, ATP production are decreased, much less is known about Ca^{2+}-dependent regulation of mitochondrial metabolism in HFpEF.[91] Recently, cardiac mitochondrial calcium kinetics have been explored in a rat model of metabolically-induced HFpEF.[92] Interestingly, in striking contrast to that observed in HFrEF models, [Ca^{2+}]m was increased in HFpEF hearts, coupled with mitochondrial functional alterations and cytosolic Ca^{2+} mishandling.[92] Despite this evidence, the specific role of [Ca^{2+}]m cycling in metabolic remodelling in HFpEF remains elusive.

A large focus of research has been directed towards the metabolic reprogramming of immune cells during the course of cardiac inflammatory processes or towards the role of inflammatory cytokines in cardiac remodelling as occurs in diabetes.[93,94] More recently, additional insights into cardiomyocyte metabolic reprogramming in response to metabolic

inflammation have emerged. Intriguingly, despite the pivotal role of Ca^{2+} in regulating many functions of both innate and adaptive immunity,[95] Ca^{2+} alterations in immune cells in the context of metabolic disease remain only partially understood.

Immune regulation of cardiac intermediary metabolism

The heart is highly responsive to external stimuli and changes in workload demand. A chronic inflammatory state, as occurs in HFpEF, impacts cardiac microenvironment and consequently its energetic state. Both immune cells and cardiomyocytes are marked by high metabolic rates, required to meet their energy demands. Therefore, the relative contribution of one or the other cell type to cardiac metabolic adaptation during chronic inflammatory stress and limited access to nutrients is difficult to assess. Crosstalk between different cell types comprises a complex network of signals, involving cytokines and metabolites. Metabolic signals link both cardiac structure and function, and metabolic remodelling is intertwined with—if not causative of—functional and structural remodelling.[96] Significant efforts have been made to improve the assessment of myocardial metabolic flux in the elucidation of HFpEF pathophysiology, including employing systems biology approaches.[97,98]

The limited number of studies currently available focusing on myocardial substrate metabolism in response to inflammation do not specifically refer to HFpEF. In an animal model of high-fat diet and IL-6 infusion, AMP-activated protein kinase (AMPK), an enzyme known to be a crucial energy sensor in cells, is suppressed.[99] In this study, blunted AMPK activity was associated with impaired glucose metabolism. Conversely, glucose oxidation increased in a different model of cardiac exposure to metabolic inflammation, featuring TNFα elevation.[100] This effect has been mechanistically linked to decreased expression of pyruvate dehydrogenase kinase 4 (PDK4) as a consequence of proliferator-activated-receptor γ coactivator-1 α (PGC-1α) inhibition by binding with p65 subunit of NF-κB.[101]

Whereas these data raise the prospect of effects of circulating cytokines on cardiac intermediary metabolism, they are not conclusive. As consequence, metainflammatory stress-dependent regulation of cardiac glucose metabolism remains controversial.

NO and iNOS as metabolic regulators

NO is a signalling molecule with a plethora of functions in the cardiovascular system, spanning regulation of endothelial homoeostasis to regulation of cardiac contraction.[102,103] Besides its role in vasodilation, NO is implicated in oxygen utilization and mitochondrial respiration, as well as in modulation of cardiac energy substrate metabolism.[104,105]

It has been proposed that reduced NO bioavailability in HFpEF exists due to diversion of NO to peroxynitrite under conditions of inflammation-induced reactive oxygen species production.[23] In light of the connection between NO biology and cardiac metabolism, one could argue that the notion of low NO availability affecting cardiac energy provision in HFpEF is a hypothesis that remains to be tested. Whereas we lack targeted studies, it is worth mentioning that acute or chronic inhibition of NO synthesis in dogs boosts cardiac glucose and lactate oxidation.[106–108] Similarly, others have taken advantage of the *ex vivo* working heart model to show that inhibition of NO synthesis provokes selective enhancement of glucose uptake.[109] Specifically, this effect has been related to decreased concentration of cyclic guanosine monophosphate (cGMP), a downstream effector of NO. The functional result of this metabolic shift is unclear. Also, a note of caution is warranted in extending this knowledge to metabolic remodelling in HFpEF, since we still know very little about cardiac metabolic adaptations in this syndrome. And as noted, a substrate shift towards glucose oxidation is a favourable energetic adaptation.[84] One might speculate that microvascular dysfunction in HFpEF is a mechanism leading to hypoxia and this might direct substrate preference towards carbohydrate oxidation. However, NO-cGMP signalling is only one of many elements in HFpEF pathophysiology, and other mechanisms may well be involved.

We recently showed that the combination of metabolic stress induced by obesity/diabetes coupled with the mechanical stress induced by hypertension recapitulates in mice most of the clinical features of HFpEF.[26] Mechanical stress and metabolic stress exert heterogeneous effects on cardiac energy metabolism. Whereas chronic pressure overload is known to induce a shift in myocardial metabolism towards glucose oxidation,[110–112] increased FA availability in obesity enhances cardiac fatty acid oxidation (FAO).[113] It is thereby reasonable to speculate that cardiac metabolism in HFpEF is challenged by conflicting metabolic needs. Also, metabolic flexibility might be hampered in the presence of fuel excess, lipotoxicity, and insulin resistance. Deciphering mechanisms of mitochondrial dysfunction and FAO pathways in HFpEF will be critical to the elucidation of specific hallmarks of cardiac metabolic alterations in this syndrome.

Metabolic reprogramming is the result of highly orchestrated interplay of signalling pathways that encompass transcriptional control and biochemical checkpoints. The recent identification of iNOS upregulation in HFpEF highlights the potential of NO-based post-translational protein modification, such as S-nitrosylation, in modulating cardiac metabolic pathways. Mainly known to act as an inflammatory master mediator, iNOS is a metabolic enzyme whose impact on cell metabolism has been explored extensively.[114] Given its role in HFpEF, the connection between iNOS activity and insulin resistance, for example, might be of relevance. Indeed, nitrosative stress in skeletal muscle has been associated with protein modifications of key elements of insulin signalling, including insulin receptor substrate-1/2 and Akt, in the context of ageing and obesity.[115,116] This heightens the complexity of insulin resistance and metainflammation in HFpEF. Interestingly, nitrosative stress might also induce post-translational modifications of key glycolytic and FAO enzymes, directly influencing metabolic fluxes.[117,118]

Metainflammation: evolutionary perspective on a potential therapeutic target in HFpEF

Metabolism and inflammation are integrated at the molecular level through highly conserved pathways. Indeed, mechanisms acting at the intersection of metabolism and inflammation underlie aspects of how cells and tissues respond to environmental changes and external stimuli in order to maintain homoeostasis. For example, it is known that pattern recognition receptors are able to operate as metabolic sensors. An example is toll-like receptor 4 activation by free fatty acids that leads to NF-κB signalling activation.[119] From an evolutionary perspective, the intersection between metabolism and inflammation can be attributed to complementary means of coping with intermittent nutrient supply and high risk of infectious disease, together promoting survival in hostile conditions.[6]

The evolutionary underpinnings of the metabolism-inflammation interplay might be informative in our understanding of HFpEF

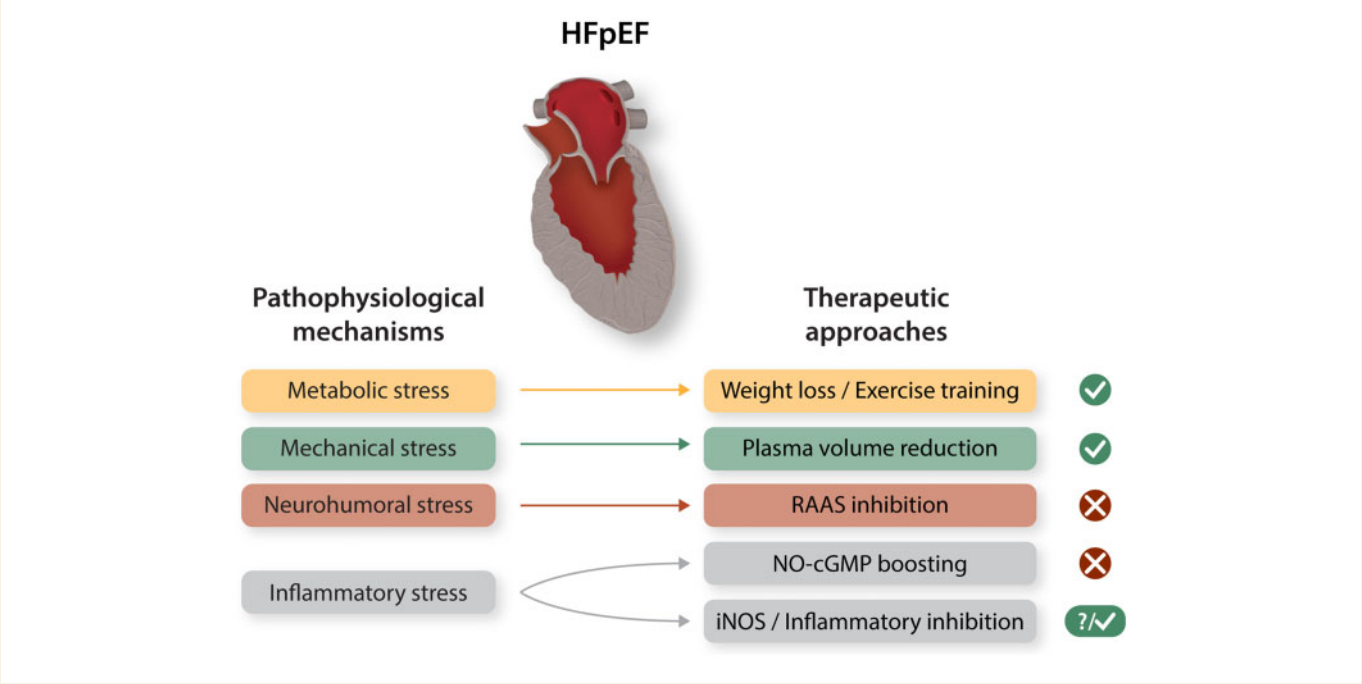

Figure 3 How to fill an empty toolbox? Potential targets and approaches in HFpEF therapy. A promising therapeutic rationale is targeting the stressors prevalent in HFpEF. Possible approaches are shown in association with the prevalent forms of stress they are able to tackle, together with the clinical efficacy they have demonstrated so far. Whereas we still lack evidence of effective HFpEF treatments from large clinical trials, encouraging evidence suggests that targeting metabolic and inflammatory stress, limiting nutrient overload, and antagonizing key inflammatory mediators hold promise and warrant further study. RAAS (Renin–Angiotensin–Aldosterone System).

pathophysiology. In cardiac remodelling, a transition from adaptive responses to those that are maladaptive can often be inferred. In the context of HFpEF, one should recognize that a mismatch between our modern environment and human evolutionary history worsens the cost-benefit trade-off of inflammation.[120] In other words, environmental factors have changed dramatically in recent centuries, and the evolutionary cost-benefit balance of inflammation in modern human populations is not optimized to the current environment.

Of course, inflammation and metabolism serve different purposes, and it is reasonable that innate immunity may induce an alteration in tissue function when fitness or even survival of the organism is threatened. A cost-benefit trade-off mismatch provides the basis for consideration of clinical intervention as a way to modulate inflammatory responses that are potentially not suited to the environmental conditions. Finally, antagonistic pleiotropy should be taken into consideration.[120] This term refers to a phenomenon explaining why biological mechanisms that positively impact fitness at young age occur at a cost in later phases of lifespan. The presence of an inflammatory substrate in many age-related syndromes, such as HF may be an example. On the basis of the role of inflammation in HFpEF, a suboptimal cost-benefit trade-off of immune responses may contribute to increased susceptibility of obese individuals to the syndrome.

Rapidly changing environmental conditions are shaping cardiovascular disease in developed countries.[121,122] Cardiac biology, in general, is highly influenced by both environmental stimuli and genetic background.[123,124] We have learned to target pathways and molecules involved in cardiac adaptation to stress and to develop therapeutic approaches accordingly. For example, neurohumoral antagonism and haemodynamic unloading are cornerstones of HFrEF therapy.[125] Whereas relieving neurohumoral and haemodynamic stresses has been fundamental to combat HFrEF to date, the evolving understanding of HFpEF as a cardio-metabolic disease challenges us to consider a different therapeutic rationale, mirroring inflammatory, and metabolic stress as potential targets of clinical intervention. Metabolic unloading in HF is already recognized to be effective. Examples include the benefit of bariatric surgery and caloric restriction on cardiac function, as well as the recent emergence of sodium/glucose cotransporter-2 (SGLT2) inhibitors in the clinical arena.[126,127] However, metabolic stress is only one side of the coin, as metabolic syndrome and fuel over-supply are coupled with inflammatory stress. Restricting fuel supply—i.e. caloric restriction—may provide indirect benefit and diminish the inflammatory burden of metainflammation.[128,129]

We have argued that innate immunity must evolve in order to be optimized for a given environment and thereby activated appropriately. The dynamic balance of metabolism is fundamental to an organism's interaction with the environment.[130] Metabolic pathways are not only involved in energy provision but also in a two-way dialogue between the cell and the entire organism. Both metabolites and cytokines participate as signals in this dialogue. Metainflammation is a state of disrupted metabolic homoeostasis. Therefore, HFpEF is a paradigmatic example of how metabolic and inflammatory alterations are intertwined in fundamental pathophysiological mechanisms.

Therapeutic modulation of metainflammation

It has been correctly noted that HFpEF represents the greatest unmet medical need in modern cardiology.[131] Survival with this condition has not improved over the last decades, and adopting the therapeutic tools

available for HFrEF have failed in HFpEF.[132] It is now increasingly recognized that HFpEF and HFrEF have distinct pathophysiological mechanisms.[133] Despite the fact that these mechanisms may potentially coexist in some cases, a growing body of evidence suggests that tackling HFpEF will require tailored strategies and *ad hoc* targets[134] (***Figure 3***). We propose that the current understanding of HFpEF involves systemic metabolic inflammation as a key driver, together with fibrosis and altered NO availability as major effects. Implementing this knowledge to develop effective therapeutic strategies is challenging.

Anti-fibrotic strategies

One of the major features of HFpEF is reactive fibrosis resulting, at least in part, from transforming growth factor beta (TGF-β) release and collagen deposition. Fibrosis is a highly dynamic process characterized by heterogeneous plasticity across different organs.[10,135] In fact, fibrosis in HFpEF can involve many organs beyond the heart. Along these lines, current medications for idiopathic pulmonary fibrosis, such as pirfenidone, have been suggested to exert beneficial effects in HFpEF.[136–138] Recently, a clinical trial commenced specifically to test this hypothesis.[139] Of note, other cardiovascular drugs with anti-fibrotic properties have been tested in HFpEF, including spironolactone, a mineralocorticoid receptor antagonist with known beneficial effects on extracellular matrix remodelling. However, despite encouraging results in secondary analyses, this study was reported as neutral.[140] Importantly, subsequent *post hoc* analyses of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial revealed possible clinical benefits with spironolactone in patients with HFpEF from the Americas (in contrast with patients enrolled from Russia and Georgia).[141,142] Therefore, the significant regional discrepancies observed in the TOPCAT trial have raised legitimate concerns regarding the true therapeutic response to spironolactone in patients with HFpEF.

TGF-β has relevant biological implications in metabolic reprogramming of different tissues and yet this remains incompletely understood in the heart.[143] Intermediary metabolism can coordinate extracellular matrix homoeostasis, and metabolic interventions might serve as a strategy to reverse fibrosis.[144]Proof-of-concept of modulating the immune system for therapeutic purposes emerged recently with the development of chimeric antigen receptor T cells targeting cardiac fibrosis.[145,146] Whether this novel strategy might have therapeutic potential in HFpEF has yet to be determined.

Tuning NO availability and anti-inflammatory therapies

Increasing NO availability has been tested in multiple large HFpEF clinical trials; the notion of reduced NO availability as a cause of myocardial stiffness in HFpEF has stimulated investigators around the world to find ways to boost NO-cGMP signalling. Phosphodiesterase 5 (PDE5) inhibitors, NO donors, soluble guanylate cyclase (sGC) stimulators have all been tested in HFpEF as potential therapeutic interventions.[147–150] Unfortunately, NO-inducing approaches have failed to improve outcomes with neutral or even negative results.[148,151]

The recent demonstration of iNOS-dependent metainflammatory events as a major source of nitrosative stress in HFpEF may provide a biological explanation for failure of such strategies. Therefore, turning attention to strategies focusing on reducing mediators of systemic metabolic inflammation, or nitrosative stress[26,152] might hold promise in HFpEF therapeutics.[114] Counteracting pro-inflammatory mediators in HFpEF also include, for example, IL-1 blockade. Anakinra, an IL-1 receptor antagonist, has been shown to ameliorate, in part, exercise intolerance and oxygen consumption in HFpEF patients.[153] These findings were not confirmed in a subsequent phase II study,[154] suggesting that targeting specific inflammatory mediators known to be involved in HFpEF pathophysiology, rather than a broad anti-cytokine approach, might represent a more valuable therapeutic strategy.

Metabolic agents with anti-inflammatory properties

Interaction between metabolism and inflammation is also suggested by the anti-inflammatory effects of metabolic agents used to mitigate cardiovascular risk factors, such as cholesterol-lowering and glucose-lowering drugs. These strategies offer the potential to tackle metabolic stress and inflammatory stress simultaneously, providing a therapeutic rationale for targeting these two pathogenetic processes concurrently.

Endomyocardial biopsies from patients with HFpEF treated with statins reveal less myocardial nitrosative stress as well as reduced cardiomyocyte hypertrophy.[23] It has also been reported that statin-treated HFpEF patients have diminished probability of developing atrial fibrillation.[155] Additional evidence in support of this notion has emerged from registry-based studies showing that statins are associated with improved outcomes in HFpEF, reducing mortality even in the absence of coronary artery disease, the typical targets of these drugs.[156,157] Despite the unquestioned need for large clinical trials to test the efficacy of statins in HFpEF, we hypothesize that the pleiotropic anti-inflammatory effects of these cholesterol-lowering drugs will attenuate some of the harmful metainflammatory pathways active in HFpEF.

In additions to statins, several glucose-lowering drugs have been shown to mitigate inflammation, suggesting potential for HFpEF therapeutics.[158] For example, recent evidence of the therapeutic benefits of SGLT2-inhibitors in HF even in the absence of diabetes mellitus[159] has paved the way to test these drugs in HFpEF. Whereas precise mechanism(s) underlying the beneficial cardiovascular effects of SGLT2 inhibition remain elusive, the possibility that they target metabolic inflammatory pathways has been proposed.[160]

Of note, metainflammation is a low-grade, systemic state. Previous experience with suppression of pro-inflammatory cytokines in HF led to inconsistent results.[161] One can hypothesize that direct anti-inflammatory strategies can increase the risk of unwanted suppression of immune responses. The complexity of immune system responses in shaping cardiovascular adaptions to stress is also evident from the variety of immune cellular subsets present in the human heart.[162] Based on this, a targeted, rather than broad and non-specific anti-inflammatory approach, might hold greater promise. Of note, it has been suggested recently that an acute immune response might mediate the beneficial effects of stem cell therapy after myocardial infarction, highlighting the need for fine-tuning manipulation of inflammatory events in cardiovascular disease.[163,164] Therefore, we suggest that anti-inflammatory properties of metabolic agents might exert more balanced effects on the immune components of the disease, targeting the primary cause of metainflammation, i.e. metabolic syndrome.

Beneficial effects of exercise training in HFpEF

Exercise intolerance is a hallmark of HFpEF presentation, with obesity and diabetes greatly contributing as underlying mechanisms.[165] Physical activity has been shown to have a stronger dose-dependent inverse association with risk in HFpEF as opposed to HFrEF.[166] Among the most

effective interventions ameliorating exercise intolerance is exercise training. As a consequence, chronic exercise training has emerged as a powerful strategy to mitigate the unfavourable natural history of HFpEF.[167,168]

Exercise training exerts a number of beneficial effects on cardiovascular function, including improvement of metabolic health, positive modulation of cardiac metabolic profile, and mitigation of mitochondrial dysfunction.[169,170] Despite the fact that some of these effects have been related to increased PGC-1α expression induced by endurance exercise, leading to enhanced mitochondrial biogenesis, the intricate mechanisms underlying exercise-induced benefits on cardiovascular function, and in HFpEF in particular, remain elusive. Chronic exercise training is also associated with complex metabolic remodelling in the heart. With respect to lipid metabolism, treadmill training in mice increases both lipid utilization and lipid accumulation,[171] suggesting that complex, incompletely characterized, regulation of lipid homoeostasis occurs in the exercised heart. In addition, accumulating evidence suggests that exercise has anti-inflammatory value.[172] Cytokines and myokines, secreted by the skeletal muscle, participate in the metabolic/inflammatory reprogramming induced by exercise. For example, irisin is a myokine released in response to physical activity that potentially mediates systemic effects against metabolic inflammation and oxidative stress.[173,174] Similarly, other myokines, myostatin, and insulin-like growth factor 1, might represent potential targets in HFpEF as well, given their role in comorbidities frequently associated with HFpEF, such as frailty and sarcopenia in the elderly. Of note, the immunomodulatory properties of skeletal muscle-derived factors integrate the decades-old 'muscle hypothesis' of HF.[175]

Another well-known exercise-induced effect is the upregulation of endothelial nitric oxide synthase (eNOS), resulting in increased bioavailability of NO leading to improved vascular function and reduced oxidative stress.[176] Despite this, the disappointing results of NO-increasing strategies in HFpEF suggest strongly that exercise training has much more complex effects on NO signalling than simple increases in NO levels. In the end, the nature and role of cellular and molecular mechanisms linking exercise-dependent metabolic and inflammatory changes in the context of HFpEF warrant further investigation.

Conclusions and perspectives

Metabolic inflammation is emerging as a critical pathophysiological mechanism in HFpEF. Epidemiological evidence pointing to obesity, hypertension, and ageing as risk factors for HFpEF support the notion that a state of subtle systemic inflammation exists in HFpEF, driving key pathophysiological events within the syndrome.

We submit that the field should foster investigations on these topics as HFpEF research priorities.[62] The arguably simplistic approach of using successful anti-HFrEF therapies to treat HFpEF has failed. Similarly, many other therapeutic approaches have not provided positive results in clinical trials due to the paucity of preclinical experimental evidence supporting a role for the targeted pathway in HFpEF pathophysiology.

A paradigm shift in HFpEF therapeutics is recommended. Despite the fact that a number of disease modifiers have yet to be identified, elucidation of mechanisms whereby metabolic and inflammatory processes contributes to HFpEF pathogenesis hold promise for therapeutic intervention in this devastating syndrome.

Conflict of interest: G.G.S. and J.A.H. are co-inventors on a patent application (PCT/US/2017/037019) that was filed in June 2017 (provisional application filed in June 2016). The patent relates to the diet used for modeling HFpEF.

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