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Role of inflammation in the pathogenesis of heart failure with preserved ejection fraction and its potential as a therapeutic target

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Abstract Heart failure (HF) with preserved ejection fraction (HFPEF) is an increasingly prevalent clinical syndrome with many unresolved issues regarding diagnosis, pathophysiology, and treatment. The major pathophysiological mechanisms underlying HFPEF are known to be fibrosis and reduced ventricular compliance, and hypertension (HTN) is perhaps the most significant risk factor for the development of left ventricular diastolic dysfunction (LVDD). Inflammation is one of the earliest events in cardiac stress situations such as pressure and/or volume overload and involves elevated levels of endothelial adhesion molecules as well as increased production and release of inflammatory cytokines and chemokines in the tissue. The latter promotes the infiltration of activated inflammatory cells, particularly monocytes, into the cardiac tissue. Increased monocyte infiltration is seen in the early and late stages of HTN and HFPEF. Once inside the tissue, monocytes differentiate into macrophages and promote cardiac inflammation, tissue injury, and myocardial fibrosis. This review focuses on inflammation as the initial and primary trigger of ventricular remodelling in HTN and LVDD, affecting progression to HFPEF. The link between inflammation and b-type natriuretic peptide (BNP), a clinical marker of cardiac pressure overload which is positively associated with cardiac dysfunction and HF, is also described. Finally, current and prospective therapeutic approaches for HFPEF based on modification of the inflammatory response are reviewed.

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Heart failure with preserved ejection fraction

Heart failure (HF) is a complex clinical syndrome with increasing prevalence, high hospitalisation, and mortality rates, but poor diagnostic and treatment options [1]. HF is classified according to the degree of structural abnormality (American College of Cardiology (ACC)/American Heart Association (AHA) guidelines [2]) and by symptoms relating to functional capacity (New York Heart Association (NYHA) classification [1]), and is based upon ejection fraction (EF) which distinguishes between HF with reduced left ventricular (LV) ejection fraction (LVEF) (HFREF) and HF with preserved LVEF (HFPEF). HFREF defines HF with an underlying abnormality in systolic function leading to reduced expulsion of blood from the ventricle with every cardiac cycle (LVEF < 40 %). On the contrary, HFPEF is diagnosed based on signs and symptoms of HF, normal or only mildly abnormal LV systolic function (LVEF > 50 % in a non-dilated LV), and evidence of diastolic dysfunction defined by prolonged LV relaxation time, increased LV diastolic stiffness, slow LV filling, and elevated LV end-diastolic pressures [3, 4].

HFPEF contributes to approximately 50 % of the total HF population, and prevalence as well as incidence of HFPEF is continuing to rise due to increased awareness, increased comorbidities, and little advancement in therapy [5–8]. One year readmission and morbidity rates are identical to those of HFREF patients, and annual mortality is between 5 and 8 % [9]. However, as opposed to HFREF for which prognosis and survival have improved due to

successful evidence-based therapies for HF, survival rates for HFPEF have remained unchanged during the last two decades [5].

In order to tackle HFPEF, major effort has been directed towards prevention and early diagnosis of the disease. Preventing disease progression at the earliest possible stage will substantially reduce the economic burden of multidrug treatment and recurrent hospitalisation, and will considerably improve patient well-being as well as the overall clinical outcome. To achieve this, an in-depth understanding of the pathophysiological events associated with early stage (pre-) HFPEF is a must. Indeed, a growing concern and a major limitation of progress in the field of HFPEF diagnosis, prognosis, and treatment is the lack of sufficient understanding of the mechanisms driving LV remodelling in HFPEF [10]. In addition, the complexity of measuring diastolic function parameters and attributing correct LV functional classification in animal models of diastolic dysfunction and HFPEF has made it difficult to identify pertinent disease mechanisms that are relevant to patients with LV diastolic dysfunction (LVDD) and HFPEF [11].

From a pathophysiological point of view, it is considered that one of the most significant risk factors and a leading cause of LVDD and HFPEF is chronic pressure overload (i.e. hypertension (HTN)), with approximately 60–80 % of the patients diagnosed with HFPEF presenting with HTN [5, 8, 12, 13]. Increases in blood pressure are directly associated with an increased risk of HF in the long term as demonstrated by the Framingham study [14]. Other molecular and cellular mechanisms promoting LVDD symptoms including slow LV relaxation and elevated diastolic LV stiffness include changes in the extracellular matrix (ECM) and cardiomyocytes, posttranslational changes in the sarcomeric protein titin including phosphorylation and isoform switch, increased nitrosative and oxidative stress, reduced bioavailability for nitric oxide, and reduced myocardial cyclic guanosine monophosphate (cGMP) and protein kinase G (PKG) signalling, and these have been comprehensively reviewed in a recent paper by van Heerebeek et al. [15].

Whilst we appreciate the multivariate nature of symptoms and causes of HFPEF, for the purpose of this review, we will focus specifically on the most established pathophysiological sequence of events causing HFPEF, namely the natural progression from chronic pressure overload and LV diastolic dysfunction to HFPEF.

Pathophysiology of HFPEF

During the progression of hypertensive heart disease, a constellation of structural and functional cardiac abnormalities including LV hypertrophy (LVH), myocardial fibrosis, ischaemia, myocyte impairment, endothelial dysfunction, and increased arterial stiffness result from the underlying chronic HTN [6, 13]. A signature event in the early response to pressure overload is the accumulation of activated inflammatory cells (especially monocytes) in the heart, which, via the release of inflammatory mediators such as monocyte chemotactic protein-1(MCP1) and tumour necrosis factor alpha (TNFα), and fibrogenic activators such as transforming growth factor beta (TGFβ), maintain and augment further pro-inflammatory and pro-fibrotic processes [16–18]. This leads to structural and mechanical remodelling of the heart muscle mainly due to excessive interstitial deposition of ECM proteins such as collagens. In parallel with these inflammatory and fibrotic changes, the myocardium responds to mechanical strain via an adaptive hypertrophic increase in cardiomyocyte diameter, myofibrillar density, and myocyte passive tension, which are reported in chronic HTN patients who subsequently develop diastolic dysfunction [19, 20]. Echocardiographic evidence of concentric LVH is found in the majority of HFPEF patients [2, 20]. In the hypertrophied heart, substantial ventricular distortion is prevented by the activation of compensatory mechanisms like interstitial myocardial fibrosis. The latter aims to ensure that the heart would not distort and that the force generated by the hypertrophied myocytes is distributed throughout the entire ventricle as efficiently as possible. However, the prolonged exposure of the heart to these "compensatory forces" ultimately overloads the heart causing severe myocardial stiffness and impaired cardiomyocyte contractility in patients with HTN. The significance of inflammation and myocardial fibrosis, two processes known to have particularly important and intriguing roles in the process of hypertensive cardiac remodelling in LVDD and HFPEF, are described in detail below.

LVDD in HTN with or without LVH occurs as a result of changes in myocardial structure determined by cellular and extracellular matrix dyssynchrony. These cause alterations in the active relaxation of the ventricle and/or changes in diastolic compliance resulting in delayed LV relaxation, reduced distensibility, and increased chamber stiffness [4, 21]. Currently, the gold standard for assessing diastolic function and diagnosing LVDD is two-dimensional transthoracic Doppler echocardiography [3, 4, 22].

Patients with LVDD can often be asymptomatic for months or years without developing symptoms of HFPEF. The borderline between LVDD and HFPEF is thin and defined primarily by the manifestation of symptoms for congestive HF, most common being breathlessness (dyspnoea) due to pulmonary congestion and lung oedema [3, 23]. Dyspnoea and fatigue on exertion develop as a result of reduced LV filling, low cardiac output as the disease

progresses, and cardiac inflammation and remodelling intensifies with a further up-regulation of pro-inflammatory mediators, including MCP1 and intercellular adhesion molecule-1 (ICAM1); increases in fibrillar collagen deposition, collagen cross-linking and fibrosis; increases in the transition of cardiac fibroblasts to myofibroblasts; reductions in matrix metalloproteinases (MMP) expression or activity; and increases in tissue inhibitors of metalloproteinases (TIMP)—all causing gradual destruction of the normal cardiac interstitium [16, 24–30]. Along with these changes, and also as a result of them, inadequate activation of various cytokines and neurohormonal factors, including the renin–angiotensin–aldosterone system (RAAS), catecholamines, and endothelin [24, 31]; increased oxidative and nitrotyrosine content; impaired nitric oxide bioavailability; and impaired myocardial cGMP and PKG signalling [15] contribute to the early and late myocardial remodelling in LV diastolic dysfunction and HFPEF. All of these processes are intertwined forming intricate self-regulating networks. This makes it hard to describe the exact natural history of HFPEF, a topic of constantly increasing interest among clinicians and researchers. A schematic of the major pathophysiological events believed to be associated with pressure-overload-induced LVDD and HFPEF is presented in Fig. 1.

With accumulating evidence demonstrating an injurious and vital impact of early cardiac and vascular remodelling in the development of HFPEF, novel, more effective therapeutic strategies for HFPEF should involve reversing or slowing down cardiac inflammation, ECM remodelling, and fibrosis in addition to treating HFPEF comorbidities (i.e. atrial fibrillation, hypertension, diabetes mellitus, and coronary artery disease (CAD)), which is advised in the 2012 ESC guidelines for the management of HFPEF [1].

Inflammation: the trigger of hypertensive HFPEF: the evidence

Inflammation in hypertensive cardiac remodelling

Initial evidence showing a role for inflammation in hypertensive cardiac remodelling and heart disease came from experimental and clinical observations of immune–inflammatory activation in patients with established chronic HF [32]. Since then, multiple studies have shown high levels of pro-inflammatory cytokines such as TNFα, interleukin (IL) 1, IL6, IL8, and MCP1 in the peripheral circulation and heart of HF patients [33–39]. Main sources for these cytokines are neutrophil granulocytes, monocytes, macrophages, and T cells, as well as platelets, endothelial cells, and vascular smooth muscle cells. These cytokines have repeatedly and consistently been shown to bring important prognostic information, which has led to the conclusion that these inflammatory mediators are critically implicated in the mechanisms of progression of HF, and, as recently described, specifically in HFPEF [40]. Accumulated evidence from such studies supports the existence of a repetitive and progressive state of immune–inflammatory activation that is strongly associated with the progression of ventricular diastolic dysfunction, a distinguishing feature in the pathogenesis of HFPEF, and is characterised by an intense release and activation of cytokines, complement, adhesion molecules, and autoantibodies in the circulation [33, 34].

In addition to the role of inflammation in late ventricular remodelling and HF stabilization, early vascular inflammation has been shown to be the most common precursor of comorbidities prevalent in HFPEF such as HTN, atherosclerosis, and CAD [29], and asymptomatic individuals with even slight evidence of low-grade vascular inflammation have been shown to have an elevated risk for subsequent major cardiovascular events [18, 41].

It is now well understood that in chronic vascular inflammatory disorders, such as atherosclerosis, CAD, and HTN, the earliest and most significant inflammatory event to initiate atherosclerotic vascular lesion formation is the recruitment of circulating inflammatory cells (primarily monocytes) that attach to the endothelium and transmigrate into the vascular lesion. Transmigration is made possible due to the interactions between specific cell surface molecules on monocytes (selectins, integrins, complement receptors) and endothelial adhesion molecules (ICAM1, vascular cell adhesion molecule-1(VCAM1)), and is directed by chemokine gradients (MCP1, IL8) secreted within the injured tissue and the activated vessel wall [42] (fig. 1). Once inside the vessel wall (or inside the myocardium), monocytes differentiate into macrophages, which play a key role in orchestrating responses to injury and promoting wound repair. Macrophage activation and function is controlled by complex cell–cell interactions and a milieu of secreted pro- and anti-inflammatory cytokines, fibrotic mediators, chemokines, and growth factors released in the tissue and the periphery. These complex interactions within the injured tissue define the specificity of macrophage activation and the phenotype of macrophages—pro-inflammatory type 1 (M1) or anti-inflammatory, pro-remodelling type 2 (M2), which dictate the function of these cells in the tissue [43, 44]. In a normal "healthy wound" situation, macrophages are called to the tissue where they deal with the injury and promote healing before they clear the tissue and/or undergo apoptosis. However, in a state of disease, exaggerated injury (e.g. sustained hypertension) or uncontrolled inflammation lead to the sustained presence of activated macrophages, which damage the tissue and potentially promote aberrant tissue

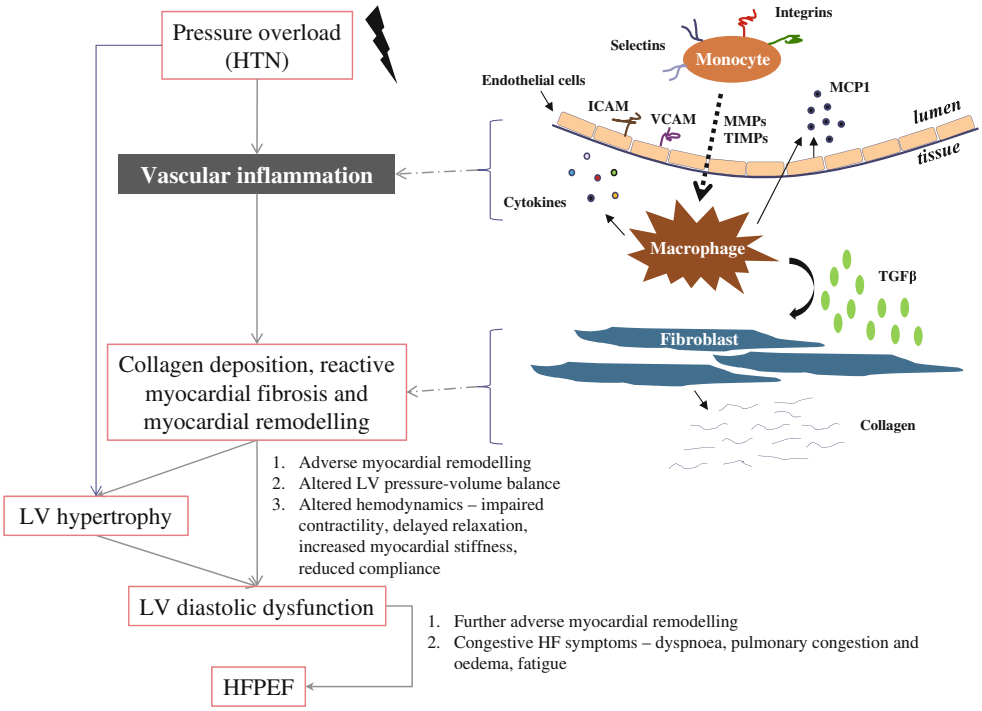

Fig. 1 The significance of inflammation and the role of monocyte/macrophage—fibroblast interaction in hypertensive cardiac remodelling and HFPEF pathophysiology. Chronic pressure overload, i.e. hypertension (HTN) regulates pro-inflammatory mechanisms and activates circulating monocytes to infiltrate into the tissue, differentiate into macrophages, and cause inflammation. The infiltration is aided by gradients of chemoattractants like MCP1 secreted by endothelial cells and tissue macrophages; the expression of adhesion molecules on endothelial cells (ICAM, VCAM) and circulating monocytes (selectins, intergrins); and the expression signature of matrix-modulating enzymes and their inhibitors (i.e. MMP, TIMP). In the tissue-differentiated, TGFβ-producing macrophages activate fibroblasts to proliferate and produce collagen which subsequently results in the development of myocardial fibrosis and remodelling. Hypertensive inflammatory and fibrotic changes subsequently cause structural and hemodynamic alterations in the heart leading to LV diastolic dysfunction either directly or by causing LV hypertrophy, a result of high LV wall tension and compensatory increase in sarcomere size. In addition, pressure overload can directly cause LV hypertrophy. In either case, the resulting myocardial remodelling, along with an altered LV pressure–volume balance, an impaired cardiac contractility, delayed relaxation, increased myocardial stiffness, and reduced compliance cause LVDD. With time, further decompensation begins to project to other systems causing dyspnoea, fatigue, pulmonary congestion, and oedema. Patients with LVDD who present with symptoms of congestion are classified as HFPEF patients

remodelling. This suggests that modulation of monocyte and macrophage activation and function may be an efficacious strategy to prevent tissue damage and improve cardiovascular function.

Inflammation in animal models of hypertensive cardiac remodelling

Initial evidence from animal studies aimed at investigating the significance of inflammation in the aetiology and progression of HTN has confirmed the significance of this process for hypertensive myocardial remodelling and has also indicated that there exists an intricate cause–effect relationship between inflammatory and fibrotic processes in the hypertensive heart. In rat models of hypertension (spontaneously hypertensive rat (SHR) and renovascular hypertensive rat), distinctive macrophage and fibroblast accumulation have been detected in perivascular regions of the pressure-overloaded heart [45, 46]. In addition, altered ICAM1 expression, observed in the endothelium of SHR, suggested that pressure overload directly regulates the abnormal inflammatory responses associated with this disease [47]. In a rat model of pressure overload caused by suprarenal abdominal aortic constriction (AC), the rapid increase in arterial pressure triggered a series of inflammatory and fibrotic changes in the intramyocardial arterial wall [16]. In this model, the earliest event detected was up-regulation of MCP1 and ICAM1 (1-day post-insult) in the intramyocardial arteries. This was followed by the accumulation of perivascular macrophages, which co-localised to sites of cytokine expression, and also resulted in enhanced TGFβ expression, fibroblast proliferation, and conversion of fibroblasts to myofibroblasts (day 3). Later in the time course of events, reactive fibrosis, LVH, and myocyte hypertrophy developed (after day 7), and LVDD was diagnosed at day 28. Similarly, rats with experimental

myocardial infarction which were treated with an angiotensin receptor blocker had attenuated LV remodelling due to reduced MCP1 expression and macrophage infiltration resulting in diminished myocardial fibrosis [48]. These models show clear evidence of a link between inflammation and fibrosis in this disease setting and establish inflammation as the initial event that triggers the onset of fibrosis in the perivascular space before expansion to the interstitium.

The induction of MCP1 to prime circulating monocytes to invade the vessel wall and thus initiate inflammation can be driven by stretch, but also by oxidative stress and activation of RAAS [49, 50], and significant activation of RAAS has been shown in HFPEF rather than in HFREF patients [51]. Angiotensin II has been shown to induce MCP1 expression in macrophages and up-regulate TGFβ in cardiac myocytes and fibroblasts in animal models of atherosclerosis [52] and pressure overload [17], suggesting that the activation of RAAS may precede the onset of inflammation and fibrosis in hypertensive heart failure. Inhibition of MCP1 with an anti-MCP1 monoclonal neutralising antibody in a rat model of developing diastolic dysfunction was shown to abolish macrophage infiltration and TGFβ induction, attenuate myocardial fibrosis, and improve diastolic function without affecting blood pressure, myocyte hypertrophy, or systolic function [16]. Similarly, MCP1 depletion in a mouse model of angiotensin II-infusion aimed at clarifying the early cellular mechanisms linking interstitial fibrosis with the onset of the tissue inflammatory response in cardiac failure showed that non-adaptive fibrosis resulting in HTN and hypertrophy requires induction of MCP1, which stimulates the differentiation of fibroblast precursor cells [53]. In addition, studies with MCP1 null mouse models of ischaemic cardiomyopathy and CCR2 (MCP1 receptor) knockout mice with HTN and LVH have shown markedly diminished interstitial fibrosis, low macrophage infiltration, and attenuated ventricular dysfunction [54, 55]. In one study, the reduction in cardiac fibrosis in angiotensin II-infused CCR2 knockout mice was attributed to impeded accumulation of bone marrow-derived fibroblast precursors in the heart [56]. Similar beneficial effects were noted also when ICAM1 function was blocked [27].

Further evidence supporting the role of leukocyte-induced inflammation in pressure overload and HF comes from a hypertensive animal model of oxidative and inflammatory stress. [57]. It was shown in deoxycorticosterone acetate and sodium chloride-treated rats (i.e. DOCA-salt hypertensive rats) that the intricate combination of inflammation and oxidative stress is a necessary basis for eliciting a chronic pathophysiological stress state—a prerequisite for initiating cardiovascular remodelling (expressed as HTN, hypertrophy, fibrosis, electrical conduction abnormalities, vascular hypertrophy, and dysfunction) and heart failure. In the same model, cardiac ECM remodelling was associated with an up-regulation of inflammatory mediators (nuclear factor kappa B (NFκB), VCAM, platelet-endothelial cell adhesion molecule (PECAM) 1), increased fibronectin, and MMP activity [58]. Finally, in two-month-old rats with hypertensive heart failure, the addition of rosuvastatin to the standard antihypertensive HF therapy (quinapril plus torasemide plus carvedilol) was able to improve cardiac remodelling associated with HFPEF, and these beneficial effects were due, at least in part, to decreased myocardial inflammation [59].

Taken together, these studies suggest that leukocyte-mediated perivascular inflammation is a key event in triggering early ECM changes, myocardial fibrosis, and LVDD in pressure overload. Therefore, targeting monocyte infiltration and macrophage function could be an effective new strategy to prevent hypertensive myocardial remodelling in HFPEF.

Inflammation in patients with hypertension-induced LVDD and HFPEF

The significance of inflammation in patients with diastolic LV dysfunction and HFPEF perhaps has been underestimated due to the complexity of diagnosing diastolic dysfunction in disease-relevant animal models and the overall lack of adequate translational models.

Existing data in patients with diagnosed HFPEF is scarce, but studies in patients with clinical conditions predisposing to and prevalent in HFPEF, such as HTN, CAD, LVDD, and metabolic syndrome, have helped to shed light on the processes involved.

In a study on cardiovascular damage in patients with metabolic syndrome, increased levels of inflammation (urinary albumin, C-reactive protein (CRP), TNFα, and TGFβ) were found to be independently associated with asymptomatic diastolic dysfunction [60]. In other studies, increased inflammation (CRP) [61], platelet activation, and endothelial dysfunction [62] were predictive of abnormal diastolic function in patients with stable CAD. Comorbidities such as HTN, CAD, obesity, and diabetes that are associated with the syndrome of HFPEF and the systemic inflammatory state (defined by high levels of peripheral IL6 and TNFα) induced by them has recently been shown to be predictive of incident HFPEF, but not incident HFREF [29]. High circulating IL6, TNFα, IL8, and MCP1 were also detected in a cross-sectional study of 275 stable hypertensive patients with and without HFPEF [30]. Two similar large cross-sectional studies, one in patients with acute dyspnoea and preserved LVEF [63] and one in HFPEF patients [64], identified the independent systemic inflammatory markers soluble ST2 (member of the IL1

receptor family) and PTX3 (pentraxin 3), respectively, to correlate with the presence of LVDD and HFPEF and to be strong predictors of mortality in these patients.

The importance of systemic inflammation, specifically in patients with HFPEF, has been highlighted in a recent study comparing physiologically distinct circulating biomarkers in HFPEF patients, HFREF patients, and community controls [40]. The authors provided important evidence of a distinguishing role for myocardial injury (high-sensitivity troponin T) with increased wall stress (N-terminal pro-BNP) in the pathophysiology of HFREF, and a role for systemic inflammation, defined by high levels of growth differentiation factor 15 (GDF15), as a crucial determinant specifically in the progression of HFPEF.

The systemic inflammatory state induced by HFPEF comorbidities starts to gradually affect the cardiac vascular endothelium resulting in increased expression of endothelial adhesion molecules including VCAM1 in the heart. This has been shown in left ventricular endomyocardial biopsy samples from HFPEF patients by Westermann et al. [28]. VCAM, among other endothelial adhesion molecules, is a marker of inflammatory endothelial activation and high expression leads to the activation and subendothelial migration of circulating leukocytes. HFPEF patients had high numbers of CD3, CD11, and CD45-positive leukocytes in the myocardium, increased inflammatory cell TGFβ expression, and increased levels of collagen I and III [28]. TGFβ is the best-known inducer of collagen production and stimulates the differentiation of fibroblasts into myofibroblasts thus altering the cardiac ECM homeostasis and predisposing to diastolic dysfunction. Based on these findings, the authors concluded that myocardial inflammation has an important role in HFPEF pathophysiology by promoting ECM changes and diastolic dysfunction. In addition, it has been demonstrated that activated myofibroblasts can themselves induce inflammation by producing cytokines and chemokines which stimulate inflammatory cell recruitment and activation [65]. This recurrent inflammatory boost may have detrimental effects on the heart by intensifying fibrosis and promoting diastolic dysfunction and subsequently HFPEF.

B-type natriuretic peptide (BNP) and cardiac inflammation: relevance to hypertension, diastolic dysfunction, and HFPEF

BNP is a circulating endocrine factor positively implicated in the regulation of blood pressure and is a useful prognostic and diagnostic marker for hypertension and HF regardless of ejection fraction [66–68]. BNP's prognostic and diagnostic significance are partially related to its implication in the regulation of fibrotic and inflammatory pathways in the pressure-overloaded heart. BNP has potent autocrine/paracrine actions in the heart that are implemented following the interaction with its receptor, natriuretic peptide receptor A (NPRA), and the subsequent production of cGMP. NPRA is expressed in most cells of the heart including cardiomyocytes, and NPRA deletion in mice ($Npr1^{-/-}$) has been shown to cause salt-resistant hypertension, cardiac hypertrophy, and fibrosis [69–71], whilst overexpression causes arterial hypotension [72]. Locally targeted overexpression of NPRA in cardiomyocytes attenuates pressure-induced LVH [73, 74]. On the other hand, myocyte-specific NPRA deletion in mice causes cardiac hypertrophy and impaired diastolic relaxation [75]. In the setting of deletion of the BNP gene ($Nppb^{-/-}$), the knockout animals develop focal cardiac ventricular fibrotic lesions and increase ventricular expression of profibrotic genes including angiotensin-converting enzyme (ACE), TGFβ3, and pro-α1-collagen [76]. The expression and function of BNP were more recently also shown in cardiac fibroblasts [77–79]. Data from in vivo studies with human cardiac fibroblasts support an important paracrine role for the peptide in the regulation of fibroblast proliferation and function in cardiac hypertrophy via opposing the actions of TGFβ, decreasing collagen synthesis, and increasing MMP activity [78–80]. Consistent with these data, our group has described protective effects of BNP in vitro in mechanically stretched fibroblasts, where treatment with the peptide attenuated the effects of TGFβ in inducing myofibroblast differentiation, indicated by a reduction in protein levels of α-smooth muscle actin [81]. In vivo studies, $Npr1^{-/-}$ mice had increased expression of fibrotic genes including MMP2, MMP9, TGFβ, TNFα, and total collagen [82]. Taken together, these studies establish BNP as a potential anti-fibrotic factor and a local regulator of ventricular remodelling in the heart.

The BNP/NPRA system has recently also been shown to regulate inflammatory networks in the diseased heart. Recent evidence from animal studies shows enhanced pro-inflammatory cytokine gene expression in $Npr1^{-/-}$ mice [83]. A three- to fivefold induction of TNFα, IL6, and TGFβ1 expression was demonstrated in the left ventricles of the knockout animals. In another study, knockout of NPRA in mice caused up-regulation of NFκB activity and TNFα expression supporting a role for BNP in counterbalancing these inflammatory mediators [82]. In line with this, cardiac-specific overexpression of TNFα and IL6 in mice proved to be sufficient to induce cardiac hypertrophy and LVDD [84, 85]. In vitro studies with neonatal rat ventricular cardiomyocytes have also shown increased synthesis and secretion of BNP following treatment of the cells with TNFα or IL1β [86]. Furthermore, the same study reported increased plasma BNP levels in the absence of

hemodynamic changes in an in vivo mouse model of sepsis and supported a unique regulatory role for BNP (but not ANP) in the setting of an inflammatory process. In summary, it seems very likely that the BNP/NPRA/cGMP system has an important anti-inflammatory role in the heart.

Recent data have shown a substantial correlation between BNP levels and serum markers of inflammation in animal models as well as patients. BNP and IL6 gene levels were consistently elevated in cardiac hypertrophy complicated with diastolic LV dysfunction in spontaneously hypertensive rats, indicating active inflammatory processes in these hearts [87]. Additionally, a significant correlation between IL6, BNP, and LV end-diastolic dimension (LVEDD) values was found in patients with idiopathic LV dysfunction [88] and elevated BNP correlated with TNF and LVEDD in chronic HF patients [89]. Ahmad et al. [90] also identified an association between TNFα, IL6, NT-proBNP, and LV function recovery in patients with dilated cardiomyopathy. In addition, N-terminal proBNP levels correlated with CRP and systolic and diastolic blood pressure in chronic renal failure patients with or without known cardiomyopathy [91].

Along with the published data, our group also identified significant correlation between central BNP levels and levels of TNFα, IL6, and IL8 in hypertensive patients at risk of developing HFPEF [92]. Furthermore, peripheral BNP levels correlated with central levels of TNFα, IL6, IL8, and MCP1. This suggested that in asymptomatic HTN patients, a peripheral BNP measurement may be a useful marker of early, sub-clinical pathological processes including inflammation, ECM alterations, and cardiac remodelling—important pathophysiological determinants of HFPEF.

Whilst it is not known what promotes the release of inflammatory mediators in high-BNP patients, it is considered that BNP could be able to modulate the inflammatory response by affecting different immune cell functions, like leukocyte migration, and activation, or by interfering with the integrity of the vasculature, i.e. the endothelial and smooth muscle layers. In fact, a study published a few years ago showed that BNP can up-regulate the production of pro- and anti-inflammatory molecules like reactive oxygen and nitrogen species, leukotriene B_4, and prostaglandin E_2; increase IL10 levels; and affect cell motility of monocytic THP1 cells [93]. In another study, co-culture of peripheral blood mononuclear cells (PBMC) from cardiac transplant recipients with BNP caused a reduction in pro-inflammatory cytokines (TNFα, IL6, IL1α), whilst expression of anti-inflammatory and regulatory cytokines (IL4, IL5, IL13) was preserved [94]. Our group has also very recently shown evidence of a cardio-protective regulatory role of BNP in an in vitro inflammatory setting where BNP was able to directly oppose human monocyte migration to MCP1 [95]. The ability of BNP to block MCP1-induced chemotaxis was attenuated in monocytes from HTN and HFPEF patients suggesting that this potentially beneficial anti-inflammatory function of BNP is likely compromised in chronic pressure overload and HFPEF [95].

Even though most of these new data are relatively descriptive, when taken together, they suggest that there exists a circumstantial relationship between BNP, leukocyte (i.e. monocyte/macrophage) function, and inflammation—a concept which needs further exploration in the context of HFPEF and heart failure in general.

Current and prospective anti-inflammatory therapeutic approaches for HFPEF

The pathophysiological mechanisms underlying HFPEF are still not well understood, which is why it is not surprising that to date, there is no effective treatment for this complex syndrome. Current ESC/HFA and ACC/AHA guidelines recommend control of blood pressure, ischaemia, tachycardia, and targeting the two most important comorbidities, i.e. diabetes and LVH, to be the most effective approaches for HFPEF [1, 2]. However, the current classes of pharmacological agents used for reduction in blood pressure, congestion, and circulation volume, and reduction in ventricular remodelling, namely β-blockers, diuretics, aldosterone antagonists, ACE inhibitors, and angiotensin receptor blockers which have shown significant benefit for treatment of HFREF failed to show particular benefit in long-term outcome (mortality) or quality of life (exercise capacity, hospitalisation) in clinical trials with HFPEF patients [96–100]. This is also the reason why there is currently no specific evidence-based therapy for HFPEF. Data from the currently completed clinical endpoint trials in HFPEF using anti-hypertensive agents including the SWEDIC, SENIORS, V-HeFT II, DIG-PEF, PEP-CHF, CHARM-Preserved, and I-PRESERVE trials have been comprehensively reviewed by Paulus et al. [10] and Kindermann et al. [101]. Briefly, the beta-blocker carvedilol had no effect on primary endpoints (cardiovascular death and hospitalisations for HF) (SWEDIC), and treatment with nebivolol reduced primary outcomes by 14 % (regardless of EF), but had no significant effect on LA volume, EF, LA dimensions, and function (Seniors); treatment with the ACE inhibitor perindopril had no effect on mortality and HF hospitalisations (i.e. primary endpoint) (PEP-CHF); similarly, treatment with the digitalis glycoside digoxin also showed no effect on primary and secondary endpoints (DIG-PEF); finally, the use of the angiotensin II receptor antagonists candesartan (CHARM-Preserved) and irbesartan (I-PRESERVE) did not improve

mortality in both trials, but a reduction in HF hospitalisations was reported in CHARM-Preserved. The negative results from these trials once again highlight the fact that controlling HTN alone in HFPEF is insufficient to treat the disease and that other medications, such as anti-inflammatories, should be used, in addition to anti-hypertensive drugs to address the multifactorial nature of HFPEF. Whilst anti-hypertensive drugs do not appear to have beneficial effects in HFPEF, the VALIDD trial (NCT00170924) showed that lowering blood pressure using a mixture of tailored anti-hypertensive agents with or without the angiotensin receptor blocker valsartan was able to improve diastolic function in LVDD patients by reducing blood pressure and increasing diastolic relaxation velocity irrespective of the type of anti-hypertensive agent used [100]. We therefore propose that therapeutic approaches intervening with the inflammatory pathways that are known to play a role in hypertensive heart disease should be utilised in addition to an anti-hypertensive treatment in at-risk patients or patients with LVDD and/or HFPEF to prevent the detrimental effects that inflammation has on matrix remodelling in the heart. This concept is supported by the recently completed Health ABC (Health, Aging, and Body Composition) study which showed strong association of inflammatory markers with HFPEF (as compared to HFREF) and pointed out the importance of identifying and targeting inflammation for improving risk stratification and reducing mortality in HFPEF [29]. Further support for the cause of targeting inflammation in HFPEF is provided by Collier et al. [30] who showed that increased pro-inflammatory cytokine levels predict future development of HFPEF in at-risk populations, i.e. hypertensive patients. The importance of inflammation in primary prevention of cardiovascular disease is also highlighted by the Jupiter trial which tested the effectiveness of rosuvastatin to reduce the rate of first major cardiovascular events (i.e. cardiovascular death, stroke, MI, hospitalisation for unstable angina, or arterial revascularization) in normoglycaemic individuals with high levels of the inflammatory mediator CRP [102]. The study found that only patients with high CRP (i.e. with evidence of systemic inflammation) benefited from the statin therapy, and by following treatment, these patients had reduced inflammation and significantly reduced incidence of major cardiovascular events [41], providing a further rationale for targeting inflammation in heart failure. Indeed, a range of broad-spectrum anti-inflammatory and immuno-modulatory approaches including anti-TNFα therapy (the RENEWAL programme), anti-oxidant therapy (A-HeFT trial), immuno-adsorption, immuno-modulation (ACCLAIM trial), and intravenous immunoglobulin therapy have been investigated and tested in clinical trials of chronic HF without significant overall benefit [103, 104]. These, however, were investigated in HFREF and not HFPEF patients. Whilst HFREF has an inflammatory component, it is unclear and unlikely that targeting inflammation in the late stages of systolic dysfunction would be of any benefit, a rationale which is supported by the negative results from these anti-inflammatory HFREF trials.

Ever since the failure of broad-spectrum anti-inflammatory therapies in HFREF, more specific treatment options have been explored in translational models of HF. Such anti-inflammatory strategies in hypertensive HFPEF-relevant animal models have shown promising results. These include targeting immunomodulatory and inflammatory cytokines and chemokines (MCP1 [16, 105], MCP3 [106], IL10 [107–109]), cytokine receptors (IL1 receptor [110, 111]), matrix-modulating enzymes (MMP) [112–119], pentraxins (PTX3) [120–122], and inflammatory signal transduction mediators (phosphatidylinositol 3-kinase gamma (PI3 Kγ) [123, 124]). Data and major conclusions from these experimental studies are summarised in Table 1.

Based on these experimental data that show a benefit of inflammatory modulation in hypertensive HFPEF-relevant animal models, it becomes evident that particular effort must be put into the precise identification of the inflammatory pathways which play a role in the immunopathogenesis of HFPEF in order to develop specific immune-modulating agents that could be used in clinical HFPEF trials. In fact, several small-scale clinical trials exploring the use of inflammatory modulators, which were shown to have beneficial effects in animal models of HFPEF, have been recently initiated. One such pilot study investigates the advantage of Anakinra, a non-glycosylated recombinant human IL1 receptor antagonist approved for the treatment of rheumatoid arthritis, in HFPEF patients (NCT01542502). The therapeutic agent is projected to have beneficial anti-inflammatory and anti-remodelling effects originating from antagonism of the pro-inflammatory cytokines IL-1α and IL-1β which are implicated in adverse ventricular remodelling, including pressure-overload-induced cardiac hypertrophy [125]. Another pilot study is currently investigating the effects of active vitamin D supplementation (paricalcitol) on left atrial volume index in HFPEF patients (NCT01630408). Paricalcitol has previously been shown to improve LV function by reducing LV mass, posterior wall thickness, and end-diastolic pressures, increasing fractional shortening, and regulating gene expression in high-salt diet fed Dahl salt-sensitive rats—a model of hypertensive HFPEF [126]. Many cardiovascular diseases including HTN, myocardial ischaemia, diabetic cardiomyopathy, and HF may arise from a low vitamin D status: low vitamin D is associated with poor prognosis in HF patients due to RAAS activation and increased inflammation [127]. However, it should be noted that the

Table 1 Emerging anti-inflammatory targets with potential benefit for HFPEF therapy

New target	Evidence	Reference
Chemokine antagonists–anti-MCP1, MCP3	Anti-MCP1 gene therapy attenuates LV remodelling and HF in a mouse model of post-MI HF	[105]
	MCP1 antagonism with a monoclonal neutralising antibody in a rat model of cardiac hypertrophy ameliorates diastolic dysfunction without affecting blood pressure or systolic function	[16]
	Administration of MCP3 neutralising antibody in MMP2 knockout mice with viral myocarditis alleviates exaggerated inflammation and improves cardiac function and survival	[106]
Immuno-modulatory cytokines-IL10	Administration of recombinant IL10 in mice with viral MI improves survival and attenuates myocardial inflammation	[107]
	Recombinant IL10 reduces levels of IL10 in HF patients.	[108]
	Recombinant IL10 reduces LPS-induced TNFα in PBMC of HF patients.	[109]
Cytokine receptor antagonists-IL1 receptor antagonist (IL1ra)	IL1ra provides cardio-protection against ischaemia–reperfusion injury in rat cardiomyocytes	[110]
	In a pilot study in patients with ST-segment, elevation acute MI IL1 blockade with Anakinra is safe and favourably affected by LV remodelling	[111]
Extracellular matrix modulation–matrix metalloproteinase (MMP) inhibitors	MMP2 and MMP9 knockout mice have reduced degradation of aortic elastin and are protected from pressure-overload-induced hypertrophy, myocardial fibrosis, and diastolic dysfunction	[112–114]
	Non-specific MMP inhibition in animal pressure-overload models alleviates cardiac remodelling, but has toxic effects and is therefore inefficient in the clinic.	[115–117]
	MMP inhibition with doxycycline has selective effects on vascular inflammation and reduces aortic wall neutrophil and cytotoxic T cell content in animal models of abdominal aortic aneurysm	[118]
	Doxycycline inhibits extracellular matrix degradation mediated by human peripheral blood monocytes/macrophages via downregulation of cytokines and MMP9 and inhibition of collagenase and MMP9 activities–potential therapeutic benefits for chronic inflammatory and cardiovascular diseases	[119]
Pentraxins (PTX)–PTX3	High levels of PTX3 are found in atherosclerotic lesions	[120]
	PTX3 is an independent predictor of mortality in patients with acute MI	[121]
	Absence of PTX3 in mice exacerbates heart damage (greater no reflow area, increased neutrophil infiltration, decreased capillary number, increased number of apoptotic cardiomyocytes). Administration of exogenous PTX3 alleviates myocardial damage in knockout animals	[122]
Signal transducer and inflammatory modulator inhibition–phosphatidylinositol 3-kinase gamma (PI3 Kγ) inhibitors	PI3 Kγ knockout mice have normal blood pressure and heart rate, but increased contractility, increased cardiac workload by transverse aortic banding, loss of myocytes, left ventricular dilatation, and death	[123]
	Inhibition of the catalytic domain of PI3Kγ inhibits inflammatory cell infiltration after ischaemia and reperfusion of the myocardium	[124]

MCP monocyte chemotactic protein, *MI* myocardial infarction, *PBMC* peripheral blood mononuclear cells, *LPS* lipopolysaccharide, *IL1ra* IL1 receptor antagonist, *MMP* matrix metalloproteinase, *PTX* pentraxin, *PI3Kγ* phosphatidylinositol 3-kinase gamma

beneficial effects of paricalcitol on LV function may likely be due to direct anti-inflammatory effects and/or anti-hypertensive effects (e.g. antagonism of RAAS) which on their own may alleviate cardiac inflammation via separate signalling pathways. Sildenafil—a selective phosphodiesterase inhibitor—is another drug-targeting inflammation that holds therapeutic promise. Sildenafil was shown to rescue LV dysfunction, inflammation, and cardiac remodelling in angiotensin II-induced heart failure in mice providing rationale for its potential use as a new treatment strategy for adverse ventricular remodelling in severe hypertension and possibly HFPEF [128]. A recently completed (NCT01156636, [129]) and an ongoing (NCT01726049) clinical trial should elucidate the precise clinical benefits of this drug in HFPEF patients with pulmonary hypertension. However, besides promising results from several experimental and clinical trials, neutral results of the recently completed multi-centre, double-blind, placebo-controlled, randomised clinical trial RELAX (NCT00763867), which showed no significant improvement in exercise capacity or clinical status with administration of sildenafil (compared to placebo) in a large cohort of HFPEF patients, have decreased the overall enthusiasm in phosphodiesterase-5 inhibition for HFPEF therapy [130].

Certainly, more large randomised clinical trials in patients with HFPEF along with a better understanding of the ongoing inflammatory reactions in hypertension and diastolic LV dysfunction—the most prevalent factors in the pathophysiological progression of HFPEF, are needed to help decrease the socioeconomic burden of this increasingly prevalent and mortal syndrome.

Conflict of interest The authors Dr. Nadezhda Glezeva and Dr. John A. Baugh have no conflict of interest to disclose.

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