Heart failure with preserved ejection fraction in hypertension

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Purpose of review
Hypertension is the most prevalent risk factor in heart failure with preserved ejection fraction (HFpEF) and plays a key role in the disease. The continued lack of effective therapies to improve outcomes in HFpEF underscores the knowledge gaps regarding the pathophysiology of HFpEF. This review builds on fundamental concepts in pressure overload-induced left ventricular modeling, and summarizes recent knowledge gained regarding the mechanisms underlying the transition from hypertensive heart disease to HFpEF.

Recent findings
The pathophysiology of hypertensive HFpEF extends beyond the development of left ventricular hypertrophy and diastolic dysfunction to myocardial contractile dysfunction, beyond left atrial structural dilatation to left atrial functional decline, beyond macrovascular stiffening to microvascular dysfunction, beyond central cardiac triggers to systemic endothelial inflammation, beyond fibrosis to titin changes, and beyond collagen deposition to qualitative changes in collagen. The central paradigm involves a systemic proinflammatory state triggering a downstream cascade of cardiac microvascular endothelial activation, oxidative stress, and abnormal myocardial cyclic guanosine monophosphate signaling, leading to microvascular rarefaction, chronic ischemia, fibrosis and progression to HFpEF.

Summary
Recent advances have provided insights into the pathophysiology of HFpEF in hypertension. Such knowledge provides novel opportunities for therapeutic strategies in the treatment of hypertensive HFpEF.

Keywords
heart failure with preserved ejection fraction, hypertension, pathogenesis, pathophysiology

INTRODUCTION

Hypertension carries the highest population attributable risk for heart failure in the general population [1], and a more than two-fold increased odds of heart failure with preserved ejection fraction (HFpEF) versus heart failure with reduced ejection fraction (HFrEF) [2]. Among patients with HFpEF, hypertension is the commonest cardiovascular risk factor, with a prevalence of 55–84%, which is higher than in patients with HFrEF [3]. At the onset of heart failure, a higher SBP increases the odds of HFpEF versus HFrEF by 13% for each 10-mmHg increase [2]. Individuals with hypertension are therefore at significantly higher risk of developing HFpEF and can be classified as having stage A HFpEF according to American College of Cardiology Foundation/American Heart Association (ACCF/AHA) stages of heart failure [4].

The transition from asymptomatic hypertensive heart disease (Stage B HFpEF) to clinically manifest Stage C HFpEF is an area of intense research, as identifying mechanisms for progression provides the opportunity to target these mechanisms in therapeutic or preventive strategies. Greater understanding is urgently needed in HFpEF, as it is the dominant form of heart failure in aging societies [5], and is associated with dismal outcomes; yet, to date, there are still no proven effective therapies that improve survival in HFpEF. The traditional understanding of disease progression in hypertension

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KEY POINTS

- Classical understanding of the pathophysiology of HFpEF in hypertension involves left ventricular hypertrophy, diastolic dysfunction, left atrial dilatation, macrovascular stiffening, and myocardial fibrosis.
- Recent findings suggest that beyond these key mechanisms, left ventricular myocardial contractile dysfunction, left atrial dysfunction, microvascular disease, systemic endothelial inflammation, alterations in titin and qualitative changes in collagen importantly contribute to the transition of hypertensive heart disease to HFpEF.
- New insights into the pathophysiology of HFpEF in hypertension provide potential novel therapeutic targets, such as the cyclic guanosine monophosphate signaling pathway.

has been 'cardiac-centric' and focused on structural left ventricular remodeling and the key role of left ventricular hypertrophy in the pathogenesis of heart failure [6]. However, fewer than half of patients with HFpEF had left ventricular hypertrophy, and this proportion was no greater than in those with asymptomatic hypertension in a population-based study [7]. Recent work has provided valuable insight into other fundamental mechanisms in the progression to HFpEF in hypertension, involving both central and peripheral factors. This review aims to summarize the new knowledge gained in this field, which importantly builds upon, yet goes beyond, established concepts such as left ventricular diastolic dysfunction, left atrial dilatation, macrovascular stiffening, and left ventricular fibrosis. Figure 1 summarizes recent breakthrough mechanisms underlying the pathophysiology of HFpEF in hypertension.

BEYOND LEFT VENTRICULAR HYPERTROPHY AND DIASTOLIC DYSFUNCTION: MYOCARDIAL CONTRACTILE DYSFUNCTION DESPITE PRESERVED LEFT VENTRICULAR EJECTION FRACTION

Hypertension imposes increased afterload on the left ventricle via elevated arterial pressure and total peripheral resistance. The left ventricular wall thickens in response to pressure overload as a

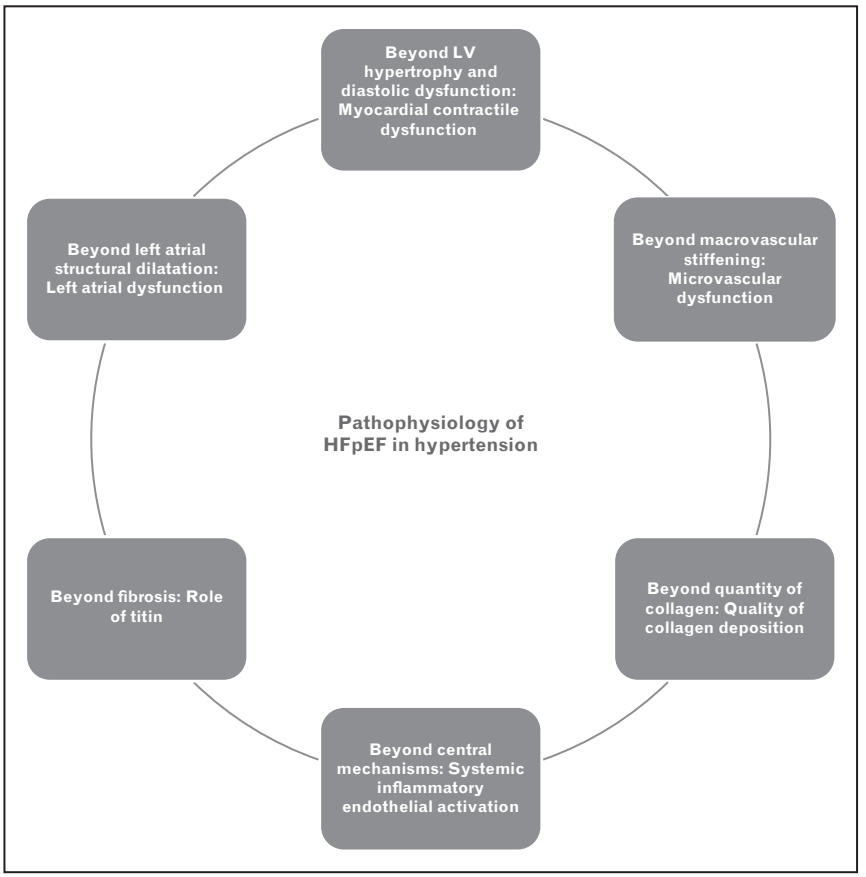

FIGURE 1. Recent breakthrough mechanisms underlying the pathophysiology of heart failure with preserved ejection fraction (HFpEF) in hypertension. LV, left ventricular.

compensatory mechanism to minimize wall stress, and this results in left ventricular hypertrophy [6] and left ventricular diastolic dysfunction as evidenced by impaired left ventricular relaxation, diminished early diastolic filling and left atrial enlargement [8▪]. Left ventricular hypertrophy and diastolic dysfunction have been identified as the key myocardial structural and functional abnormalities induced by hypertension, leading to hypertensive heart disease and HFpEF [8▪,9].

In spite of preserved left ventricular ejection fraction (LVEF) in HFpEF, patients with HFpEF have subtle systolic dysfunction not reflected by the ejection fraction [8▪,10]. Left ventricular myocardial contractility, measured as midwall fractional shortening, was impaired in HFpEF, but enhanced in people with hypertension compared with nonhypertensive controls, despite similar LVEF [11]. Impaired regional strain, as quantified by speckle tracking echocardiography, was reported in both hypertensive heart disease [12] and HFpEF patients [13▪]. In addition, Rosen *et al.* demonstrated that in asymptomatic patients, left ventricular concentric remodeling was associated with decreased regional systolic function on myocardial tagged MRI [14]. In aggregate, these data provide strong evidence of myocardial contractile dysfunction in HFpEF despite preserved overall chamber function, and suggest a role of progressive systolic dysfunction, on top of diastolic dysfunction, in the transition from hypertensive heart disease to overt HFpEF. Furthermore, myocardial contractile dysfunction is a prognostic marker in HFpEF patients, correlating with increased mortality, hospitalization for heart failure, cardiovascular death or aborted cardiac arrest [11,13▪], thus supporting a pathophysiologic role in disease progression.

BEYOND LEFT ATRIAL STRUCTURAL DILATATION: LEFT ATRIAL DYSFUNCTION

Left atrial enlargement reflects cardiac structural remodeling and is an early sign of hypertensive heart disease. Left atrial enlargement usually occurs before left ventricular hypertrophy and is much more common (up to three-fold) than LVH in hypertensive patients. Hypertensive patients who are older and have a longer duration of hypertension are more likely to develop left atrial enlargement [15]. Left atrial enlargement is present in the majority of hypertensive patients with HFpEF, and the prevalence is higher than in hypertensive patients without HFpEF [15,16]. Melenovsky *et al.* showed that left atrial volumes were 68% larger in HFpEF compared with age-matched controls, and 40% larger in patients with hypertensive heart disease without heart failure. In fact, left atrial volume (along with left ventricular mass) best distinguished HFpEF from hypertensive heart disease [16]. Beyond structural changes, left atrial *functional* changes are increasingly recognized in HFpEF. Patients with HFpEF had reduced atrial total, passive, and active emptying fractions, as well as reduced atrial contractile reserve in response to handgrip, compared with controls and hypertensives in Melenovsky's cohort [16]. Tan *et al.* also demonstrated reduced left atrial functional reserve on treadmill exercise in HFpEF, where late diastolic mitral annular velocity on exercise was lower in HFpEF, compared with hypertensive subjects and healthy controls, and correlated with exercise capacity [17]. The inability to increase left atrial contribution to left ventricular filling during exercise was postulated to lead to raised left atrial pressure and breathlessness on exertion in HFpEF. More recently, increased left atrial stiffening and greater left atrial pressure pulsatility was shown in HFpEF compared with hypertensive controls and patients with HFrEF [18▪]. A substudy of HFpEF patients from the angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction (PARAMOUNT) trial further reported worse left atrial reservoir, conduit, and pump function, as well as reduced systolic left atrial strain compared with age- and sex-matched healthy controls [19]. Importantly, left atrial dysfunction is a potent prognostic factor in hypertensive patients [20▪] and patients with HFpEF [20▪,21], independently of left atrial structural remodeling. The ultimate expression of left atrial dysfunction may be the development of atrial fibrillation. Indeed, recent longitudinal epidemiologic studies have highlighted the intimate relationship between HFpEF and atrial fibrillation, where one condition begets the other, and atrial fibrillation was found to occur in more than 60% of patients with HFpEF during the course of their disease [22▪]. In fact, compared with HFrEF, patients with HFpEF were more likely to have prevalent atrial fibrillation (23% versus 32%); conversely, prevalent atrial fibrillation tended to predict incident HFpEF [hazard ratio (HR): 2.34, 95% confidence interval (CI): 1.48–3.70, no atrial fibrillation as referent] more strongly than HFrEF (HR 1.32, 95% CI: 0.83–2.10; *P* for difference 0.06) [22▪].

BEYOND MACROVASCULAR STIFFENING: MICROVASCULAR DYSFUNCTION

Macrovascular stiffening is present in patients with hypertension and HFpEF, associated with matched increases in left ventricular systolic stiffness (elastance) so as to preserve arterial–left ventricular

coupling for maximal cardiac efficiency [16,23]. However, during exercise there was blunted increase in left ventricular contractility and blunted vasodilation in HFpEF, resulting in abnormal arterial–LV coupling reserve and exertional intolerance [24]. Apart from macrovascular stiffening, *microvascular* dysfunction has been demonstrated in HFpEF, as evidenced by lower resting endothelial-related microvascular vasomotion by laser Doppler flowmetry, and impaired reactive hyperemia (reduced slope of the rise in forearm cutaneous blood flow and decreased forearm cutaneous peak blood flow after release of arterial occlusion), compared with hypertensive control subjects matched for age, sex, and diabetes [25▪▪]. Lee *et al.* recently reported reduced brachial flow-mediated dilatation (FMD) and reactive hyperemia in HFpEF compared with healthy controls, indicating the presence of both macrovascular and microvascular endothelial dysfunction in HFpEF. Importantly, when brachial FMD was normalized for hyperemia-induced shear stimulus (as the shear stimulus is a measure of microvascular function), there was no significant difference in FMD between HFpEF and controls, indicating that the macrovascular dysfunction was, at least in part, contributed by microvascular dysfunction [26▪]. Microvascular dysfunction may result in impaired stress-induced myocardial perfusion, leading to myocardial ischemia, microvascular infarction, rarefaction, and fibrosis with ensuing HFpEF [27]. Mohammed *et al.* [28▪] provided valuable insights from human myocardial autopsy samples showing that patients with HFpEF had more coronary microvascular rarefaction and myocardial fibrosis than in controls. Microvascular rarefaction was postulated to play a role in limiting systolic and diastolic reserve, predisposing to chronic microvascular ischemia, fibrosis, and progression to HFpEF. In fact, evidence has very recently emerged to show that microvascular ischemia results in abnormal diastolic reserve during exertion in HFpEF [29]. This was demonstrated by higher peak exercise pulmonary capillary wedge pressure despite a lower workload and significantly lower transcardiac oxygen gradient in HFpEF compared with controls and hypertensive patients without heart failure. The difference in the response between the hypertensive patients and the HFpEF patients suggests that microvascular ischemia might play a role in the progression to Stage C HFpEF.

BEYOND CENTRAL MECHANISMS: SYSTEMIC INFLAMMATORY ENDOTHELIAL ACTIVATION

In the landmark paper by Paulus and Tschope, attention was turned from a cardiac-centric trigger (such as acute myocardial infarction in HFrEF) to a *systemic* trigger in HFpEF, where a widespread proinflammatory state secondary to comorbidities was responsible for a cascade of events resulting in left ventricular diastolic dysfunction and HFpEF [30]. According to this paradigm, common comorbidities in HFpEF, such as hypertension, obesity, and diabetes mellitus, trigger systemic inflammation, including coronary microvascular endothelial inflammation. Coronary microvascular endothelial inflammation, in turn, decreases the bioavailability of nitric oxide and cyclic guanosine monophosphate (cGMP) content, resulting in decreased protein kinase G (PKG) activity in cardiomyocytes. The low PKG activity leads to cardiomyocyte hypertrophy, concentric left ventricular remodeling, hypophosphorylation of the giant cytoskeletal protein titin, and increased myocardial stiffness.

Further evidence in support of this paradigm was recently provided by Frannssen *et al.,* who looked at myocardial biopsies of HFpEF patients (compared with patients with aortic stenosis and HFrEF) in conjunction with findings in obese diabetic fatty/spontaneously hypertensive HFpEF rats (compared with control rats) [31]. Firstly, in the myocardium of HFpEF patients and HFpEF rats, they found higher levels of vascular adhesion molecules Intercellular Adhesion Molecule-1 and E-selectin, which were attributed to the higher metabolic risk profile, and favored myocardial infiltration of inflammatory cells. Secondly, they showed striking upregulation of NADPH oxidase expression in endothelial cells of HFpEF patients and rats but not cardiomyocytes. This is in line with the hypothesis that endothelial activation is responsible for myocardial remodeling in HFpEF, in contrast to cardiomyocyte cell death in HFrEF. Thirdly, in HFpEF patients and HFpEF rats there was uncoupling of endothelial nitric oxide synthase, leading to reduced nitric oxide production and downstream cGMP and PKG effects as described above and shown in prior work from the group [32].

Interestingly, in the setting of hypertensive heart disease, it may be that a 'second hit' triggers HFpEF; that is, a concomitant metabolic comorbidity (such as diabetes mellitus) is superimposed on hypertension to produce the syndrome of HFpEF. Indeed, compared with patients with aortic stenosis without diabetes mellitus, patients with diabetes mellitus were more likely to have more myocardial fibrosis, increased advanced glycation end product deposition in the intramyocardial vasculature and higher cardiomyocyte resting tension [33], resulting in greater disposition to HFpEF in the diabetic patients. This suggests that diabetes acted as a metabolic trigger in addition to the pressure overload state to

produce HFpEF. However, hypertension alone may also be associated with oxidative stress and inflammation, and very recent evidence suggests that this predisposition may be related to genetic factors. Fazakas *et al.* [34▪] showed that the genetic predisposition to oxidative stress in the setting of hypertension was associated with HFpEF. They determined a genetic score from the prevalence of six single nucleotide polymorphisms of genes encoding enzymes related to various components of oxidative stress. Using 94 60-year-old or older patients with hypertension and 18 age-matched controls with normal ejection fraction, they report that a high genetic risk score for oxidative stress was significantly associated with diastolic dysfunction.

BEYOND FIBROSIS: ROLE OF TITIN

Titin is a giant myofilament protein that functions as a complex spring and is responsible for cardiomyocyte passive tension. Multiple experiments have shown that other than collagen, titin is also associated with the myocardial stiffness that is fundamental in the pathophysiology of HFpEF [35,36]. Importantly, the relative contribution of collagen versus titin changes was recently correlated to myocardial stiffness measured directly in left ventricular myocardial strips from patients with HFpEF: Zile *et al.* [37▪▪] elegantly demonstrated that *both* components are important: collagen accounted for a larger proportion of left ventricular stiffness at longer sarcomere lengths, and titin for a larger proportion of left ventricular stiffness at shorter sarcomere lengths. The investigators also detailed the type of titin modification responsible for increased left ventricular stiffness: titin modifications may include change in the titin isoform (N2BA versus N2B isoforms) or change in phosphorylation status at various sites of titin. Compared with hypertensive patients without heart failure and controls without hypertension, patients with hypertensive HFpEF had increased titin phosphorylation on a protein kinase C site in the PEVK element and decreased phosphorylation of a protein kinase A/protein kinase G site in the N2B element. In contrast to Van Heerebeek *et al.* [32] and Borbely *et al.* [38], Zile *et al.* found no differences in the N2BA/N2B titin ratio in HFpEF. The varying results were postulated to be related to differences in disease severity, with more advanced stages of HFpEF included in the former studies compared with the latter.

BEYOND QUANTITY OF COLLAGEN: QUALITY OF COLLAGEN DEPOSITION

In the same study, Zile *et al.* [37▪▪] also showed that the increased collagen-dependent stiffness found in HFpEF patients correlated with an increase in total and *insoluble* collagen in the group, whereas the soluble collagen levels were similar in all three groups. Insoluble collagen, but not soluble collagen, was therefore deemed to be the culprit for myocardial stiffness. These were insoluble fibers with increased thickness, formed when collagen fibrils were covalently linked together by the enzyme lysyl oxidase in the process called collagen cross-linking (CCL). More recently, López *et al.* [39▪] went on to show that excessive myocardial CCL, determined as the ratio between insoluble and soluble collagen in endomyocardial biopsies of 38 patients with hypertensive heart failure, was increased in patients compared with controls, and associated with higher risk of subsequent hospitalization for heart failure.

CLINICAL IMPLICATIONS

Contemporary guideline recommendations for the management of HFpEF have been largely confined to the use of diuretics for symptom relief and treatment of comorbidities [4]. Large phase III HFpEF clinical trials looking at rennin–angiotensin–aldosterone system inhibition have failed to demonstrate reduction in cardiovascular events in HFpEF [40▪], and reasons for this have been discussed in recent reviews [41,42]. New drugs that may boost myocardial cGMP offer hope [43▪], and include a long-acting phosphodiesterase-5 inhibitor Udenafil (phase III ULTIMATE-HFpEF Trial; ClinicalTrials.gov Identifier: NCT01599117), a soluble guanylate cyclase stimulator Vericiguat (phase IIb SOCRATES-PRESERVED trial; ClinicalTrials.gov Identifier: NCT101951638), and an angiotensin receptor-neprilysin inhibitor LCZ 696 (phase III PARAGON-heart failure trial; ClinicalTrials.gov Identifier: NCT01920711). Particularly in the setting of hypertensive HFpEF, nonpharmacological interventions deserve mention: in a small study of 13 hypertensive patients with HFpEF, the sodium restricted Dietary Approaches to Stop Hypertension diet was associated with favorable changes in left ventricular diastolic function, arterial elastance, and ventricular–arterial coupling [44], as well as altered metabolic profile with improved energy substrate utilization [45]. A larger randomized controlled trial, involving 100 obese and predominantly hypertensive older patients with HFpEF, demonstrated that low calorie diet and aerobic exercise training improved exercise capacity with increased peak oxygen consumption [46]. The potential mechanisms underlying the beneficial effects of healthy diet and exercise in HFpEF may be because of reduced inflammation, enhanced mitochondrial function, attenuated reactive oxygen species generation, increased

nitric oxide bioavailability, and improved microvascular function [46].

CONCLUSIONS

Hypertension is the commonest risk factor for the development of HFpEF. Recent work has provided valuable insights into the mechanisms underlying the transition from hypertension to HFpEF, showing that the pathophysiology extends beyond left ventricular hypertrophy and diastolic dysfunction to myocardial contractile dysfunction, beyond left atrial structural dilatation to left atrial functional decline, beyond macrovascular stiffening to microvascular dysfunction, beyond central cardiac triggers to systemic endothelial inflammation, beyond fibrosis to titin changes, and beyond collagen deposition to qualitative changes in collagen. Such understanding importantly offers new therapeutic opportunities beyond reduction of blood pressure.

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Conflicts of interest

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