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TOPICAL REVIEW

Insights into the pulmonary vascular complications of heart failure with preserved ejection fraction

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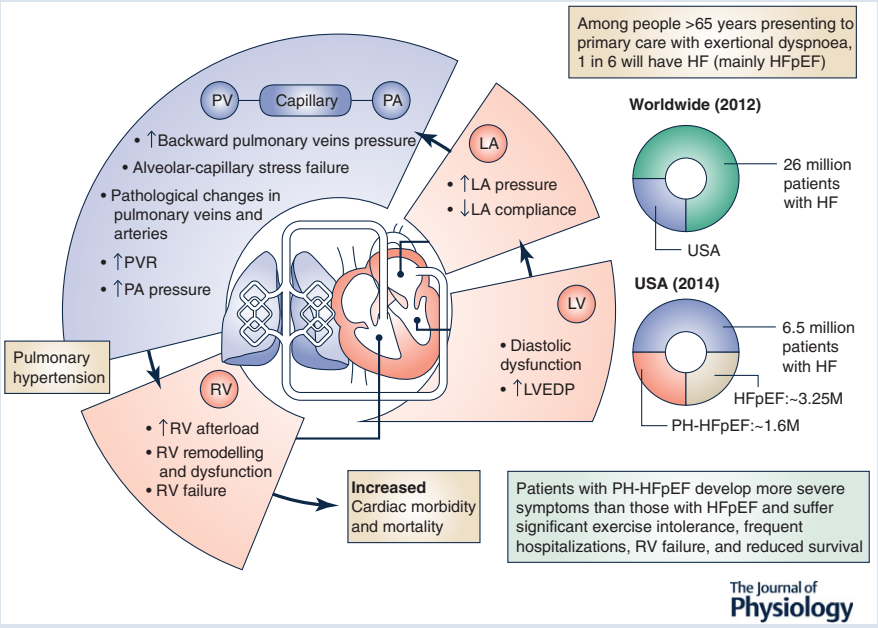

Abstract Pulmonary hypertension in the setting of heart failure with preserved ejection fraction (PH-HFpEF) is a growing public health problem that is increasing in prevalence. While PH-HFpEF is defined by a high mean pulmonary artery pressure, high left ventricular end-diastolic pressure and a normal ejection fraction, some HFpEF patients develop PH in the presence of pulmonary

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vascular remodelling with a high transpulmonary pressure gradient or pulmonary vascular resistance. Ageing, increased left atrial pressure and stiffness, mitral regurgitation, as well as features of metabolic syndrome, which include obesity, diabetes and hypertension, are recognized as risk factors for PH-HFpEF. Qualitative studies have documented that patients with PH-HFpEF develop more severe symptoms than those with HFpEF and are associated with more significant exercise intolerance, frequent hospitalizations, right heart failure and reduced survival. Currently, there are no effective therapies for PH-HFpEF, although a number of candidate drugs are being evaluated, including soluble guanylate cyclase stimulators, phosphodiesterase type 5 inhibitors, sodium nitrite and endothelin receptor antagonists. In this review we attempt to provide an updated overview of recent findings pertaining to the pulmonary vascular complications in HFpEF in terms of clinical definitions, epidemiology and pathophysiology. Mechanisms leading to pulmonary vascular remodelling in HFpEF, a summary of pre-clinical models of HFpEF and PH-HFpEF, and new candidate therapeutic strategies for the treatment of PH-HFpEF are summarized.

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Abstract figure legend Prevalence and pathophysiology of pulmonary hypertension (PH) in patients with heart failure with preserved ejection fraction (HFpEF). LA, left atrium; LV, left ventricle; LVEDP, left ventricular end-diastolic pressure; PA, pulmonary artery/arterial; PV, pulmonary vein; PVR, pulmonary vascular resistance; RV, right ventricle.

Pulmonary hypertension (PH) due to left heart disease (LHD) is the most frequent form of PH and is a growing public health problem with associated high morbidity and mortality (Vachiery *et al.* 2013). PH-LHD was originally classified under category 2 (pulmonary venous hypertension) with predominant cause of left-sided valvular or myocardial diseases by the World Health Organization (WHO) in 1998. During the Fifth World Symposium on Pulmonary Hypertension held in Nice, France in 2013, the classification was updated and the subcategories of Group 2 PH/PH-LHD were classified into four distinct aetiologies: left ventricular (LV) systolic dysfunction, LV diastolic dysfunction, valvular disease, and congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies (Simonneau *et al.* 2013). Most recently, the 2015 European Society of Cardiology (ESC) and the European Respiratory society (ERS) guidelines further expanded the definitions to include congenital/acquired pulmonary vein stenosis in Group 2 PH (Galie *et al.* 2016*a*). Among all of these LHD endophenotypes, PH attributable to LV diastolic dysfunction, also referred to as PH associated with heart failure with preserved ejection fraction (PH-HFpEF), is clearly the most common (Willens & Kessler, 1993; Lam *et al.* 2009). Although the true prevalence of PH-HFpEF remains unknown due to a general lack of standardization in study design (mostly retrospective and single centre), with accompanying variation in the definitions and diagnostic methods used (most data are based on echocardiography estimation rather than invasive haemodynamic measurement with right heart catheterization), the range in the reported prevalence of PH is between 23% and 83% of patients with HFpEF (see recent reviews for detailed information: Vachiery *et al.* 2013; Guha *et al.* 2016; Levine *et al.* 2018).

Qualitative studies have documented that patients with PH-HFpEF develop more severe symptoms than those with HFpEF and suffer significant exercise intolerance, frequent hospitalizations, right ventricular (RV) failure and reduced survival (Guazzi, 2014; Mohammed *et al.* 2014; Dalos *et al.* 2016; Gorter *et al.* 2016, 2018*b*; Santas *et al.* 2017; Vanderpool *et al.* 2018). Despite increasing interest and a growing number of related publications, no approved specific medication or consensus therapeutic strategy for PH-HFpEF is available at present, mainly due to significant gaps in understanding of the pathophysiological processes and parameters that can help to accurately define PH-HFpEF, as well as the complex associated comorbidities seen with HFpEF in general (metabolic syndrome, renal dysfunction, advancing age, etc.). In this review, we aim to provide an updated overview of the pulmonary vascular complications in HFpEF in terms of clinical definitions, epidemiology and pathophysiology. Mechanisms leading to pulmonary vascular remodelling in HFpEF, as well as pre-clinical models which aid evaluation of the putative therapeutic strategies for the treatment of PH-HFpEF, will also be discussed.

Definitions, classification of subtypes and diagnostic factors of PH-HFpEF

One-half of approximately 6.5 million heart failure patients >20 years of age in the USA are estimated to

suffer from HFpEF (Benjamin *et al.* 2017). Roughly half of these patients (a wide range from 23 to 83%, depending on the definitions employed) have associated high pulmonary artery pressures (i.e. PH), imposing an economic burden of about $7.7 billion per annum (Farr *et al.* 2016; Savarese & Lund, 2017).

Evaluation of a patient with suspected PH in HFpEF requires comprehensive clinical, echocardiographic and haemodynamic assessments. Exertional dyspnoea and exercise intolerance are the most common symptoms in HFpEF patients and, together with orthopnoea and paroxysmal nocturnal dyspnoea, are often the first clues to the presence of PH. Individuals with PH-HFpEF are often elderly, female and more likely to present with multiple comorbidities, including obesity, diabetes mellitus, hypertension, renal dysfunction, coronary artery disease and atrial fibrillation. Findings from physical examination may reveal signs of fluid retention (e.g. peripheral oedema, ascites and crackles) and cardiac examination will reveal the presence of an S3 heart sound. Additionally, chest X-ray may show pulmonary vascular congestion, pleural effusion and pulmonary oedema. Screening echocardiography often reveals evidence of left atrial enlargement, LV hypertrophy, right atrial enlargement, LV diastolic dysfunction (e.g. abnormal LV relaxation, filling, dispensability or diastolic stiffness), and preserved LV systolic function (e.g. LV ejection fraction $\geq$50% and indexed LV end-diastolic volume $<$97 mL/m^2) (Rich & Rabinovitch, 2008; Guazzi & Borlaug, 2012; Perez *et al.* 2012). Although mean pulmonary artery pressure (mPAP) can be estimated by echocardiography based on tricuspid regurgitant jet velocity, the accuracy of this is low. Thus, despite echocardiography being a good screening tool, it should never be used to establish a diagnosis of PH-HFpEF without proceeding with a right heart catheterization (Lai *et al.* 2014). Diagnosis of PH-HFpEF is typically confirmed when the mPAP exceeds 25 mmHg and when pulmonary arterial wedge pressure (PAWP; also called pulmonary capillary wedge pressure (PCWP) or pulmonary artery occlusion pressure (PAOP)) is greater than 15 mmHg at rest (Fig. 1). It is important to note that PAWP should be measured at end-expiration to minimize respiratory pressure swings. If there is further concern for coronary disease or discrepancy from previous right heart catheterization, left ventricular end-diastolic pressure (LVEDP) can be measured directly by left heart catheterization (Lai *et al.* 2014). Elevated plasma levels of brain natriuretic peptide (BNP) (BNP $\geq$35 pg/mL and/or N-terminal prohormone of BNP (NT-proBNP) $\geq$125 pg/mL) are also frequently detected in patients with PH-HFpEF. Increased LA volume and higher pulmonary artery-to-aorta ratio measured by

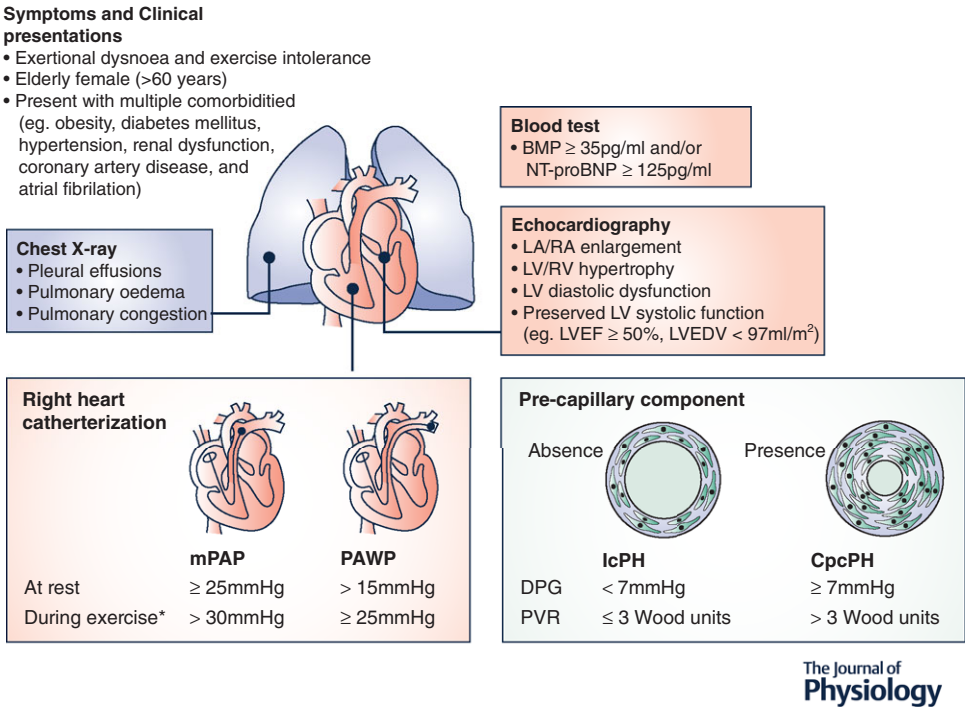

Figure 1. Classification of subtypes and diagnostic factors of PH-HFpEF
CpcPH, combined post-capillary and pre-capillary pulmonary hypertension; DPG, diastolic pressure gradient (defined as diastolic pulmonary artery pressure – PAWP); IpcPH, isolated post-capillary pulmonary hypertension; LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RA, right atrium; RV, right ventricle.

cardiac magnetic resonance, as well as higher size ratio of left atrium to right atrium measured by non-gated CT angiography (CTA), may be additional diagnostic features for identifying patients with PH-HFpEF, although none of these have been sufficiently validated (Crawley *et al.* 2013; Karakus *et al.* 2015; Huis In 't Veld *et al.* 2016). As atrial fibrillation was observed in more than 65% of HFpEF patients and was correlated with right ventricular dysfunction in patients with HFpEF, (Zakeri *et al.* 2013; Melenovsky *et al.* 2014; Lam *et al.* 2017; Sartipy *et al.* 2017), it is not surprising that the presence of atrial fibrillation was reported in 28–48% of patients with PH-HFpEF (Salamon *et al.* 2014; Berthelot *et al.* 2017). Nonetheless, future studies are needed to determine whether the presence of atrial fibrillation can be employed as a diagnostic factor for PH-HFpEF.

While most PH diagnoses rely on resting haemodynamics, HFpEF patients experience worsening symptoms indicative of PH more often during exercise due to a number of impairments in cardiovascular reserve function and skeletal muscle vasodilatory reserve with exercise. The use of exercise stress testing has been increasingly recognized as a valuable tool for the reproduction of symptoms and early diagnosis of PH-HFpEF, especially in patients with unexplained exertional symptoms and normal resting haemodynamics or in patients with intermediate probability of PH-HFpEF (Borlaug *et al.* 2010; Borlaug *et al.* 2011; Obokata *et al.* 2018). The type of exercise stress testing can vary widely and may include the six-minute walk test (6MWT), cardiopulmonary exercise testing (CPET) and CPET combined with echocardiography and/or both right and left heart catheterization. Standard/non-invasive CPET records parameters such as oxygen uptake ($\dot{V}_{O_2}$), carbon dioxide production ($\dot{V}_{CO_2}$) and minute ventilation ($\dot{V}_E$) during exercise, which can aid in diagnosis and risk stratification of PH-HFpEF as very low upright $\dot{V}_{O_2}$ at peak exercise ($<$14 mL/kg/min) and increased $\dot{V}_E/\dot{V}_{CO_2}$ slope ($</\geq$36), have been reported in patients with PH-HFpEF (Borlaug *et al.* 2010; Guazzi *et al.* 2013*b*; Reddy *et al.* 2018). Using invasive CPET, a mPAP cut-off value of $>$30 mmHg at a cardiac output (CO) $<$10 L/min or a total pulmonary resistance (defined as mPAP/CO) $>$3 Wood units and a PAWP cut-off value of $\geq$25 mmHg during exercise have been proposed for the diagnosis of PH in patients with HFpEF (Fig. 1) (Borlaug *et al.* 2010; Lewis *et al.* 2013; Maor *et al.* 2015). In a recent study by Obokata *et al.*, which employed a simultaneous use of non-invasive and invasive CPET, it was shown that increased left heart filling pressure and pulmonary artery pressure during exercise directly correlated with reduced exercise capacity, increased ventilatory drive, severity of dyspnoea, altered breathing patterns, lower RV systolic function, and worse functional class (Obokata *et al.* 2018). These data reveal a new insight into the connection between haemodynamic derangements, clinical symptoms and gas exchange alterations in patients with PH-HFpEF. Additionally, limited data suggest that a PAWP cut-off value of 18 mmHg after fluid challenge with 7 mL/kg saline may be useful for the diagnosis of patients with post-capillary PH. Although the use of exercise exposure was suggested for detection of diastolic dysfunction in the current guidelines for the diagnosis and treatment of heart failure, the current guidelines for the diagnosis and treatment of pulmonary hypertension recommend against the use of these stress-inducing measures due to insufficient validation and lack of standardized protocols (Borlaug *et al.* 2010; Robbins *et al.* 2014; Ponikowski *et al.* 2016; Galie *et al.* 2016*b*; D'Alto *et al.* 2017; Obokata *et al.* 2018).

Still, these definitions do not account for the presence or absence of progressive pulmonary vascular remodelling (also known as the pre-capillary component) associated with the development of PH in patients with HFpEF. Depending on the extent of the pre-capillary component, the backward transmission of the elevated LV filling pressure can lead to an increase in pulmonary artery pressure passively (1:1 ratio) or disproportionately ($>$1:1 ratio). Patients with no significant pulmonary vasoconstriction or pre-capillary component often exhibit passive/proportional PH (now termed isolated post-capillary PH, IpcPH) and are responsive to medications which lower their PAWP, such as diuretics, nitroprusside and other systemic blood pressure control drug. If, on the other hand, chronically elevated LV filling pressure triggers pulmonary vasoconstriction and pathological pre-capillary remodelling to a point of having increased pulmonary vascular resistance (PVR, defined as transpulmonary gradient (TPG)/CO) and high TPG (where TPG is defined as mPAP $-$ PAWP), patients exhibit out of proportion PH (now termed combined pre-capillary and post-capillary PH, CpcPH). While increased PVR ($>$3 Wood units) and high TPG ($>$12 mmHg) are commonly used to differentiate patients with CpcPH from IpcPH (PVR $<$3 Wood units and TPG $\leq$12 mmHg), these parameters may not accurately reflect the presence of the pre-capillary component for their interdependence on CO and PAWP (Galie *et al.* 2009; Task Force for *et al.* 2009). As diastolic pressure gradient (DPG, defined as diastolic PAP $-$ PAWP) is independent of pulmonary blood flow and is not influenced by PAWP, a new haemodynamic definition for distinguishing CpcPH from IpcPH was proposed based on elevated DPG ($\geq$7 mmHg) during the Fifth World Symposium on PH (Stevens, 1975; Buchbinder & Ganz, 1976; Chemla *et al.* 2002; Gerges *et al.* 2013; Vachiery *et al.* 2013). Beyond diagnosis, recent reports also showed the prognostic value of DPG, as elevated DPG was associated with increased mortality and poor long-term outcomes (Gerges *et al.* 2013; Ibe *et al.* 2016). In accord with this, a large retrospective

cohort study (Pittsburgh cohort, single centre with 10,023 subjects undergoing right heart catheterization during 2005–2012) revealed that multiple haemodynamic definitions of the pre-capillary component (elevated DPG, PVR and TPG) all independently predicted mortality and cardiac hospitalizations in patients with CpcPH-HFpEF (Vanderpool *et al.* 2018). This study found that TPG >12 mmHg (an easily obtained measure) captures more patients as having CpcPH and independently predicts hospitalization and increased mortality in patients with HFpEF. Furthermore, this study suggested that DPG measurement can lead to underestimation of CpcPH based on artefactual negative DPG values.

There is an increasing controversy regarding the use of DPG, as several retrospective studies have shown that DPG does not have predictive ability for survival and outcomes (Tedford *et al.* 2014; Brittain *et al.* 2015; Tampakakis *et al.* 2015; Adir *et al.* 2017). As mentioned above, another apparent major problem with using DPG comes from the reliability of its measurement, since even small errors in obtaining diastolic PAP (e.g. negative values caused by catheter 'whip', high frequency noise, excessive respiratory variation, and/or inadequate calibration) and PAWP (e.g. inaccurate wedging or large V-waves) may significantly impact DPG, given its relatively low absolute value (Tampakakis *et al.* 2015; Nagy *et al.* 2017). While further research is needed to determine whether or not haemodynamic definition by DPG is clinically meaningful, the current guidelines included both PVR and DPG, and redefined IpcPH as DPG <7 mmHg and/or PVR ≤3 Wood units and CpcPH as DPG ≥7 mmHg and/or PVR >3 Wood units (Fig. 1) (Galie *et al.* 2016*b*).

Chronic elevation in LV filling pressure and the progressive pulmonary vascular remodelling leads to reduced pulmonary artery compliance (PAC, defined as stroke volume/pulmonary artery pulse pressure), resulting in RV contractile impairment, increased pulsatile RV afterload, and eventually right heart failure. Within this context, PAC has been proposed as a new haemodynamic marker for diagnosis and prognosis of CpcPH-HFpEF (Al-Naamani *et al.* 2015; Dragu *et al.* 2015; Sugimoto *et al.* 2016). Of note, PAC was found as the strongest predictor of mortality, compared to DPG, PVR and TPG, with low PAC (<1.1 mL/mmHg) associated with nearly a fivefold increased risk of death in patients with PH-HFpEF in a recent study (Al-Naamani *et al.* 2015). Additionally, index of RV contractile function and its coupling with pulmonary circulation (RV-PC coupling), such as measurements of the ratio between end-systolic elastance (E_{es}) and arterial elastance (E_a), as well as the ratio between tricuspid annular plane systolic excursion (TAPSE) and pulmonary artery systolic pressure (PASP), were found useful for stratifying clinical phenotypes and predicting outcomes of patients with CpcPH-HFpEF. For instance, Gauzzi *et al.* showed that depressed TAPSE/PASP ratio predicts CpcPH-HFpEF and a TAPSE/PASP cut-off ratio of <0.36 is associated with worse prognosis. Gerges *et al.* also reported that poor RV-PC coupling is associated with reduced survival (Guazzi *et al.* 2013*a*, 2017; Gerges *et al.* 2015; Gorter *et al.* 2018*a*). Most recently, Gorter *et al.* showed that CpcPH-HFpEF patients display greater reduction in PA compliance associated with higher PVR and E_a during exercise due to impaired RV contractile reserve, suggesting that measurement of these exercise haemodynamic parameters is important for identifying CpcPH-HFpEF patients (Gorter *et al.* 2018*a*). This study also provides new evidence that RV function and functional preserve may be potential therapeutic targets for management of CpcPH-HFpEF in the future (Gorter *et al.* 2018*a*). The use of PAC, E_{es}/E_a and TAPSE/PASP, either at rest or during exercise, is undergoing validation for clinical utility at this time.

How common is CpcPH-HFpEF?

Data from several recent catheter-based studies are available, although varying definitions are being used. In a large retrospective University of Pittsburgh Medical Center (UPMC) cohort, the prevalence of a high DPG, PVR and TPG was evaluated in patients with HFpEF who had a mean PAP ≥25 mmHg. In this study the prevalence of DPG ≥7 mmHg, PVR ≥3 Wood units and TPG >12 mmHg in 2587 patients with PH-HFpEF was 13.7%, 34.2% and 48.9%, respectively (Vanderpool *et al.* 2018). In Austria, retrospective and prospective studies found CpcPH (DPG ≥7 mmHg) in 22.6% and 18.8% of 217 and 138 patients with PH-HFpEF, respectively (Gerges *et al.* 2015). A recent study with the combined Northwestern/San Paolo cohort, CpcPH (DPG ≥7 mmHg) was met by 10% of 219 patients with HFpEF (Guazzi *et al.* 2017). For a smaller sample size, a recent multicentre retrospective study across Italy and Israel found CpcPH (DPG ≥7 mmHg) in 38% of 86 patients with PH-HFpEF (Adir *et al.* 2017). In addition, a prospective cohort at Tufts Medical Center found that 36% of 73 patients with PH-HFpEF met the CpcPH definition of a DPG ≥7 mmHg (Al-Naamani *et al.* 2015).

Regardless of whether LVEF is preserved or reduced, the prevalence of CpcPH in patients with left heart disease in the UPMC cohort was 11.7%, 36.2% and 45.9%, based on DPG (≥7 mmHg), PVR (≥3 Wood units) and TPG (>12 mmHg), respectively (Vanderpool *et al.* 2018). CpcPH (DPG ≥7 mmHg) was also noted in 13% of patients with left heart disease in a Johns Hopkins cohort and 13% of patients with PH in a Vanderbilt cohort (Tampakakis *et al.* 2015; Assad *et al.* 2016; Vanderpool *et al.* 2018). In cohorts from Austria and the Netherlands, CpcPH (DPG ≥7 mmHg) was noted

in 12% of patients with heart failure and in 24.7% of patients with PH, respectively (Gerges *et al.* 2015; Gorter *et al.* 2018*b*). In Japan, 3% of heart failure patients met the CpcPH definition of a DPG ≥7 mmHg (Ibe *et al.* 2016). Accordingly, if heart failure affects approximately 6.5 million patients in the USA, then roughly 0.4 million (ranging between 0.2 and 0.6 million) of those patients are estimated to suffer from CpcPH-HFpEF.

What causes pulmonary vascular complications in HFpEF?

The left ventricle is designed to be filled with and to eject blood against the high-resistance systemic circulation, producing adequate cardiac output of 4–6 L of blood per minute to provide oxygen to the entire body. Each single beat of the heart consists of two major components, diastole, the period of LV relaxation and filling, and systole, the period of LV ejection. In a healthy heart, 75–90% of LV filling occurs during early diastole, and the remainder of LV filling occurs during late diastole when there is atrial contraction. The healthy left ventricle can effectively pull in blood to an adequate preload volume (EDV) at a normal filling pressure, but in patients with HFpEF, due to abnormal active relaxation and increased passive stiffness of the left ventricle, normal cardiac filling and output can only be achieved by a compensatory elevation in filling pressure within the left ventricle and a high LA pressure to push blood into the chamber. In this setting, increased LA pressure can then back up into the pulmonary circulation, leading to increased pulmonary venous pressure, which is in turn transferred to pulmonary capillaries, causing damage to the alveolar–capillary barrier (also known as alveolar–capillary stress failure) (West & Mathieu-Costello, 1995). The alveolar–capillary barrier of the human lung is extremely thin to allow rapid gas exchange by passive diffusion. It consists of three layers, the capillary endothelium, the extracellular matrix (interstitial space) and the alveolar epithelium, with sufficient strength to maintain its integrity and to limit fluid leak into the interstitial space and alveolus. Normally, the endothelial permeability within the alveolar–capillary barrier is very low (approximately 4 times less than pulmonary veins or arteries) with low intracellular Ca^{2+} levels to keep the interendothelial junctions closed, and fluid is continuously cleared from the alveolar surface by Na^+ transport through the epithelial sodium channel (ENaC) and the Na^+/K^+-ATPase (see reviews in depth by Sukriti *et al.* 2014; Huppert & Matthay, 2017). Pressure-induced elevation of intracellular calcium-mediated endothelial retraction, activation of the calcium-permeable transient receptor potential vanilloid 4 (TRPV4) channels, and impaired resorption of alveolar fluid by ENaC are apparently involved in disruption of the integrity of the alveolar–capillary unit, characterized by increased capillary permeability, fluid filtration into interstitial space and reduced fluid removal from the alveolar surface. This leads to pulmonary oedema, which impairs gas exchange and leads to hypoxaemia and dyspnoea. When elevation in filling pressures is sustained, the alveolar–capillary membrane can undergo a compensatory remodelling process characterized by increased extracellular matrix thickening and proliferation, which, along with increased fluid storage/clearance, protect against pulmonary oedema in patients with chronic heart failure (Dixon *et al.* 2013). However, over time, excessive extracellular matrix remodelling, inflammation, endothelial dysfunction, myofibroblasts proliferation and alveolar fluid reabsorption contribute to a persistent decrease in capillary–alveolar membrane conductance and gas exchange, ultimately leading to further dyspnoea with even mild exertion (see reviews in depth by Dayeh *et al.* 2016; Guazzi & Naeije, 2017). In fact, a low diffusion capacity for carbon monoxide (DLCO) of <45% has been found even at rest in nearly half of the patients with PH-HFpEF (Hoeper *et al.* 2016). As disease progresses further, structural and functional changes regulated by chronic elevation in capillary pressure also trigger vasoconstriction and promote remodelling in the pulmonary arteries and veins, with various combinations of intimal proliferation, medial hypertrophy and adventitial thickening (Delgado *et al.* 2005; Rich & Rabinovitch, 2008; Chen *et al.* 2012; Hunt *et al.* 2013; Lai *et al.* 2016; Guazzi & Naeije, 2017; Fayyaz *et al.* 2018). Particularly noteworthy, using urokinase plasminogen activator receptor (uPAR) as an anatomical venous marker, a recent study found that intima, media and adventitia in veins and arteries were significantly remodelled to similar degrees in patients with PH-LHD and in rats with aortic banding (Hunt *et al.* 2013). Additionally, medial hypertrophy of muscular pulmonary arteries appears to be the most common pathological finding in patients with at-risk PH-LHD. The greater medial hypertrophy is correlated with higher pulmonary pressure (Delgado *et al.* 2005). It is also noted that pulmonary arterial intimal remodelling is the least common pathological feature and has the weakest correlation with PH severity (Lai *et al.* 2016; Fayyaz *et al.* 2018). In a recent study, venous and small vessel intimal thickening were found to be more severe than arterial intimal thickening in patients with PH-HFpEF (Fayyaz *et al.* 2018). Collectively, the above attributes describe the patients with CpcPH-HFpEF – patients whose PH involves remodelling of alveolar–capillary and pre-capillary small pulmonary arteries in addition to the passive increase in pulmonary artery pressure. This is in contrast to the patients with IpcPH-HFpEF, whose PH simply rises passively in response to the increase in filling pressure without significant small pulmonary artery remodelling (Fig. 2).

Animal models of PH-HFpEF

At present, the management of PH-HFpEF is mostly based on the treatment and relief of the underlying HFpEF. While current guidelines recommend management of optimal volume and cardiac filling pressure with diuretics and systemic blood pressure control, no specific therapies are available for reducing mortality and hospitalization in patients with PH-HFpEF. Thus, there is an important unmet need for developing and using animal models to explore potential mechanisms and new treatment options for this disease. Current animal models of PH-HFpEF are adopted from HFpEF models or are developed based on pathophysiological features, comorbidities and other confounding factors, including cardiac pressure overload models, obesity and diabetes models, metabolic syndrome models and models that combine all attributes. Aortic banding, either transverse aortic constriction or supracoronary aortic banding, is the most common and successful surgical model for pressure overload-induced cardiac hypertrophy and HFpEF (Rockman *et al.* 1991; Litwin *et al.* 1995). Aortic-banded mice and rats were found to develop PH, which was evident from increased lung weight, pulmonary fibrosis and remodelling, elevated pulmonary artery pressure and RV hypertrophy (Dai *et al.* 2004; Chen *et al.* 2012; Hunt *et al.* 2013; Lu *et al.* 2016). In addition, elevated NT-proBNP plasma levels, alveolar–capillary wall thickening and perivascular fluid cuff formation along extra-alveolar vessels were observed in a recently established aortic-banded cat model of PH-HFpEF (Wallner *et al.* 2017). However, aortic banding models cause acute and severe pressure overload compared to the chronic process observed in the human disease. The Dahl salt-sensitive rat, which is hypersensitivity to sodium intake, is another commonly used model for HFpEF-based studies. When fed with a high-salt diet (8% NaCl in most studies) from the age of 7–9 weeks, Dahl salt-sensitive rats exhibit progressive LV concentric hypertrophy, diastolic dysfunction, preserved LVEF and renal failure at the age of 12 weeks (Doi *et al.* 2000; Klotz *et al.* 2006; Lee *et al.* 2017). Pulmonary oedema and pulmonary vein fibrosis have also been observed in this model, but no catheter-based haemodynamics have been reported (Doi *et al.* 2000; Nishi *et al.* 2006; Iwasaki *et al.* 2016).

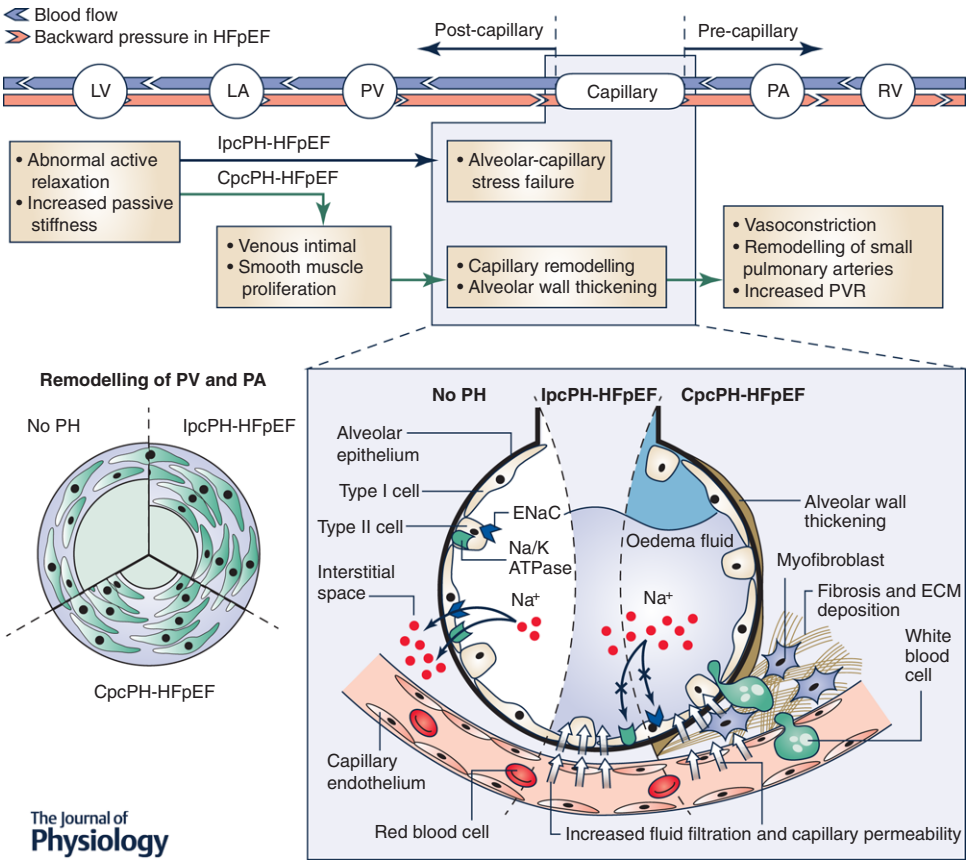

Figure 2. Pulmonary vascular complications in HFpEF
ENaC, epithelial sodium channel; LA, left atrium; LV, left ventricle; PA, pulmonary artery; PV, pulmonary vein; PVR, pulmonary vascular resistance; RV, right ventricle.

While some patients with HFpEF develop CpcPH-HFpE or IpcPH-HFpEF, it is noted that some patients never develop PH-HFpEF, suggesting that pathological changes of pulmonary capillaries and small arteries in response to increased filling pressure are not the only factors involved in the development of PH-HFpEF (Thenappan *et al.* 2011). Recent studies have found that features of metabolic syndrome, including obesity, diabetes, hyperglycaemia, insulin resistance, hypertension and coronary artery disease (CAD), may affect the development of PH in the setting of HFpEF (Oktay *et al.* 2013; Farr *et al.* 2016). In fact, the prevalence of metabolic syndrome is observed in more than 94% of patients with PH-HFpEF (Robbins *et al.* 2009). The mouse with leptin deficiency (*ob*/*ob*) is the most used obesity and diabetic animal model. In addition to evident diastolic dysfunction with impaired LV relaxation, *ob*/*ob* mice have been shown to exhibit macrophage infiltration, myofibroblast proliferation, pulmonary arterial remodelling and RV hypertrophy at the age of 12 weeks (Christoffersen *et al.* 2003; Van den Bergh *et al.* 2008; Aytekin *et al.* 2014). The high fat diet (HFD)-fed mouse is another commonly used model for obesity, impaired glucose tolerance, insulin resistance, type 2 diabetes and LV diastolic dysfunction. Komuro & Rosenzweig (1967) reported that combined HFD (2 g/kg of lanolin, composed of cholesterol and oxycholesterol) and pneumonectomy induced pulmonary hypertension and pulmonary atherosclerosis in rabbits. HFD treatment (60% lipids/kcal, ranging from 8–20 weeks) has also been shown to induce LV hypertrophy, increased LVEDP with preserved LVEF, pulmonary arterial remodelling, elevated pulmonary artery pressure and RV hypertrophy in the most widely used C57BL/6J mice and in apolipoprotein (apoE)-deficient mice (Hansmann *et al.* 2007; Kelley *et al.* 2014, 2017; Meng *et al.* 2017). Recently, Kelly *et al.* exposed 36 inbred and wild-derived mouse strains to 20 weeks of HFD and identified AKR/J as the strain most susceptible to HFD-induced PH-HFpEF (Kelly *et al.* 2017). Of note, the observed increase in severity of PH in HFD-exposed AKR/J mice (RV systolic pressure ∼37 mmHg) was close to that observed in patients with PH-HFpEF (RV systolic pressure range 46–51 mmHg). Interestingly, despite HFD-treated C57BL/6J and AKR/J mice developing a comparable degree of obesity, glucose intolerance and hyperglycaemia, changes in RVSP were moderate in C57BL/6J mice (Kelly *et al.* 2017; Meng *et al.* 2017). Kelly *et al.* also found that the NOD/ShiLtJ mouse, which develops autoimmune type 1 diabetes, was the most resistant strain to HFD-induced PH-HFpEF. In contrast, the NON/shiLtJ mouse, which is sensitive to HFD-induced type 2 diabetes, was highly susceptible to the development of PH-HFpEF, suggesting that type 2 diabetes may be an important pathophysiological abnormality potentially leading to the development of PH-HFpEF (Kelly *et al.* 2017; Meng *et al.* 2017).

Another recently discovered HFpEF model is the obese ZSF1 rat, which is generated by crossing lean female Zuker diabetic fatty rats (ZDF, +/*fa*) with lean male spontaneous hypertensive heart failure rats (SHHF, $+/fa^{cp}$) (Tofovic *et al.* 2000). At the age of 8 weeks, obese ZSF1 rats are diabetic with hyperglycaemia, dyslipidaemia and hypertension (Bilan *et al.* 2011). As disease progresses, obese ZSF1 rats show elevated LVEDP, preserved LVEF, LV hypertrophy, LA dilatation, increased cardiomyocyte stiffness, pulmonary congestion, effort impairment and signs of renal failure at age 20 weeks (Hamdani *et al.* 2013; Leite *et al.* 2015; Franssen *et al.* 2016; van Dijk *et al.* 2016). With the combined treatment of SU5416 (commonly known as Sugen), a vascular endothelial growth factor (VEGF) receptor blocker known to induce lung endothelial injury and apoptosis (Taraseviciene-Stewart *et al.* 2001), in 8-week-old obese ZSF1 rats for 14 weeks, the SU5416-exposed obese ZSF1 rats displayed PH-HFpEF characterized by elevated RV systolic pressure (∼38 mmHg) accompanied with increased PVR, pulmonary arterial remodelling and RV hypertrophy (Lai *et al.* 2016). Interestingly, a correlation between impaired glucose uptake by skeletal muscle and elevated pulmonary pressures was observed using this model (Lai *et al.* 2016), suggesting a broader set of mechanisms contributed by multiple organs may be involved in the regulation of PH-HFpEF. Additionally, several large animal models, such as aged dogs with renal wrapping-induced diastolic dysfunction, Ossabaw swine with metabolic syndrome and high fat/cholesterol diet-exposed diabetic pocrine, have demonstrated the role of ageing and metabolic syndrome in the development of HFpEF; however, their cardiopulmonary function and structure require future studies (Munagala *et al.* 2005; Trask *et al.* 2012; van den Heuvel *et al.* 2012).

Summary and future directions

While we still have no approved specific therapy or even a consensus treatment strategy at present for patients with PH in the setting of HFpEF, recent studies have advanced our knowledge and understanding in terms of more precise haemodynamic definitions, classification of subtypes, underlying pathophysiology, standardization of diagnosis and prognosis methodologies, as well as the development of new and relevant animal models. Although the search for effective therapies for PH-HFpEF remains challenging due to phenotypic heterogeneity of the disease, substantial efforts made by researchers over the years have helped to shape a consensus that targeted therapies to specific subtypes of PH-HFpEF may be essential for providing a significant positive impact on patient outcomes.

We would propose five major areas that could advance the field:

(1) Precision medicine targeting of the more severe CpcPH populations of HFpEF and HFrEF. Trials of PAH-specific drugs have consistently shown clearer therapeutic signals in the groups with higher PVR and lower LVEDP values. Efforts to move forward with drugs targeting the pulmonary vasculature should focus on tight management of left ventricular filling pressures with protocolized diuretic and systemic blood pressure control regimens while enriching the cohort for intervention with patients with high PVR, TPG or DPG values. Efforts to consider this group with CpcPH an 'orphan disease' population with the FDA seems appropriate and will advance the field, based on the cost and challenge of strict end-ophenotyping populations.
(2) Considering the use of provoked response as an end-point (e.g. exercise haemodynamics and capacity). While the use of haemodynamic exercise testing and/or fluid challenge are at present not included in the current recommended guidelines, more effort is required to assess whether the use of these methods can be valuable in future diagnostic and prognostic evaluations.
(3) Developing drugs that target the pulmonary vasculature and metabolic features of disease. New mechanism-based therapeutics should attempt to target the diverse phenotype of disease by improving metabolism and pulmonary vascular remodelling. Suggested models include AMPK and sirtuin activators based on metformin, perhaps in combination with pulmonary vasodilatory agents, similar to experiences with nitrite and metformin (Lai *et al.* 2016). Combination therapy targeting the pulmonary vasculature, metabolic syndrome and left ventricular relaxation may be required.
(4) Limiting the confounding effect of deconditioning. In our experience, our HFpEF patients are extremely sedentary and deconditioned. Simple participation in our trials increases their activity and confidence in ability to exercise, with observed effects that are much greater than the 'learning effect' observed with repeat six-minute walk testing. This creates background noise for any outcome measure based on exercise. We would propose lead-in cardiopulmonary rehabilitation prior to enrolment, similar to strategies that were shown effective with lung volume reduction surgery (Fishman *et al.* 2001, 2003).
(5) Continuing to advance development of robust and predictive pre-clinical models of HFpEF and PH-HFpEF. Ultimately, the field may be advanced by the discovery of molecular therapies that directly improve the diastolic function of the left ventricle at rest and during exercise or fluid challenge stress. It will be necessary to test these agents in appropriate models and then advance to the clinic in well-defined patient populations.

In conclusion, establishing a definitive consensus for haemodynamic phenotyping is still a critical first step in providing important new insights into this emerging disease and in driving the research field of PH-HFpEF forward. As individuals with phenotypic variations are noted to have different response to drug treatments, future trials with well-defined and carefully selected patient populations may help to identify the corresponding prevention and treatment strategies. Finally, referral to PH care centres is recommended for treatment of patients in an effort to optimize clinical decision making and potential outcome.

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Additional information

Competing interests

M.T.G. is a co-inventor on a National Institutes of Health government patent for the use of sodium nitrite for the treatment of cardiovascular diseases. The other authors report no competing interests.

Author contributions

All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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