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CURRENT OPINION

Pulmonary hypertension in heart failure with preserved ejection fraction: a plea for proper phenotyping and further research†

Marius M. Hoeper,[1]* Carolyn S.P. Lam,[2] Jean-Luc Vachiery,[3] Johann Bauersachs,[4] Christian Gerges,[5] Irene M. Lang,[5] Diana Bonderman,[5] Karen M. Olsson,[1] J. Simon R. Gibbs,[6] Peter Dorfmuller,[7] Marco Guazzi,[8] Nazzareno Galiè,[9] Alessandra Manes,[9] M. Louis Handoko,[10] Anton Vonk-Noordegraaf,[11] Mareike Lankeit,[12] Stavros Konstantinides,[13] Rolf Wachter,[14] Christian Opitz,[15] and Stephan Rosenkranz[16]

[1]Department of Respiratory Medicine and German Centre of Lung Research (DZL), Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany; [2]National Centre Singapore and Duke-National University of Singapore, 5 Hospital Dr, Singapore 16960; [3]Pulmonary Vascular Disease and Heart Failure Clinic, CUB Hopital Erasme, Route de Lennik 808, 1070 Brussels, Belgium; [4]Department of Cardiology and Angiology, Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany; [5]Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna, Spitalgasse 23, 1090 Vienna, Austria; [6]National Heart and Lung Institute, Imperial College, Sydney St, Chelsea, London SW3 6NP and National Pulmonary Hypertension Service, Hammersmith Hospital, Du Cane Rd, White City, London W12 0HS, United Kingdom; [7]Department of Pathology and INSERM UMR-S 999, Paris-South University, Marie Lannelongue Hospital, Le Plessis Robinson, 15 Rue Georges Clemenceau, 91400 Orsay, France; [8]Department of Cardiology, University of Milano, IRCCS Policlinico San Donato, Piazza Edmondo Malan, 1, 20097 San Donato Milanese, Milano, Italy; [9]Department of Experimental, Diagnostic and Speciality Medicine, Bologna University Hospital, Via Zamboni, 33, 40126 Bologna, Italy; [10]Department of Cardiology, VU University Medical Center, De Boelelaan 1117, 1081 Amsterdam, The Netherlands; [11]Department of Pneumology, VU University Medical Center, De Boelelaan 1117, 1081 Amsterdam, The Netherlands; [12]Department of Cardiology, Charité University Medicine Berlin, Campus Virchow Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany; [13]Centre for Thrombosis and Haemostasis, University Medical Centre Mainz, Langenbeckstraße 1, 55131 Mainz, Germany; and Department of Cardiology, Democritus University of Thrace, University Campus, 69100 Komotini, Alexandroupolis, Greece; [14]Department of Cardiology, University of Göttingen, and German Cardiovascular Research Center (DZHK), Robert-Koch-Str. 40, 37099 Göttingen, Germany; [15]Department of Cardiology, DRK-Kliniken Berlin, Spandauer Damm 130, 14050 Berlin Germany; and [16]Department of Cardiology and Cologne Cardiovascular Research Centre (CCRC), University of Cologne, Kerpener Strasse 62, 50937 Köln, Germany

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Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) is a common disease affecting the elderly in particular. Up to 80% of these patients develop pulmonary hypertension (PH), which is associated with worse symptoms and increased mortality.[1] It is a matter of concern that drugs approved for pulmonary arterial hypertension (PAH) are sometimes used in such patients despite insufficient data for their safety and efficacy. On the other hand, the impact of PH and right ventricular (RV) dysfunction on morbidity and mortality in HFpEF call for proper attention both at the clinical and scientific level. Here we discuss the clinical problem, pathophysiology, diagnostic shortfalls, gaps in evidence, and future strategies for PH-HFpEF.

Epidemiology, natural history, and diagnosis of HFpEF

HFpEF is currently the dominant form of HF in aging societies globally. Epidemiologic trends over the past two decades showed that HFpEF increased relative to HF with reduced ejection fraction (HFrEF).[2] Overall mortality did not improve over time, with more than 50% dead in 5 years from diagnosis.[2]

Differences between epidemiologic and trial populations of HFpEF reflect potential selection bias and lack of uniformity of diagnostic criteria. Epidemiologic studies utilize the most widely applicable definition of HFpEF: (i) clinically diagnosed HF (e.g. by Framingham criteria) and (ii) preserved EF (e.g. ≥50%).[2] While such definitions capture the broad unselected population with the syndrome of HFpEF, they are rarely

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* Corresponding author. Tel: +49 511 532 3530, Fax: +49 511 532 8536, Email: hoeper.marius@mh-hannover.de

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specific enough for clinical trials since the accurate diagnosis relies on symptoms and signs of HFpEF, both non-discriminating particularly in elderly patients with multiple comorbidities. The ESC guidelines included additional criteria, i.e. elevated levels of natriuretic peptides or objective evidence of left ventricular (LV) hypertrophy, left atrial enlargement, and/or LV diastolic dysfunction.[3] Yet, the diagnosis of HFpEF remains difficult as many presumably healthy elderly patients fulfil at least some of these echocardiographic criteria. Invasive demonstration of increased pulmonary arterial wedge pressure (PAWP) or LV end-diastolic pressure (LVEDP), abnormal LV relaxation, and increased LV diastolic stiffness support the diagnosis.

PH in HFpEF

Post-capillary PH is defined by a mean pulmonary artery pressure (PAPm) ≥ 25 mmHg and a PAWP > 15 mmHg[4] and is further subdivided into isolated post-capillary PH (IpcPH) and combined post- and pre-capillary PH (CpcPH). The current PH guidelines base the distinction between IpcPH and CpcPH on a diastolic pressure gradient (DPG, the gradient between diastolic pulmonary artery pressure and PAWP) ≥7 mmHg and/or a pulmonary vascular resistance (PVR) >3 Wood units.[4] The DPG criterion was introduced to replace the transpulmonary gradient (TPG, the gradient between PAPm and PAWP), as DPG was believed to be less dependent on pulmonary blood flow, less sensitive to elevated left atrial pressures, and a stronger predictor of mortality than TPG.[4–7] There is, however, increasing controversy about using DPG as it does not have major advantages over TPG in distinguishing between CpcPH and IpcPH.[8] In addition, its predictive value has been confirmed in some series[5,9,10] but not in others.[11–15] Currently, the evidence remains conflicting,[16,17] and further research is needed to determine whether PVR, DPG, or other variables such as pulmonary artery capacitance[10,12] are most suitable to identify a clinically relevant pre-capillary component in patients with post-capillary PH due to left heart disease.

PH is common in patients with HFpEF. A population-based study of 244 patients with HFpEF reported echocardiographic signs of PH in 83%.[1] The estimated systolic PAP was a predictor of mortality (hazard ratio 1.3 per 10 mmHg increase; $P < 0.001$). In a catheter-based study,[18] PH was found in 168 of 219 (77%) prospectively evaluated patients with HFpEF, 26 (12%) of whom had CpcPH (defined as elevated DPG and PVR). Patients with CpcPH, unlike those with IpcPH, had impaired RV to pulmonary vascular coupling and their survival was worse. Consistently, a prospective series demonstrated that right HF was the cause of death in 55% of patients dying with PH-HFpEF (Bonderman *et al.*, unpublished data).

Patients with CpcPH-HFpEF typically present with the same risk factors and co-morbidities as patients with HFpEF in general, including obesity, hypertension, coronary artery disease, diabetes, and atrial fibrillation.[18,19] Little is known about additional risk factors promoting the development of PH in patients with HFpEF. In a cross-sectional study,[19] HFpEF patients with and without PH had almost identical risk factors, co-morbidities, left-sided echocardiographic findings, and left-sided filling pressures.

Recent data have shown that the haemodynamic features of patients with CpcPH-HFpEF resemble those seen in PAH with equally high PAPm and equally low cardiac output, except for a higher PAWP (by definition >15 mmHg) and a lower PVR.[20]

In addition, it was noted that a subgroup of patients fulfilling the haemodynamic criteria of PAH (including PAWP ≤ 15 mmHg) have multiple risk factors for left heart disease and share clinical features of a HFpEF. Provocative measures such as volume loading[21,22] or exercise challenge[23–25] have been proposed to unmask post-capillary PH in such patients. However, current guidelines note that none of these measures have been sufficiently validated.[4,7] Some authors have defined this clinical entity 'atypical' PAH alluding to a well-defined specific subset.[20] The current state of knowledge though does not allow a clear and unequivocal identification of this subgroup. The descriptive definition of 'PAH with cardiovascular risk factors' appears more accurate and less prone to misunderstandings. It should be noted that current evidence supports PAH and PH due to HFpEF being distinct entities rather than part of a continuous spectrum of the same disease.

In this context, it appears relevant whether PAWP and/or LVEDP as the sole determinants can properly distinguish between pre- and post-capillary PH. PAWP and LVEDP measurements are not always reliable as they may be affected by numerous confounders including volume status, intrathoracic pressures, respiratory pressure swings, and technical problems. It may be more useful to develop a clinical distinction between PAH and PH due to left heart disease based on a comprehensive assessment utilizing the clinical presentation and echocardiographic findings, particularly the size of the left atrium, in addition to haemodynamics.[26] In any case, this approach needs to be properly validated.

Pathology and pathophysiology of PH and RV dysfunction in HFpEF

In HFpEF, chronic congestion is associated with functional and morphological alterations of pulmonary vessels, which include muscularization of pulmonary venules, haemangiomatosis-like endothelial cell proliferation in pulmonary capillaries, and pulmonary arterial remodelling (*Figure 1*), resulting in chronically increased afterload of the right heart. Of note, Borlaug *et al.*[27] recently provided evidence suggesting that blunted pulmonary vasodilation and impaired RV function in response to exercise occur in the earliest phases of HFpEF, before there is PVR elevation or structural remodeling of the RV.

The changes in the pulmonary capillaries and post-capillary venules may cause alterations in pulmonary function, in particular the diffusion capacity of the lungs for carbon monoxide (DLCO). In a recent study,[28] about half of the enrolled patients with PH-HFpEF had a low DLCO (<45% of the predicted value). These patients had a significantly higher mortality than their counterparts with higher DLCO values (hazard ratio 6.6; 95% confidence interval 2.6–16.9; $P < 0.001$), despite similar haemodynamics. A reduced diffusion capacity has also been linked to impaired exercise capacity in patients with HFpEF.[29]

Signs of RV failure have been described in 21–33% of patients with HFpEF and have been attributed to afterload mismatch and RV contractile impairment.[30,31] The presence of RV dysfunction in HFpEF is an independent predictor of mortality, making it a potential therapeutic target.[30,31]

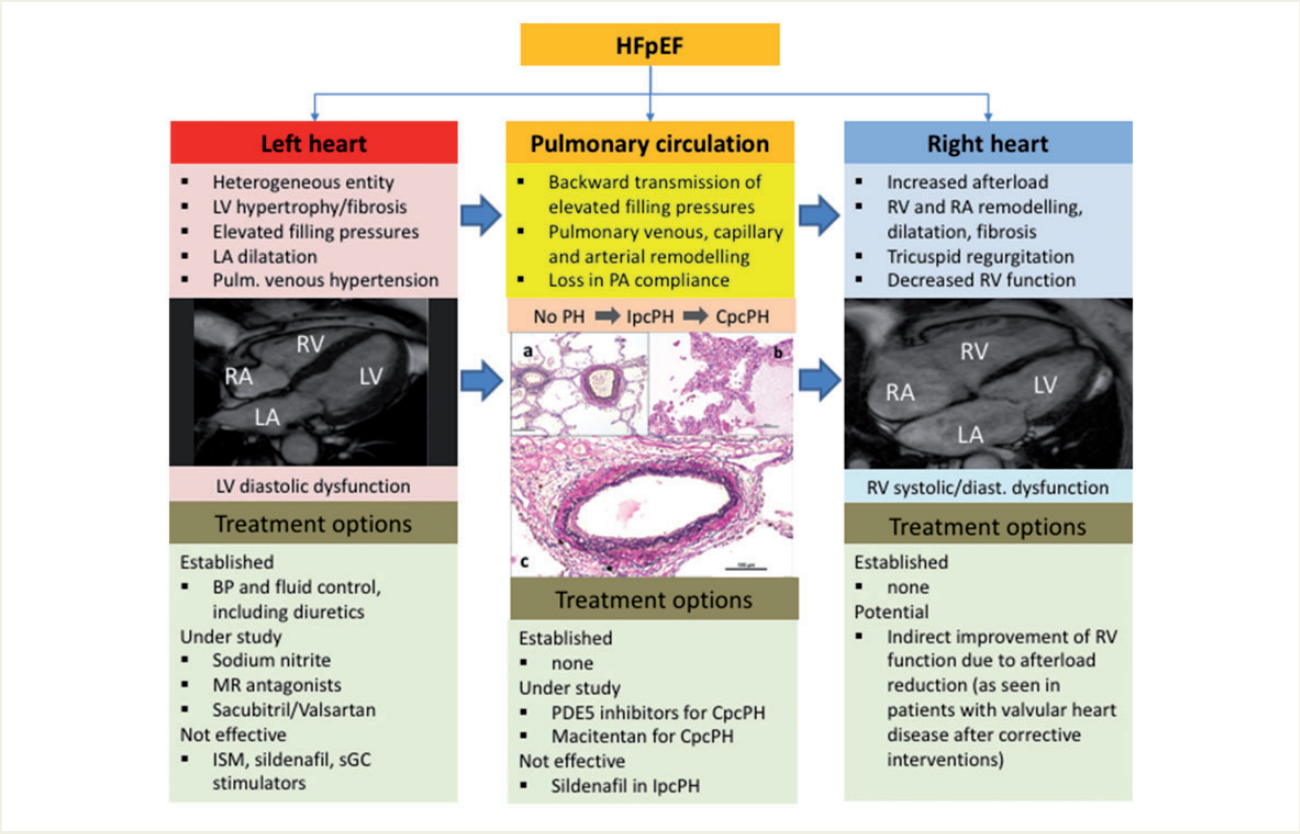

Figure 1 PH-HFpEF, features, and treatment options. The middle photo-inlet shows histological features of pulmonary vascular remodelling including (*A*) mild medial hypertrophy of a pulmonary artery, (*B*) haemangiomatosis-like endothelial cell proliferation of pulmonary capillaries, and (*C*) pulmonary venous remodelling. The cardiac magnetic resonance images show signs of HFpEF (LV hypertrophy, LA dilatation) without (left inlet) and with (right inlet) signs of PH. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; PA, pulmonary artery; BP, blood pressure; PH, pulmonary hypertension; IpcPH, isolated precapillary pulmonary hypertension; CpcPH, combined post- and precapillary pulmonary hypertension; HFpEF, heart failure with preserved ejection fraction; MR, mineralocorticoid receptor; ISMN, isosorbide mononitrate; sGC, soluble guanylate cyclase; PDE5, phosphodiesterase-5.

Treatment approaches

Treatment of HFpEF

Numerous studies have failed to show a benefit of HF therapies in HFpEF (reviewed in Refs. 26 and 32). Potential future strategies currently under investigation include (i) mineralocorticoid receptor antagonists such as spironolactone[33]; (ii) sodium nitrite, which improved exercise haemodynamics in subjects with HFpEF[34]; (iii) the neprilysin/angiotensin receptor inhibitor sacubitril/valsartan, which demonstrated a significant reduction of NT-proBNP serum levels in HFpEF in the phase II PARAMOUNT trial,[35] and which is currently investigated in the phase III PARAGON study; and (iv) soluble guanylate cyclase stimulators such as vericiguat, which did not change the co-primary endpoints, NT-proBNP or left atrial volume, at 12 weeks compared with placebo in the recently reported Phase II SOCRATES-PRESERVED trial (Pieske *et al.*, presented at Heart Failure 2016, Florence, Italy).

Treatment of PH-HFpEF

The first approach to treatment of PH in HFpEF is effective decongestion of the pulmonary vascular bed. Examples for the effectiveness of this approach include the potential reversal of PH, including CpcPH, after successful aortic or mitral valve repair, or after implantation of LV assist devices in HF patients. In HFpEF, optimization of diuretic and vasodilator therapy based on home transmission of PAP with an implanted pressure sensor reduced HF-associated hospitalizations.[36] In fact, decongestion may improve not only the passive component of PH but also the pre-capillary component as well.[37] Pulmonary arterial compliance, RV to PA coupling, and RV function may also be improved by β-adrenergic stimulation,[38] but further studies are required to determine the clinical effects of such therapy.

Presently, no multicentre randomized controlled trial (RCT) targeting any of the three pathways tested in PAH has met its primary endpoint. The response to such therapy likely depends on precise haemodynamic characterization and proper phenotyping of individual patients. Two trials in PH-HFpEF, predominantly IpcPH, were negative: In DILATE-1, no significant haemodynamic changes were observed 6 h after treatment with the soluble guanylate cyclase stimulator riociguat in 36 clinically stable patients.[39] A study of sildenafil, a phosphodiesterase-5 (PDE5) inhibitor, in 52 patients showed no improvement in haemodynamics and exercise capacity over 12 weeks.[40]

In contrast, in a single-centre study of patients with mainly CpcPH-HFpEF, 12 months of sildenafil treatment was well tolerated with significant improvements in haemodynamics and RV function compared to placebo.[41] The results of a multicentre phase II trial (MELODY-I) evaluating the safety and efficacy of the endothelin receptor antagonist macitentan in patients with CpcPH-HFpEF are awaited (ClinicalTrials.gov Identifier NCT02070991).

We caution against the widespread use of PAH drugs in clinical practice, especially outside expert centres, given the absence of clinical outcome data, and their effects in HF without PH where they caused no benefit at best or were detrimental in some cases. Perhaps the clue to advancement lies in the only positive study, which used sildenafil in carefully selected patients with a CpcPH-HFpEF phenotype.[41] Whether the observed benefit is reproducible and drug specific is yet to be determined. Registry data indicate that PAH drugs, predominantly PDE5 inhibitors are occasionally used to treat patients with CpcPH-HFpEF and stress the need for proper outcome trials.[20]

In summary, there is a disparity between an urgent medical need to treat PH-HFpEF safely and effectively and a lack of robust scientific evidence. Closing this gap will be an important endeavour for future research activities in the field.

Recommendations for the future approach to PH-HFpEF

- The most effective prevention and therapy of PH-HFpEF may be effective treatment of HFpEF. To this end, establishing strategies that improve LV diastolic function and decongest the pulmonary circulation will be crucial.
- No drug approved for PAH has thus far been shown to be safe and effective in PH-HFpEF or in any form of PH associated with left-sided heart disease. Patients with IpcPH-HFpEF should not be treated with such drugs since two multicentre RCTs have not shown beneficial effects.
- Patients with CpcPH-HFpEF may have a unique pulmonary vasculopathy affecting all segments of the pulmonary vascular bed. Mortality is high, and right-sided HF contributes to death. Preliminary data from a single-centre clinical trial suggest that PDE5 inhibitors may be safe and effective in this selected patient population. However, the available evidence is insufficient to make a recommendation to use PDE5 inhibitors or other drugs approved for PAH as treatments for CpcPH-HFpEF. Instead, there is an urgent need for multicentre clinical outcome trials in this area.
- Robust evidence on the safety and efficacy of treatments targeting PH requires randomized, controlled, long-term multicentre trials in the subset of patients with CpcPH-HFpEF. Patients must be haemodynamically well characterized, which includes right heart catheterization, in clinically stable condition and on optimized background therapy, including diuretics. Since there are no validated surrogate markers for the efficacy of treatments for PH-HFpEF, RCTs should assess exercise capacity, functional class, and quality of life as well as outcome measures including cardiac hospitalizations and all-cause mortality.

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