Diagnosing heart failure with preserved ejection fraction with pulmonary vascular disease

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In patients with heart failure (HF) with a preserved left ventricular ejection fraction (HFpEF), pulmonary hypertension (PH) is common, is a marker of poor prognosis and may represent a therapeutic target. The presence of PH in HFpEF is typically the consequence of the backwards transmission of elevated left atrial pressure into the pulmonary circulation. This is reflected by an increased mean pulmonary artery wedge pressure (mPAWP), which directly leads to an increase in the mean pulmonary artery pressure (mPAP). Initially, the mPAP elevation is a purely passive phenomenon, and the transpulmonary gradient (the difference between mPAP and mPAWP) and the pulmonary vascular resistance (PVR; transpulmonary gradient divided by cardiac output) are normal, respectively. This most frequent PH constellation in HFpEF is referred to as isolated post-capillary PH (IpcPH). There is a subset of patients with HFpEF, however, in whom a sustained mPAWP elevation leads to the development of an additional component of pulmonary vascular disease.[1] In contrast to pulmonary arterial hypertension, this type of pulmonary vascular remodelling seems to affect primarily the venules rather than the arterioles. The net result of this process in terms of haemodynamics is a rise in PVR. Thus, both an elevated mPAWP and transpulmonary gradient (product of PVR and cardiac output) contribute to the elevated mPAP. This constellation is referred to as combined prae-capillary and post-capillary PH (CpcPH). Although this concept is now generally accepted, its exact haemodynamic definition has been under intense discussion and has changed several times over the last years.[2–4]

The 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) PH guidelines defined CpcPH as an mPAP ≥25 mm Hg, an mPAWP >15 mm Hg and a diastolic pressure gradient (DPG; the difference between the diastolic pulmonary artery pressure and the mPAWP) ≥7 mm Hg AND/OR a PVR >3 Wood units (WU).[2] Because IpcPH was defined as a DPG <7 mm Hg AND/OR a PVR ≤3 WU, there were unclassifiable patients, that is, those with discrepant DPG and PVR. Clinical studies therefore often only used the PVR criterion or modified the IpcPH definition to 'DPG <7 mm Hg AND PVR ≤3 WU' to avoid unclassifiable patients. The 2018 PH World Symposium proposed a reduction of the mPAP cut-off for the definition of any PH from ≥25 to >20 mm Hg to account for the fact that a normal mPAP is only 14±3 mm Hg, and CpcPH was defined as an mPAWP >15 mm Hg in combination with a PVR ≥3 WU (no DPG criterion anymore).[3] At the same time, the diagnosis of prae-capillary PH was amended by the compulsory requirement of a PVR≥3 WU in addition to an mPAWP ≤15 mm Hg to make sure that there was evidence of pulmonary vascular disease rather than only increased pulmonary flow. This was particularly important after reduction of the mPAP cut-off because patients with an mPAP just above 20 mm Hg and an mPAWP just below 15 mm Hg could have a relatively low transpulmonary gradient, which would not correspond to a PVR ≥3 WU.[3] Patients with mPAP >20 mm Hg and both mPAWP ≤15 mm Hg and a PVR <3 WU (high pulmonary blood flow) remained officially undefined in the 2018 proposal but are now retrospectively classified as 'unclassified PH' in line with the new labelling of this constellation in the 2022 ESC/ERS guidelines. The recently published 2022 ESC/ERS guidelines went a step further than the 2018 proposal and also changed the PVR criterion for CpcPH and prae-capillary PH from '≥3 WU' to '>2 WU' because a normal PVR had been found to be approximately 2 WU.[4]

Sera *et al*[5] for the first time evaluated the impact of the different PH definitions in a cohort of patients with HFpEF. They studied 219 patients with HFpEF admitted with acute heart failure and undergoing right heart catheterisation after decongestion and before discharge. Patients represented a subgroup of a larger registry, and selection of patients for and timing of right heart catheterisation was at the discretion of the treating physician. Patients undergoing right heart catheterisation were generally younger, had higher N-terminal-pro-B-type natriuretic peptide (NT-proBNP) and received more aggressive treatment than those not doing so. The median interval between admission and cardiac catheterisation was 11 days. The diagnosis of HFpEF was relatively evident given that these patients fulfilled clinical criteria for HF, had an LVEF ≥50% in the absence of severe valve disease, often had left atrial dilatation and displayed very high NT-proBNP plasma concentrations. According to the 2015 definition, the prevalence of any PH was 60 out of 219 (27%). Most patients had IpcPH, and only nine patients had CpcPH, and seven had prae-capillary PH. As highlighted by the authors the patients with 'prae-capillary PH' most likely had 'occult' CpcPH after aggressive diuretic therapy given their borderline mPAWP of 13–15 mm Hg and large left atrial size, although provocative testing (eg, volume challenge) was not performed. Patients with a 'prae-capillary component of PH' (CpcPH and 'prae-capillary PH'), that is, patients with HFpEF and evidence of pulmonary vascular disease, had significantly worse 1-year event-free survival (all cause death or HF hospitalisation). The two classification steps (application of the 2018 and 2022 definition; figure 3 in the paper by Sera *et el*[5]) led to a substantial reclassification of the cohort with a net increase in the number of patients with any PH by 82% (from 60 to 109), which was driven by an increase in CpcPH and 'prae-capillary PH' patients by 222% (from 9 to 29) and 314% (from 7 to 29), respectively. In contrast, the number of patients with IpcPH remained overall unchanged, and the number of 'unclassified PH' patients was low. Figure 1 highlights the impact of the change in PH definition on the classification of different haemodynamic constellations. This figure shows that it is 'easier' to receive a diagnosis of CpcPH or prae-capillary PH with the 2022 definition compared with the 2015 and 2018 definitions. Importantly, in contrast to the 2015 definition, neither the 2018 nor the 2022 PH categorisation provided significant prognostic information. When inspecting the Kaplan-Meier plot for the 2018 definition, the patients with a 'prae-capillary component' of PH (CpcPH and 'pre-capillary PH') were still separated from the other groups (figure 4 in the manuscript by Sera *et al*[5]), and the lack of statistical significance may have been due to a lack of power. This is in line with a recent analysis in a more than twice as large aortic stenosis population showing

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	mPAP ≥25 mmHg					
	mPAWP >15 mmHg			mPAWP ≤15 mmHg		
	PVR ≥3 WU	PVR <3 and >2 WU	PVR ≤2 WU	PVR ≥3 WU	PVR <3 and >2 WU	PVR ≤2 WU
2015[2 a]	CpcPH	IpcPH	IpcPH	praecPH[b,c]	praecPH[b]	praecPH[b,d]
2018[3]	CpcPH	IpcPH	IpcPH	praecPH[c]	Unclassified PH[e]	Unclassified PH[d,e]
2022[4]	CpcPH	CpcPH	IpcPH	praecPH[c]	praecPH[c]	Unclassified PH[d]
	mPAP 21-24 mmHg					
	mPAWP >15 mmHg			mPAWP ≤15 mmHg		
	PVR ≥3 WU	PVR <3 and >2 WU	PVR ≤2 WU	PVR ≥3 WU	PVR <3 and >2 WU	PVR ≤2 WU
2015[2a]	No PH	No PH	No PH	No PH	No PH	No PH
2018[3]	CpcPH	IpcPH	IpcPH	praecPH[c]	Unclassified PH[e]	Unclassified PH[e]
2022[4]	CpcPH	CpcPH	IpcPH	praecPH[c]	praecPH[c]	Unclassified PH

Figure 1 Illustration of the impact of the different pulmonary hypertension definitions on the classification of different haemodynamic constellations. CpcPH, combined prae-capillary and post-capillary pulmonary hypertension; IpcPH, isolated post-capillary pulmonary hypertension; mPAP, mean pulmonary artery pressure; mPAWP, mean pulmonary artery wedge pressure; praecPH, prae-capillary pulmonary hypertension; PH: pulmonary hypertension; PVR, pulmonary vascular resistance, WU, Wood units. [a]For simplification, the diastolic pressure gradient criterion is not considered (as this has been done in several clinical studies). In addition, the PVR criterion in the 2015 definition was '>3 WU'; for simplification, this was considered equivalent to '≥3 WU'. [b]According to the 2015 definition, there is no explicit PVR criterion for the definition of praecPH. [c]In case of a borderline mPAWP of 13–15 mm Hg in combination with features suggestive of post-capillary PH (typically left atrial dilatation), 'occult CpcPH' is likely, and unmasking by provocative testing (volume challenge, exercise) has to be considered. [d]In patients with mPAP ≥25 mm Hg and mPAWP ≤15 mm Hg, the transpulmonary gradient is at least 10 mm Hg, and in the presence of a normal or reduced cardiac output, the PVR will be at least 2 WU. Thus, this constellation is unlikely to be found in clinical practice except for patients with high cardiac output. [e]This constellation was not officially defined in the 2018 definition but in keeping with 2022 definition the term 'unclassified PH' is also used for the 2018 definition.

that those with CpcPH and pre-capillary PH according to the 2018 definition still had a significantly worse long-term mortality after valve replacement than patients with IpcPH or no PH.[6] However, the 2022 definition obviously did not discriminate anymore regarding prognosis (figure S2 in the paper by Sera *et al*[5]), which is a new and potentially relevant finding. Thus, it seems that the change in the mPAP cut-off from 25 to 20 mm Hg (2015→2018 definition) did not critically affect the prognostic power of the PH definition but the change in the PVR cut-off from ≥3 to >2 WU (2018→2022 definition) did. Notably, in the key study showing an increase in mortality already at 2.2 WU and thereby representing an important basis for the reduction of the PVR cut-off in the 2022 guidelines, the HR for a PVR ≥2.2 WU versus <2.2 WU was substantially higher for patients with an mPAWP ≤15 mm Hg than for those with an mPAWP >15 mm Hg.[7] In the above-mentioned aortic stenosis cohort, patients with a PVR 3≥WU had a more than four times higher long-term risk of death compared with those with PVR <3 WU. However, patients with a PVR between 2 and 3 WU had similar higher mortality compared with those with PVR <2 WU.[6]

Intense research over the last years has resulted in a clearer picture of CpcPH in terms of pathophysiology and prognostic relevance.[1 8] Studies concurred that independent of the underlying left heart pathology (HFpEF, aortic stenosis), patients with CpcPH have substantially worse symptoms and prognosis than those with IpcPH or no PH. Combined non-invasive and invasive studies (eg, the recent study by Omote *et al*[1]) have improved our understanding of the mechanisms underlying the symptoms of patients with CpcPH . Importantly, the studies compiling this evidence used the 2015 CpcPH definition as inclusion criterion (most often by using only the PVR ≥3 WU criterion).[1 8] Thus, Sera *et al*[5] for the first time demonstrated the substantial effect of the change in the PH definition from the 2015 to the 2022 guidelines when classifying PH in patients with left heart disease. Although the rationale for 2022 definition is sound from an epidemiological and probably also pathophysiological point of view, the data by Sera *et al*[5] raise the possibility that the new criteria may not be selective enough to identify those HFpEF patients with clinically relevant pulmonary vascular disease and poor prognosis who may be candidates for studies evaluating innovative therapies beyond treatment of the underlying left heart pathology. However, given the limited number of patients in the present study, its results are hypothesis-generating only, and further larger studies are needed.

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