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Pulmonary hypertension in patients with advanced heart failure with reduced ejection fracion. Impact of the new definition of pulmonary hypertension

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Introduction and aim

Post-capillary pulmonary hypertension (PH) is a frequent component of the heart failure (HF) (1). It develops as a result of a passive transmission of high left atrial pressure. 2022 ESC PH guidelines introduced a change in its definition. Currently, PH is defined by mean pulmonary artery pressure (mPAP) > 20 mmHg (2). Evidence of post-capillary PH requires the finding of an elevated pulmonary artery wedge pressure (PAWP) > 15 mmHg. Pulmonary vascular resistance (PVR) is reflecting the pre-capillary component of PH and is essential for identifying patients with a combined PH phenotype (PVR > 2 WU) (3). Pre-capillary pulmonary vasculature remodelling in patients with post-capillary PH is referred as pulmonary vascular disease (PVD). PVD contributes to the right ventricular dysfunction and is a negative prognostic factor in patients with HFrEF affecting hospitalization and mortality rate (4).

Prevalence of PH in patients with heart failure with reduced ejection fraction (HFrEF) varies, depending on the diagnostic modality used and on the characteristics of the patient population itself. With echocardiography being used as a diagnostic tool, the prevalence of PH in patients with HFrEF is estimated to be 35-48% (5). Studies based on right heart catheterization in patients with de novo HFrEF have demonstrated the prevalence of PH in 46%-72% (6, 7). With a discriminative PVR of 3 WU valid until 2022, 55% of patients met criteria for combined pre- and post-capillary PH (CPC PH) (8). These data reflect the hemodynamic status of patients with a relatively stable course of HFrEF. Data on the prevalence of PH or its phenotypes in patients with advanced HFrEF according to the new definition are not known.

This retrospective cohort study is aimed at describing the prevalence of PH and its phenotypes in patients with advanced HFrEF and to search for factors associated with CPC PH phenotype using the new PH definition.

Patients and methods

Patients referred for hospitalization in 2017-2020 for advanced HFrEF or HFrEF resistant to conventional pharmacotherapy were included in the retrospective analysis, regardless of disease duration. Inclusion criteria was left ventricular systolic dysfunction, defined as LVEF < 40%. All patients underwent RHC. Selected clinical,

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anthropometric, laboratory, electrocardiographic, echocardiographic, and hemodynamic data were extracted from the medical records, which were maintained in a standard protocol manner.

A total of 175 patients were enrolled – 39 women and 136 men. The most common cause of LV dysfunction was dilated cardiomyopathy (73 patients), followed by coronary artery disease (66 patients). Other, less frequent causes, included hypertensive heart disease, burnt-out hypertrophic cardiomyopathy, non-compaction cardiomyopathy, chronic myocarditis and failed valvular heart disease (36 patients). The basic characteristics of the cohort are presented in **Table 1**. RHC was performed after reaching a euvolemic state in case of congestion being present during admission. Under standard conditions, RHC was performed within 24 hours of echocardiographic examination and peripheral blood sampling for laboratory parameters. Based on the complete hemodynamic profile, patients were classified into one of three groups according to the ESC guidelines (2) – patients in whom invasive testing did not prove the presence of PH, patients with isolated post-capillary PH (IPC PH), and patients with CPC PH. The IPC PH phenotype was assigned to patients with mPAP > 20 mmHg, PAWP > 15 mmHg, PVR ≤ 2 WU. If PVR was > 2 WU, patients were classified as CPC PH.

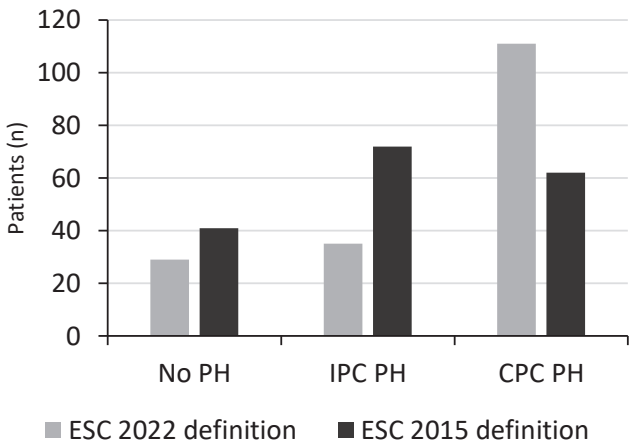

Figure 1 Number of patients without PH or with PH and IPC PH/CPC PH phenotype according to the new definition compared to the definition from 2015 ESC PH guidelines

CPC PH – combined pre- and post-capillary pulmonary hypertension, ESC – European Society of Cardiology, IPC PH – isolated post-capillary pulmonary hypertension, PH – pulmonary hypertension

Results

PH was not present in 29 (17%) patients, 146 (83%) patients had post-capillary PH. Criteria for IPC PH, resp. CPC PH were met in 35 (20%), resp. 111 (63%) patients (**Figure 1**). Patients with PH regardless of its phenotype had a longer history of HFrEF (6.8 ± 5.6 vs 3.8 ± 4.6 years, p<0.01), lower systolic (108 ± 13 vs 120 ± 20 mmHg, p<0.01) and diastolic blood pressure (71 ± 10 vs 75 ± 15 mmHg, p<0.05). Among echocardiographic parameters, PH patients had significantly lower LVEF (21 ± 6 vs 26 ± 8, p<0.001), larger left atrium (51 ± 7 vs 45 ± 7 mm, p<0.001) and right ventricle (39 ± 9 vs 34 ± 8 mm, p<0. 01). They were more likely to have moderate or severe mitral regurgitation (42 vs 13%, p<0.05), while there was no significant difference in either the presence or the severity of tricuspid regurgitation, but a trend could be observed (p=0.06). Right ventricular systolic dysfunction expressed as TAPSE was more pronounced in the PH group (14 ± 4 vs 18 ± 6 mm, p<0.001). Patients with PH had a higher prevalence of atrial fibrillation (36 vs 17%, p<0.05) and renal insufficiency as assessed by KDIGO classification (59 vs 29%, p<0.05). Among laboratory parameters, presence of PH was associated with lower serum sodium concentration (139.6 ± 3.1 vs 140.8 ± 2.0 mmol/L, p<0.05), higher NT-proBNP concentration (4565.0 ± 4087.0 vs 1975.7 ± 2375.9 ug/L, p<0.001), uric acid (468. 5 ± 140.7 vs 381.5 ± 105.0 umol/L, p<0.005), alkaline phosphatase (1.6 ± 0.8 vs 1.3 ± 0.3 ukat/L, p<0.01), gamma-glutamyl transferase (2. 0 ± 2.3 vs. 0.8 ± 0.7 ukat/L, p<0.001) and serum bilirubin concentration (18.9 ± 10.5 vs. 12.6 ± 11.6 umol/L, p<0.005). The only electrocardiographic parameter reaching statistical significance was a wider QRS complex in PH patients (117 ± 28 vs 98 ± 23 ms, p<0.005). Lung function parameters (FEV1, FVC, FEV1/FVC) were comparable in both groups.

Comparing PH phenotypes, CPC PH patients were older (54 ± 10 vs 47 ± 13 years, p<0.001), had lower exercise capacity expressed by the 6-MWD (390 ± 126 vs 439 ± 74 meters, p<0.05), higher prevalence of renal insufficiency (33 vs 14%, p<0.05) and type 2 diabetes (32 vs 11%, p<0.05). Renal insufficiency was defined by a glomerular filtration rate less than 90 mL/min/1.73 m^2. Among the selected echocardiographic parameters, only higher non-invasively determined sPAP was as-

sociated with the CPC PH phenotype (56 ± 14, vs 44 ± 13 mmHg, p < 0.001) (**Figure 2a**). The alteration of hemodynamic parameters in the pulmonary circulation was more pronounced in the CPC PH group with higher sPAP (55 ± 14 vs 38 ± 7 mmHg, p<0.001), dPAP (29 ± 6 vs 23 ± 5 mmHg, p<0.001), mPAP (40 ± 9 vs 29 ± 5 mmHg, p<0.001), PAWP (27 ± 6 vs 22 ± 5 mmHg, p<0.001) (**Figure 2b**), and lower cardiac index (CI) (1.9 ± 0.4 vs 2.3 ± 0.5 L/min/m^2, p<0.001) (**Figure 2c**). The only hemodynamic parameter that did not reach a level of statistical significance when comparing IPC PH and CPC PH was RAP (10.9 ± 6.2 vs 11.9 ± 5.4 mmHg, p=0.37). There was no significant difference in the degree of obstruction (FEV1), lung restriction (FVC), or Tiffeneau-Pinneli index (FEV1/FVC) between the IPC PH and CPC PH groups, respectively. The complete spectrum of parameters comparing both groups is shown in **Table 1**. As for the differentiation of post-capillary PH phenotypes, sPAP > 55 mmHg determined by echocardiography was able to delineate patients with CPC PH in the population of patients with advanced HFrEF with relatively reliable specificity (C-statistic 0.76, sensitivity 47%, specificity 81%).

Conclusions

The new PH definition is unlikely to significantly affect the prevalence of PH in the population of patients with HF, but a disproportionate increase in the CPC PH phenotype can be expected. Lowering the PVR threshold for defining the pre-capillary component of PH increases variability within the CPH PH phenotype.

Table 1 Baseline characteristics

Number of pts		175
Men (n/%)		136/78
Age (years)		54.1 ± 10.8
HF etiology	DCMP (n/%)	73 (42)
	CAD (n/%)	66 (38)
	Other (n/%)	36 (20)
Duration of the HF (months)		112 ± 103
LVEF (%)		21.9 ± 6.7
NYHA I/II/III/IV (n)		0/11/124/40

CAD – coronary artery disease, DCMP – dilated cardiomyopathy, HF – heart failure, LVEF – left ventricular ejection fraction, NYHA – New York Heart Association

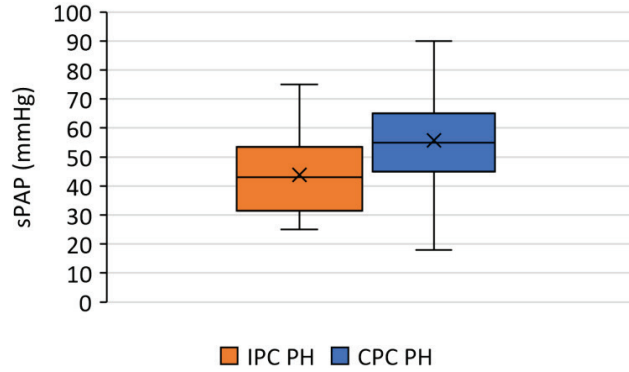

Figure 2a Difference in echocardiographically measured sPAP in IPC PH/CPC PH patients
CPC PH – combined pre- and post-capillary pulmonary hypertension, IPC PH – isolated post-capillary pulmonary hypertension, sPAP – systolic pulmonary artery pressure

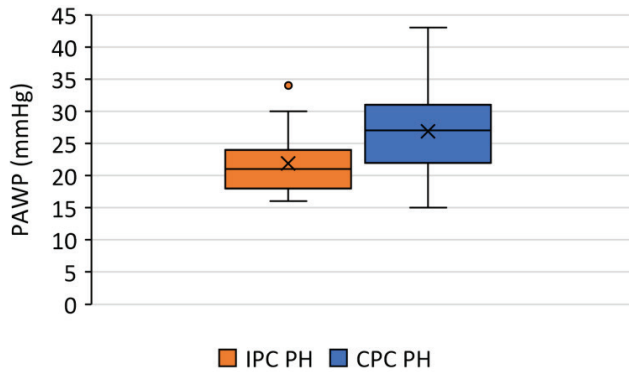

Figure 2b Difference in PAWP in IPC PH/CPC PH patients
CPC PH – combined pre- and post-capillary pulmonary hypertension, IPC PH – isolated post-capillary pulmonary hypertension, PAWP – pulmonary artery wedge pressure

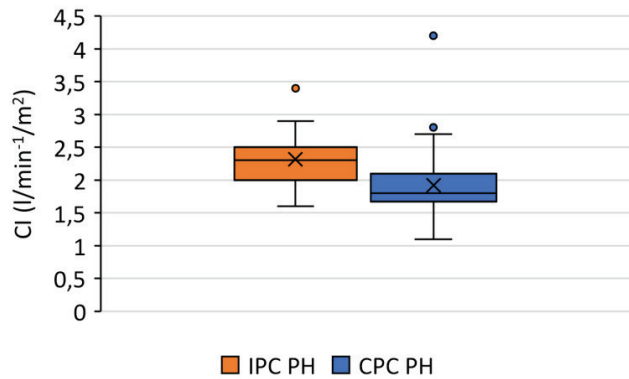

Figure 2c Difference in CI in IPC PH/CPC PH patients
CI – cardiac index, CPC PH – combined pre- and post-capillary pulmonary hypertension, IPC PH – isolated post-capillary pulmonary hypertension

This fact probably complicates attempts for non-invasive selection of patients with PVD in HFrEF. We found sPAP >55 estimated by echocardiography as the only non-invasive parameter delineating patients with CPC PH in the population of advanced HFrEF. As a result of the new PH definition, the spectrum of patients with differently expressed PVD becomes more disparate. This may complicate the design of future clinical trials aimed at pre-capillary component of PH, e.g., the use of specific pulmonary arterial hypertension (PAH) therapy in patients with HF and PH.

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