How to define pulmonary hypertension due to left heart disease

To the Editor:

Current 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines for the diagnosis and treatment of pulmonary hypertension (PH) [1, 2] have adopted new insights in the understanding of PH due to left heart disease (PH-LHD, group 2).

The new guidelines present two subsets of PH-LHD: 1) isolated post-capillary PH (Ipc-PH), previously labelled as "passive" PH-LHD, defined by a mean pulmonary artery pressure (PAP) ⩾25 mmHg, mean pulmonary artery wedge pressure (PAWP) >15 mmHg, diastolic pulmonary vascular pressure gradient (DPG) <7 mmHg and/or pulmonary vascular resistance (PVR) ⩽3 Wood units (WU); and 2) combined post- and pre-capillary PH (Cpc-PH), previously labelled as "reactive" or "out of proportion" PH-LHD, defined by a mean PAP ⩾25 mmHg, mean PAWP >15 mmHg, DPG ⩾7 mmHg and/or PVR >3 WU [1, 2].

However, the previous definition of PH-LHD and the associated terminology of "passive" and "reactive" or "out-of-proportion" PH-LHD have been unsatisfactory for the characterisation of patients. Transpulmonary pressure gradient (TPG) is sensitive to changes in cardiac output, recruitment and distension of pulmonary vessels decreasing upstream transmission of left atrial pressure. Furthermore, pulmonary blood flow is pulsatile with systolic PAP and mean PAP, determined by stroke volume and arterial compliance [3–5]. At the fifth World Symposium on Pulmonary Hypertension in Nice, France, in 2013 and in the recently published ESC/ERS guidelines for the diagnosis and treatment of PH, the definition of PH-LHD was revised [1, 2, 5], mainly based on the observations that DPG is less flow dependent and less sensitive to elevation of left atrial pressure than TPG [4], and reflects pulmonary vascular remodelling [6].

Despite initial disagreement with DPG as a prognostic indicator [7, 8], the predictive value of DPG ⩾7 mmHg in PH-LHD has been confirmed by other groups in the meantime [9–12].

We would like to support the guideline PH-LHD classification. In a recent manuscript we have clarified that Cpc-PH (mean PAP >15 mmHg and DPG ⩾7 mmHg) [13] is truly a distinct entity. We are demonstrating that Cpc-PH is occurring in ∼12–13% of systolic heart failure and diastolic heart failure cases [13]. Cpc-PH is associated with a worse prognosis compared to Ipc-PH in both heart failure subsets [13]. To substantiate that DPG is relevant we have demonstrated a continuous impact of increasing DPG on the pulmonary vascular resistance (PVR)-compliance (C_{PA}) relationship with a downward-rightward shift, illustrating that heart failure patients with higher DPGs have higher right ventricular (RV) afterload [13]. Interestingly, PVR-C_{PA} relationship in Cpc-PH is similar to that in idiopathic pulmonary arterial hypertension [13]. RV to pulmonary vascular (RV-PV) coupling is worse in patients with Cpc-PH than in Ipc-PH, possibly explaining our previous findings that survival is significantly shorter in Cpc-PH [6, 13]. These data illustrate that Cpc-PH represents heart failure patients with decreased RV function and pulmonary arteriopathy.

However, there is a problem with the diagnostic criteria of the new classification. The new guidelines bring PVR into the definition. According to our data, a stratification using a PVR ⩾3 WU did not provide prognostic implications [6]. In our database, PH-LHD patients with DPG <7 mmHg and PVR >3 WU (n=76) had preserved RV-PV coupling (end-systolic elastance (E_{es}); arterial elastance (E_a) mean±SD 1.4±0.3) while RV-PV coupling was poor in those with DPG ⩾7 mmHg and PVR >3 WU (n=41; E_{es}/E_a mean±SD 1.1±0.3, p<0.001). We acknowledge that MILLER *et al.* [14] demonstrated that prognosis was worse when PVR was ⩾3 WU. However, MILLER *et al.* [14] only analysed heart failure patients with reduced ejection fraction, excluding patients who had heart failure with preserved ejection fraction and valvular heart disease. Furthermore, in contrast to our study [6], a TPG >12 mmHg was not predictive of outcome in the study by MILLER *et al.* [14].

Using the discriminative term of and/or PVR >3 WU for the definition of both Ipc-PH and Cpc-PH, one discovers that almost 30% of patients with PH-LHD fall into both categories (table 1). For example, a patient with PH-LHD and DPG of 6 mmHg but a PVR of 4 WU could be classified as having Ipc-PH (DPG <7 mmHg) and as having Cpc-PH (PVR >3 WU). On the background of our 1506 patients with PH-LHD, 28.7% of PH-LHD patients were unclassifiable using the guideline definition (table 1).

TABLE 1 Patients with pulmonary hypertension (PH) due to left heart disease (n=1506, mean pulmonary artery pressure ⩾25 mmHg, and mean pulmonary artery wedge pressure >15 mmHg) stratified by diastolic pulmonary vascular pressure gradient (DPG) and pulmonary vascular resistance (PVR)

	DPG <7 mmHg	DPG ⩾7 mmHg
PVR ⩽3 WU n (%)	858 (57.0)[#]	**44 (2.9)**
PVR >3 WU n (%)	388 (25.8)	216 (14.3)[¶]

Numbers in bold indicate the number of patients (432 (28.7%)) with DPG/PVR combinations that are unclassifiable using the current definition of the 2015 European Society of Cardiology and the European Respiratory Society guidelines [1, 2]. WU: wood units. [#]: isolated post- and pre-capillary PH with DPG <7 mmHg and/or PVR ⩽3 WU; [¶]: combined post- and pre-capillary PH with DPG ⩾7 mmHg and/or PVR >3 WU.

According to the current definition of the 2015 ESC/ERS guidelines, patients were classified as Ipc-PH (DPG <7 mmHg and/or PVR ⩽3 WU, n=858 (57.0)) *versus* Cpc-PH (DPG ⩾7 mmHg and/or PVR >3 WU, n=216 (14.3%)). The numbers in bold in table 1 indicate the number of patients with DPG/PVR combinations that are unclassifiable using the current definition (n=432 (28.7%)).

If one were to reclassify PH-LHD using the definition: Ipc-PH corresponding to DPG <7 mmHg and PVR ⩽3 WU, and Cpc-PH corresponding to DPG ⩾7 mmHg and/or PVR >3 WU, one would get 57% and 43% cases, respectively, which does not reflect the clinical observation that only a minority of patients with PH-LHD experience significantly shorter survival [6]. Therefore, we suggest defining Ipc-PH as PH-LHD with a DPG <7 mmHg and/or PVR ⩽3 WU and Cpc-PH as PH-LHD with a DPG ⩾7 mmHg and PVR >3 WU. Under these conditions, 14.3% of PH-LHD would be classified as Cpc-PH in accordance with our observations in a large patient population [13]. The current proposal should stimulate independent validation in series of PH-LHD from other centres.

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A retrospective cohort study of patients with pulmonary embolism: the impact of comorbidities on patient's outcome

To the Editor:

Despite considerable advances in diagnosis and treatment, pulmonary embolism (PE) remains is an important clinical entity with a high risk of death. Due to pulmonary bed obstruction, PE can result in acute right ventricular failure, a life-threatening condition.

If untreated, acute PE is associated with a significant mortality rate (as high as 30%) whereas the case–fatality ratio of diagnosed and treated PE drops to 8% [1]. It is well known that comorbidities can affect one or more diseases through several potential aetiological mechanisms of direct causation, associated risk factors, heterogeneity and independence. In particular, in patients with venous thromboembolism (VTE) the presence of comorbidities can hinder clinical assessment and timely diagnoses [2] and exacerbate the risk of recurrence, complications and death [3].

In order to identify the burden of PE, as well as the most common diagnoses associated with hospital admissions for PE, we analysed the hospitalisation data available for Sardinia (Italy) between 2009 and 2011. The secondary aim was to analyse the difference in comorbidity rates between survivors and patients who died. The study was conducted by analysing data from hospital discharge records (HDR; SDO in Italian) featuring the International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM) code for PE (415. 1x) over the period 2009–2011 in Sardinia. Data were obtained from the Department of Health and Hygiene of the "Regione Autonoma della Sardegna" (RAS) Sardinian Regional Government. The HDR includes information pertaining to the hospitalisation and discharge of patients, both resident and non-resident in Sardinia, from all public and private hospitals located in this Italian region. All hospitals are required to provide the Department of Health and Hygiene at RAS with this information in electronic format. Information contained in the HDR is encoded according to the ICD-9-CM. It includes patient demographic characteristics, the field of primary diagnosis (defined as the main reason for hospitalisation), up to six fields for secondary diagnoses, hospital identification codes and diagnostic procedures. The Regional Epidemiological Observatory is a Division of the Department of Health and Hygiene at RAS devoted, among other things, to the management of healthcare information for epidemiological purposes.

Data were processed and descriptive statistics provided using MedCalc software (version 13.3.0.0; Ostend, Belgium). Analysis comprised all hospitalisations with PE as a primary hospital discharge diagnosis from 2009 to 2011. Data were expressed as absolute numbers, percentage and mean±SD. The rates were standardised to the Sardinian population between 2009 and 2011.