The difficult diagnosis of pulmonary vascular disease in heart failure

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Definition and diagnosis of pulmonary vascular disease in heart failure: still an unclear rebus
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Pulmonary hypertension (PH), defined as a mean pulmonary arterial pressure (PAP) ⩾25 mmHg, is a well-recognised complication of left heart disease (LHD). PH prevalence is variable ranging from 25% to 80% of LHD patients according to the methods of assessment, cut-off values and characteristics of the patient population [1–3]. All aetiological types of LHD are affected, including heart failure with reduced (HFrEF) or preserved (HFpEF) left ventricular ejection fraction, and valvular LHD. The presence of PH-LHD is associated with advanced symptoms, reduced exercise capacity and impaired outcome after medical, interventional or surgical therapy [1, 3, 4].

The relevance of PH-LHD is highlighted by the recognised epidemiological predominance of this condition, which represents the most common form among the five groups included in the PH clinical classification, accounting for 65–80% of the PH cases [1, 3, 5, 6]. PH-LHD is distinctively characterised by an increase of the pulmonary artery wedge pressure (PAWP) >15 mmHg [5, 6], an accepted surrogate for left atrial pressure.

Historically, two different subsets of PH-LHD have been recognised from the pathological, pathophysiological and haemodynamic points of view [7–9]. The first form, traditionally defined as "passive" PH, is characterised by the pure backward transmission of the increased left atrial pressure through the pulmonary veins and capillaries up to the pulmonary arteries. The second form, called "reactive" or "out-of-proportion" PH, includes a specific distal pulmonary artery disease, which contributes to further increase the PAP in an addition to the passive component. More recently, the two forms have been relabelled isolated post-capillary PH (Ipc-PH) and combined post- and pre-capillary PH (Cpc-PH), respectively [1, 5, 6]. There is agreement on the observation that the latter subgroup portends a worse prognosis [1, 5, 6].

Gerges *et al.* [10], in this issue of the *European Respiratory Journal*, entertain the "vexata quaestio" of the haemodynamic definition of the two subtypes of PH-LHD and of the parameter(s) that can capture the different outcome.

The recent increased interest in this topic is testified by the flourishing of the medical literature in this field with different and sometimes contradictory results. The importance of the argument is not confined to sophisticated pathophysiological reasoning, but may influence the clinical decision-making. In fact, the presence, the extent and the type of PH affects the medical, interventional and surgical management of patients with PH-LHD [1–6].

Before analysing the novel proposals of Gerges *et al.* [10] it may be of interest to revise briefly the two different PH-LHD subsets according to the known pathology and pathobiology and the changes in nomenclature and definitions observed over time.

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The traditional description of the pulmonary vascular pathological changes in patients with PH-LHD includes enlarged and thickened pulmonary veins, pulmonary capillary dilatation, interstitial oedema, alveolar haemorrhage, lymphatic vessels and lymph nodes enlargement [11]. In addition, the pre-capillary circulation may also be involved at the level of distal pulmonary arteries, which may be affected by different degrees of obstructive remodelling such as medial hypertrophy and intimal fibrosis and proliferation. The presence of this pre-capillary component, which is considered exclusive to the Cpc-PH form has been described in the past [11] and confirmed in more recent analyses from biopsies, autopsies and lung resections [12, 13]. Interestingly, all the haemodynamic parameters involved in the characterisation of the two subsets of PH-LHD have been correlated with the presence of the pre-capillary obstructive component including: the transpulmonary pressure gradient (TPG) [12], defined as the difference between the mean PAP and the PAWP; the pulmonary vascular resistance (PVR) [12], defined as the ratio between TPG and cardiac output; and the diastolic pressure gradient (DPG) [13, 14], defined as the difference between diastolic PAP and PAWP.

The pathobiological mechanisms responsible for the development of the pre-capillary vascular obstructive component in a proportion of PH-LHD patients are poorly understood. They may include endothelial dysfunction of pulmonary arteries that may favour constriction and proliferation of the cells of the distal pulmonary arteries walls [15].

The functional portion of the pre-capillary component is acutely reversible, at least in part, as demonstrated by pharmacological challenges performed in subjects with Cpc-PH that are candidates for heart transplantation [1, 16]. The regression of the fixed obstructive lesions over time can be achieved after effective treatment of the valvular LHD [17]. In addition, reduction of PVR as early as after 3 days and complete normalisation in 6 weeks has been observed in potential candidates for heart transplantation with left ventricular assist devices [18]. Unfortunately, all multicentre randomised controlled studies performed, to date, in patients with PH-LHD using drugs approved for pulmonary arterial hypertension have failed so far [1, 3]. Data from small single-centre studies have been contradictory [19, 20].

The most intriguing and controversial issue remains the haemodynamic definition of the two forms, which has sparked intense debates and influenced the nomenclature changes over time. Different haemodynamic parameters have been proposed, but the most common have been PVR, TPG and DPG, either individually or combined.

The observation that PVR was too sensitive to the level of cardiac output, in particular under pharmacological challenge, led to the suggestion to use only TPG, the "pressure" component of the PVR formula, to identify the pre-capillary component. The term "out-of-proportion PH" was coined to outline the disproportionate increase of mean PAP as compared with PAWP in patients with high TPG. In the 2009 European Society of Cardiology (ESC)/European Respiratory Society (ERS) PH guidelines a TPG >12 mmHg identified patients with reactive/out-of proportion PH-LHD [7–9].

At the world PH symposium held in Nice in 2013 the new acronyms Ipc-PH and Cpc-PH were adopted to introduce a more descriptive wording and to outline the importance of the pre-capillary component [1]. In addition, it was decided to define Ipc-PH by a DPG <7 mmHg and Cpc-PH by a DPG ⩾7 mmHg. The implementation of DPG was based on its theoretical independence from stroke volume and PAWP [21] and on the data published by Gerges *et al.* [13] reporting its prognostic value in patients with PH-LHD and TPG >12 mmHg. These results were eventually confirmed by the same group in an analysis that included all patients irrespective of TPG value [14].

In the 2015 ESC/ERS PH guidelines [5, 6] experts decided to modify this approach, including PVR in the definition because no independent confirmation of the prognostic value of DPG when used alone was achieved at that time [22, 23]. In addition, it was recognised that DPG measurement was prone to technical errors given its low absolute value, potentially influenced by procedural artefacts.

The following updated invasive haemodynamic criteria for PH-LHD were proposed in these guidelines: a mean PAP ⩾25 mmHg and a PAWP >15 mmHg to define post-capillary PH; Ipc-PH was defined by a DPG <7 mmHg and/or PVR ⩽3 Wood Units (WU); Cpc-PH was defined by a DPG ⩾7 mmHg and/or PVR >3 WU. Interestingly, these definitions include patients with isolated increases of DPG ⩾7 mmHg or of PVR >3 WU in both groups testifying the heterogeneity and uncertainties of the available data.

In this issue of the *European Respiratory Journal*, Gerges *et al.* [10] would like to support the guideline PH-LHD haemodynamic classification using both PVR and DPG, but not in the present form.

The rationale for this is based on the following four major points derived from analysis of their database of 1506 patients. 1) PVR ⩾3 WU did not provide prognostic implications [13]. 2) Patients with PVR >3 WU and DPG <7 mmHg had preserved right ventricle (RV) to pulmonary vascular (PV) coupling, while it was poor in those with DPG ⩾7 mmHg and PVR >3 WU [14]. 3) Patients with an increase of

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PVR >3 WU (and DPG <7 mmHg) or DPG ⩾7 mmHg (and PVR ⩽3 WU) can be included in both Ipc-PH or Cpc-PH groups and should be considered unclassifiable (28.7% of their series) [10]. 4) In the hypothesis that these patients are also considered Cpc-PH, then this group will increase to 43% of the entire population and this large cluster with predicted poor prognosis is not compatible with the current clinical observations [13].

As a consequence, Gerges *et al.* [10] propose to include the unclassifiable patients in the Ipc-PH group, the definition of which is unchanged, and suggest that Cpc-PH is defined only in the case of a concomitant increase of DPG ⩾7 mmHg and PVR >3 WU.

The major limitation of the above reasoning is that it is based on the analysis of data from a single database, which still awaits confirmation by other large datasets, possibly multicentre studies. Moreover, if we consider the individual points we could argue that PVR >3 WU does provide prognostic implication in different series of patients with predominantly HFrEF [23–25]. DPG as an individual predictor has been confirmed in some series [4, 25, 26], but not in others [22, 23]. The RV to PV coupling data were obtained from a prospective relatively small series of patients without survival information [14]. In addition, quite sophisticated RV function data were measured without the support of high fidelity catheters and magnetic resonance imaging for RV volumes calculation [14]. A single centre series of patients cannot be considered paradigmatic to define "*a priori*" the percentage of subjects with poor prognosis.

The heterogeneity of the data in the literature supports the flexibility provided by the current ESC/ERS guidelines haemodynamic classification. In fact, combined low or high DPG and PVR define Ipc-PH or Cpc-PH, respectively, while the isolated increase of either parameter is classified in both groups pending further confirmatory data. This latter patient population may also constitute a specific group of subjects with an intermediate prognosis between Ipc-PH and Cpc-PH as assessed by the combination of the two parameters.

A proposal to be confirmed in future multicentre studies may be the concept of the probability for pulmonary vascular disease (PVD): Ipc-PH patients, defined by the combination of DPG <7 mmHg and PVR ⩽3 WU, may be considered to have a low probability for PVD; patients with DPG ⩾7 mmHg or PVR >3 WU may be at intermediate probability for PVD; and Cpc-PH patients, defined by the combination of DPG ⩾7 mmHg and PVR >3 WU, may be at high probability for PVD. This proposed stratification, if supported by prospective data, may better accommodate the wide spectrum of PVD and the related prognostic impact in patients with PH-LHD, limiting the artificial constraint of defined borders. Finally, an additional relevant question to be addressed is whether all aetiological types of PH-LHD (HFrEF, HFpEF and valvular LHD) should be classified with an identical combination of parameters or not.

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