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Phenotyping pulmonary hypertension in systemic sclerosis: a moving target

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To the Editor

Pulmonary hypertension (PH) is a pathophysiological disorder that complicates various clinical conditions including cardiovascular and respiratory diseases.[1] The current classification of PH identifies five distinct groups sharing similar clinical presentation, pathological findings, and hemodynamic characteristics.[1,2]

Phenotyping patients and assigning the correct type of PH is essential during diagnostic work-up in order to adopt the most appropriate therapeutic strategy. In this context, invasive assessment of pulmonary hemodynamics and cardiac output by means of right heart catheterization (RHC) plays a crucial role. In particular, from a hemodynamic standpoint, beyond the presence of mean pulmonary arterial pressure $\geq$25 mmHg (definition of PH), mean pulmonary arterial wedge pressure (PAWP) value $\leq$15 mmHg further distinguishes pre-capillary from post-capillary PH (typically group 2 due to left heart disease), which is characterized by a PAWP >15 mmHg. The latter type of PH may present with isolated post-capillary PH or combined PH with a pre-capillary component, defined by an elevated diastolic pressure gradient and/or an increase in pulmonary vascular resistance, both calculations taking into account PAWP value.[1] Thus, the importance of PAWP measurement is evident in identifying the correct PH group for individual patients, although it is based on a rather arbitrary cut-off.

Unfortunately, PAWP measurements are often affected by calibration issues, respiratory variation, and are dependent on the operator's skills as suggested by poor inter-observer reliability.[3] In addition, PAWP measurement can significantly be affected by methodological issues,[4] and may vary from individual patients' measurements of left ventricular end-diastolic pressure.[5] Furthermore, a one-time measurement of PAWP could be affected by volume status or diuretic intake at a specific moment in time (e.g. patients with group 2 PH may have a normal PAWP in conditions of optimal medical treatment and volume depletion with diuretics), thus not necessary allowing distinction between pre- and post-capillary PH.

To further complicate the situation, in spite of the clarity and apparent simplicity of this classification, PH categories may actually co-exist in several clinical settings (i.e. the so-called atypical idiopathic pulmonary arterial hypertension [PAH]: hemodynamic features of pre-capillary PH, but associated with multiple risk factors for left-sided heart failure such as systemic hypertension, obesity, diabetes, and atrial fibrillation).[6] Such a complex situation is typified by PH associated with connective tissue disease, particularly systemic sclerosis (scleroderma [SSc]). Patients with SSc are indeed a unique group of patients since they are prone to developing PH that may fit in any of the first four groups of PH, whether they have a predominantly vascular disease with little evidence of parenchymal disease (group 1), or PH associated with left heart disease (group 2), chronic lung diseases (group 3 with, for instance, interstitial lung disease but also obstructive sleep apnea), or in the presence of chronic thromboembolic disease (group 4). SSc patients are also generally older than patients with idiopathic PAH and thus more prone to having co-morbid conditions such as left heart disease from systemic hypertension, diastolic dysfunction, and atrial arrhythmias, and to developing lung fibrosis.

In this issue of *Pulmonary Circulation*, Lammi et al. deal with the change of PH classification based on changes in PAWP that occurred over a median time of about 1.4 years in the prospective observational PHAROS (Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma) registry cohort of patients with SSc complicated by PH.[7] The study was limited to patients who had at least two RHC procedures performed. A total of 120 patients were included in the analysis. While there was an overall average change in PAWP from 11 ± 5 to 13 ± 6 mmHg, about 30% of patients were found to have a change in PAWP values that eventually required a change in PH hemodynamic classification. Patients initially classified as group 2 PH (post-capillary PH) were most likely to change PAWP class (to pre-capillary PH) over time. The authors conclude that PAWP values commonly change over time in patients with SSc-associated PH and warn about using a single time-point PAWP to define classification groups in this patient population.

The results of the current study are not too surprising. Phenotyping these patients, in terms of the cause of

pulmonary vascular disease, can be quite challenging and a change in classification over time is not unexpected. In particular, it is not surprising that patients initially classified as group 2 PH would be most likely to change PAWP class over time. Patients in this particular group are indeed likely to be truly group 2 patients who had better control of their fluid status and resulting pulmonary pressures on subsequent RHC. They may be left with some pre-capillary PH after adequate diuresis, as is the case for many patients with heart failure with preserved ejection fraction. This would be one of the most likely explanations for the change. Alternatively, a patient initially classified in group 1 because of a PAWP $\leq$ 15 mmHg may, however, be truly a group 2 patient in the right clinical setting of left ventricular hypertrophy, coronary artery disease, or perhaps an element of diastolic dysfunction on echocardiography. It would not be surprising that, on a follow-up RHC and after initiation of pulmonary vasodilators, the patient would be found with a PAWP > 15 mmHg. In this regard, there has been an interest recently in ''unmasking'' these patients with normal PAWP by a provocation maneuver either in the form of exercise[8] or fluid challenge test[9] during RHC while monitoring PAWP, although to date neither method has been standardized or included in the current guidelines recommendations.

There are several obvious limitations to this study, some of which are readily acknowledged by the authors. Most prominent among these is the fact that there was no strict protocol for PAWP measurement and no central adjudication of the RHC tracings. Another major source of concern is that the authors could not take into account the clinical background and existence of other specific co-morbid conditions such as systemic hypertension, diabetes mellitus, the metabolic syndrome, sleep apnea, or thyroid disorder (which were not prospectively collected by the PHAROS study). In addition, a more in-depth characterization of heart function and performance (aside from left ventricular ejection fraction, left atrial size, and presence or absence of diastolic dysfunction) was not available. It would have been useful to assess, for instance, the degree of diastolic dysfunction and presence of left ventricular hypertrophy.

In conclusion, while observations from this study are useful for clinicians, they also highlight the concept that, when it comes to PH, phenotyping is crucial and should not solely rely on hemodynamic measurements and an arbitrary PAWP cutoff. Phenotyping and proper group assignment should emanate from a thorough evaluation of clinical characteristics, co-morbidities, imaging data (e.g. echocardiography, cardiac magnetic resonance, thoracic computed tomography), hemodynamic data including provocation maneuvers (e.g. exercise or fluid challenge), and probably much more. This is true whether for SSc but also other diseases associated with PH. This is indeed the very focus of an ongoing National Institutes of Health (NIH)/National Heart, Lung and Blood institute (NHLBI) sponsored initiative, the PVDOMICS (Redefining Pulmonary Hypertension through Pulmonary Vascular Disease Phenomics), which is aimed at augmenting the current PH classification based on shared biological features.[10] The protocols and procedures are available online (https://pvdstudy.ccf.org/pvd/) and the results of these studies will be broadly available for future investigations.

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Valentina Mercurio[1,2] and Paul M. Hassoun[1]

[1]Johns Hopkins University, Division of Pulmonary and Critical Care Medicine, Department of Medicine, Baltimore, MD, USA; [2]Federico II University, Department of Translational Medical Sciences, Naples, Italy

Corresponding author:
Paul M. Hassoun, Division of Pulmonary and Critical Care Medicine, 1830 East Monument Street, Baltimore, MD 21287, USA.
Email: phassoun@jhmi.edu