Adding an important piece to the pulmonary vascular resistance puzzle in pulmonary arterial hypertension

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Clinical outcomes in pulmonary arterial hypertension (PAH) have improved substantially in the modern era, owing to greater clinician awareness, availability of numerous pulmonary vasodilator therapies and, now, more than two decades of sound clinical trial data informing optimal strategies for treating patients [1]. This arc of progress began with therapeutic interventions that aimed to simply delay mortality in patients with end-stage disease, at a time in which PAH was regarded as by-and-large uniformly fatal. The evolution of PAH into a contemporary and treatable disease has been marked by specific sentinel transition points, including proven efficacy of prescription exercise, sequential add-on treatment with different drug classes, and up-front combination therapy in newly diagnosed patients [2]. This has resulted in a collective shift toward greatly enhanced goals for defining treatment success in clinical practice, such as minimal symptom burden, preserved exercise tolerance, and favourable haemodynamic parameters [3].

In line with this trend, early PAH diagnosis has emerged as the next major front in the battle to optimise quality of life, decrease morbidity and improve upon hard clinical event rates that remain unacceptably elevated. This emphasis coincides with accumulating clinical and epidemiological research findings suggesting that opportunities may exist to refine the haemodynamic criteria defining pulmonary hypertension, generally, and PAH, specifically [4, 5]. Indeed, the upper limit of normal mean pulmonary artery pressure (mPAP) converges with data showing that decreased functional capacity and increased mortality in patients at risk for PAH begins at ∼20 mmHg [6]. To modernise clinical practice, the 6th World Symposium on Pulmonary Hypertension (Nice, France) recommended changing the mPAP threshold defining PAH from ⩾25 mm to >20 mmHg [7].

A principal objective of this revision was to capture patients with early-stage PAH, for whom diagnosis and management is overlooked at present. Importantly, an increase in pulmonary vascular resistance (PVR) driven, at least in part, by plexigenic, fibrotic and hypertrophic effacement of pulmonary arterioles is a hallmark feature of PAH [2]. Yet, patients with mildly elevated mPAP are unlikely to meet the PVR threshold of >3.0 WU used to diagnose PAH currently, derived mainly from historical consensus opinion [8]. Thus, revising the mPAP threshold to >20 mmHg also established a need to clarify the optimal PVR for diagnosing PAH inclusive of early stage (mild) disease. Accomplishing this goal in PAH will need to

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draw on information framing PVR values that are normative, pathogenic and associated with favourable response to therapy.

In this issue of the *European Respiratory Journal*, Ratwatte *et al.* [9] add a key piece to the PVR puzzle by leveraging the unique clinical practice patterns in Australian and New Zealand, in which PVR ⩾3.0 WU is not obligatory for treating PAH. The investigators assembled data for 2378 PAH patients enrolled in the PHSANZ registry between 2011 and 2018, and focused on 82 patients for whom the PVR was <3.0 WU. This subgroup had the following haemodynamic profile (medians presented with interquartile ranges): PVR 2.2 (1.9–2.7) WU, mPAP 27 (IQR 25–30) mmHg, pulmonary artery wedge pressure 13 (11–14) mmHg. All patients were prescribed at least an endothelin receptor antagonist (80.4%) or phosphodiesterase type-V inhibitor (19.5%), and 17% were on dual therapy. After a median follow-up of 5 months, 6-min walk distance increased on average by 46 m and one-third of patients improved ⩾1.0 New York Heart Association functional class, with greater effects observed in idiopathic rather than connective tissue disease-associated PAH.

Beyond these findings suggesting salutatory clinical benefit for the study population in the early phase of treatment, some important insights were gained during the long-term follow-up spanning a median 65 months after diagnosis. First, the PVR progressed to >3.0 WU in seven (27%) of the 26 patients undergoing repeat right heart catheterisation at 1 year. This suggests that for some patients, PVR progresses to levels classically associated with PAH (*i.e.* ⩾3.0 WU) soon after diagnosis, and this vulnerable subgroup may be captured earlier when considering a PVR range beginning ∼2.2 WU. Second, the 3-year and 5-year survival rates for the study population were 89% and 83%, respectively, which are more favourable than for other real-world outcome data in PAH populations, including from studies with only dual therapy patients [10]. Taken together, these data begin an important narrative exploring potential opportunity to affect outcome in PAH when considering a PVR threshold <3.0 WU.

As the authors assert, the study population was unique, but modest in size; when coupled with the retrospective study design, this may limit generalisability of the findings to other PAH populations. Further, results of this study do not clarify the optimal cardiopulmonary haemodynamic spectrum to define PAH, or that which should be used to initiate therapy. Indeed, patients with mPAP 21–24 mmHg, now included in the modern-day PAH definition, were not part of the current study. It is noteworthy, however, that PVR ∼2.0–2.2 WU has already been described as the upper limit of normal [5], and is associated with increased clinical events in large unselected populations [11] and connective tissue disease patients [12]. Nevertheless, data from this study are not ready for use in clinical practice, which as the authors clearly state will require further rigorous prospective investigations clarifying how best to interpret PVR <3.0 WU at point-of-care. Results extrapolated from this study could also be used to guide national screening programmes for detecting early stage PAH, already underway in some countries, including France [13].

Ratwatte *et al.* [9] are to be congratulated on these important data, which help build a much-needed framework for contemporising the PAH haemodynamic criteria relative to PVR. These findings should stimulate additional investigations using definitive clinical research methodologies, which were not yet available at the time the current work was assembled, to understand the association between PVR <3.0 WU and therapeutic response in PAH. It is in this way that the field moves toward further improving clinical outcome and, possibly, an era of preventative medicine.

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