**The challenge of an expanded therapeutic window in pulmonary hypertension**

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Our understanding of the causes and consequences of pulmonary hypertension is limited. Consequently, its most distinctive forms with the worst prognosis have been the focus for diagnosis and treatment. We highlight the emerging challenge of reframing the prevalence and prognostic implications of pulmonary hypertension, focusing on the optimal therapeutic window to address the high mortality linked to this condition.

**Historical perspective**

Until the past 5 years, the public health importance of pulmonary hypertension has been largely underestimated. This underestimation largely reflects the practicalities of directly measuring and monitoring mean pulmonary arterial pressures (mPAP) via the gold-standard method of invasive right heart catheterization (RHC).1 The challenges associated with mPAP evaluation predicate that much of the natural history and disease burden of pulmonary hypertension has remained hidden from clinical sight. Consequently, the vast majority of studies on pulmonary hypertension have focused on patient populations characterized by late clinical presentations associated with end-organ damage (most commonly irreversible right heart failure (RHF))2 and by referrals to expert centres for management of specific subtypes of severe pulmonary hypertension with specific therapeutic options (see discussion below).

The classification of pulmonary hypertension predominantly discriminates between precapillary and postcapillary forms of the disease, with underlying lung disease and left heart disease predominant as secondary causes of pulmonary hypertension.1 However, regardless of the aetiology, all patients with a severe form of pulmonary hypertension have a poor prognosis.3Early research on pulmonary hypertension focused purely on pulmonary arterial hypertension (PAH), which was initially referred to as primary pulmonary hypertension. Allowing for diagnostic variability, pulmonary hypertension was arbitrarily defined as a mPAP of >25 mmHg.1 However, on the basis of physiological studies demonstrating that the normal distribution of mPAP is 14.0±3.3 mmHg and rarely exceeded 19.6 mmHg in the absence of disease, the current recommendation is to define pulmonary hypertension as a mPAP of >20 mmHg.4

If we were to rely on specialist centres in pulmonary hypertension to apply RHC investigation alone to detect and then treat newly diagnosed patients with pulmonary hypertension based on these new thresholds, probably nothing much would change for those individuals. First, as noted above, specialist centres by their very nature focus on patients with more advanced pulmonary hypertension with markedly elevated mPAPs and obvious RHF. Second, even if specialist centres were to proactively search for and diagnose milder cases of pulmonary hypertension, beyond comprehensively characterizing the underlying cause, specialist treatment options are limited. However, with the emergence of echocardiography as a reliable, noninvasive surrogate measure of underlying pulmonary hypertension,5 at the very least our capacity to detect this often insidious condition in many more patients has expanded exponentially. Most commonly derived from the peak tricuspid regurgitation velocity with the use of the modified Bernoulli equation (added to the estimated right atrial pressure), an estimated right ventricular systolic pressure (eRVSP) of >30 mmHg is equivalent to the new threshold of pulmonary hypertension (mPAP >20 mmHg).5 In the absence of clinically significant pulmonary stenosis, therefore, eRVSP is a reliable indicator of mPAP.. The challenge of course is to identify not only an abnormal state, but to identify the underlying disease process and to treat it cost-effectively.

**[H1] Current treatment options**

Reflective of the historical context of pulmonary hypertension (from the diagnostic definition to the identification of clear therapeutic targets), a disproportionate focus has been placed on developing therapeutic options for individuals with the rarer, more distinctive forms of precapillary pulmonary hypertension, most notably PAH. Largely driven by commercial interests and the preference for conducting highly focussed clinical trials in small and homogeneous patient populations, an expanding therapeutic armoury is available for targeting the prostacyclin, endothelin, cyclic GMP, calcium channel and nitric oxide pathways involved in increasing pulmonary vascular resistance (PVR) in PAH.1 Almost none of the agents developed and now commonly prescribed for PAH (increasingly as combination therapy) are cheap. Moreover, these agents are typically prescribed to young and very sick individuals with a poor prognosis (owing to a very high mPAP from increased PVR and resultant RHF), and their broader effects if prescribed to more individuals with pulmonary hypertension and on prolonging life rather than providing symptomatic palliation remain unknown.1 Addressing these unknowns will require a substantial amount of investment (from the clinical researchers to the pharmaceutical industry) to develop new therapies for a potentially much larger and heterogeneous patient population. The critical question, of course, is how many more individuals have pulmonary hypertension according to the new diagnostic criteria. Moreover, is there any incentive to expand the therapeutic window in this condition by developing new treatment modalities for an expanded patient population or by testing pharmaceutical agents that are known to therapeutically decrease PVR?

**Reframing pulmonary hypertension**

In support of the reframing of the definition of pulmonary hypertension in 2019 on the basis of physiological observations,4 compelling evidence suggests that mild-to-moderate forms of pulmonary hypertension should not be considered benign. A meta-analysis of 15 studies including a total of 16,482 individuals showed that mPAP above this new threshold is associated with an overall adjusted 1.52-fold (95% CI 1.32–1.74; *P* <0.001) increased risk of death compared with individuals with a normal mPAP (quantified by RHC or echocardiography).6 Whether this increased mortality reflects the effect of related morbidity rather than early, deleterious changes in the right ventricle in response to even mildly elevated pulmonary hypertension remains open to conjecture.7 However, consistent with the latter hypothesis, Huston and colleagues showed in a large, well characterized patient cohort that even mild pulmonary hypertension is associated with prognostically important right ventricular dysfunction and worse right ventricular–pulmonary artery coupling compared with individuals without pulmonary hypertension .8 Moreover, findings from the large, NEDA study9 demonstrated a clearly delineated threshold for the risk of all-cause death and cardiovascular-related death at eRVSP >30 mmHg. Given that this specific finding is consistent with the new diagnostic threshold of pulmonary hypertension ( mPAP >20 mmHg obtained during RHC),4 this result provides a strong case for further exploring prognostically important changes in the pulmonary vasculature and right ventricular structure occurring in response to much lower levels of mPAP than first suspected.

A more granular analysis of the survival profile of the NEDA cohort based on a minimum 5-year profile (*n* = 67,067) and the eRVSP (around 50% of the NEDA cohort had an eRVSP evaluation) offers important and tantalising insights into the number of patients and the life-years they might gain if a broader therapeutic window for pulmonary hypertension was successfully treated (Fig. 1). As can be appreciated in Figure 1, despite the potential confounding of age, a clear inverse relationship exists between the total number of patients with increasingly severe pulmonary hypertension (with fewer patients as the eRVSP increases) and the accumulated premature life-years lost (owing to higher and more premature mortality in patients with more severe elevation of eRVSP than in those with milder eRVSP elevation ). Accordingly, consistent with the current therapeutic focus on those individuals with severe forms of pulmonary hypertension, the ratio of the number of patients (purple bars in Figure 1) to life-years lost (red bars in Figure 1) was the highest for those with an eRVSP >40 mmHg. However, of clinical and therapeutic significance is the additional one in three patients with an eRVSP 30.0–39.9 mmHg, who accumulated 25% of the total number of premature life-years lost in the entire cohort. Overall, >50% of deaths in this substantive group were premature and were associated with 8–10 life-years-lost each time such an even occurred. Through a combination of individuals with a younger age profile and 5-year death rates of >35% overall in this eRVSP range, for each 100 women and 100 men with an eRVSP of 30.0–39.9 mmHg, a total of >200 and >250 premature life-years were lost, respectively. Such numbers are encouraging from a number-needed-to-treat and cost-effective perspectives if a suitable therapy can be found to lower mild-to-moderately elevated mPAP and to prevent RHF and its clinical sequelae.

**[H1] Conclusions**

The exponential improvements in our capacity to accurately screen for pulmonary hypertension via echocardiography and to link observed measurements to long-term outcomes have led to an enormous correction in our estimates of the number of individuals who have this condition, particularly when reframing the normal boundaries of mPAP. Unfortunately, owing to the infancy of research and the heterogeneous nature of pulmonary hypertension (particularly in old individuals in whom multiple pathological pathways might be involved), evidence-based, specific treatment options for the vast majority of patients with mild-to-moderate forms of pulmonary hypertension are almost nonexistent.10 The challenges to rectify this treatment gap are enormous. However, as highlighted in this Comment article, the existence of a substantial patient population who might derive gains in survival and, most notably, in life-years offers clinicians and industry alike with a strong incentive to expand successfully the therapeutic window of pulmonary hypertension.

**References**

1 Galie, N. *et al.* 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* **37**, 67-119, doi:10.1093/eurheartj/ehv317 (2016).

2 Strange, G. *et al.* Time from symptoms to definitive diagnosis of idiopathic pulmonary arterial hypertension: The delay study. *Pulm Circ* **3**, 89-94, doi:10.4103/2045-8932.109919 (2013).

3 Assad, T. R. *et al.* Prognostic Effect and Longitudinal Hemodynamic Assessment of Borderline Pulmonary Hypertension. *JAMA Cardiol* **2**, 1361-1368, doi:10.1001/jamacardio.2017.3882 (2017).

4 Simonneau, G. *et al.* Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J* **53**, doi:10.1183/13993003.01913-2018 (2019).

5 Parasuraman, S. *et al.* Assessment of pulmonary artery pressure by echocardiography-A comprehensive review. *Int J Cardiol Heart Vasc* **12**, 45-51, doi:10.1016/j.ijcha.2016.05.011 (2016).

6 Kolte, D. *et al.* Mild Pulmonary Hypertension Is Associated With Increased Mortality: A Systematic Review and Meta-Analysis. *J Am Heart Assoc* **7**, e009729, doi:10.1161/JAHA.118.009729 (2018).

7 Kovacs, G., Douschan, P., Maron, B. A., Condliffe, R. & Olschewski, H. Mildly increased pulmonary arterial pressure: a new disease entity or just a marker of poor prognosis? *Eur J Heart Fail* **21**, 1057-1061, doi:10.1002/ejhf.1570 (2019).

8 Huston, J. H. *et al.* Association of Mild Echocardiographic Pulmonary Hypertension With Mortality and Right Ventricular Function. *JAMA Cardiol*, doi:10.1001/jamacardio.2019.3345 (2019).

9 Strange, G. *et al.* Threshold of Pulmonary Hypertension Associated With Increased Mortality. *J Am Coll Cardiol* **73**, 2660-2672, doi:10.1016/j.jacc.2019.03.482 (2019).

10 Maron, B. A. & Wertheim, B. M. Toward Early Diagnosis of Pulmonary Hypertension: Lessons From Oz. *J Am Coll Cardiol* **73**, 2673-2675, doi:10.1016/j.jacc.2019.03.473 (2019).

**Competing interests**

The authors declare no competing interests other than that the National Echocardiography Database of Australia (NEDA) was initially co-funded with industry support (including from Actelion Pharmaceuticals).

Fig. 1 | **Relationship between increasing eRVSP and premature all-cause mortality**. The graphs show the relationship between estimated right ventricular systolic pressure (eRVSP) and premature all-cause mortality in women and men during 5 years of follow-up in the NEDA study9. Combined, the 17,065 women (mean age 58±18 years) and 14,750 men (mean age 59±18 years) with no evidence of pulmonary hypertension represented 47% of the cohort (data not shown). At the other end of the spectrum, patients with eRVSP >40 mmHg — which are the most likely to attract clinical attention according to historical diagnostic thresholds and recognition of high risk of death — accounted for 18.5% (median age >77 years) and 19.3% (median age >75 years) of women and men, respectively. Individuals within the new expanded therapeutic window comprised 33.1% (median age 69–74 years) and 34.0% (median age 68–72 years) of women and men, respectively.