Gas exchange: the neglected piece in the PAH puzzle

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Pulmonary arterial hypertension (PAH) remains a deadly disease despite the use of modern therapy, which consists essentially of vasodilators targeting three different pathways, the endothelin, nitric oxide and prostacyclin signalling pathways [1]. Factors helping the clinician to predict prognosis have long been sought after to identify patients at risk for poor survival [2], in order to guide therapy. More recently, the European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines provided a comprehensive, multidimensional risk assessment table based on parameters most frequently used in pulmonary hypertension (PH) centres [3]. These variables would be obtained on regular visits with the understanding that not all would necessarily be checked at each visit. While most of the chosen variables and their cut-off criteria were based on expert opinion, the risk stratification assessment hence proposed was rapidly validated, mainly retrospectively, by various groups using their own PAH cohorts [4–6]. Boucly *et al.* [6] further demonstrated, in a subgroup of patients, that achieving adequate thresholds for three non-invasive criteria (World Health Organization/New York Heart Association functional class, 6-min walk distance and brain natriuretic peptide/N-terminal pro-BNP) at first re-evaluation also helped discriminate prognostic groups. Interestingly enough, markers of gas exchange are not part of current risk assessment strategies.

In this issue of the *European Respiratory Journal*, Valentin *et al.* [7] performed a retrospective analysis of the French Registry of Pulmonary Hypertension to determine the clinical characteristics and outcomes of incident, treatment-naïve patients with PAH displaying a greater than 3% decrease in arterial oxygen haemoglobin saturation (S_{aO_2}) while receiving treatment with PAH drugs. Patients with congenital heart disease and PAH associated with features of venous/capillary involvement were excluded for obvious concerns of oxygen desaturation in these patients. 24% out of the total studied cohort of 719 PAH patients were identified as having >3% desaturation on treatment. When re-evaluated in follow up, using a risk stratification methodology based on the ESC/ERS guidelines [3], these patients were less likely to be in the low risk stratification category, more likely to have required long-term supplemental oxygen, and were found to have an overall poorer survival. In a multivariate Cox analysis, the authors determined that a ⩾3% decrease in S_{aO_2} was a prognostic factor independent of age, when using ESC/ERS risk stratification at follow-up. The message conveyed by this study is that a relatively significant proportion of PAH patients, when started on PAH drugs, develop oxygen desaturation, which portends somber clinical implications, including poor survival.

This study brings a novel prognostic indicator to the risk assessment of patients with PAH. Despite its retrospective nature, it was well conducted, and large enough due to its inclusion of multiple centres. In addition, exclusion criteria were appropriate, and one is to assume there was adequate phenotyping of PAH patients under the aegis of the French Registry of PH. However, there are limitations to this study that need emphasis, some of which are appropriately addressed by the investigators, such as the retrospective nature of the study. There was a fair number of missing data from the registry patients, a problem inherent to any retrospective analysis, which led to the exclusion of almost 20% of the cohort for the proposed analysis.

However, there were no significant differences in demographics, lung function and haemodynamic data between included and excluded patients, which is certainly reassuring.

The relatively large proportion of smokers or ex-smokers (no casual smokers considering the average 31 pack-year history in the relatively small subgroup of patients in whom a smoking history could be obtained) combined with the lack of imaging studies cannot obviate the fact that some patients may have had co-morbid conditions such as emphysema, COPD or mild interstitial lung disease [8, 9]. This admixture of smokers/ex-smokers may explain why mean oxygen saturation was overall relatively low in this cohort. This could also explain that some patients were more prone to oxygen desaturation in response to vasodilators (by virtue of worsening ventilation/perfusion mismatch) and were, therefore, more susceptible to complications including death from a co-morbid burden. The inclusion of patients with connective tissue disease (CTD) was also a concern, considering these patients tend to have a lower diffusion capacity to carbon monoxide (D_{LCO}), may be more susceptible to the effect of vasodilators, and have worse survival compared to other forms of group 1 PAH disease [10]. To their credit, the investigators performed sensitivity analyses that confirmed that the prognostic value of desaturation was no different between idiopathic PAH and CTD-PAH patients.

It is also noteworthy that among considered co-morbid conditions (table 1 in the study [7]), COPD was not included. In this regard, a concerning result is the finding that the >3% decrease in S_{aO_2} loses its predictive value when incorporating D_{LCO} in the multivariate Cox analysis, which suggests that these two values are linked and may reflect some underlying parenchymal lung disease or a distinct pulmonary vasculopathy in the cohort with oxygen desaturation at reassessment. The patients who had S_{aO_2} drop greater than 3% were also older (64 *versus* 58 years old) and had on average a D_{LCO} of 42±17% of predicted. This particular group of patients is known to have higher mortality [11]. Therefore, one might speculate that baseline D_{LCO}, which is an indirect assessment of gas exchange and the integrity of the alveolar gas exchange unit is sufficient for adequate prediction. Thus, why would there be a need for a complex approach with measurement of oxygen saturation the way obtained in this study (*i.e.* calculated using the Severinghaus' equation, which requires blood gas analysis)? A final note on this measurement and PAH prediction is that D_{LCO} less than 40% predicted is included in the REVEAL risk score calculator 2.0 [12] but not included in the ESC/ERS risk stratification [5] or the newly revised REVEAL Lite 2 calculator [12].

What are the practical implications of this study? First, gas exchange must be higher on the radar of physicians treating patients with PAH. It has already been shown that a low arterial carbon dioxide tension at baseline and during follow-up has prognostic relevance independent of established variables [13], and now we learn that the same is true for the trajectory of S_{aO_2} during follow-up. Second, there is very little data from randomised clinical studies on the effects of approved PAH drugs on gas exchange. Therefore, it is important that future clinical trials collect and report such data, at least as safety parameters. Third, the present study adds to the accumulating evidence showing that among patients with PAH, there is a phenotype characterised by a particularly low D_{LCO}, which is probably a marker of a widespread loss of pulmonary capillaries and post-capillary venules [11, 14, 15]. While the mechanisms leading to such a particular pulmonary vasculopathy may be different in patients with idiopathic PAH, CTD-PAH or other forms of PAH, the common notion is that these patients tend to respond poorly to PAH drugs, may experience a drop in their oxygen saturation when receiving PAH medications, and have a particularly poor survival. It is unknown whether the drop in oxygenation observed in such patients is simply a biomarker indicating the presence of a distinct pulmonary vasculopathy or a contributor to the heightened mortality risk in such patients. In any case, oxygen saturation needs to be monitored on a regular basis during the course of the disease and taken into account when making treatment decisions. Lastly, this study brings up one of the limitations of our treatment-oriented classification system, which aims at grouping patients who might be managed similarly while ignoring pathophysiologic heterogeneity within a PAH subgroup, as highlighted in the present study. Perhaps it is time to also consider underlying pathophysiology in identifying homogeneous subgroups of patients within the PH classification.

Valentin *et al.* [7] should be commended for their meticulous work. In refining prognostic factors that might be important in a lethal disease such as PAH, investigators have focused on simplicity to propose specific, preferably non-invasive, parameters [4–6, 12]. While it is wise to use Occam's razor whenever possible, one should however not lose sight of the context and other factors that might explain certain destinies.

Conflict of interest: P.M. Hassoun serves on a scientific advisory board for Merck. R. Souza has no potential conflicts of interest to disclose. M.M. Hoeper has received fees for lectures and/or consultations from Acceleron, Actelion, Bayer, GSK, Janssen, MSD and Pfizer.

References

1 Galie N, Channick RN, Frantz RP, *et al.* Risk stratification and medical therapy of pulmonary arterial hypertension. *Eur Respir J* 2019; 53: 1801889.

2 D'Alonzo GE, Barst RJ, Ayres SM, *et al.* Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991; 115: 343–349.

3 Galie N, Humbert M, Vachiery JL, *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). *Eur Respir J* 2015; 46: 903–975.

4 Hoeper MM, Kramer T, Pan Z, *et al.* Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. *Eur Respir J* 2017; 50: 1700740.

5 Kylhammar D, Kjellstrom B, Hjalmarsson C, *et al.* A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. *Eur Heart J* 2018; 39: 4175–4181.

6 Boucly A, Weatherald J, Savale L, *et al.* Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. *Eur Respir J* 2017; 50: 1700889.

7 Valentin S, Maurac A, Sitbon O, *et al.* Outcomes of patients with decreased arterial oxyhaemoglobin saturation on pulmonary arterial hypertension drugs. *Eur Respir J* 2021; 58: 2004066.

8 Lewis RA, Thompson AAR, Billings CG, *et al.* Mild parenchymal lung disease and/or low diffusion capacity impacts survival and treatment response in patients diagnosed with idiopathic pulmonary arterial hypertension. *Eur Respir J* 2020; 55: 2000041.

9 Godinas L, Harari S, Barbera JA, *et al.* Mild parenchymal lung disease is still lung disease. *Eur Respir J* 2020; 56: 2003542.

10 Chung L, Liu J, Parsons L, *et al.* Characterization of connective tissue disease-associated pulmonary arterial hypertension from REVEAL: identifying systemic sclerosis as a unique phenotype. *Chest* 2010; 138: 1383–1394.

11 Trip P, Nossent EJ, de Man FS, *et al.* Severely reduced diffusion capacity in idiopathic pulmonary arterial hypertension: patient characteristics and treatment responses. *Eur Respir J* 2013; 42: 1575–1585.

12 Benza RL, Kanwar MK, Raina A, *et al.* Development and validation of an abridged version of the REVEAL 2.0 risk score calculator, REVEAL lite 2, for use in patients with pulmonary arterial hypertension. *Chest* 2021; 159: 337–346.

13 Harbaum L, Fuge J, Kamp JC, *et al.* Blood carbon dioxide tension and risk in pulmonary arterial hypertension. *Int J Cardiol* 2020; 318: 131–137.

14 Hoeper MM, Vonk-Noordegraaf A. Is there a vanishing pulmonary capillary syndrome? *Lancet Respir Med* 2017; 5: 676–678.

15 Hoeper MM, Pausch C, Grunig E, *et al.* Idiopathic pulmonary arterial hypertension phenotypes determined by cluster analysis from the COMPERA registry. *J Heart Lung Transplant* 2020; 39: 1435–1444.