Floating the invisible swan: noninvasive prediction of haemodynamics

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Pulmonary hypertension (PH) describes a heterogeneous set of diseases associated with increased morbidity and mortality, regardless of the aetiology [1–4]. The gold standard for diagnosing and phenotyping PH remains invasive measurement *via* right heart catheterisation [5]. Noninvasive estimation of pulmonary haemodynamics is an attractive alternative to reduce procedural risk and to more broadly study patient subsets who do not uniformly undergo right heart catheterisation for evaluation of PH (*e.g.* most patients with PH due to left heart disease) [5–7]. However, imperfect correlations between invasive and noninvasive measurements limit broad adoption of noninvasive strategies for the evaluation of PH [8–13].

In this issue of the *European Respiratory Journal*, Obokata *et al.* [14] identified an important contributor to the noninvasive estimation of pulmonary artery (PA) pressure with exercise: right atrial (RA) hypertension. In their study of 97 patients who underwent simultaneous collection of echocardiographic estimates and invasive measures of haemodynamics, the authors showed a moderate-to-strong correlation between invasive measurements and noninvasive estimates of PA pressure, right ventricle (RV) to PA gradient, and RA pressures at rest. In agreement with previous studies, Bland–Altman analysis of their data confirmed minimal bias between invasive and noninvasive measurements despite large limits of agreement [15, 16]. In other words, noninvasive estimates performed well on a population level but individual level correlations were weaker, which introduces important concerns for misclassification. At peak exercise, echocardiographic measures consistently underestimated true PA pressure estimates (by 3–6 mmHg on average), largely driven by underestimation of RA pressure during exercise (by 5 mmHg on average). In contrast, the measurement of the RV–PA gradient (*i.e.* tricuspid regurgitation peak velocity) correlated with invasive measurements with almost no bias (r=0.73, 0–1 mmHg bias), suggesting this measure in isolation may be the most valuable for identifying patients with elevated pulmonary pressures noninvasively. Of note, these findings were limited by the ability to estimate PA systolic pressure in only 16% of patients during exercise, largely driven by the inability to visualise the inferior vena cava.

The work by Obokata *et al.* [14] has two important implications. The first is that their work highlights the importance and under-recognised contribution of RA hypertension to the development of exercise-induced PH. Recent studies have identified RA dysfunction as both prevalent and prognostically important in patients with World Health Organization (WHO) group 1 PH [17]. However, detailed pathophysiological study of exercise-induced PH has been hampered by the lack of consensus regarding thresholds for diagnosis, the variability in protocols utilised for exercise, and the invasive nature of the

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study required for diagnosis [18]. Although Obokata *et al.* [14] contribute to the known literature by showing similar abnormalities in the RA in their subset of patients highly enriched for WHO group 2 PH, the broadly generalisability of this finding to all subsets of patients with either exercise-induced or resting PH remains unclear. Furthermore, since elevations in RA pressure can occur through various mechanisms (post-capillary venous hypertension and increased back flow, increased pericardial restraint or pressure, abnormalities in RV–PA coupling, or primary abnormalities of RA function), replication of the findings by Obokata *et al.* [14] is necessary to understand the role of RA pressure and function in all subsets of patients with PH.

The second implication of this important work by Obokata *et al.* [14] is the finding that noninvasive estimation of RA pressure poorly correlated with and consistently underestimated true RA pressure using the standard American Society of Echocardiography methods for estimating RA pressure [19]. This bias was notably mitigated, but not eliminated, by using a modified Mayo Criteria for RA pressure estimation. As noted by the authors, the discrepancies between invasive and noninvasive PA pressure estimates was almost entirely accounted for by discrepancies in RA pressure estimate, a finding that may explain previous discrepancies between invasive and noninvasive haemodynamic measures [8–13]. This finding highlights a call to action to identify better noninvasive methods of estimating RA pressure. In addition to refining noninvasive haemodynamic measurements of pulmonary and post-capillary pulmonary pressures, measurement of RA pressure has clear implications for everyday practice (*e.g.* jugular venous pressure estimation). On a population level, most patients at risk for exercise-induced PH or RA hypertension (*i.e.* patients with heart failure or COPD) do not routinely undergo invasive right heart catherisation, thus making accurate noninvasive estimates even more important.

Finally, the study by Obokata *et al.* [14] contributes to the growing literature that has demonstrated the feasibility of population-level noninvasive estimations of haemodynamics [15, 16]. Key gaps in our understanding of the pathophysiology of pulmonary vascular disease and inconsistent translation from pre-clinical models to patients has led to a greater interest in the use of large patient-derived datasets for gaining insight into the pathogenesis of pulmonary vascular disease [20, 21]. Additionally, exercise studies are challenging, require specific expertise, and are not performed at all centres. These limitations have led to inconsistent understanding of the clinical, biological and prognostic implications of altered haemodynamics during exercise [22, 23]. Aggregate data utilising noninvasive measures would not only include subsets of populations that otherwise would not be included in studies limited to invasively measured haemodynamics, but also ultimately help to standardise the technique of assessing exercise-induced PH. Fortunately, large scale efforts are already ongoing through the "pulmonary haemodynamics during exercise – research network" (PEX-NET) to address the current lack of standard in exercise pulmonary haemodynamics based on invasive haemodynamics [24]. Findings from the PEX-NET research network will only further inform adequate endpoints in noninvasive estimation of haemodynamics during peak exercise.

In summary, the authors are congratulated on a study that has clear clinical implications. In addition to identifying RA hypertension as an important contributor to exercise-induced PH, their work also raises awareness that exercise-induced PH may be underdiagnosed due to underestimation of noninvasive estimates of RA pressure. Beyond identifying future avenues of investigation to improve noninvasive prediction of invasive haemodynamics, their work also paves the way to utilising vast and growing data from real world populations to study the pathophysiology of cardiopulmonary disease.

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