Pulmonary hypertension at high altitude

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In the present issue of the *European Respiratory Journal*, Soria *et al.* [1] report on a meta-analysis of echocardiographic estimates of systolic pulmonary artery pressure (sPAP) in 287 patients (nine studies) with chronic mountain sickness (CMS) at rest and in 142 of them (five studies) also at exercise. The results are surprising. Mean pulmonary artery pressure (mPAP), here recalculated as 0.6×sPAP+2 mmHg [2], was on average 18 mmHg (95% CI 16–20 mmHg) at rest and 31 mmHg (95% CI 29–33 mmHg) during exercise, suggesting no pulmonary hypertension (PH) at rest but mild PH during exercise. The same authors had previously reported on a similar meta-analysis in a larger number of 834 healthy high altitude dwellers at rest, showing a mPAP of 18 mmHg and a maximum of 24 mmHg, compared to 13 mmHg and a maximum of 20 mmHg, respectively, in sea level controls [3]. On the basis of these data altogether, Soria *et al.* [1] conclude that high altitude dwellers with or without CMS have no PH at rest, but CMS patients commonly present with exercise-induced PH, which may be of symptomatic and of prognostic relevance. This is provocative, as altitude is listed as "hypoxia without lung disease" in the updated classification of PH, and experts remain unconvinced about the notion of exercise-induced PH [4].

The upper limit of normal of resting mPAP is 20 mmHg [5]. PH used to be defined by mPAP ⩾25 mmHg, allowing for a 5 mmHg safety margin to decrease the likelihood of false-positives [6–8]. This cut-off value was most recently brought down to 20 mmHg based on the evidence of prognostic and functional relevance of all-cause higher than normal values [4]. In the meantime, altitude experts still define PH by mPAP ⩾30 mmHg (sPAP ⩾50 mmHg) [9]. Thus, altitude dwellers have PH or not, depending on definitions. With the "traditional" definition of a mPAP ⩾25 mmHg, less than 1% of high altitude dwellers would suffer from PH. With the definition of mPAP⩾30 mmHg, PH at high altitudes should be very rare. A consensus evidence-based revised definition of PH at high altitudes is obviously needed. As it is, one does not know whether PH is a public health problem or a rarity for the estimated 120 million people living at altitudes higher than 2500 m.

Exercise increases mPAP because of associated increases in cardiac output (CO) and pulmonary artery wedge pressure (PAWP). The upper limits of normal for mPAP–CO and PAWP–CO relationships have been proposed to be 3 mmHg·min·L^{-1} and 2 mmHg·min·L^{-1}, respectively [10, 11]. These cut-off values were recently confirmed [12, 13]. Thus, total pulmonary vascular resistance (PVR), or mPAP/CO should not normally exceed 3 mmHg·min·L^{-1} during exercise, and higher values define "exercise PH" [14]. Exercise PH would also be defined by PVR or (mPAP−PAWP)/CO exceeding 2 mmHg·min·L^{-1} [11]. Soria *et al.* [1] estimated exercise PVR of 2.7±0.3 mmHg·min·L^{-1} in CMS patients and 2.2± 0.6 mmHg·min·L^{-1} in healthy highlander controls, suggesting that mild exercise PH might indeed be common at high altitudes. However, a correction for haematocrit using a recently introduced diagram [15]

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smoothed out the difference between CMS patients and controls. The authors did not address the issue of the contribution of increased haematocrit to high altitude exercise PH.

Altitude exposure is associated with adaptive increase in red blood cell mass. In CMS, this response is excessive, resulting in polycythaemia (*i.e.* greater than mean+2SD of healthy altitude controls), severe hypoxaemia and neurological symptoms, such as headache, somnolence, fatigue and depression [9]. CMS occurs in native or long-term residents above 2500 m, and is reversible at lower altitudes. Diagnostic cut-off values are haemoglobin $\geqslant$21 g·dL^{-1} in men, and $\geqslant$19 g·dL^{-1} in women. The underlying mechanism accounting for CMS is a loss of ventilatory adaptation to altitude [16]. Increased haemoglobin levels in these patients contribute to hypoventilation by allowing for more carbon dioxide output at any given level of carbon dioxide tension [17].

Increased red blood cell mass during high altitude exposure increases blood viscosity. The relationship between PVR and blood viscosity is linear. The relationship between haematocrit and blood viscosity is curvilinear. Estimates of PVR for the diagnosis of pulmonary vascular disease at high altitudes can be corrected for haematocrit, which is easier to measure than viscosity. Correction equations are complex, and thus best replaced by a diagram plotting PVR as a function of haematocrit [15]. It is intriguing that haematocrit-corrected PVR was found to be similar in high altitude Andean Quechua, Himalayan Sherpa or high altitude sojourners [18]. Pioneer studies in the 1950s had already concluded that hypoxic PH on the Andean altiplano was mainly explained by an increased haematocrit [19].

One could wonder if exercise PH, at the level seen at high altitudes, could impair the coupling of right ventricular (RV) function to the pulmonary circulation. This does not seem to happen. Echocardiographic studies of the RV in CMS patients at rest and at exercise have shown an adequate increase in RV contractility to preserve RV–pulmonary artery (PA) coupling [20]. Combined cardiopulmonary exercise testing and echocardiographic examinations have shown that maximum oxygen uptake is preserved in spite of steep mPAP–CO relationships in CMS patients, suggesting no RV limitation to aerobic exercise capacity [21]. Steep mPAP–CO relationships in exercising CMS patients have been shown to be associated with increased lung water, as assessed by lung ultrasound measurements [22], but the clinical significance of this observation is uncertain.

All this is not to say that severe PH never occurs at high altitudes. It has been reported by field invasive studies, though in small numbers and probably fraught with referral bias [23]. It has been occasionally confused with idiopathic pulmonary arterial hypertension triggered in children by chronic hypoxic exposure [24]. Severe PH has been reported as a cause of high altitude pulmonary oedema [25] or high altitude-induced right heart failure [26] in altitude sojourners with uncommonly brisk hypoxic pulmonary vasoconstriction. Right heart failure syndromes have been reported as "brisket disease" in cattle [27] or as "subacute mountain sickness" in children [28] or adults [29] during prolonged stays at high altitudes. Brisket is a butchery term, and CMS has per definition no heart failure component or any preceding acute or sub-acute stages. Therefore, these terminologies are therefore better replaced by the more easily understood "high altitude-induced right heart failure".

The study by Soria *et al.* [1] could be criticised for relying exclusively on Doppler echocardiography of the pulmonary circulation. However, as underscored by the authors, sPAP calculated from the maximum velocity of tricuspid regurgitation compared to its invasive measurement has been shown to be accurate (no bias on Bland and Altman analysis) but with limited precision (wide limits of agreement on Bland and Altman analysis) at rest [30] and at exercise [31]. Accurate methods with limited precision are adequate for population studies, but less so for individual decision-making [30]. The accuracy of Doppler echocardiography for estimates of CO and PAWP at rest has been shown to be acceptable as well [30], but may require further validation in exercise [32]. In general, exercise stress echocardiography is nowadays a sufficiently validated approach for the detection and diagnosis of a variety of cardiovascular conditions, including PH and RV-PA uncoupling [32].

Soria *et al.* [1] are to be commended for setting the stage for a better understanding of purely hypoxic PH and its place in current PH classifications. Their studies are enlightening, but also show how much remains to be done. Altitude experts should be invited to participate in future PH expert meetings to agree on revised definitions and terminology. Noninvasive approaches should be further validated and extensively implemented. To what extent PH and right heart failure are public health problems or rarities in high altitude communities needs to be addressed with updated methodology and large scale population studies.

Conflict of interest: None declared.

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