Proposed new definition of exercise pulmonary hypertension decreases false positive cases

To the Editor:

The exercise part of the haemodynamic definition of pulmonary hypertension (PH) was used between the first (1973) [1] and fourth (2008) [2] world conferences on PH for patients with a mean pulmonary arterial pressure (mPAP) >30 mmHg during exercise. However, at the World Symposium on Pulmonary Hypertension in Dana Point in 2008, this part of the PH definition was abandoned, mainly due to the fact that pulmonary arterial pressure (PAP) values during exercise are strongly dependent on age and exercise level [3], and a definition based on a single parameter such as PAP may not be reliable. The analysis of historical studies [3, 4] and the generation of novel data [5–8] have led to a better understanding of exercise haemodynamics. HERVE et al. [7] suggest a new definition of exercise-PH that includes not only PAP, but also total pulmonary resistance (TPR), calculated as mPAP/cardiac output, representing the steepness of PAP increase during exercise. According to this definition, exercise-PH may be diagnosed if during maximal exercise mPAP >30 mmHg and TPR >3 Wood units (WU). This may reduce the number of false positive exercise-PH diagnoses in healthy subjects who develop high mPAP values at excessive exercise levels.

We applied the old and the suggested new definition of exercise-PH to a historical cohort of normal subjects whose individual invasively assessed haemodynamic data were published in the scientific literature [3, 4]. In addition, we asked whether the assessment of pulmonary arterial wedge pressure (PAWP) and pulmonary vascular resistance (PVR) during exercise in addition to TPR might provide additional information about subjects with elevated PAP values during exercise.

Our databank contains all invasively assessed haemodynamic data at rest and during exercise of 1187 subjects, which were published in 47 historical studies. We assumed that all subjects were healthy in terms of haemodynamics. Exercise was performed on a cycle ergometer in the supine position in the majority of cases. Only subjects for whom at least mPAP and cardiac output and systemic blood pressure were available at rest and during exercise were included. Subjects with PAWP values at rest and exercise, where PVR could be calculated, were analysed separately. We did not correct or exclude implausible values, which were detected in a few cases. To describe the correlation between mPAP and PAWP as well as PVR and TPR, Spearman rank correlation was used, and p<0.05 was considered statistically significant.

We included 160 subjects out of 13 studies with complete mPAP and cardiac output values (female/male/unknown 26/120/14; mean±SD age 33±18 years, height 176±8 cm and weight 69±11 kg). Out of these, PAWP and thus PVR values were also available in 104 subjects. 22 out of 160 (13.8%, 95% CI 8.5–19.1%) subjects fulfilled the historical definition of exercise-PH (mPAP >30 mmHg at maximal exercise). Assuming that all subjects were healthy, this means that one out of eight subjects would have been falsely classified as exercise-PH (fig. 1a). The proposed new definition (mPAP >30 mmHg and TPR >3 WU at maximal exercise) would only classify four out of 160 subjects (2.5%, 95% CI 0.1–4.9%) as exercise-PH (fig. 1a). Interestingly, all these four subjects were aged >65 years. Another four subjects (three of them aged >65 years) fulfilled the criteria of the proposed new definition at a submaximal, but not at the maximal exercise level. PAWP was strongly correlated with mPAP at maximal exercise (p=0.72, p<0.001; fig. 1b). Among the eight subjects with TPR >3 WU at maximal exercise, depending on their maximal PAWP values, subjects with high and low PVR values could be distinguished (fig. 1c), providing an opportunity for further haemodynamic differentiation based on PVR.

A strong increase in PAP during exercise has always been considered to be an inadequate adaptation of the pulmonary circulation, which may be due to different pathological mechanisms including pulmonary vascular disease, left heart dysfunction or air trapping in obstructive pulmonary diseases. Based on physiological considerations and recent studies [9], the steepness of the mPAP/cardiac output slope was suggested instead of the mPAP alone as decisive parameter for exercise-PH. This has been supported by the study by HERVE et al. [7] and is reflected in the proposed new definition of exercise-PH. In our analysis we confirm that the use of this definition reduces the number of false positive cases compared to the historical definition, and may represent an important step forward.
However, the analysis of the historical data revealed some new insights that could further refine our understanding of exercise-PH:

1) In a few subjects the criteria of the suggested new definition were fulfilled at a submaximal exercise level, but no more at maximal exercise. Such individuals would be categorised as exercise-PH if they were to stop exercise prematurely. Such subjects have a PAP/cardiac output slope flattening out at higher exercise values, resulting in a late decrease of TPR < 3 WU. This pattern may be quite typical in elderly subjects, where the filling resistance of the left ventricle increases during mild exercise before it decreases during heavy exercise [4].

2) There may be subjects with maximal cardiac output < 10 L·min$^{-1}$, e.g. due to muscular limitation, where the interpretation of exercise data is difficult (fig. 1d). These subjects may have a TPR > 3 WU without reaching mPAP > 30 mmHg (fig. 1a and d). According to the suggested new definition these individuals are not considered as exercise-PH although their TPR is suggestive of pulmonary vascular disease (increased PVR), left heart dysfunction (increased PAWP) or both.

3) An increased TPR during exercise may have several causes. There may be some degree of pulmonary vascular disease which is recognised if PVR is closely monitored. Alternatively, there may be increased...
PAWP values due to a latent diastolic left heart disease, and finally there may be some air trapping, even in mild obstructive pulmonary diseases. Such an air trapping causes an increase in both mPAP and PAWP and increases TPR, but leaves PVR unchanged [10]. This means that an increased PVR should be more specific for pulmonary vascular changes. Unfortunately we have no international consensus on the normal range of PVR during exercise. Based on our previous study [4] the upper level of normal (mean+2 sd) for PVR in normal subjects at higher exercise levels may be ~1.5 WU. This corresponds to mPAP 22.7±5.6 mmHg, PAWP 11.8±4.5 mmHg and cardiac output 17.8±4.2 L·min⁻¹. These values might provide a basis to define pulmonary vascular disease.

Interestingly, all four presumably healthy subjects in our analysis fulfilling the proposed criteria for exercise-PH were aged >65 years. This might suggest that the novel definition needs to be validated and, potentially, modified in elderly subjects. In these individuals exercise haemodynamics may be significantly different from younger individuals and in most studies only very few elderly subjects were included.

One of the important limitations of our analysis regards the subject population analysed. We accepted the statements of the primary authors that all participating subjects were healthy, or that their diseases did not influence pulmonary haemodynamics, yet we cannot exclude the possibility that unidentified diseases influenced pulmonary pressure or flow. Nevertheless, this collective represents the largest available database with invasive pulmonary haemodynamic data during exercise and we believe that the findings are suitable to raise important questions for further scientific discussions.

In conclusion, the proposed new definition of exercise-PH by Herve et al. [7] decreased the rate of false positive findings in healthy subjects from 13.7% to 2.5%. The additional consideration of cardiac output and PVR during exercise may provide further information and help to distinguish patients with latent left heart disease from those with early pulmonary vascular disease.

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The proposed novel definition for exercise-PH reduces numbers of false positives and may be an important step forward http://ow.ly/U2z7n

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