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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 (figure 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 (figure 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 (ρ=0.72, p<0.001; figure 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 (figure 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

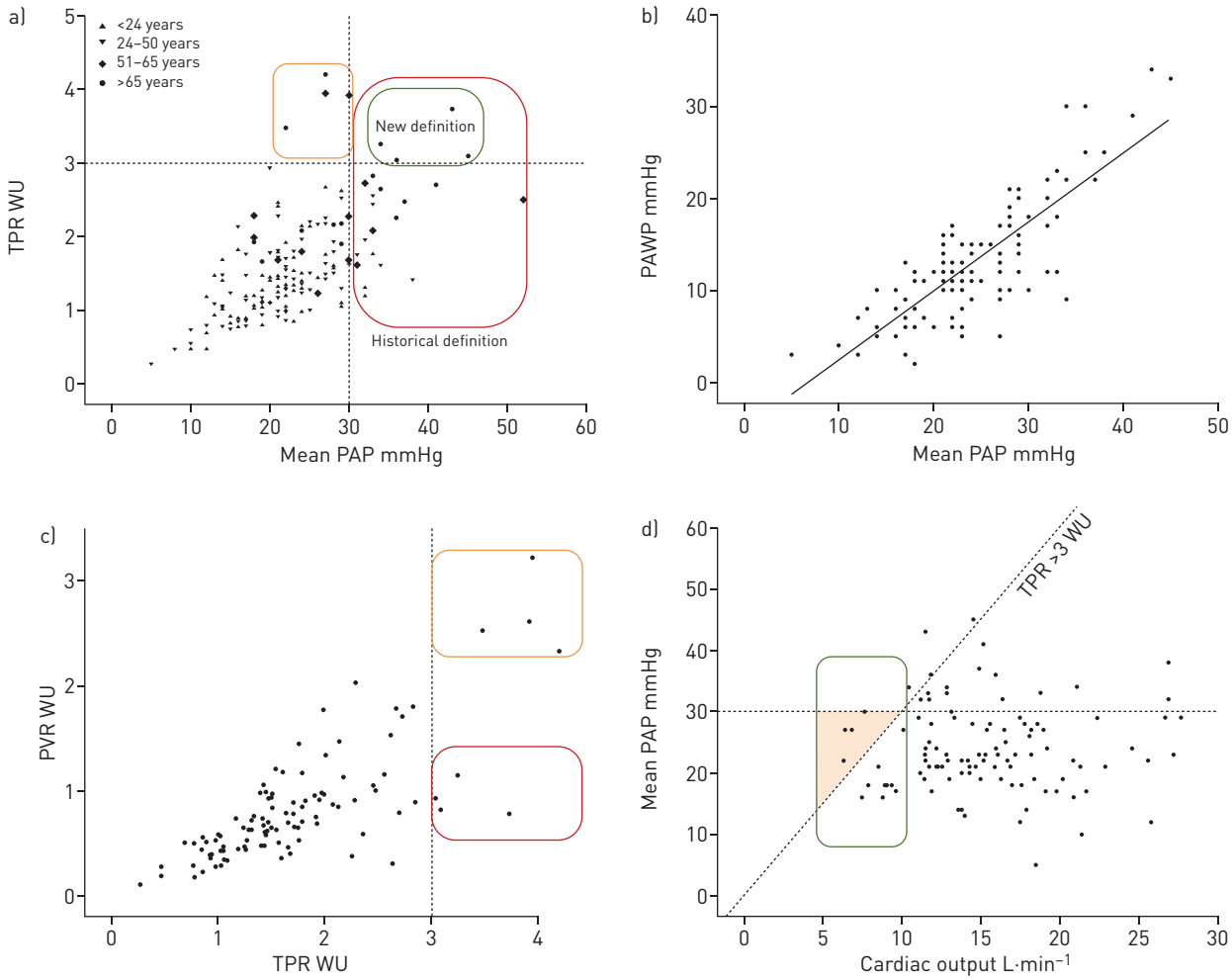

FIGURE 1 a) Mean pulmonary arterial pressure (mPAP) *versus* total pulmonary resistance (TPR) in 160 healthy individuals at maximal exercise. Patients with exercise pulmonary hypertension (PH) according to the historical definition (mPAP >30 mmHg) and patients with exercise-PH according to the suggested new definition (mPAP >30 mmHg and TPR >3 Wood units (WU)) are shown; the orange area (see also orange triangle in fig. 1d) represents subjects with TPR >3 WU (either due to increased pulmonary vascular resistance (PVR) or increased pulmonary arterial wedge pressure (PAWP)), but mPAP ⩽30 mmHg, due to peripheral muscular limitation. b) PAWP *versus* mPAP in 104 healthy individuals at maximal exercise (ρ=0.72). c) TPR *versus* PVR in 104 healthy individuals at maximal exercise. Among subjects with TPR >3 WU, depending on their PAWP values (red box: subjects with higher PAWP and lower PVR; orange box: subjects with lower PAWP and higher PVR during exercise), individuals with substantially different PVR values may be distinguished (ρ=0.74, p<0.001). d) mPAP *versus* cardiac output in 160 subjects at maximal exercise. The lines represent the thresholds of the proposed new definition of exercise-PH (mPAP >30 mmHg and TPR >3 WU). The green box shows subjects not reaching a maximal cardiac output of 10 L·min^{-1}. Among these, some subjects had a TPR >3 WU (orange triangle), which might represent early pulmonary vascular disease or left heart dysfunction (see also orange area in figure 1a).

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 $L \cdot min^{-1}$, *e.g.* due to muscular limitation, where the interpretation of exercise data is difficult (figure 1d). These subjects may have a TPR >3 WU without reaching mPAP >30 mmHg (figure 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 $L \cdot min^{-1}$. 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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Tuberculosis in migrants from 106 countries to Italy, 2008–2014

To the Editor:

Tuberculosis (TB) is a major infectious disease worldwide. Over recent years, TB caused by multidrug-resistant (MDR) *Mycobacterium tuberculosis* strains (resistant to at least isoniazid and rifampicin) and extensively drug-resistant (XDR) strains (MDR strains resistant to any fluoroquinolone and to at least one injectable second-line drug (SLD), *i.e.* kanamycin, capreomycin or amikacin) has emerged as a public health concern in industrialised countries, due to increasing migration from regions where TB is endemic.

In Italy, while the number of TB cases decreased from 4220 in 2004 to 3153 in 2013 (7.3 and 5.3 cases per 100 000 population, respectively) [1, 2], notifications from foreign-born persons (FBPs) increased from 39.4% in 2004 to 63% in 2013. The association of MDR-TB with immigrant status was previously reported [3, 4] but a systematic study of the country of origin of migrants was not performed. The European Centre for Disease Prevention and Control (ECDC) published a report on key infectious diseases (including TB) affecting migrant populations in the European Union/European Economic Area for the years 2000–2010 [5]. Here, we conducted a retrospective analysis in Italy over the period 2008–2014 in order to estimate TB burden and MDR/XDR-TB in FBPs by country of origin, in comparison with Italian-born persons (IBPs), and to determine resistance to SLDs in MDR/XDR *M. tuberculosis* clinical isolates.

Our laboratory network, the Italian Multicentre Study on Resistance to Antituberculosis drugs (SMIRA), is composed of 35 hospital reference laboratories located in 18 out of 20 regions. All the laboratories are periodically examined by first-line drug (FLD) and SLD proficiency testing exercises by the World Health Organization (WHO) Supranational Reference Laboratory in Rome [6]. In 2013, the SMIRA network covered 74.5% of nationwide notified cases, contributing the majority of cases included in the annual ECDC/WHO TB report [2].

TB cases with positive *M. tuberculosis* cultures were routinely examined by the SMIRA laboratories for susceptibility to FLD and SLD. Table 1 shows data on drug resistance of 13 030 *M. tuberculosis* strains with known country of origin (6869 from FBPs and 6161 from IBPs) isolated from 13 030 different patients in 2008–2014. Due to difficulties in obtaining a reliable history of prior treatment in FBPs, we were not able to distinguish new cases from previously treated cases, thus the number of TB cases included both categories. MDR-TB cases decreased from 3.7% in 2008 to 3.1% in 2014.

M. tuberculosis strains were isolated from migrants coming from 106 countries, including patients with MDR strains from 37 countries and with non-MDR strains from 69 countries (table 1). Data of MDR strains from