EDITORIAL

The new definition of pulmonary hypertension

M.M. Hoeper

Despite the progress that has been made in the field of pulmonary hypertension (PH) [1–3], there is no unifying and globally accepted definition of the condition. The first official haemodynamic definition of PH was proposed at the First World Symposium on Pulmonary Hypertension which took place in 1973 in Geneva, Switzerland as a World Health Organization (WHO)-sponsored meeting [4]. This conference was triggered by the previous epidemic of PH associated with the appetite suppressant aminorex [5]. As such, the focus of that meeting was primary pulmonary hypertension (PPH), as compared to the other forms of PH. After a long and sometimes heated debate the consensus was to define PPH by a mean pulmonary artery pressure ($P_{pa}$) $>25$ mmHg at rest or $>30$ mmHg during exercise in the presence of a pulmonary capillary wedge pressure ($P_{pcw}$) $\leq 15$ mmHg.

This definition was later extended to other forms of pulmonary arterial hypertension (PAH) [6]. It stood the test of time for $>30$ yrs, but was challenged during the Fourth World Symposium on Pulmonary Hypertension, which took place in 2008 in Dana Point, CA, USA. There were several reasons for this: 1) the old definition did not take into account other forms of PH; 2) the threshold of $P_{pa}$ $>25$ mmHg at rest does not reflect the upper limit of normal; 3) clinically relevant PH can be present, despite the $P_{pa}$ being $<25$ mmHg at rest; 4) the cut-off value of 30 mmHg during exercise was arbitrarily chosen and not supported by published data; and 5) PH is often present in conjunction with elevated $P_{pcw}$ levels.

Some of these points are addressed in a paper by Kovacs et al. [7] published in the present issue of the European Respiratory Journal. In preparation for the Dana Point meeting, they performed a comprehensive review of the literature published since 1947 in English, German or French language searching for right heart catheterisations performed in healthy individuals. Altogether, they were able to identify data obtained from 1,187 individuals in 47 studies. A meta-analysis of these data showed that the normal $P_{pa}$ at rest is $14.3\pm 3.3$ mmHg. These values are virtually age-independent. Following the customary approach to define an upper level of normal as the mean plus two standard deviations, the upper level of normal for the $P_{pa}$ at rest would be 20 mmHg. However, provided that the $P_{pa}$ is normally distributed, one in 40 healthy people will be above this threshold, i.e. 25,000 per million population. Even if the threshold is increased to 25 mmHg, the theoretical prevalence of individuals above this level would still be far beyond the known prevalence of PAH. Conversely, some studies indicate that even $P_{pa} >17$–20 mmHg may be associated with a poor prognosis, especially in patients with chronic lung diseases [8–11]. As is often the case in medicine, there exists a grey zone where a given value can be considered high, normal or already pathological, depending on the clinical context.

Of equal importance, the findings by Kovacs et al. [7] challenge the exercise component of the old PH definition. The problem with the 1973 WHO consensus was that the cut-off level of 30 mmHg during exercise was not supported by evidence. Kovacs et al. [7] show that, in younger persons aged $<50$ yrs, $P_{pa}$ of 35 mmHg can be considered normal during sub-maximal or maximal exercise. More importantly, in contrast to the $P_{pa}$ at rest, the $P_{pa}$ during exercise is largely age-dependent, presumably as a result of increasing stiffness of the left ventricle and the pulmonary vessels. $P_{pa}$ $>30$ mmHg during mild exercise is seen in $\sim 50\%$ of apparently healthy subjects aged $>50$ yrs, and $P_{pa}$ up to 45 mmHg during exercise appear to be normal in this population. Thus, with the previous definition many individuals were incorrectly labelled as pulmonary hypertensive that in fact had simply a physiological exercise response. Taking into account all these variables, it seems impossible to come up with a solid definition of PH during exercise. Further research is ongoing in this field to generate the data that are needed to move forward in this important area of pulmonary vascular disease [12, 13].

The consequences of the findings by Kovacs et al. [7] were intensively discussed at the Fourth World Symposium on Pulmonary Hypertension in Dana Point and it was decided to abandon the exercise criterion. With regard to the definition of PH at rest, it was proposed to introduce the term “borderline PH” for patients with $P_{pa}$ 20–25 mmHg, but this term was eventually rejected, as it was felt that patients presenting with $P_{pa}$ in this range should be further studied before being labelled with a diagnosis of PH. Thus, in the proceedings of the Dana Point meeting, the new haemodynamic definition of PH will be a $P_{pa}$ at rest $\geq 25$ mmHg [14]. This definition, which covers all forms of PH, will be adopted by the revised joint PH guidelines of the European Society of Cardiology and the European Respiratory Society, in which PH will be divided into pre-capillary and post-capillary forms, based on whether mean $P_{pcw}$ is $\leq 15$ or $>15$ mmHg, respectively [15, 16].

The revised haemodynamic definition of PH constitutes an improvement over the old definition, since it takes into account recent data and has broader applicability. Abandoning the exercise criterion is justified by the findings of Kovacs et al. [7] and it will prevent many false diagnoses of PH, as well as unjustified therapies. Limiting the current PH definition to a
$P_{pa}$ at rest $\geq 25\text{ mmHg}$ is also comprehensible for the time being. All treatment studies performed so far in the field of PH have included only patients fulfilling this criterion. Milder forms of PH, i.e. resting $P_{pa}$ 20–25 mmHg, are usually found among patients with underlying lung or heart disease, and medical therapies for these forms of PH have not been sufficiently studied. Eventually, with the broadening of our knowledge, the PH definition may have to be revised again.

Kovacs et al. [7] are to be commended for their invaluable contribution and it is likely that their manuscript will serve as a reference paper for a very long time.

STATEMENT OF INTEREST
A statement of interest for M.M. Hoeper can be found at www.erj.ersjournals.com/misc/statements.dtl

REFERENCES