



# The new haemodynamic definition of pulmonary hypertension: evidence prevails, finally!

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The proposal to redefine pulmonary hypertension by lowering the mean pulmonary artery pressure threshold from 25 mmHg to 20 mmHg is supported by strong scientific evidence <http://ow.ly/eajR30nHA2E>

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Since the 1st World Health Organization Symposium on Pulmonary Hypertension, which took place in 1973 in Geneva, Switzerland, every medical student around the world learnt, or at least should have learnt, that pulmonary hypertension (PH) is defined by a mean pulmonary arterial pressure (mPAP)  $\geq 25$  mmHg at rest (in fact, the original cut-off was  $>25$  mmHg [1, 2], but was changed to  $\geq 25$  mmHg during the 4th World Symposium on Pulmonary Hypertension, held in 2009 in Dana Point, CA, USA [3, 4]).

During the 6th World Symposium on Pulmonary Hypertension, which took place in 2018 in Nice, France, a working group led by G. Simonneau proposed revising the haemodynamic definition of PH and lowering the threshold from  $\geq 25$  mmHg to  $>20$  mmHg [5]. To many participants, this proposal came as surprise and critical voices were raised arguing that there is no need to change the PH definition, that the old definition was the basis of all treatment trials, that we don't know how to treat patients with mPAP between 20 and 24 mmHg, and that the new definition may lead to overdiagnosis and overtreatment of PH.

Some of these concerns are reasonable, others not, but we will come back to this later. First, we need to underscore where the 25 mmHg threshold came from [5]. The 1973 WHO conference was held in the aftermath of an epidemic of so-called primary PH in Germany, Austria and Switzerland that was caused by aminorex fumarate, an anorexigen [6]. The conference was focused primarily on PH while most other forms of PH were not addressed in detail. In the proceedings from this meeting, the authors stated that *the mean pressure in the pulmonary artery does not normally exceed 15 mmHg when the subject is at rest in a lying position. This value is little affected by age and never exceeds 20 mmHg. Hypertension is definitely present if the pressure exceeds 25 mmHg* [1]. Hence, the participants of the Geneva conference acknowledged that 20 mmHg is the upper limit of normal, which was later confirmed by KOVACS *et al.* [7] in a systemic review of the available evidence, rigorously showing that normal mPAP is 14.0 mmHg with a standard deviation of 3.3 mmHg. Thus, the 25 mmHg threshold was pragmatic, not scientific, in order to

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discriminate rare but severe cases of primary PH from other more common causes of PH due to chronic lung or heart diseases, which usually present with much lower mPAP.

We have been aware for many years of the gap between 20 mmHg, the upper level of normal, and 25 mmHg, our old PH threshold. In Dana Point, we discussed and rejected introducing the term “borderline PH” for mPAP from 21 to 24 mmHg [8], but the voices calling for a new PH definition became louder [9]. What has led SIMONNEAU *et al.* [5] to propose the change now? Well, the evidence that mildly elevated mPAP is associated with morbidity and mortality has simply become too strong to ignore any longer, and consistent data come from pulmonary arterial hypertension (PAH) as well as from other forms of PH.

Accumulating evidence from PAH associated with systemic sclerosis is teaching us that patients with mPAP between 21 and 24 mmHg have symptoms comparable to those who fulfil the classic definition, have an increased risk to progress to  $\geq 25$  mmHg and have a higher mortality than patients with mPAP  $\leq 20$  mmHg [10–13]. Although these data have been known for several years, there is still no recommendation to treat these patients before their mPAP reaches 25 mmHg. For patients with systemic sclerosis, symptoms of PAH and mPAP between 21 and 24 mmHg, this created the paradoxical situation that early PAH was evidently present but treatment not “permitted” because of lack of randomised controlled data due to inclusion criteria based on a biased PH definition, while, at the same time, the community was calling for early diagnosis and even introduced screening programmes [14–16]. The new definition will help these patients to receive proper management and will facilitate their inclusion in future clinical trials.

In recent years, early detection programmes have also been offered to patients with heritable PAH with identification of early pulmonary vascular disease relentlessly progressing to severe disease [17, 18]. Similarly, chronic thromboembolic pulmonary hypertension (CTEPH) is another major pre-capillary pulmonary vascular disease where mPAP below 25 mmHg is associated with significant exercise limitation, progressive haemodynamic compromise and poor outcomes [19]. Major improvements after successful desoblation argue for therapeutic interventions in selected patients with symptomatic pulmonary vascular disease but mPAP  $< 25$  mmHg [20, 21].

Perhaps even more importantly, while the PH field has focused for many years on PAH and CTEPH, two relatively rare forms of PH, we came to learn that the largest PH burden is carried by patients with chronic left heart diseases and chronic lung diseases and that in these conditions, the development of PH is associated with a 2–3 fold increased mortality risk [22]. Hence, our focus has to broaden and has to include these forms of PH as well, and for that we need an evidence-based, comprehensive haemodynamic definition.

And the evidence is there, strong and clear. For patients with chronic lung diseases, it has been known for some time that even mildly elevated PH pressures are associated with an increased risk of death [23, 24]. More recently, similar observations have been made in mixed patient populations [25]. In the largest series so far, MARON *et al.* [26], analysing data of more than 21 000 patients from the US veteran’s system, found that the hazard ratio of death for patients with mPAP between 19 and 24 mmHg compared to those with a mPAP  $< 19$  mmHg was 1.23 (95% CI 1.12–1.36;  $p < 0.001$ ). Of note, these patients were not suffering from PAH. These were patients we encounter much more frequently in daily practice, *i.e.* mostly elderly patients of whom approximately 75% had left heart disease and about 30% COPD. The findings of MARON *et al.* [26] were confirmed by the Vanderbilt group, who analysed data from 4343 patients and found an increased risk of death for patients with mPAP of 19–24 mmHg compared to patients with mPAP  $< 19$  mmHg (HR 1.31, 95% CI 1.04–1.65;  $p < 0.001$ ) [27].

Taken together, the revised definition is strongly supported by evidence, but does it also come with an increased likelihood of patients being misdiagnosed and mistreated as PH? The answer is probably yes and no at the same time. Yes, because some less experienced physicians may misinterpret the new definition and inappropriately treat (more) patients with drugs approved for PAH; and no, because a diagnosis of PH does not imply a treatment indication *per se* but requires a sophisticated work-up in expert centres, as strongly recommended in PH guidelines [28, 29]. Expert centres should be able to make a correct diagnosis and treatment decision independently of the old or new haemodynamic definition.

No single cut-off value is perfect. Moving it to the right, or in case of PH, leaving it at 25 mmHg, lowers the likelihood that patients are wrongly labelled with PH but increases the likelihood that patients who suffer from PH (or PAH) have their condition not diagnosed and not treated. The systemic sclerosis example mentioned earlier should teach us a lesson. Opponents may argue that lowering the threshold to 20 mmHg increases the likelihood of over-diagnosing PH, but again, the evidence is incontrovertible that anything above 20 mmHg is not normal and associated with an increased mortality risk. Over-treatment?

For PH associated with left heart disease and lung disease, even with the current definition we have no specific PH treatment [30, 31], so the revised definition should not change anything, except for better identifying patients in need of a therapy and helping to include them into future clinical trials. For pre-capillary PH, especially PAH, SIMONNEAU *et al.* [5] reinforced the requirement of a pulmonary vascular resistance  $\geq 3$  Wood units, which is currently the best criterion for pre-capillary pulmonary vascular disease. Hence, the revised definition will have little effect on how we treat patients with PH today, but it will foster future research that no longer leaves behind a sizeable and important group of patients in need for better treatments.

In summary, there is no debate that the upper limit of normal mPAP is 20 mmHg and that any value above that is abnormal. There is no debate either that this cut-off value does not define a disease *per se*. An elevated mPAP can have different causes, such as an increased cardiac output, left to right cardiac shunts, elevated pulmonary artery wedge pressure due to left heart disease, increased blood viscosity and, in a minority of cases, a true pre-capillary pulmonary vascular disease. Pre-capillary PH due to pulmonary vascular disease will be diagnosed when mPAP  $>20$  mmHg is associated with abnormal PVR  $\geq 3$  Wood units. With such a conservative approach, retrospective analysis of large registries from expert pulmonary vascular centres showed that the number of patients diagnosed with pre-capillary PH would increase by less than 10% with the revised haemodynamic definition (G. Simonneau, H-A. Ghofrani and R. Souza, personal communication). This number will have to be confirmed in prospective registries. Additionally, as stated by the task force members, a change in the haemodynamic definition of PH due to pulmonary vascular diseases does not imply treating these additional patients, but highlights the importance of further research, close monitoring and individualised management [5]. Last but not least, mPAP  $>20$  mmHg is a biomarker of worse outcomes in different settings, irrespective of the presence of a treatable pulmonary vascular disease, for example in the highly prevalent PH groups due to left heart diseases and/or chronic lung diseases. With all these considerations at hand, SIMONNEAU *et al.* [5] had no reasonable choice other than to propose redefining PH and they are to be congratulated for making this long-awaited decision.

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