Debating the new haemodynamic definition of pulmonary hypertension: much ado about nothing?

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The change in the haemodynamic definition of PH represents a step towards physiological haemodynamic thresholds, but does not relevantly increase the number of patients that will be classified as having pre-capillary PH associated with SSc http://bit.ly/2xZGoDC

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The introduction of the new haemodynamic definition of pulmonary hypertension (PH) was admittedly the most significant and controversial recommendation of the 6th World Symposium on Pulmonary Hypertension (WSPH) [1]. According to the previous definition, PH was limited to levels of mean pulmonary arterial pressure (mPAP) ⩾25 mmHg, whereas the new definition closed the gap to the upper level of physiological mPAP and included values ⩾21 mmHg for both pre- and post-capillary PH (table 1) [2]. Since the WSPH conference in 2018, there have been arguments for and against the new definition in the scientific community, and recent editorials in the *European Respiratory Journal* urged further analysis of large databases in order to understand the "real-life" clinical relevance of the change in the definition [3, 4]. This is of particular importance for patients suffering from systemic sclerosis (SSc), because PH is considered to be one of the leading causes of death in these patients and there was some hope that lowering the pressure threshold may lead to earlier recognition and treatment of pulmonary vascular disease.

In the current issue of the *ERJ*, Jaafar *et al.* [5] present their very timely study and compare the stratification of their n=268 SSc patients treated at the University of Michigan according to the previous and current definition of PH. Their analysis reveals that in a cohort of n=131 patients who had no PH according to the previous haemodynamic definition, just n=4 (3.1%) turned out to have pre-capillary PH according to the new haemodynamic definition. Among these four, only one had pulmonary arterial hypertension (PAH), the other three had PH due to lung disease based on abnormalities in their pulmonary function tests and computed tomography imaging. What are the haemodynamic characteristics of these four patients? They all have a mildly elevated mPAP (22–23 mmHg), a lower normal to normal pulmonary arterial wedge pressure (PAWP; 6–10 mmHg), mildly reduced cardiac output (3.43–4.37 L·min^{-1}) and a mildly increased pulmonary vascular resistance (PVR; 3.4–5.0 WU). Only four out of 131 patients: this appears to be a very rare condition!

The authors provide detailed haemodynamic data for n=87 SSc patients from their University of Michigan cohort, who had mPAP ⩾21 mmHg and no relevant left heart (PAWP ⩽15 mmHg) or interstitial lung

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TABLE 1 Proposed haemodynamic definitions of pulmonary hypertension (PH) [2]

Definition	Haemodynamics
Pre-capillary PH	mPAP >20 mmHg, PAWP ⩽15 mmHg, PVR ⩾3 WU
Isolated post-capillary PH	mPAP >20 mmHg, PAWP >15 mmHg, PVR <3 WU
Combined pre- and post-capillary PH	mPAP >20 mmHg, PAWP >15 mmHg, PVR ⩾3 WU

mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance.

disease. Out of these, n=40 had a PVR ⩾3 WU (46.0%), but n=39 (98.9%) had mPAP ⩾25 mmHg and only n=1 (1.1%) had mPAP values between 21 and 24 mmHg. Is it because mPAP 21–24 mmHg was so rare in this group? No, there were n=28 such patients. However, 27out of 28 patients with mPAP 21–24 mmHg had a PVR <3 WU. This suggests that in most patients with pulmonary vascular disease, the PVR increase was accompanied by mPAP ⩾25 mmHg. The combination of PVR ⩾3 WU and mildly elevated mPAP (21–24 mmHg) appears to be a very rare finding among patients with SSc!

Figure 1 illustrates the discussed haemodynamic relationships. According to the previous definition, all patients with mPAP ⩾25 mmHg were classified as PH, while those with mPAP <25 mmHg were not. The diagonal lines in the figure represent 3 WU "isoresistance" lines corresponding to a PAWP of 8, 12 and 15 mmHg, respectively. This means that all mPAP–cardiac output coordinates left from these lines represent patients with PVR >3 WU. In order to fulfil the new haemodynamic criteria of pre-capillary PH, but not the previous haemodynamic criteria for PH, the coordinates must lie in the mPAP range of 21–24 mmHg and left from the 3 WU "isoresistance" lines. The mentioned single "new" PAH patient from the University of Michigan cohort (mPAP 22 mmHg, PAWP 8 mmHg and cardiac output 4.1 L·min^{-1}) is represented by a black dot. As seen in the figure, the remaining 27 patients of the University of Michigan cohort with mPAP 21–24 mmHg had PVR <3 WU and are found in the area to the right of the 3 WU "isoresistance" lines.

One might argue that the rarity of SSc patients with PVR ⩾3 WU and mPAP 21–24 mmHg could be characteristic for the University of Michigan cohort, although some initial analyses of other patient

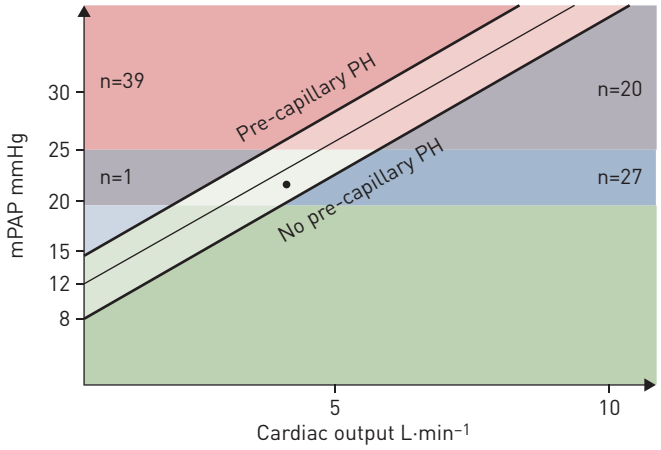

FIGURE 1 Stratification of systemic sclerosis (SSc) patients based on their pulmonary haemodynamics. Red area: pulmonary hypertension (PH) according to previous and pre-capillary PH according to new definition (mean pulmonary arterial pressure (mPAP) ⩾25 mmHg, pulmonary vascular resistance (PVR) ⩾3 WU). Purple area right from the 3 WU "isoresistance" lines: PH according to previous, but no pre-capillary PH according to new definition (mPAP ⩾25 mmHg, PVR <3 WU). Purple area left from the 3 WU "isoresistance" lines: no PH according to previous, but pre-capillary PH according to new definition (mPAP >20 mmHg, PVR ⩾3 WU). Blue, light blue and green areas: no PH according to previous and no pre-capillary PH according to new definition (blue area: mPAP >20 mmHg, PVR <3 WU; light blue area: mPAP ⩽20 mmHg, PVR ⩾3 WU; green area: mPAP ⩽20 mmHg, PVR <3 WU). The diagonal lines in the figure represent 3 WU "isoresistance" lines corresponding to a pulmonary arterial wedge pressure (PAWP) of 8, 12 and 15 mmHg, respectively. The numbers in the figure represent the number of SSc patients from the University of Michigan collective who had mPAP ⩾21 mmHg and no relevant left heart (PAWP ⩽15 mmHg) or interstitial lung disease according to their stratification. The black dot represents the single subject out of this patient cohort who had no PH according to the previous, but pre-capillary PH according to the new definition.

cohorts indicate similar results [4]. Of course, confirmation of such data in independent cohorts is needed. However, it is also possible that in the early stage of pulmonary vascular disease, cardiac output is usually not yet compromised and, in most cases, a significant increase in PVR (⩾3 WU) actually results in an elevated mPAP ⩾25 mmHg. Of note, for patients with "high normal" PAWP (12–15 mmHg) it is even more difficult to fulfil the new haemodynamic criteria of pre-capillary PH, because in these patients the 3 WU "isoresistance" line is shifted to the left and patients need even lower cardiac output values to match the criteria. In other words, from a physiological point of view, it appears difficult for patients to fulfil the new haemodynamic criteria if they had not fulfilled the old criteria.

However, why do we stick to a PVR of 3 WU for the definition of pre-capillary PH? If this was lowered from 3 to 2 WU, which is probably the upper limit of normal PVR [2, 6, 7], the "isoresistance" lines in figure 1 would shift to the right and many more patients would fulfil the criteria of pre-capillary PH. For example, in the current analysis of Jaafar *et al.* [5], out of the n=87 SSc patients with mPAP ⩾21 mmHg and no relevant left heart and interstitial lung disease, the number of patients with pre-capillary PH would increase from one to nine. This indeed would represent a significant difference in the stratification of patients. Of course, it would also ignite further discussions, if patients with such mildly elevated mPAP and PVR should be treated with PAH medication. We actually need to consider the question if such mild haemodynamic changes require different management strategies than more severe haemodynamic changes. We know that in SSc, even mild alterations can be alarming signs [8]. Similarly, in patients with chronic thromboembolic disease and in relatives of idiopathic PAH patients, mild changes of pulmonary haemodynamics can indicate early stages of an aggressive pulmonary vascular disease. However, controlled clinical trials showing evidence for beneficial effects of drugs are missing. The situation is less controversial in patients with significant lung or left heart disease. In these patients, mild elevation of mPAP and PVR is mainly the expression of the underlying disease. It is prognostically relevant, but the available data do not provide evidence for beneficial effects of targeted PAH therapy.

Figure 1 may drive our attention to another important issue. There are patients with clearly elevated mPAP (⩾25 mmHg) and no relevant left heart disease (PAWP ⩽15 mmHg), who fail to fulfil the haemodynamic criteria of pre-capillary PH, because they have a high cardiac output and a low PVR (PVR ⩽3 WU). These patients are found in the purple area right from the 3 WU "isoresistance" lines in figure 1. This combination of haemodynamic parameters appears to be quite frequent in SSc: among the mentioned n=87 patients in the University of Michigan cohort, n=20 belonged to this group. In fact, many of these patients may have a hyperdynamic circulation or obesity without relevant pulmonary vascular disease.

In summary, the valuable data of Jaafar *et al.* [5] provide important food for thought on the new definition of PH and stimulate the discussion on the diagnosis of early pulmonary vascular disease in SSc. The change in the haemodynamic definition of PH represents a step towards physiological haemodynamic thresholds but does not relevantly increase the number of patients that will be classified as pre-capillary PH associated to SSc. Although the number of SSc patients with mPAP 21–24 mmHg is relatively high, PVR ⩾3 WU remains a rare condition among these patients.

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