REGULAR ARTICLE

POINT: Is It Time to Lower the Cut-off for Increased Pulmonary Vascular Resistance? Yes

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Background: For decades, pulmonary hypertension (PH) used to be defined by a mean pulmonary artery pressure (mPAP) ≥25 mm Hg; however, this criterion was not based on data that were systematically collected. With the availability of contemporary datasets however, it was evident that the upper limit of normal mPAP was ~20 mm Hg, which is also the level of mPAP above which adverse outcomes increase. In addition, it is now evident that the specificity of mPAP >20 mm Hg to denote precapillary pulmonary vascular disease could be enhanced by adding pulmonary vascular resistance (PVR) to the precapillary PH definition. Finally, after characterizing large groups of normal individuals, akin to observations for mPAP, it was recently demonstrated that a PVR of ~2.0 Wood units (WU) is the upper limit of normal, and the lower level associated with all-cause mortality in at-risk patients.
Clinical Implications: The current hemodynamic criteria for PH are positioned to capture more patients compared to the classical definition, with particular implications for earlier diagnosis. Importantly, pulmonary vasodilator therapies have not been tested adequately in patients with mPAP <25 mm Hg or PVR between 2 to 3 WU and, thus, should not be administered in these patients. Mild PH is an active focus of clinical trial design; at present, these patients should be referred to expert PH centers earlier for individualized therapeutic planning.
Conclusions: The revised definition of precapillary PH uses a PVR threshold of >2 WU. This value is evidence-based, and exceeding this threshold is associated with adverse clinical outcomes. This revision places focus on early diagnosis, close monitoring, and consideration for certain treatments. Further studies are needed that test the efficacy and safety of pulmonary arterial hypertension-specific therapy in precapillary PH patients with PVR 2 to 3 WU.

INTRODUCTION: SETTING THE STAGE FOR DEFINING PRECAPILLARY PH USING PULMONARY VASCULAR RESISTANCE 2.0 WU

In 1973, a small group of clinicians relied on personal experience and consensus opinion to determine that mean pulmonary artery pressure (mPAP) >25 mm Hg alone should be used to diagnose pulmonary hypertension (PH). This determination was made without 2 pieces of information that are crucial for defining diseases characterized by a continuous variable: normative values and data associated with clinical events.[1-4] Despite this shortcoming, the definition of PH that was used in clinical practice remained unchanged for over 4 decades, which was due, in part, to the fact that virtually all patients in that era were initially diagnosed with advanced stage disease, often in the setting of a mPAP that was substantially greater than 25 mm Hg.

Then, Kovacs and colleagues reported on data from >1000 healthy individuals whose mean mPAP was 14±3.3 mm Hg. Thus, they determined that the upper limit of normal mPAP was 20 mm Hg, based on a conventional biostatical calculation that considers 2 standard deviations (SD) above the mean to be abnormal.[5] Supporting the 20 mm Hg upper limit are large cohort studies involving unselected referral populations, where a continuous relationship between mPAP and mortality was observed when the mPAP of approximately 20 mm Hg was exceeded.[6,7] The relationship between mPAP was affirmed for PH-relevant endpoints by studies focusing on well-phenotyped but smaller cohorts of patients with various cardiopulmonary diseases.[8,9] These observations led the scientific community to revise the mPAP threshold for diagnosing PH from ≥25 to >20 mm Hg in 2019.[10]

Generically, lowering the mPAP threshold from 25 to 20 mm Hg

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increases the pool of patients with a diagnosis of PH; however, immediately reversible and nonpathogenic conditions that increase pulmonary blood flow can elevate pulmonary artery pressure without indicating pulmonary vascular pathology. In order to maintain adequate specificity for classifying a patient with pulmonary vascular disease, the hemodynamic classification system of PH was expanded to include pulmonary vascular resistance (PVR) threshold. In 2019, PVR of ≥3.0 WU was used to delineate patients with a component of precapillary PH in all PH groups. However, this PVR threshold was not based on normative or outcome data collected systematically. Rather, this threshold was repurposed using deductive reasoning from pulmonary arterial hypertension clinical trials that used this threshold, and because poorer outcomes in patients with congenital heart lesions and PH had been reported when shunt closure was performed with PVR exceeding 3.0 WU.[10] Until relatively recently, data to inform of an outcomes-derived PVR threshold were lacking.

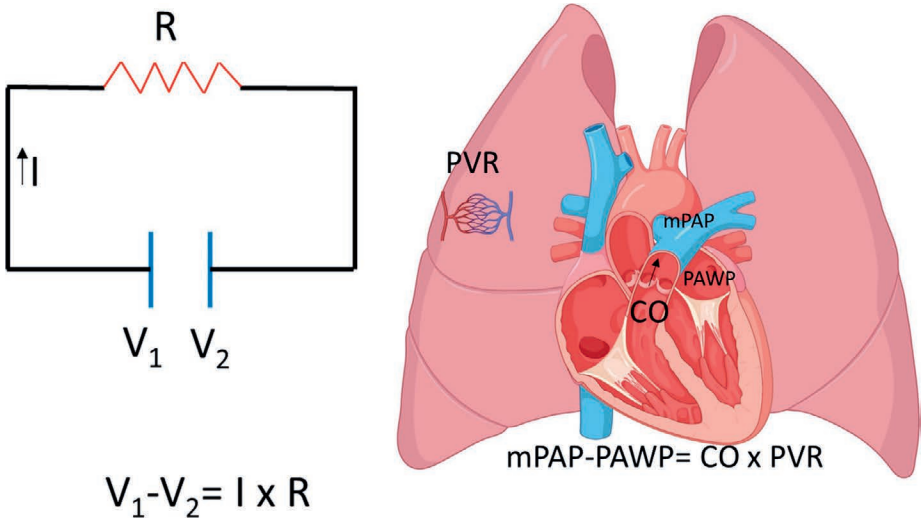

Figure 1: Analogy of the pulmonary circulation to an electrical circuit for purposes of application of Ohm's law in the calculation of pulmonary vascular resistance. CO indicates cardiac output; I, current; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure (to approximate left atrial pressure); PVR, pulmonary vascular resistance; R, resistance; V, voltage.

PVR AND THE DEFINITION OF PH

The Biophysics of Blood Flow in the Pulmonary Circulation

Under normal conditions, the pulmonary vasculature is a high-flow, low-resistance circuit oriented in parallel. PVR is the resistance against blood flow from the pulmonary artery to the left atrium (LA). It is estimated by applying Ohm's law on the pulmonary circulation (Figure 1). According to Ohm's law, the difference in potential (V) across a resistor is proportional to the electrical current (I) times the resistance (R) or V = IR. In the pulmonary circulation, the pressure gradient that drives the flow of blood from the right ventricle to the left atrium is the difference between the mPAP and the pulmonary artery wedge pressure (PAWP). By applying Ohm's law we get mPAP – PAWP = cardiac output (CO) × PVR.[11] Therefore, PVR helps distinguish increased mPAP owing to states of increased flow (such as obesity, anemia, and others) from increased mPAP when due to pulmonary vascular remodeling.[12,13] PVR is measured in mm Hg × min/L or in dynes/sec/cm^5. The units of mm Hg × min/L are referred to as Wood units (WU), the namesake of cardiologist Paul Wood, who was one of the pioneers of hemodynamic interpretation.[10,14,15] One WU equals 80 dynes/sec/cm^5.[15]

The Historical Basis of PVR in Defining PH. (Figure 2)

A normal PVR has been reported to be between 150 to 300 dynes/sec/cm^5 (1.9-3.8 WU), although the number of subjects that were assessed for this value in this study was not povided.[4] In 1998, the 3rd World Symposium on Pulmonary Hypertension (WSPH) formally included PVR into the definition of pulmonary *arterial* hypertension (denoted as primary pulmonary hypertension then). The task force set the cut-off at >3 WU but did not provide rationale to support this decision.[16] In 2008 the 4th WSPH committee acknowledged that a normal PVR was likely <2 (or 3) WU, indicating that the exact threshold was not known.[17]

Normative Values for PVR

In 2012, Kovacs and colleagues published a meta-analysis summarizing PVR data from studies on normal volunteers. They analyzed 88 subjects and found that the PVR in their cohort was 69±28 dynes/sec/cm^5 in individuals younger than 50 years old versus 88±28 dynes/sec/cm^5 in older volunteers.[18] Considering the statistical definition of normality, the upper limit of normal for PVR in that study was 135 dynes/sec/cm^5 (~1.7 WU), which was later supported by the 5th WSPH that acknowledged the upper level of normal PVR is likely ~2 WU.[10]

Using Outcomes Data to Calibrate the Definition of PH

The first study to reconsider the association between PVR and outcome that also incorporated the mPAP threshold of 20 mm Hg to define PH was by Xanthouli and colleagues[19] involving 208 patients with systemic sclerosis. The authors found that patients with mPAP 21 to 24 mm Hg and PVR ≥2 WU (selected based on the findings by Kovacs et al[18]) had reduced tricuspid annular planar systolic excursion (21±6 vs 24±4 mm, P = .004), decreased 6-minute walk distance (6MWD) (414±100 vs 488±101 m, P < .001) and decreased pulmonary artery compliance (4±1.3 vs 6.2±2.8 mL/mm Hg, P < .001) compared to patients with mPAP <21mm Hg. These findings show that right ventricle and functional impairment is prevalent even in patients with mild PH and PVR 2 to 3 WU, which was internally consistent with findings on survival. Compared to patients with mPAP >20

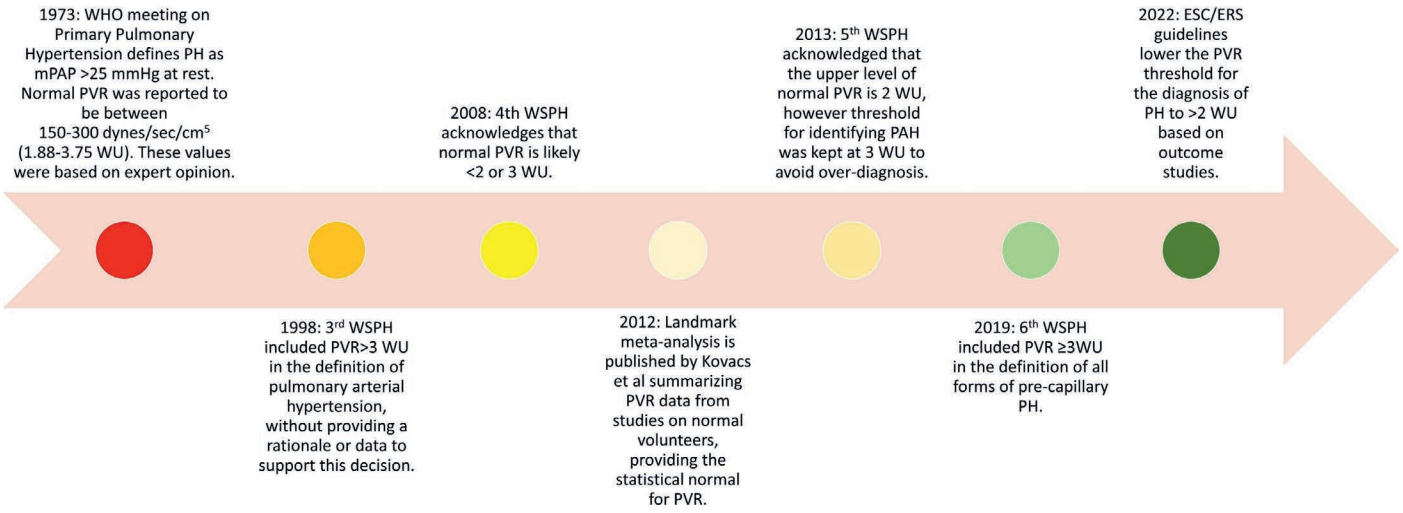

Figure 2: Timeline of pulmonary vascular resistance in the definition of pulmonary hypertension. ESC indicates European Society of Cardiology; ERS, European Respiratory Society; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WSPH: World Symposium on Pulmonary Hypertension; WU, Wood units; WHO: World Health Organization.

mm Hg and PVR <2.0 WU, patients with mPAP >20 mm Hg and PVR ≥2.0 WU had lower survival at 1 year (97.7% vs 100%), 3 years (90.7% vs 94.2%), 5 years (79.4% vs 91%) and 7 years (54.3% vs 84.2%) (age-adjusted Cox regression $P = .028$). Interestingly 25% of the mortality in the PVR <2 WU was reported to be due to pulmonary vascular disease vs 50% in the PVR ≥2 WU group.[19]

Our group[7] investigated the relationship between PVR and hard clinical events in patients referred for right heart catheterization in the Veterans Affairs Clinical Assessment, Reporting, and Tracking (VA-CART) Program, which included a total of 32 725 individuals with mPAP ≥19 mm Hg who underwent right heart catheterization between October 2008 and September 2016. This study found that all-cause mortality increases continuously beginning at PVR 2.0 to 2.2 WU (Figure 3). When PVR was dichotomized at 2.2 WU, patients with PVR ≥2.2 WU had higher 1-year (20.5% vs 11.3%) and 5-year (43.5% vs 28.5%) mortality rates, and higher 1-year (15.6% vs 10.1%) and 5-year (22.6% vs 16.1%) all-cause hospitalization rates. The association between PVR and mortality was maintained when restricting the analysis to patients with mPAP 19-24 mm Hg alone. Importantly, these data were validated in a second cohort of patients from Vanderbilt University Medical Center. This cohort included a similar number of female and male patients, which is important to consider since the VA-CART cohort is mostly comprised from male patients. These collective findings provide clinical endpoint data that support lowering the PVR cut-off for defining PH to 2 WU (Table).

Increasing Sensitivity in PH Diagnosis

"It is better to prevent than to cure" is a traditional adage attributed to Hippocrates with implications to pulmonary vascular disease: most patients are diagnosed at an advanced stage, as evidenced by the AMBITION trial, in which the mean mPAP at time of PAH diagnosis was ~48 mm Hg corresponding to World Health Organization functional class III in most patients.[20] Early diagnosis of PH and referral to expert centers for evaluation and treatment could lead to prevention of right ventricular failure and increased survival. It has been shown that the risk of adverse outcomes in association with PH increases from mPAP >20 mm Hg, and PVR >2 WU. Nevertheless, lowering of PH threshold to 20 mm Hg has a small effect on capturing more patients with PH when maintaining a PVR threshold of 3.0 WU.[21]

In the study by Xanthouli et al,[19] 50 patients with Group I PH had mPAP between 21 to 24 mm Hg. Of those, 48% had PVR between 2 to 3 WU. Additionally, of the 54 Group I PH patients with mPAP ≥25 mm Hg in that study, 35.2% had PVR between 2 to 3 WU. In 2018, Coghlan et al[22] reported outcomes of a 3-year follow-up of patients with systemic sclerosis and mPAP <25 mm Hg. Notably, patients with mPAP between 21 to 24 mm Hg had nigher incidence of "frank" PH (defined by mPAP >25mm Hg at that time) in the 3-year follow-up period

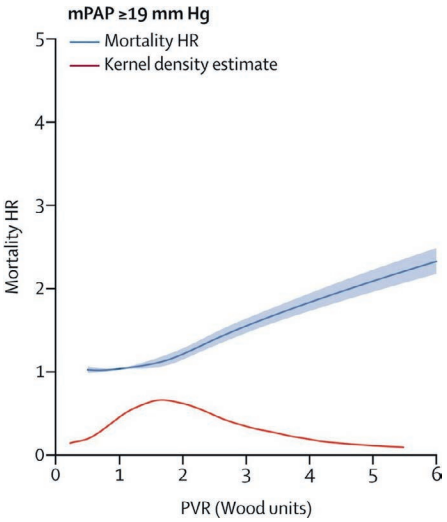

Figure 3: Hazard ratio (95% confidence interval) for all-cause mortality is plotted for PVR 1-6 WU relative to a reference value of 1.0 WU in patients with mean pulmonary artery pressure ≥19 mm Hg. All-cause mortality increases form PVR ~ 2 WU. mPAP indicates mean pulmonary artery pressure; PVR, pulmonary vascular resistance; WU, Wood units. Reproduced with permission from Elsevier.[7]

Table. Studies evaluating the significance of PVR>2 WU in patients with PH.

Study	PH group	Duration of follow-up	Outcomes	Comments/interpretation
Coghlan et al[22] 2018	Scleroderma patients (WHO Groups I, II, & III)	3 years	Patients with mPAP 21-24 had mean PVR of 2.35, which progressed to >3 WU within 3 years	Most patients with mild PH have PVR 2-3 WU, and these patients progress to more severe PH that warrants treatment
Xanthouli et al[19] 2020	Scleroderma patients with Group I	3.5 years	48% of patients with mPAP 21-24 mm Hg had PVR 2-3 WU. Patients with PVR ≥2 WU had decreased TAPSE (21 ± 6 vs 24 ± 4 mm, $P = .004$), 6MWD (414 ± 100 vs 488 ± 101 m, $P < .001$) and PAC (4 ± 1.3 vs 6.2 ± 2.8 mL/mm Hg, $P < .001$) compared to patients without PH. PVR was independently associated with survival.	Lowering PVR threshold for diagnosing PH captures more patients. Patients with mild PH and PVR ≥2 WU have impaired functional and cardiac status compared to patients without PH
Maron et al[7] 2020	Any group (I-V)	~2 years	Mortality increases progressively over a PVR ≥2 WU when PVR is plotted as a continuous variable	Identified the PVR cut-off above which the risk of adverse outcomes increases. Outcomes-based method of identifying "abnormal"

Abbreviations: 6MWD, 6-minute walk distance; mPAP, mean pulmonary artery pressure; PAC, pulmonary artery compliance; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; TAPSE, tricuspid annular place systolic excursion; WHO, World Health Organization; WU, Wood units

of that study compared to those with mPAP <21 mm Hg (33.3% vs 22%, respectively). Finally, in the larger study conducted by Maron and colleagues[7] lowering the PVR threshold to 2.2 WU would capture an additional 55.9% of patients with PH. From the above it is evident that lowering PVR to 2 WU helps diagnose PH in a significantly larger percentage of patients, compared to lowering of the mPAP threshold to 20 mm Hg alone.

PERSPECTIVES ON THE NEW PH DEFINITION

Despite the above, lowering the PVR cut-off used to define PH to >2 WU should not equate to treating patients with PVR 2 to 3 WU with PAH-specific therapies, as the safety and efficacy of our current medical treatment of PH has not been established for individuals with PVR <3 WU.[23] The EDITA study is the only randomized controlled trial to evaluate the safety and efficacy of PAH-specific therapies in those with mPAP 21 to 24 mm Hg.[24] In this study, 38 patients received either placebo or ambrisentan for 6 months. Treatment with ambrisentan decreased progression to mPAP ≥25 mm Hg (3 vs 0 patients) and improved cardiac index (CI) and PVR (CI 0.36 ± 0.66 l/min/m^2 vs −0.31 ± 0.71 l/min/m^2, $P = .010$; PVR −0.70 ± 0.78 WU vs 0.01 ± 0.71 WU, $P = .012$). The adverse events reported were among those already known for ambrisentan (edema, diarrhea, epistaxis).

Ratwatte and colleagues report data from the Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ) Registry on treatment of patients with Group I PH with mPAP ≥25mm Hg and PVR <3 WU. The study included 82 patients with a median PVR or 2.2 WU. Patients were initially treated with monotherapy with either an endothelin receptor antagonist or a phosphodiesterase type-5 inhibitor (PDE5i). Patients were followed on average for 5.5 years. During the follow-up period, 14% of patients needed to be escalated to combination therapy. The mediations were well tolerated and there were no treatment interruptions. The patients' functional capacity improved (+46 m median increase in 6-minute walk distance, 35% of patients improved New York Heart Association functional class). In addition, PAH therapy increased the patients that would fall under the low-risk REVEAL 2.0 category from 61% to 72%.[25]

The results of these studies should be viewed as exploratory but somewhat encouraging given the improvement in functional capacity of the patients. Larger studies are needed to determine whether treating patients with mPAP >20 mm Hg and PVR >2 WU with PAH-specific therapies would be safe and effective.

CONCLUSIONS

The new definition of precapillary PH uses a PVR cutoff of >2 WU, which is based on data from healthy populations determining the normal cut-off as mean ± 2 SD, as well as from data associated with clinical outcomes. This approach facilitates earlier stage diagnosis, which is positioned to test strategies that delay or prevent clinical worsening, including the development of right ventricular failure and death. In this regard, patients with mPAP 20 to 25 mm Hg and PVR 2 to 3 WU should be monitored closely, referred to expert centers, and considered for clinical trials that are designed to assess the safety and efficacy of multidimensional care plans, perhaps inclusive of PAH-specific therapies.

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