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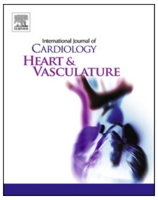

Acute pulmonary vasoreactivity: a simple test revisited in the contemporary era – a narrative review

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ABSTRACT

The acute vasodilator challenge during right heart catheterization (RHC) provides a deeper understanding of the pulmonary circulation by assessing vasoreactivity. The current criteria for a positive acute vasoreactivity test (AVT) are simplified to steady-state metrics, based on cutoff points derived from expert opinion. A positive AVT identifies a specific, but very rare, PH phenotype that may respond long-term to calcium-channel blockers. Growing evidence supports updating the role and criteria of AVT in pulmonary arterial hypertension, broadening its use to other PH groups, and potentially offering new insights for predicting risk and/or treatment outcomes.

This study aims to revisit the uses, criteria, and goals of AVT in patients with PH beyond group 1 and to propose a new approach for phenotyping the pulmonary vascular response to the acute vasodilator challenge during diagnostic RHC. We propose a continuous multi-parameter criterion to evaluate the entire right ventricular afterload during AVT, such as the pulmonary vascular resistance-pulmonary arterial capacitance curve and alpha distensibility coefficient. AVT could assess the residual vasoreactive reserve of the pulmonary circulation as a provocative test for predicting risk outcomes and/or treatment responses.

1. Introduction

Pulmonary hypertension (PH) is clinically defined as a mean pulmonary artery pressure (mPAP) of 20 mmHg or more at rest, as measured by right heart catheterization (RHC). PH involves vasoconstriction and arterial vascular wall remodeling, including the venocapillary sector. It may also be associated with thrombosis and plexiform lesions. The prognosis depends on right ventricular (RV) function and its coupling with dynamic afterload [1].

Acute vasoreactivity testing (AVT), as a provocative test, can be performed during RHC for several reasons [2]. In patients with pulmonary arterial hypertension (PAH), the detection of pulmonary vasoreactivity may identify candidates for long-term response to calcium-channel blockers (CCBs), characterized by sustained clinical and hemodynamic improvement after 1 year of treatment, and it helps predict survival. In patients with PAH associated with congenital heart disease and an intracardiac shunt, it is used to assess operability. In patients with PH associated with left heart disease, candidates for heart transplantation should undergo evaluation to evaluate the reversibility of the precapillary PH component.

Abbreviations: AVT, acute vasoreactivity testing; CCB, calcium channel blocker; CO, cardiac output; CTEPH, chronic thromboembolic pulmonary hypertension; DT-PAH, drug and toxin-associated PAH; FCSA, fractional pulmonary capillary surface area; HPAH, heritable-PAH; HR, heart rate; iNO, inhaled nitric oxide; IPAH, idiopathic PAH; LV, left ventricle; mPAP, mean pulmonary arterial pressure; PAC, pulmonary arterial capacitance; PAH, pulmonary arterial hypertension; PAOP, pulmonary arterial occlusion pressure; PH, pulmonary hypertension; pPAP, pulse pressure arterial pressure; PVR, pulmonary vascular resistance; RHC, right heart catheterization; RV, right ventricle; RVAC, right ventricular arterial coupling; SV, stroke volume; SVR, systemic vascular resistance; TPR, total pulmonary resistance; WU, wood unit.

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The ideal vasodilatory agent for AVT should be selective for the pulmonary circulation (with little effect on ventricular performance and systemic vascular resistance -SVR-) and short-acting (short biological half-life). Inhaled nitric oxide (iNO, 20–80 ppm) [3,4] and aerosolized iloprost (0.3–0.5 μg/kg administered by inhalation for 15 min) [5] meet the criteria mentioned earlier and are typically recommended for AVT in adults. They act predominantly on small arteries and/or venules (<100–200 μm) at a short distance from alveoli. There is similar evidence for i.v. epoprostenol; however, due to certain caveats (incremental dose increases, repetitive measurements that require more extended duration, and systemic hypotension associated with increased cardiac output and sympathetic tone), it becomes less feasible and less interpretable. Adenosine i.v. is no longer recommended due to frequent side effects [1].

The work aims to revisit the uses, criteria, and goals of the AVT in patients with PH beyond group 1 and to propose a new approach for phenotyping the pulmonary vascular response to acute vasodilator challenge.

2. Methods

This is a narrative review conducting a critical clinical analysis of relevant published articles on acute pulmonary vasoreactivity in PH [6,7].

Databases including PubMed/MEDLINE, SCOPUS, and Web of Science were searched up to July 2025, using the predefined search terms: “acute vasoreactivity testing,” “acute pulmonary vasoreactivity,” “pulmonary vasoreactivity,” and related phrases. The inclusion criteria were articles that involved only adult humans and were published in PubMed. We included review and research articles, conference abstracts, case reports, editorials, and short communications written in English, French, or Spanish. From the articles identified in the initial search, we also found additional references through manual searches of the cited references.

A total of 689 articles were screened based on the following items: key findings, the quality of the results obtained, the interpretation of those results, and the impact of the conclusions on the field. Of these, those publications that were considered to contain important and novel data were included in this narrative review.

3. Current Indications and criteria for acute vasoreactivity response in pulmonary arterial hypertension patients

Evidence supports conducting the AVT in specific patient subgroups with PAH. Among clinical group 1 of PAH -idiopathic (IPAH), heritable (HPAH), and drug-toxin-related (DT-HAP)- patients have the highest rates of both acute vasoreactivity-positive response (13–15 %) and sustained clinical response (6–9 %) when treated with CCBs [8]. AVT value is uncertain in patients with PAH with features of venous/capillary (PVOD/PCH) involvement, PAH associated with congenital heart disease, or connective tissue disease, because of the lack of long-term CCB response and the risk of developing pulmonary edema or clinical deterioration after starting CCB. Although uncommon, some PAH patients with HIV infection or porto-PH may have a long-term response to CCB [9]. A positive AVT percentage of 3.5 % (3 of 84 patients) was observed in patients with Schistosomal PAH and showed a nonsignificantly more preserved hemodynamic profile [9].

Although positive AVT results are critical to identify the subset of PAH patients ‘super-responders’, its definition remains controversial, leading to the wide variation in reported positive AVT rates, which range from 6.5 % to 60 % [2].

Three main hemodynamic criteria are generally used according to Barst [10], Rich [11], and Sitbon [12]:

a) Barst criteria (1986): decrease in mPAP of ≥ 20 %, unchanged or increased cardiac index, and decreased or unchanged pulmonary vascular resistance (PVR) to SVR ratio (PVR/SVR);
b) Rich criteria (1992): reduction in mPAP and PVR of ≥ 20 %;
c) Sitbon criteria (2005): decrease in mPAP of ≥ 10 mm Hg reaching an mPAP value of ≤ 40 mm Hg, and an increased or unchanged cardiac output (CO).

The Barst criteria are frequently used in children, as they have significant prognostic value for long-term survival in children with IPAH [13]. The Rich criteria were the first commonly used criteria for adults. To standardize and validate AVT criteria, Sitbon et al. retrospectively analyzed clinical data from 557 patients with PAH who had undergone an acute pulmonary vasodilator challenge (28 % with Epoprostenol and 72 % with iNO). Thirteen percent (70/557) met the AVT criteria set by Rich and colleagues. Among these acute responders, only 54 % (n = 38) experienced a sustained benefit with CCB. During AVT, these patients showed the same percent reduction in PVR as patients who fail; in contrast, they reached a significantly lower level of mPAP and PVR [14]. Based on these data, experts at the 3rd World Symposium on PH proposed a dichotomous nature of vasoreactivity. They defined positive AVT responsiveness as a reduction in mPAP greater than 10 mmHg to a level at or below 40 mmHg, with no change or an increase in CO [15]. These criteria were retrospectively analyzed using data from Sitbon et al., which showed a higher percentage of long-term responders among acute responders associated with a more ‘strict’ criteria [12] (Fig. 1). Long-term CCB responders are defined as patients in NYHA functional class I or II who have shown sustained hemodynamic improvement after at least 1 year of CCB therapy, without requiring additional treatments such as epoprostenol, prostacyclin analogues, or endothelin receptor antagonists. These Sitbon criteria are currently recommended in international guidelines for adult patients with PAH, but not for children [16]. However, when we analyze the accuracy of the Sitbon criterion, 16 % of patients (6/38) with a long-term response would not receive CCBs (sensitivity, 84 %), and 31 % (10/32) without a long-term response would be treated with CCBs (specificity, 70 %) [17]. Beyond the hemodynamic variables and their cut-off points used in different historical criteria of vasoreactivity, all employ a dichotomous criterion within an outdated hemodynamic definition of PH.

Fig. 2 illustrates how PH hemodynamic thresholds have evolved over the past 50 years, along with the criteria and definitions for AVT responders. Although the PH hemodynamic thresholds are based on large *meta*-analyses of data from healthy individuals, the criteria for responders, proposed since 2003, are based on expert opinion. Since 2018, the acute response of pulmonary circulation to vasodilator challenge has been incorporated into the clinical classification of PH.

At the 6th World Symposium of PH, a subgroup called “PH long-term responders to CCB” was proposed within PAH as a separate category, based on the argument that these patients have a significantly better prognosis and a different pathophysiology, driven mainly by vasoconstriction rather than pulmonary arterial remodeling. The positive AVT group tends to have less severe hemodynamic abnormalities at baseline and an earlier stage of pulmonary vasculopathy compared to those with a negative AVT, supporting the idea of long-term CCB therapy. However, this proposal raises unresolved issues: patients can only be classified into this subgroup after one year of follow-up, and those who lose their response to CCBs also lose their favorable prognosis and experience disease progression similar to patients with idiopathic PAH [18].

In the 2022 ESC/ERS PH guidelines, the “PH long-term responders to CCB” subgroup was removed and replaced by a distinction between “acute responders at vasoreactivity testing” (subgroup 1.1.2) and “nonresponders at vasoreactivity testing” (subgroup 1.1.1) within IPAH. Again, there are some questionable issues: there are patients in subgroups 1.2 and 1.3, responders and non-responders who are not included in the clinical classification; acute responders are a mix of long-term responders to CCBs and those who will require management with

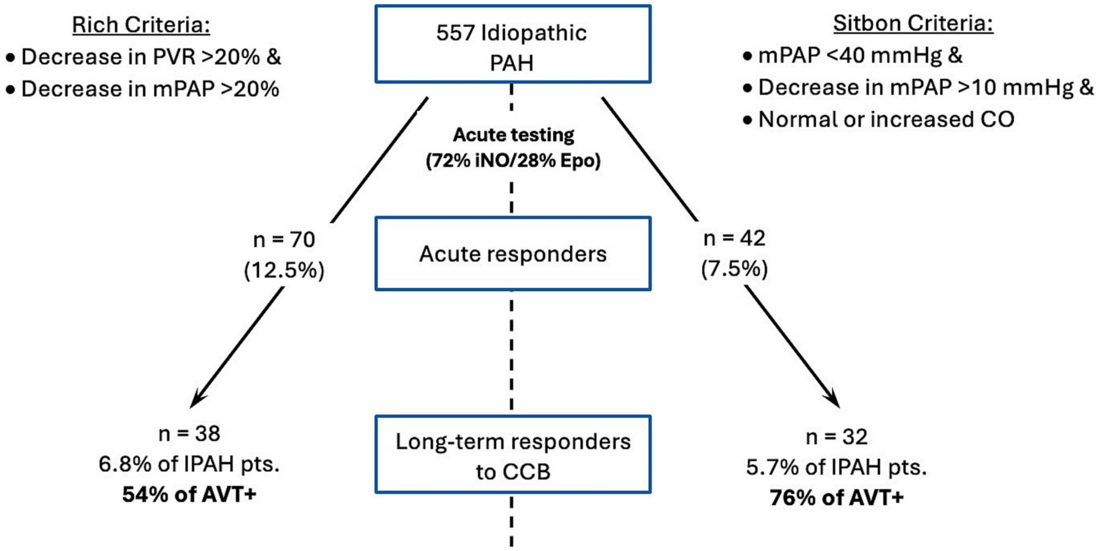
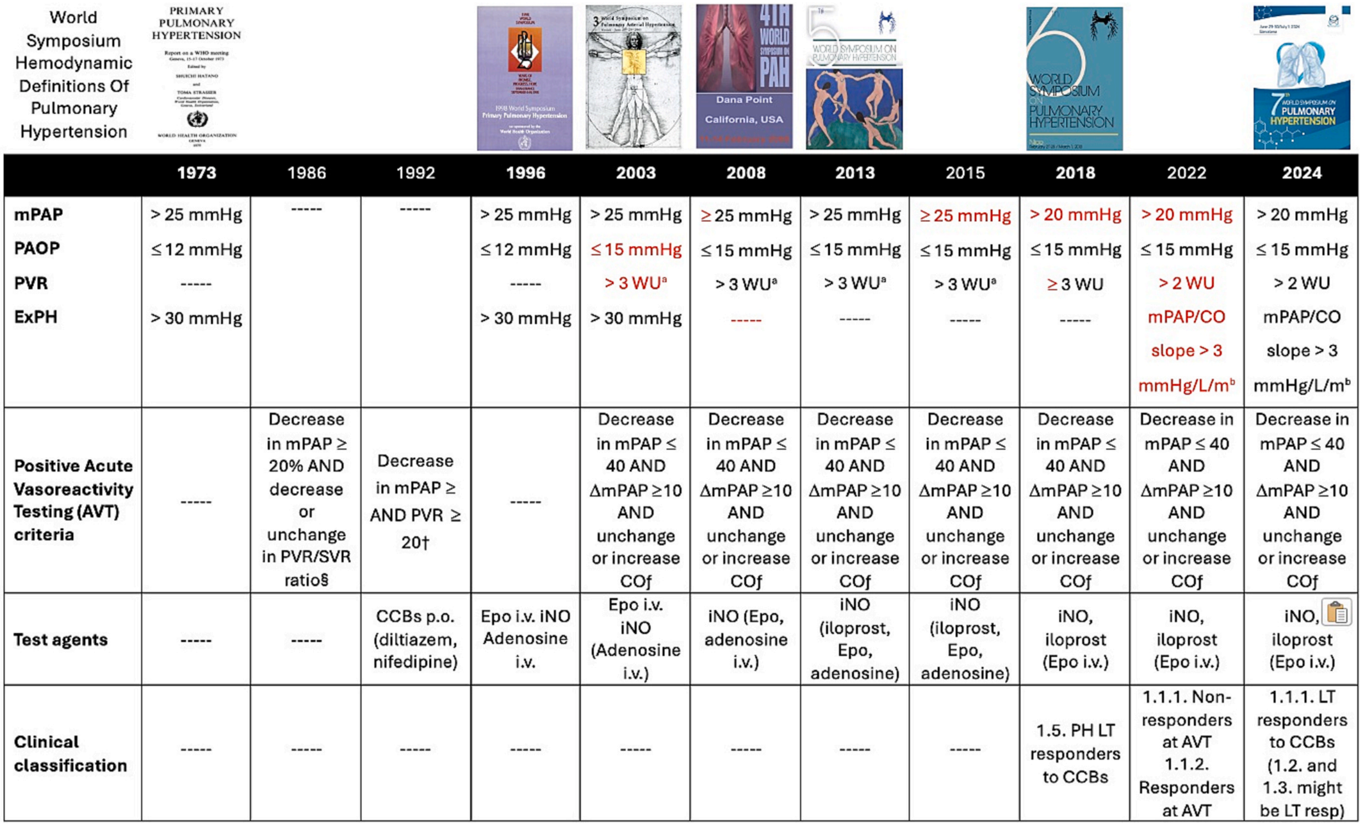


Fig. 1. Diagram comparing the proportions of acute vasoresponders screened using Rich (left panel) and Sitbon (right panel) criteria, along with the corresponding long-term responders to calcium-channel blockers (CCBs) based on a historical cohort published by Sitbon et al.[12]. AVT: acute vasoreactivity testing; CO: cardiac output; Epo: epoprostenol; iNO: inhaled nitric oxide; mPAP: mean pulmonary arterial pressure; PAH: pulmonary arterial hypertension; PVR: pulmonary vascular resistance.



World Symposium Hemodynamic Definitions Of Pulmonary Hypertension	1973	1986	1992	1996	2003	2008	2013	2015	2018	2022	2024
mPAP	> 25 mmHg	-----	-----	> 25 mmHg	> 25 mmHg	≥ 25 mmHg	> 25 mmHg	≥ 25 mmHg	> 20 mmHg	> 20 mmHg	> 20 mmHg
PAOP	≤ 12 mmHg			≤ 12 mmHg	≤ 15 mmHg	≤ 15 mmHg	≤ 15 mmHg	≤ 15 mmHg	≤ 15 mmHg	≤ 15 mmHg	≤ 15 mmHg
PVR	-----			-----	> 3 WU[a]	> 3 WU[a]	> 3 WU[a]	> 3 WU[a]	≥ 3 WU	> 2 WU	> 2 WU
ExPH	> 30 mmHg			> 30 mmHg	> 30 mmHg	-----	-----	-----	-----	mPAP/CO slope > 3 mmHg/L/m[b]	mPAP/CO slope > 3 mmHg/L/m[b]
Positive Acute Vasoreactivity Testing (AVT) criteria	-----	Decrease in mPAP ≥ 20% AND decrease or unchange in PVR/SVR ratio§	Decrease in mPAP ≥ AND PVR ≥ 20†	-----	Decrease in mPAP ≤ 40 AND ΔmPAP ≥10 AND unchange or increase COƒ	Decrease in mPAP ≤ 40 AND ΔmPAP ≥10 AND unchange or increase COƒ	Decrease in mPAP ≤ 40 AND ΔmPAP ≥10 AND unchange or increase COƒ	Decrease in mPAP ≤ 40 AND ΔmPAP ≥10 AND unchange or increase COƒ	Decrease in mPAP ≤ 40 AND ΔmPAP ≥10 AND unchange or increase COƒ	Decrease in mPAP ≤ 40 AND ΔmPAP ≥10 AND unchange or increase COƒ	Decrease in mPAP ≤ 40 AND ΔmPAP ≥10 AND unchange or increase COƒ
Test agents	-----	-----	CCBs p.o. (diltiazem, nifedipine)	Epo i.v. iNO Adenosine i.v.	Epo i.v. iNO (Adenosine i.v.)	iNO (Epo, adenosine i.v.)	iNO (iloprost, Epo, adenosine)	iNO (iloprost, Epo, adenosine)	iNO, iloprost (Epo i.v.)	iNO, iloprost (Epo i.v.)	iNO, 📋 iloprost (Epo i.v.)
Clinical classification	-----	-----	-----	-----	-----	-----	-----	-----	1.5. PH LT responders to CCBs	1.1.1. Non-responders at AVT 1.1.2. Responders at AVT	1.1.1. LT responders to CCBs (1.2. and 1.3. might be LT resp)

Fig. 2. Table showing the evolution of positive acute pulmonary vasoreactivity testing criteria, the vasodilators used, and the clinical classification, alongside changes in PH hemodynamic thresholds over the past 50 years. Updates are highlighted in red. (CCB: calcium channel blocker; CO: cardiac output; Epo: epoprostenol; ExPH: exercise pulmonary hypertension; LT: long-term; mPAP: mean pulmonary arterial pressure; PAOP: pulmonary arterial occlusion pressure; PVR: pulmonary vascular resistance; SVR: systemic vascular resistance; WU: Wood unit). [a]: applies only to Group 1 PAH; [b]: mean pulmonary artery pressure to cardiac output slope (mPAP/CO slope) measured between rest and exercise. §: Barst criteria [11]; †: Rich criteria [12]; *ƒ*: Sitbon criteria [13]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

PAH-targeted drugs; therefore, this clinical group should not have a common pathophysiological mechanisms [1].

Recently, at the 7th World Symposium of PH (2024), a subgroup of “long-term responders to CCB” was reintroduced within IPAH (subgroup 1.1.1), adding that patients with HPAH (subgroup 1.2) or DT-PAH (subgroup 1.3) may also be long-term responders to CCBs. Therefore, it is recommended that not only IPAH but also HPAH and DT-PAH must undergo AVT during the diagnostic RHC to identify those who should be treated with CCBs, while maintaining the dichotomous criteria for responsiveness. Although the reintroduction of this subgroup emphasizes the importance of AVT in IPAH, HPAH, and DT-PAH, it still does not address predicting long-term responders, nor does it consider the potential role of pulmonary arterial capacitance (PAC) improvement (both change and achieved value) as the best predictor of long-term CCB therapy success [19].

4. Areas of certainty and Controversy

4.1. Certainties

Certain aspects about the vasoreactive PAH population can be stated with certainty. As we discussed earlier, a small subgroup of patients with PAH, including 1.1, 1.2, and 1.3 (~10–12 %), shows significant hemodynamic improvement after acute exposure to short-acting inhaled vasodilators (‘super responders’), and about half of these vasoreactive patients have long-term responsiveness to CCBs. The difference in outcomes between long-term responders and non-long-term responders has led to speculation that the AVT responsiveness phenotype may indicate different diseases or a less advanced stage of the disease [20]. Although recent cohorts of patients with PAH show more preserved resting hemodynamics, the extent of pulmonary vascular remodeling remains substantial. Vasoreactive patients are not necessarily those with the least remodeling due to early diagnosis. Recent cohorts have shown no significant differences in resting hemodynamics between positive and negative AVT and between long-term responders and non-long-term responders [19,21]. These facts suggest that these are distinct diseases, with a naturally slower progression in cases of ‘super responders’. Accordingly, recent evidence suggests that a more responsive circulation may indicate a distinct patient phenotype [22,23].

4.2. Controversies

There is no link between resting hemodynamics and hemodynamic changes during AVT (the vasoreactive phenotype varies unpredictably with pulmonary vasculopathy and hemodynamic abnormalities). Being a vasoresponder (beyond the criteria used: −20 % mPAP and PVR or mPAP $<$ 40, delta mPAP $>$ 10 with normal or increased CO) is beneficial (with less disease progression and longer survival).

The definition of long-term CCB responders has evolved to the most recent, stricter criteria: patients who are alive and remain on initial therapy, either as CCB monotherapy or CCB combined with other initial PAH treatments, and are classified as WHO-FC I/II or low risk at 12 months follow-up [19]. Additionally, we may question how to interpret the hemodynamic response during AVT, given the lower diagnostic thresholds of mPAP and the increasing number of IPAH patients with comorbidities [24].

Current guidelines for AVT do not standardize O_2 co-administration with iNO. Considering the effects of alveolar O_2 pressure on pulmonary vasoresponsiveness in PH patients, this creates another uncertainty [25,26]. Adding 100 % O_2 to iNO would allow identification of hypoxic vasoconstriction during the hemodynamic response to an acute vasodilator challenge [27].

Little is known about whether repeating AVT provides benefits for PAH patients. Acute pulmonary vasoreactivity may vary over time due to disease progression and/or changes in PAH-specific therapies. Loss of AVT over time may be associated with a decrease in response to CCBs [28,29].

5. Interpreting and understanding the magnitude of vasoresponsiveness (phenotype) during an acute vasodilator challenge

5.1. Complete hemodynamic response during a vasodilator challenge

Physiologically, the different hemodynamic criteria of AVT may identify distinct patient populations, each exhibiting unique levels of pulmonary vascular tone, vascular remodeling, and RV dysfunction.

According to the Poisseuille equation, mPAP is dependent on the resistance of the pulmonary vessels (PVR), pulmonary blood flow (CO), and left-sided filling pressures (PAOP) as represented with the following equation:

$$\mathrm{mPAP} = \mathrm{CO} \times \mathrm{PVR} + \mathrm{PAOP}$$

where PAOP refers to pulmonary arterial occlusion pressure.

While PVR measures stationary pulmonary vascular load, PAC reflects the pulsatile load caused by vessel wall stiffness and wave reflections. PAC represents the elastic properties of the entire pulmonary vascular system and is defined by the change in volume per unit pressure change (SV/pPAP, mL/mmHg). It is a measure of the overall ability of the entire PA circuit to respond to pulsatile flow, resulting in an attenuation of pulse pressure as it propagates to distal pulmonary vessels. A decline in PAC occurs earlier in the course of pH than an increase in PVR, indicating that PAC can be an earlier or more sensitive marker of elevated RV load [30].

Replacing CO with SV and heart rate (HR), and SV with PAC multiplied by pPAP, allows us to incorporate the pulsatile component of the afterload:

$$\mathrm{mPAP} = \mathrm{PAC} \times \mathrm{pPAP} \times \mathrm{PVR} \times \mathrm{HR} + \mathrm{PAOP}$$

Based on large meta-analyses reviewing resting hemodynamic data from healthy individuals, the estimated mean ± SD mPAP was 14.0 ± 3.3 mmHg, with an upper limit of normal (ULN) defined as two SDs above the mean at 20.6 mmHg [31]. For PVR, the mean ± SD was 1.1 ± 0.5 WU, with an ULN of 2.1 WU [32]. For PAOP, the mean ± SD was 9.4 ± 1.8 mmHg, with an ULN of 13.0 mmHg and a gray zone between 12 and 15 mmHg, recommending that PAOP be interpreted in the clinical context [33,34]. The latest PH guidelines (2022) propose a normal PAC value greater than 2.3 mL/mmHg [1]. Considering these normal resting hemodynamic values, we can suggest that the primary determinant of mPAP is the left heart diastolic properties (PAOP, ~67 %). In healthy, highly distensible pulmonary vessels, as PAOP rises, the PAOP is transmitted in a less one-to-one ratio (i.e., a one mmHg rise in PAOP results in a $<$ 1 mmHg rise in mPAP), with a reduced or unchanged transpulmonary gradient and PVR. However, as the PAC decreases, mPAP increases disproportionately relative to PAOP, leading to increases in transpulmonary gradient and PVR [35,36]. In case of a significant increase in PAOP during AVT (which could indicate left heart dysfunction), the concomitant change in PVR will reflect the functional status of the pulmonary vasculature.

The current criteria for defining a positive AVT, proposed as an expert opinion over 20 years ago, are based on mPAP and CO (a decrease in mPAP by 10 mmHg to below 40 mmHg while maintaining CO, which necessarily involves a significant drop in PVR). They evaluate the steady hemodynamic response, which can be referred to as ‘steady vasoreactivity,’ and this does not predict who will be a long-term responder [12].

Cheng et al. performed AVT with inhaled iloprost in 308 incident cases of IPAH and found that PAC was higher in the positive AVT group, suggesting that it may predict a long-term response to CCBs [21]. Eleven percent of patients (35/308) met the AVT responder criteria. Of these, 69 % (24/35) were classified as long-term responders -patients who remained in WHO FC I-II after one year on CCB monotherapy and had never been hospitalized for worsening or RV failure- showing a greater increase in PAC, a higher final PAC, and a greater PAC change during AVT, with similar baseline hemodynamics compared to non-long-term responders. Limitations included a retrospective design, patients from a single PH center, and the lack of reassessment of hemodynamic changes by RHC after 1 year of CCB therapy. Lastly, a recent multicenter study revealed that, among positive AVT responders, PAC value at AVT, low-risk status, and normal NT-proBNP levels during early follow-up were associated with long-term response to CCBs and predicted survival. Therefore, the PAC response during AVT, which measures the pulsatile hemodynamic response (‘pulsatile vasoreactivity’), may identify a subgroup of vasoresponders with a sustained response to CCBs, less disease progression, and an improved prognosis [19]. However, the study’s limitations included the retrospective nature of the analysis, missing data, and the relatively small number of patients.

While PAC measures overall pulmonary distensibility, the alpha (α) coefficient proposed by Linehan et al. is a measure of distal vascular distensibility [37]. Alpha distensibility is a mechanical property defined as the percentage (relative change) increase in diameter (or area) of the distal resistive pulmonary vessels per mmHg increase in pressure (%/mmHg). Since the microvasculature accounts for nearly 80 % of the total pulmonary circulation, alpha serves as a marker of pulmonary vascular health and microvascular reserve [38]. Linehan’s distensible model of pulmonary circulation is a nonlinear equation relating alpha with mPAP at constant hematocrit according to the following formula:

$$\mathrm{mPAP} = \frac{\left[(1+\alpha \mathrm{PAOP})^{5} + 5\alpha \mathrm{TPR} \times \mathrm{CO}\right]^{1/5} - 1}{\alpha}$$

This model has been validated in healthy humans, where the increase in diameter is 1.2 ± 0.4 % per mmHg (ULN 2 %/mmHg) [39]. Similar to PVR, the alpha coefficient is more accurately determined from maneuvers that provide repeated hemodynamic measurements during increased CO, such as passive leg raises or exercise hemodynamics (multi-point pressure-flow data) [40]. However, it can also be analyzed for changes between single-point values [41]. Loss of distal vascular distensibility (alpha decrease) during exercise is an early hemodynamic marker of pulmonary vascular disease [42]. Additionally, alpha may improve after therapy with pulmonary vasodilators [41].

It is well known that the response to inhaled vasodilators (most commonly NO or iloprost) mainly reflects pulmonary microvascular vasoreactivity. Only a recent study examined the alpha distensibility coefficient during AVT in 75 treatment-naïve patients with PH-associated interstitial lung disease (PH-ILD). An alpha distensibility cutoff of ≥ 21 % change could accurately distinguish 6-month inhaled treprostinil treatment success with an AUROC of 0.83. The authors did not examine the relationship between AVT response and changes in alpha distensibility [27]. Although the data were derived from a strict selection criterion to define PH-ILD, the sample size was small and the study was conducted at a single tertiary center, which may limit generalizability.

6. Potential role of acute vasoreactivity testing across pulmonary hypertension clinical groups

The frequency and importance of hemodynamic changes during AVT in patients other than those with PAH are less well known. However, there is growing interest in studying acute vasoresponsiveness across different patient groups with PH, as it can guide therapy and predict outcomes. Recognizing that vasoreactivity may result from multiple mechanisms and have different implications across PH groups is crucial.

Krasuski et al. investigated the ability of the vasoreactive response (iNO 40 ppm) to predict survival in a cohort of patients with different clinical PH groups ($n = 197$, including 134 in group 1-85 with IPAH-, 39 in group 3, and 24 in groups 4 and 5 of Dana Point). Vasoresponders were defined as those who achieved an mPAP of 40 mmHg and a reduction in mPAP of at least 13 % (median value of the cohort). There were 51 deaths (26 %) over an average of 2.3 years. Vasoresponders showed improved survival regardless of whether they had idiopathic or nonidiopathic PH, or belonged to group 1 or non-group 1. In a multivariate analysis, a positive vasoresponse was associated with better survival, along with younger age, lower RAP, and improvement in functional class [43].

6.1. Pulmonary hypertension associated with congenital heart disease

The best approach for managing patients with shunt lesions and increased PVR remains uncertain. Reversibility testing with O_2 and vasodilators is an essential step in the preoperative evaluation of congenital heart disease with left-to-right shunt-induced PH and a PVR of 4–8 WU·m^2. The main goal of the AVT is to determine whether the rise in PAP is mainly due to advanced pulmonary vasculopathy or increased pulmonary blood flow [44]. Patients with unrepaired moderate-to-large defects and mildly to moderately elevated PVR (less than 4 WU·m^2) who have predominantly left-to-right shunt may still be suitable for repair. Conversely, those with physiology closer to Eisenmenger syndrome (when PVR exceeds 8 WU·m^2) are unlikely to be candidates for repair [45]. Although AVT can assist in decision-making regarding correction, the entire clinical picture, patient age, and anatomical type of shunt should also be considered.

D’Alto et al. investigated whether residual pulmonary vascular responsiveness to intravenous epoprostenol predicts clinical outcomes in patients with Eisenmenger syndrome who received chronic bosentan therapy ($n = 38$). The mean follow-up was 33 ± 17 months; three patients died, resulting in an overall survival rate of 92 %. A PVR of less than 25 % after epoprostenol infusion predicted clinical worsening, with a sensitivity of 56 %, a specificity of 100 %, and an area under the ROC curve of 0.77. In the multivariate Cox proportional hazards regression model, PVR was identified as the only independent predictor of clinical worsening ($HR = 0.973$; $p = 0.01$) [46]. Limitations include an open-label, retrospective, non-randomized, and monocentric design.

6.2. Pulmonary hypertension associated with left heart disease

In a prospective cohort of 73 patients with pulmonary hypertension due to left heart disease (PH-LHD) associated with heart failure with preserved ejection fraction, 78 % underwent AVT with iNO. No adverse side effects or events occurred during iNO testing, despite 30 patients (55 %) experiencing an increase in PAOP of 1–16 mm Hg. Ten subjects (18 %) met the Rich definition of acute vasodilator response, of whom 2 (4 %) also met the more stringent Sitbon definition. Responders, regardless of the criteria used, showed no difference in survival compared with nonresponders [47].

A single-center, retrospective study of 69 patients with PH-LHD found that an increase in PAOP during AVT was the only significant predictor of all-cause death or hospitalization for heart failure after one year in a multivariate analysis (HR 4.35; $p = 0.019$) [48]. Patients with group 2 PH are likely to tolerate the iNO vasoreactivity test. Patients with PH-LHD associated with heart failure with preserved ejection fraction showed an increase in PAOP. In contrast, those with heart failure with reduced ejection fraction showed less tolerance to iNO, indicating greater tolerance in the former. The authors proposed that iNO shifts pressure from the RV to the LV via selective pulmonary arterial dilation, potentially increasing left ventricular (LV) filling pressure in patients lacking LV diastolic reserve [48]. However, in a more recent cohort of 104 patients with either PH-LHD, involving combined precapillary and postcapillary PH, or PAH with a post-capillary component overlapping PAH and PH-LHD, Krishtopaytis E et al. hypothesized that the iNO challenge (40 ppm during 5 min) could relax the pulmonary circulation and increase LV preload, affecting PVR and PAOP to varying degrees and providing valuable information for guiding treatment and prognosis. They found that the iNO challenge is safe and significantly decreases PVR (mainly due to a reduction in transpulmonary gradient by about 86 %), particularly in patients with more severe PH, while increasing PAOP. Changes in PAOP and PVR during iNO administration did not correlate with tolerance to PAH-specific medications, heart failure-related hospitalization, or survival [49]. This was a single-center, retrospective cohort study with measurement variations in the repeated PAOP, which can limit the usefulness of iNO in combined postcapillary PH.

Irreversible PH places potential heart transplant candidates at high risk of RV failure after transplantation. When sPAP reaches 50 mmHg and either the transpulmonary gradient is 15 mmHg or PVR exceeds 3 WU with systolic blood pressure above 85 mmHg, candidate selection requires AVT. The degree of PVR reversibility with pulmonary vasodilators predicts better outcomes in transplant candidates, provided systemic hypotension does not occur. According to the International Society for Heart and Lung Transplantation, an appropriate response to a vasodilator challenge would be a reduction in the transpulmonary gradient to $\leq$ 12 to 15 mmHg and in PVR to $\leq$ 2.5 to 3 WU. If PVR is reversible but systolic blood pressure falls below 85 mmHg with pharmacologic maneuvers, the risk of RV failure remains high [50]. Although several drugs have been used to evaluate PH reversibility, iNO (40 ppm, 10 min) is the drug of choice for AVT [51,52]. It is a short-acting drug without systemic side effects, though it may increase LV filling pressure due to increased venous return to a poorly compliant LV. Inhaled iloprost is an alternative, but it has more systemic effects, primarily systemic vasodilation, due to its slower inactivation [53].

6.3. Pulmonary hypertension associated with chronic lung diseases

Strick et al. studied vasoreactivity and mortality in thirty-six patients diagnosed with group 3 PH (seventeen with Chronic Obstructive Pulmonary Disease, twelve with Interstitial Lung Disease, and six with Combined Pulmonary Fibrosis and Emphysema). Only 8 % of patients met the current criteria for acute vasoreactivity. The median survival time for all subjects was 31.7 months after diagnosis, while non-vasoreactive patients had a median survival of 25.4 months. Patients were grouped based on baseline and absolute changes in mPAP (35 mmHg and 5 mmHg) and PVR (6.3 WU and 1.2 WU) during AVT. Interestingly, only patients with a PVR reduction of more than 1.2 WU during the iNO challenge showed a statistically significant increase in mortality risk. Changes in mPAP, CO, and PAOP all contributed to the decrease in PVR within this group; baseline PVR was higher, and PAOP increased more, suggesting that iNO may reveal a component of left-sided heart dysfunction [54].

In PH associated with interstitial lung disease, the microvascular response -measured as the change in alpha distensibility coefficient- from baseline to iNO resulted in an absolute median increase of 0.15 % per mmHg in distensibility (53 %), along with an absolute median reduction in mPAP and PVR of 6.0 mmHg and 1.8 WU, respectively, which corresponded to relative values of 16.3 % and 28.7 %. Four patients (5.3 %) met the current criteria of mPAP falling $\geq$ 10 mmHg to below 40 mmHg without a reduction in CO, and 23 patients (30.7 %) met the Rich criteria with a $\geq$ 20 % reduction in both mPAP and PVR. Patients with six months of inhaled treprostinil (iTre) improvement showed large relative increases in distensibility with O_2 + iNO (versus failure, 76.0 % versus 15.3 %, $p = 0.004$). Conversely, iTre failure was associated with increased distensibility when oxygen was administered alone (26.8 % versus -3.9 % iTre improve, $p = 0.045$). This opposing response to vasodilator challenges may reflect the distinct roles of hypoxic vasoconstriction and remodeling in patients with PH associated with interstitial lung disease [27].

Recently, Takano et al. evaluated the clinical impact of AVT with iNO (20 ppm for 10 min) in forty-eight patients with severe PH related to chronic lung disease (nineteen Chronic Obstructive Pulmonary Disease, nine Interstitial Lung Disease, and twelve Combined Pulmonary Fibrosis and Emphysema). iNO testing was safe and did not worsen gas exchange. Patients were divided based on the median PVR response to iNO (-15 %). The vasoreactive group had a higher proportion of patients started on pulmonary vasodilators and showed more severe baseline hemodynamics. Univariate Cox regression analysis indicated that prognostic factors for survival included age, vasoreactivity, and initiation of pulmonary vasodilator therapy. However, only age remained as a significant predictor of death in the multivariable Cox regression analysis [55]. This is a single-center, retrospective, exploratory study with a small sample size, including patients who had already received pulmonary vasodilators before iNO testing.

6.4. Chronic thromboembolic pulmonary hypertension (CTEPH)

Ulrich et al. have shown that patients with PAH ($n = 35$) and CTEPH ($n = 22$) exhibit similar acute vasoreactivity to iNO (40 ppm) and inhaled iloprost (10 μg), suggesting possible shared pathophysiological pathways in both conditions. According to the criterion of a $\geq$ 20 % reduction in mPAP (pressure responders) or PVR (resistance responders), and the Sitbon criteria, more patients responded to iloprost (21 %, 48 %, and 12 %) than to iNO (7 %, 41 %, and 5 %), respectively [56].

In a cohort of 103 CTEPH patients (1994–2006), Skoro-Sajer et al. reported that none of the patients who did not undergo pulmonary endarterectomy ($n = 41$) met the Sitbon AVT criteria. Among the 62 patients who underwent endarterectomy, 12.9 % were vasoreactive responders [57]. Additionally, 80 out of 103 (77.7 %) exhibited some level of acute vasoresponse. A reduction in mPAP of more than 10.4 % with inhaled NO predicts better long-term survival and freedom from lung transplantation in adults with CTEPH undergoing pulmonary endarterectomy [57]. This pilot study has established the cutoff value for ΔmPAP based on a small, single-center sample, with few events observed and no validation cohort.

In CTEPH patients enrolled in PVDOmics (Pulmonary Vascular Disease Omics) and who underwent vasodilator challenge with O_2 plus iNO ($n = 49$), Frantz et al. found that 20 % and 8 % met the Rich and Sitbon criteria, respectively [58]. This includes patients with prior PEA ($n = 14$) and those undergoing medical therapy ($n = 35$, including two with balloon pulmonary angioplasty). Patients on riociguat had a lower response rate than patients on phosphodiesterase-5 inhibitors [58].

7. Revisiting the acute vasoreactivity testing: a new approach for phenotyping the pulmonary vascular response to acute vasodilator challenge

As previously mentioned, pulmonary vascular health can be assessed by the hemodynamic afterload faced by the RV, which includes both steady and pulsatile components. The mPAP and pPAP represent opposition to steady and pulsatile loads, respectively [60]. The steady load is reflected in the PVR and total pulmonary resistance (TPR), which are commonly used in diagnosing PH. However, 30 % to 50 % of RV work is to meet the pulsatile load, such as overall vessel stiffness and wave reflections [59]. As mentioned before, alpha pulmonary vascular distensibility and PAC enable the quantification of this load. The ability of the pulmonary vasculature to cushion arterial pulsatility (high PAC) and to dilate with increasing pulmonary flow (alpha) helps protect the RV from excessive increases in steady and pulsatile afterload during exercise, and reduces the progression of pulmonary vascular disease in PH patients. These parameters can also be sensitive indicators for detecting an early rise in RV afterload.

The current hemodynamic response of the pulmonary circulation during an acute vasodilator challenge in PAH patients is simplified to steady-state metrics, with the additional drawback of being assessed dichotomously using cutoff points set by expert opinion [12]. The alpha distensibility coefficient and PAC are excluded from routine assessments (to diagnose PH) and AVT (to define pulmonary vasoreactivity). Both parameters are key hemodynamic parameters that complete the description of pulmonary vascular function and RV afterload and can be derived from hemodynamic data collected during the diagnostic RHC.

Like PVR, the alpha distensibility coefficient should be measured across different pulmonary flows (multi-point plots), since a curvilinear relationship exists between them and CO [61]. CO can be changed by the passive leg rise (PLR) maneuver, which is comparable to alpha with exercise [40]. Additionally, alpha distensibility can be pharmacologically modified with selective pulmonary vasodilator therapy and by the related change between single-point measurements [41,62]. A lower alpha coefficient can help identify patients with early pulmonary arteriopathy and those at risk for PH who have exercise-induced PH and normal resting hemodynamics, which are associated with a poorer prognosis [63]. Alpha is reduced in exercise-induced PH, chronic hypoxia, and PH, but can be improved with long-term pulmonary vasodilator therapy [39,41]. Changes in the alpha coefficient during AVT can estimate the degree of recruitable microcirculatory reserve in response to an acute vasodilator challenge [64].

Wang et al. have identified PAC as a key prognostic marker in PH. Among patients with elevated mPAP, a protective association between PAC and all-cause mortality was observed, starting at 3 ml/mmHg and progressing to 7 ml/mmHg. These data support prospective studies that consider PAC as a new therapeutic target for PH [65]. In a cohort of patients with HFpEF and PH-LHD, PAC was the strongest predictor of mortality, with a PAC < 1.1 ml/mm Hg associated with nearly a 5-fold increased risk of death [47].

Unlike systemic circulation, where arterial compliance is mainly limited to the proximal aorta and resistance is primarily found in the distal arterioles, in pulmonary circulation, resistance and compliance change together throughout the entire vascular bed [66,67]. These anatomical and functional features create an inverse hyperbolic relationship between PVR and PAC (R-C curve) in pulmonary circulation. In early PH, small increases in PVR are associated with large decreases in PAC. Conversely, at high PVR (>3–4 WU), there is minimal additional change in PAC [68]. As with the calculation of PVR, PAC relates pressure and pulmonary blood flow; however, PAC worsens even before changes occur in PVR in PAH [24]. PAC depends on pressure (mPAP and PAOP, an extrinsic mechanism) as well as on pulmonary vascular wall remodeling (where collagen and fibrosis replace elastic fibers, an intrinsic mechanism). Therefore, PAC can be impaired by two mechanisms: a) an increase in pressure (mPAP and/or PAOP), which saturates the elasticity of arterial elastic fibers and recruits stiffer collagen fibers; and b) less reversible wall remodeling (with an accumulation of collagen and loss of elastin fibers) [36]. An effective way to distinguish these mechanisms when PAC decreases is to analyze changes in isobaric PAC [69]. For similar hemodynamic values, a greater change in PAC would depend on the addition of an intrinsic mechanism (structural or functional remodeling) to the change in mPAP (extrinsic mechanism). The PVR/PAC response of patients located to the left of the R-C curve is more dependent on the intrinsic mechanism (less structural/functional remodeling) compared to those to the right of the R-C curve. One method to detect the presence of an intrinsic mechanism in PAC improvement could be an increase in the alpha distensibility coefficient.

The study by Gerhardt et al. provides new insights, especially regarding the current criteria for predicting responsiveness to long-term CCB therapy, particularly the calculation of PAC. They found that PAC increased by 78.2 % in AVT responders. A subgroup of patients who may exhibit a prolonged response to CCB therapy includes those who demonstrate a significant improvement in PAC (in addition to meeting vasoreactivity criteria) [19]. Fig. 3 plots the R-C data of the Gerhardt cohort with positive AVT, distinguishing long-term from non-long-term CCB responders. The higher PAC response observed in long-term responders compared to non-long-term responders may be due to better preserved structural and/or functional remodeling of the vascular wall. This suggests that only in long-term responders, an intrinsic mechanism (vessel wall) could contribute to the extrinsic mechanism of PAC improvement (associated with similar decreases in mPAP), explaining the higher PAC response during the vasodilator challenge. Three vasoreactive patients with an intermediate risk from a historical cohort of

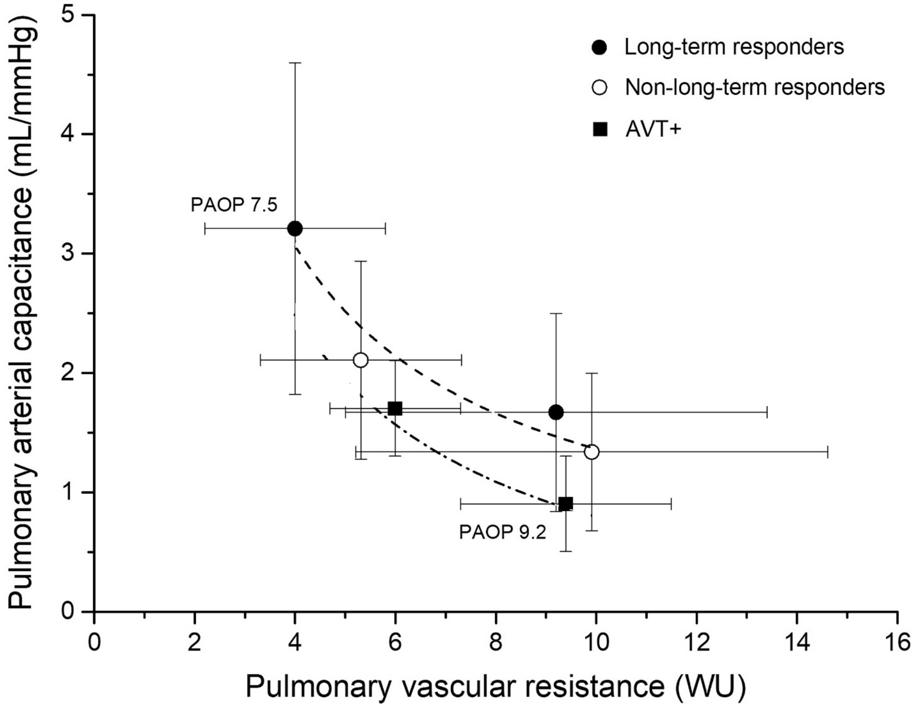


Fig. 3. Plot representing the PAC-PVR mean ± SD values relationship for long-term responders (black circle, n = 88) and non-long-term responders (unfilled circle, n = 74) based on the cohort published by Gerhardt et al. [20], and for positive vasoresponders from our cohort (black square) [70]. PAOP: pulmonary arterial occlusion pressure.

our group, who exhibited a behavior similar to that of the non-long-term responders in the Gerhardt cohort of positive vasoreactive patients, were also included in Fig. 3 [70]. Despite positive vasoreactivity, the alpha distensibility coefficient did not change during AVT (0.22 ± 0.04 vs 0.20 ± 0.04 %/mmHg) with a resting RV arterial coupling (TAPSE/sPAP ratio) of 0.3 ± 0.05 mm/mmHg (unpublished data). This supports the idea that an increase in alpha coefficient during AVT would be linked to a greater rise in PAC through an intrinsic mechanism that adds the extrinsic one. The higher PAOP would explain the downward and leftward shift of the R-C curve.

Considering the prognostic significance of baseline RV-arterial coupling (RVAC), it is logical to evaluate RV response during AVT. Tello et al. reported the first evidence of improved acute vasoreactivity in RVAC-related disease using an invasive multibeat approach. The significant increase in the ratio of end-systolic ventricular elastance to arterial elastance from 0.71 to 1.84 was primarily due to a decrease in arterial elastance [71].

8. Discussion and future directions

Resting hemodynamic variables are prognostic factors in PAH, included in various risk scores, and recent efforts have focused on examining the prognostic value of hemodynamic parameters through RHC during follow-up [72,73]. The use of the acute vasodilator challenge, along with other provocative tests such as exercise or passive leg raising during RHC, enables a deeper understanding of the pulmonary circulation's condition by assessing vasoreactivity and resistance to increased flow (depending on recruitment and vascular distension), respectively. The response of the pulmonary circulation to increased pulmonary flow (caused by physical or pharmacological stress, or increased venous return) is well understood, and it has been included in the PH guidelines since 2022 [1,74]. It enables early detection of pulmonary vascular disease or left-heart diastolic dysfunction, as well as prognostic assessment. In contrast, the current AVT is often underused.

The present work aims to reconsider what should be measured in pulmonary vasoreactivity and its current importance during the diagnostic RHC. The acute hemodynamic response to a vasodilator challenge offers more information for most PAH patients than the parameters currently used to identify the minority who can be successfully treated with CCB [64]. Based on criticisms of the current vasoreactivity criteria, the proposed new analysis of AVT could more thoroughly evaluate the remaining vasoreactive reserve of the pulmonary circulation. On the one hand, calculating alternative variables from the parameters obtained during diagnostic RHC without adding more complexity to the study can also accurately reflect the extent of remodeling and vasomotor tone in the pulmonary tree. On the other hand, analyzing the continuous changes in these variables can help better define 'degrees' of vasoreactivity. The only additional action is to estimate the concomitant TAPSE/sPAP ratio by echocardiography, which would complete the picture of the right ventricular function during the vasoreactive response (Fig. 4). However, as a proposal, it will need further studies to confirm the reproducibility and validity. Evidence has grown to support updating the role and criteria of AVT, as well as its use as a dynamic, provocative test that could become a new metric for predicting risk, specific treatment response, and outcomes. Despite ongoing debates, whenever some degree of vasoreactivity is demonstrated and sustained, the prognosis for PH patients could improve [64].

Currently, pulmonary vasoreactivity testing during RHC is recommended only for patients with IPAH, HPAH, or DT-PAH to identify a small subgroup, known as super-responders, a specific but very rare phenotype. These 'super-responders' may help identify long-term responders to CCBs, leading to excellent survival outcomes. Historically, finding patients suitable for high-dose CCB therapy made sense as a cheap option for individuals without comorbidities and limited alternatives. However, today, the availability of modern vasodilator/antiproliferative drugs and a treatment approach based on a comprehensive global risk assessment restricts the current criteria for AVT use. It would be very cautious to initiate long-term CCB monotherapy in patients with WHO Functional Class late III or IV and severely abnormal hemodynamics, even if they show a positive AVT response [24]. A comprehensive characterization of a PAH phenotype with pulmonary vasoreactive reserve should involve continuous, multiparametric metrics that assess the entire hemodynamic response to a vasodilator challenge, rather than simply meeting current criteria for CCB therapy. Additionally, we may suggest using the AVT to adjust overall risk and treatment response by analyzing responses of other hemodynamic

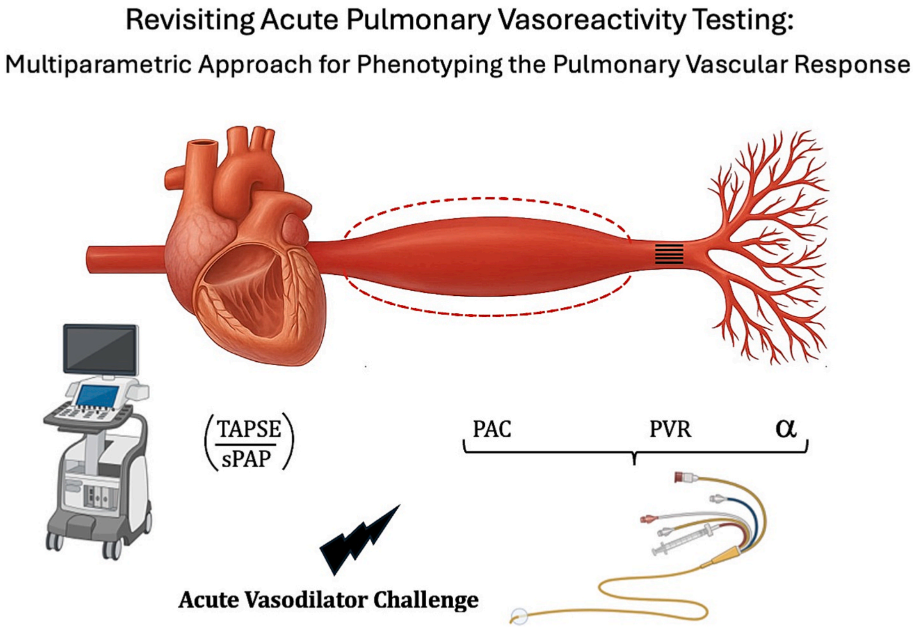


Fig. 4. Diagram illustrating the comprehensive analysis of different hemodynamic parameters during vasodilator challenge in right heart catheterization at rest. Concomitant echocardiography can enhance the evaluation of right ventricular function. α: distensibility coefficient; PAC and PVR: pulmonary arterial capacitance and vascular resistance, respectively; TAPSE/sPAP: tricuspid annular plane systolic excursion/systolic pulmonary arterial pressure ratio. Created with Biorender.com.

variables that reflect the pulsatile load (PAC, alpha), including RVAC, estimated by the TAPSE/sPAP ratio during an acute vasodilator challenge. Based on PAH-designed three-strata, four-strata, or continuous risk scores (REVEAL score) have predictive power in a large multicenter cohort of pH patients (whether considered as a whole or separately for each PH group) [75], the current proposal should motivate future prospective studies to analyze the role and interpretation of AVT across all PH subgroups.

We must consider some limitations associated with the use of the various hemodynamic parameters. The Poisseuille equation is limited because it assumes a purely linear relationship between mPAP and CO. It is well-known that normal pulmonary vasculature can distend and recruit additional closed vessels to accommodate increased blood flow, leading to an attenuated rise in mPAP and a curvilinear relationship with CO, which accounts for the decreased PVR at higher CO levels [61]. By performing joint density analysis and physiologically constrained hemodynamic simulations, Hungerford S et al. reproduced with high fidelity the inverse hyperbolic relationship between PVR and PAC that has been reported in clinical studies [68], along with the influence of PAOP [76–78]. These findings indicate that this relationship might not solely reflect an inherent property of the pulmonary vasculature but could also result from plotting mathematically linked variables with a predictable shift based on PAOP [79]. The most reliable methods for accurate PAC estimation are the area method and the logarithmic pressure difference method [80]. The value obtained from the ratio SV/pPAP, though commonly used and validated, tends to overestimate true PAC because part of the SV exits the arterial system toward the periphery [81]. Further research using more accurate PAC methods is necessary to confirm whether this relationship is consistently valid across all PH subtypes or is simply a mathematical artifact [82]. Although alpha assessment based on single-point values is less reliable than using multi-point pressure-flow data, performing a passive leg raise may be equally predictive of clinical outcomes as the alpha coefficient obtained with exercise [40].

9. Conclusion

With the lowering of the diagnostic threshold for pulmonary hypertension (PH), the development of new vasodilator drugs and more aggressive treatment strategies, and changes in PH epidemiology, the value of the current pulmonary vasoreactivity criterion has become very limited.

In the present work, we support a continuous multi-parameter criterion to evaluate changes in whole RV afterload during acute vasoreactivity testing, such as the R-C curve and the alpha distensibility coefficient.

The new approach could provide more detailed information on the acute vasoreactivity test without adding complexity to the invasive study, thereby expanding the analysis of the vasodilator challenge response. It would be especially useful for patients with comorbidities, early-stage PH (mPAP > 20 mmHg), and various clinical PH groups, as well as for predicting risk outcomes and assessing responses to new pulmonary vasodilators. In other words, the proposed multiparametric, continuous metrics might identify different levels of vasoreactive reserve beyond PH group 1, even in patients with normal resting hemodynamics. However, as a proposal, it will require further studies to verify its usefulness, reproducibility, and validity [83].

CRediT authorship contribution statement

Juan C Grignola: Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Pedro Trujillo:** Validation, Investigation, Formal analysis, Data curation, Conceptualization. **Julio Sandoval:** Validation, Formal analysis, Data curation, Conceptualization. **Enric Domingo:** Validation, Formal analysis, Data curation, Conceptualization. All authors read and approved that final manuscript.

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Declaration of competing interest

The author declares that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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