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Partitioning of Pulmonary Vascular Resistance in Primary Pulmonary Hypertension

SOPHIA ABDEL KAFI, MD, CHRISTIAN MÉLOT, MD, PHD, JEAN-LUC VACHIÉRY, MD, SERGE BRIMIOULLE, MD, PHD, ROBERT NAEIJE, MD, PHD

Brussels, Belgium

Objectives. **This study sought to determine the site of increased pulmonary vascular resistance (PVR) in primary pulmonary hypertension by standard bedside hemodynamic evaluation.**

Background. **The measurement of pulmonary vascular pressures at several levels of flow (Q) allows the discrimination between active and passive, flow-dependent changes in mean pulmonary artery pressure (Ppa), and may detect the presence of an increased pulmonary vascular closing pressure. The determination of a capillary pressure (Pc′) from the analysis of a Ppa decay curve after balloon occlusion allows the partitioning of PVR in an arterial and a (capillary + venous) segment. These approaches have not been reported in primary pulmonary hypertension.**

Methods. **Ppa and Pc′ were measured at baseline and after an increase in Q induced either by exercise or by an infusion of dobutamine, at a dosage up to 8 μg/kg body weight per min, in 11 patients with primary pulmonary hypertension. Reversibility of pulmonary hypertension was assessed by the inhalation of 20 ppm nitric oxide (NO), and, in 6 patients, by an infusion of prostacyclin.**

Results. **At baseline, Ppa was 52 ± 3 mm Hg (mean value ± SE), Q 2.2 ± 0.2 liters/min per m^2, and Pc′ 29 ± 3 mm Hg. Dobutamine did not affect Pc′ and allowed the calculation of an averaged extrapolated pressure intercept of Ppa/Q plots of 34 mm Hg. Inhaled NO had no effect. Prostacyclin decreased Pc′ and PVR. Exercise increased Pc′ to 40 ± 3 mm Hg but did not affect PVR.**

Conclusions. **These findings are compatible with a major increase of resistance and reactivity at the periphery of the pulmonary arterial tree.**

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The arterial occlusion technique, initially developed in isolated perfused lungs (1), has been applied to intact animals and to patients for the partitioning of pulmonary vascular resistance (PVR) into an arterial segment and a (capillary + venous) segment (2,3). The method has been used mainly for the determination of pulmonary capillary pressure (Pc′), but has been shown to overestimate the "effective" capillary pressure as measured by the reference isogravimetric method in experimental acute lung injury models (3). There are experimental data suggesting that the (capillary + venous) segment as determined from single arterial occlusion also includes small pulmonary arterioles 100 to 150 μm in diameter (4).

Another bedside approach to get a deeper insight into the nature of PVR is based on the determination of multipoint mean pulmonary artery pressure (Ppa)/flow (Q) plots. In most cardiac and pulmonary diseases, Ppa/Q plots are well described by a linear approximation, but their extrapolation to the pressure axis (Pi) may be higher than occluded Ppa (Ppao) or left atrial pressure (5–8). An increased Pi can be explained by an increased closing pressure of small pulmonary arterioles or capillaries, or both (5–8).

The objective of the present study was to test the hypothesis that pathologic changes at the periphery of the pulmonary arterial tree increase the Pi of Ppa/Q plots and Pc′ as obtained by arterial occlusion in patients with primary pulmonary hypertension. Histologic studies indicate that increased PVR in these patients is mainly due to a disease of small pulmonary arteries and arterioles, but the extent of associated pathologic changes upstream is not known exactly (8). There has been no previous report on pulmonary vascular pressure/flow relations or on the partitioning of PVR using the arterial occlusion method in primary pulmonary hypertension.

Methods

Patients. Ten women 33 to 65 years of age (mean 49) and one man 62 years of age with primary pulmonary hypertension gave informed consent to this study, which was approved by the Ethical Committee of the Erasme University Hospital. The diagnosis of primary pulmonary hypertension required both the documentation of pulmonary hypertension, with a Ppa >25 mm Hg and the absence of the following secondary

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Address for correspondence: Dr. Robert Naeije, Department of Intensive Care, Erasme University Hospital, Route de Lennik 808, 1070 Brussels, Belgium. E-mail: rnaeije@ulb.ac.be.

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Abbreviations and Acronyms

NO = nitric oxide
Pc′ = pulmonary capillary pressure
Pi = extrapolated pressure intercept of Ppa/Q plots
P_{O_2} = partial pressure of oxygen
Ppa = mean pulmonary artery pressure
Ppao = pulmonary artery occluded pressure
Pra = right atrial pressure
Psa = mean systemic arterial pressure
PVR = pulmonary vascular resistance
Q = pulmonary blood flow

causes: congenital abnormalities of lungs, thorax or diaphragm; congenital or acquired valvular or myocardial disease; pulmonary thromboembolism; obstructive lung disease; interstitial lung disease; pulmonary artery or pulmonary valve stenosis; pulmonary venous hypertension; central hypoventilation with hypoxemia and hypercapnia; parasitic disease affecting the lungs; sickle cell anemia; and collagen vascular disease. To exclude secondary pulmonary hypertension an algorithm was used on the basis of a mandatory chest radiograph, respiratory function, perfusion lung scan, echocardiogram, right heart catheterization and measurement of arterial blood gases (9). Eight of the 10 female patients had previously been exposed to appetite suppressants, either dexfenfluramine or compound preparations containing fenfluramine. The one male patient had liver cirrhosis. None of them were treated with vasodilators. All were dyspneic, class II to III of the New York Heart Association classification.

Procedures and measurements. Catheterization of the right side of the heart was performed without premedication, with the patient lying supine and breathing room air. A balloon-tipped flow-directed pulmonary catheter (Model 131H-7F Baxter) was inserted under local anesthesia into an internal jugular vein and floated under constant pressure wave monitoring into a pulmonary artery to measure pulmonary artery pressures, Ppa, Ppao, Pc′ (computed from the Ppa decay curve), right atrial pressure (Pra) and mixed venous blood sampling. A small polyethylene catheter was inserted into a radial or a femoral artery to measure systemic arterial pressures and for arterial blood sampling. Pulmonary and systemic arterial pressures were measured using Gould Statham P50 transducers (Gould Inc.) connected to a bedside hemodynamic and electrocardiographic monitoring system (SIRECUST 404, Siemens, Erlangen, Germany). The pressure transducers were zero referenced at midchest, and vascular pressures were measured at end expiration. Heart rate was determined from a continuously monitored electrocardiographic lead. Q was measured by thermodilution using injections of 10 ml of 5% cold dextrose in water and a computer (9520-A, Edwards Laboratories) and was calculated as the mean of three determinations. Arterial and mixed venous blood gases were measured by an automated analyzer (ABL 2, Radiometer, Copenhagen, Denmark) immediately after drawing the samples and corrected for temperature.

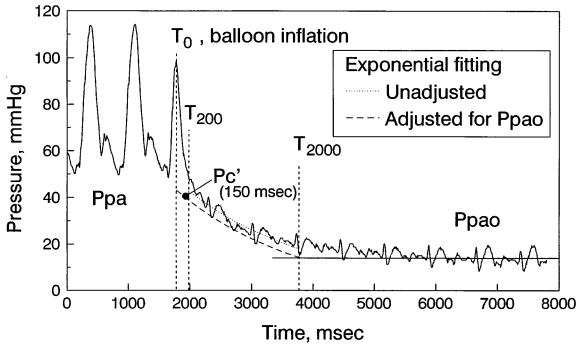

Figure 1. Typical pulmonary artery single-occlusion recording to estimate effective Pc′ by the extrapolation to 150 ms after the instant of occlusion (To) of a single exponential fitting of the Ppa decay curve between 200 ms (T_{200}) and 2,000 ms (T_{2000}) after the occlusion, with secondary adjustment for mean Ppao.

Nitric oxide (NO) was supplied from a pure NO source tank (Oxhydrique, Machelen, Belgium) and delivered through a face mask. The inspired fraction of NO was monitored by chemiluminescence after calibration against standard NO concentration (Model 42 chemiluminescence NO-NO2-NOx analyzer, Thermo Environmental Instruments Inc.).

The pulmonary vascular pressure signals were sampled at 200 Hz using an analog/digital converter (RTI 800, Analog Device) and stored and analyzed on a personal computer. Pc′ was computed in duplicate from the Ppa decay curves after inflation of the balloon of the pulmonary artery catheter. For this measurement the patients were asked to stop breathing at the end of a normal tidal volume for a period of 8 s. Time zero was defined as the time when pulmonary arterial pressure began to deviate from the normal wave. This instant was chosen because in the clinical setting, pressure is the only signal usually available for this purpose. The Ppa decay curve was fitted by an exponential equation on the basis of a least squares analysis applied to a set of data between 0.2 and 2.0 s after the occlusion, adjusted for Ppao, and extrapolated back toward time 0 + 150 ms. This time lag after occlusion corresponds to the delay from the beginning of occlusion to zero flow reached in the capillaries (10). A typical Ppa decay curve with analysis for Pc′ is shown in Figure 1.

Study protocol. As soon as steady-state conditions (stable heart rate, Psa and Ppa for 20 min) were ensured, a baseline set of hemodynamic and blood gas measurements was obtained. The measurements were repeated, each of them after a 20-min equilibration period, during the following conditions: 1) pedaling in the supine position without load, 2) rest, 3) an infusion of dobutamine at the doses of 4 μg/kg body weight per min and 8 μg/kg per min, 5) rest, 6) 20 ppm of inhaled NO, 7) rest, and, in six of the patients, 8) an infusion of prostacyclin (Flolan, Glaxo-Wellcome). Only six patients were tested with prostacyclin because this drug was not available in Belgium at the start of the study. For the same reason, in three of these patients, the prostacyclin measurements were obtained between 6 and 12 months after the other seven steps of the study

Table 1. Hemodynamic and Blood Gas Responses to Exercise, Dobutamine and Nitric Oxide in 11 Patients With Primary Pulmonary Hypertension*

Variables	Baseline	Exercise	Dobutamine	Nitric Oxide
Q (liter/min per m^2)	2.2 ± 0.2	3.1 ± 0.4§	2.8 ± 0.2‡	2.2 ± 0.2
Heart rate (beats/min)	82 ± 2	102 ± 3§	91 ± 4‡	82 ± 3
Psa (mm Hg)	102 ± 4	118 ± 6§	92 ± 4‡	101 ± 4
PVR (dynes·s·cm^{-5}·m^2)	1,841 ± 240	1,717 ± 231	1,560 ± 216†	1,825 ± 278
Ppa (mm Hg)	52 ± 3	67 ± 2‡	56 ± 4	50 ± 4
Pc′ (mm Hg)	29 ± 3	40 ± 3§	29 ± 4	27 ± 3
Ppao (mm Hg)	10 ± 1	15 ± 2§	10 ± 1	10 ± 1
Pra (mm Hg)	8 ± 2	15 ± 2§	5 ± 2‡	7 ± 2
pHa	7.47 ± 0.01	7.46 ± 0.01	7.49 ± 0.01	7.47 ± 0.01
Pa_{O_2} (mm Hg)	64 ± 4	60 ± 5	68 ± 4	61 ± 4
Pa_{CO_2} (mm Hg)	28 ± 1	26 ± 1	26 ± 1	28 ± 2
Pv_{O_2} (mm Hg)	35 ± 2	28 ± 3§	37 ± 1	34 ± 1

*Values are expressed as mean value ± SE. †$p < 0.05$, ‡$p < 0.01$, §$p < 0.001$ versus baseline. Dobutamine was infused at the dose of 8 μg/kg per min, and nitric oxide inhaled at the dose of 20 ppm. Pa_{CO_2} = arterial P_{CO_2}; Pa_{O_2} = arterial P_{O_2}; Pc′ = effective pulmonary capillary pressure; pHa = arterial pH; Ppa = mean pulmonary artery pressure; Ppao = occluded Ppa; Pra = right atrial pressure; Psa = mean systemic arterial pressure; Pv_{O_2} = mixed venous P_{O_2}; PVR = pulmonary vascular resistance; Q = cardiac output.

protocol, at the start of a continuous prostacyclin infusion as a bridge to transplantation. Prostacyclin was increased by 2 ng/kg per min increments every 15 min until intolerable side effects as defined by a decrease in Psa by >30%, an increase in heart rate by >30% or nausea, vomiting or headache (11). NO was given at the dose of 20 ppm, two times the dose previously shown to offer a maximum pulmonary vasodilating effect in patients with primary pulmonary hypertension (11). The dose of dobutamine was chosen to reproduce about the same increase in Q as exercise, and, on the basis of previous animal studies (12), unlikely to affect pulmonary vascular tone.

Statistical analysis. Results are expressed as mean value ± SE. The Ppa/Q coordinates obtained by the infusion of dobutamine and by exercise were pooled and analyzed using a method allowing for mild nonlinearities or state dependent variability, or both (13) to yield averaged slopes and Pi of two- or three-point Ppa/Q plots. The blood gases and hemodynamic data were analyzed by a repeated measures analysis of variance. When the F ratio of the analysis of variance reached a $p < 0.05$ critical level, specific comparisons were made using modified *t* tests, that is, *t* tests computed with the residual variance of the analysis of variance (14).

Results

The main hemodynamic and blood gas measurements are summarized in Table 1. At baseline, the hemodynamic and blood gas profile of the patients was similar to that of previously reported large series of patients with primary pulmonary hypertension (9), with very high Ppa, moderately high Pra, normal Ppao, decreased Q, respiratory alkalosis, moderate arterial hypoxemia and decreased mixed venous partial pressure of oxygen (P_{O_2}). Pc′ was markedly elevated, to a mean value of 29 mm Hg.

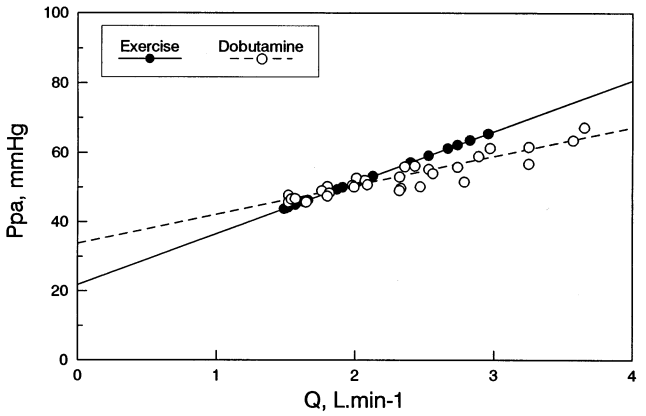

Figure 2. Pooled Ppa versus Q relations with Q increased by exercise **(solid circles)** or dobutamine **(open circles)** in 11 patients with primary pulmonary hypertension. The calculated regressions are represented by the **lines.** The extrapolated pressure intercept of the dobutamine-induced Ppa/Q relation was higher than the extrapolated pressure intercept of the exercise-induced Ppa/Q relation.

Exercise increased Q by an average of 0.9 liter/min per m^2, increased all vascular pressures including Pc′ and decreased mixed venous P_{O_2}. Pc′ increased more than Ppao (by an average of 11 and 5 mm Hg, respectively). Pooled exercise-induced Ppa/Q relations had a slope of 15 mm Hg/liter per min and a Pi of 22 mm Hg (Fig. 2).

Dobutamine at the dose of 8 μg/kg per min increased Q by an average of 0.6 liter/min per m^2, but had no effect on blood gases or vascular pressures, except for slight decreases in Psa, Pra and PVR.

Pooled dobutamine-induced relations had a slope of 8.3 mm Hg/liter per min and a Pi of 34 mm Hg (Fig. 2).

NO 20 ppm had no effect on pulmonary hemodynamics or blood gases. Individual changes in Ppa and in PVR associated with inhaled NO ranged respectively from +3 to −10 mm Hg and from +258 to −408 dynes·s·cm^{-5}·m^2.

In six of the patients, (three of them 6 to 12 months after the initial study) an infusion of prostacyclin 4 to 10 ng/kg per min had no effect on blood gases, Ppa, Pra or Ppao, but decreased Pc′, PVR and Psa and increased Q (Table 2). Individual changes in Ppa and PVR ranged respectively from +5 to −16 mm Hg and from −310 to −1,288 dyne·s·cm^{-5}·m^{-2}. The effects of dobutamine in these 6 patients were the same as in the group of 11 patients (not shown).

Discussion

The present results show that in severe primary pulmonary hypertension, both Pi and Pc′ are increased, suggesting that the main site of increased resistance is at the periphery of the pulmonary arterial tree, and possibly is a cause of an increased closing pressure.

Exercise-induced Ppa/Q relations. Ppa/Q relations, with Q increased by exercise, had a lower Pi and a higher slope than

Table 2. Hemodynamic and Blood Gas Responses to Prostacyclin in Six Patients

Variable	Baseline (Mean ± SD)	Prostacyclin* (Mean ± SD)
Q (liter/min per m^2)	1.8 ± 0.2	2.5 ± 0.3‡
Heart rate (beats/min)	87 ± 3	91 ± 2
Psa (mm Hg)	97 ± 7	80 ± 6‡
PVR (dyne·s·cm^{-5}·m^2)	2,479 ± 366	1,718 ± 244‡
Ppa (mm Hg)	63 ± 3	62 ± 3
Pc′ (mm Hg)	37 ± 4	32 ± 3†
Ppao (mm Hg)	13 ± 1	12 ± 1
Pra (mm Hg)	11 ± 2	11 ± 2
pHa	7.47 ± 0.01	7.48 ± 0.01
Pa_{O_2} (mm Hg)	57 ± 4	56 ± 4
Pa_{CO_2} (mm Hg)	27 ± 1	24 ± 2
Pv_{O_2} (mm Hg)	34 ± 2	34 ± 2

*Prostacyclin was infused at an average dose of 6.8 ng/kg per min (range 4 to 10). †$p < 0.05$, ‡$p < 0.01$ versus baseline. Abbreviations as in Table 1.

dobutamine-induced Ppa/Q relations. Previously reported exercise-induced Ppa/Q plots in patients with pulmonary vascular disease or left heart failure frequently presented with higher than normal slopes and low or even negative Pi (15,16). A negative Pi is physically impossible and can only be explained by an increase in Ppa at the highest Q because of exercise-induced pulmonary vasoconstriction (16). Causes of pulmonary vasoconstriction at exercise include a decreased mixed venous P_{O_2} (by 7 mm Hg in our patients) and sympathetic nervous system activation (7).

Dobutamine-induced Ppa/Q relations. We hypothesized that an infusion of dobutamine to increase Q would be more likely than exercise to allow us to construct passive Ppa/Q plots, on the basis of previous animal work suggesting that low dose dobutamine does not affect pulmonary vascular tone (12). Infusing dobutamine to increase Q led to Ppa/Q plots with a very high Pi. An increased Pi can be explained by a pulmonary vascular closing pressure acting as an effective outflow pressure higher than left atrial pressure (estimated by Ppao) (5–7). This explanation is based on a reference Starling resistor model viewing the pulmonary vasculature as a recruiting system of parallel units with fixed resistance and a distribution of opening pressures (17). There is an alternative viscoelastic model (18) that explains a Pi that is higher than left atrial pressure by an increase in resistance and compliance of small order arterioles (6). This viscoelastic model was found to be superior to the Starling resistor model of the pulmonary circulation in experimental embolic pulmonary hypertension (19). However, the considerable remodeling, including fibrotic changes seen at the microscopic examination of pulmonary vessels of patients with primary pulmonary hypertension (8), is not suggestive of an increased compliance at the site of increased resistance. Both the Starling resistor and the viscoelastic models of the pulmonary circulation predict that Ppa/Q relations with an increased Pi are due to an increased resistance of small pulmonary arteries and arterioles at the periphery of the pulmonary arterial tree.

Effects of inhaled NO and intravenous prostacyclin. In the present study, pulmonary hypertension was on average not reversible with inhaled NO. Sitbon et al. (11) showed in a series of 35 patients with primary pulmonary hypertension that changes in PVR during NO inhalation or prostacyclin infusion are closely correlated, and that a maximum pulmonary vasodilation can be obtained with 10 ppm NO. However, in six of our patients unresponsive to 20 ppm inhaled NO, prostacyclin decreased PVR by 29% (range 18% to 41%). This change occurred without significant changes in Ppa, but with a decrease in Pc′, indicating that the decrease in PVR was not just an artifact caused by increased Q (5–7), but truly corresponded to a decreased pulmonary vascular tone. Nevertheless, none of our patients was a "high responder" to prostacyclin, as defined by a >50% decrease in PVR (20). Such a response to prostacyclin was observed in only 9 of 91 patients with primary pulmonary hypertension in a recent study (20).

Method of measurement of Pc′. A variety of electrical analog models and methods of analysis of the pressure decay curve after pulmonary artery occlusion have been reported for the estimation of Pc′ as a determinant of fluid filtration and edema in the lung (1–3). Gilbert and Hakim (10) reported laser Doppler flow measurements in intact dogs to validate a Pc′ measurement obtained by a back extrapolation to 152 ms after the initial change in pulmonary artery pressure of a single exponential fitting of the pressure decay curve between 0.2 to 2 s. A monoexponential fitting is based on a simple electrical analog model of a single compartment with a large capillary compliance between arterial and venous resistances. We modified this model to provide for a parallel structure of the pulmonary vascular bed at the level of small resistance arteries, corresponding to inhomogenous distribution of obstruction and showed that it still predicts that a monoexponential fitting gives a reasonable approximation of the Ppa decay curve (21). Applied to intact normal dogs, the modified model allowed the calculation of a (capillary + venous) component of PVR ~25%, somewhat lower than in several previous studies using different methods of analysis (21). It is thus unlikely that in the present study the method of analysis of the Ppa decay curve would have overestimated Pc′.

Interpretation of increased Pc′. In the present study, Pc′ was markedly increased, to levels that would be expected to produce hydrostatic lung edema (2,3). However, lung edema is not a feature of primary pulmonary hypertension (9). Several studies have shown that the arterial occlusion technique may overestimate the effective Pc′ as determined by the isogravimetric method or the double occlusion technique in diseased lungs (3). Obstruction of small resistive arteries with 100-μm glass beads increases Pc′ without changes in capillary pressure as measured by isogravimetry or by the double arterial and venous occlusion technique (22,23). Hakim and Kelly (4) compared pressure measurements with micropuncture, a small retrograde catheter and arterial and venous occlusion in isolated perfused dogs lungs and found that the arterial occlusion technique measures pressure in vessels of a diameter between 50 and 900 μm, probably on average ~100 μm. We

therefore believe that Pc′ in our patients reflects an increased pressure in small resistive arteries and arterioles, rather than an increased pressure in capillaries. It is of interest that prostacyclin in our patients decreased Pc′, compatible with an acute effect at the main site of increased resistance.

Histologic studies have shown that primary pulmonary hypertension is primarily a disease of the small muscular pulmonary arteries and arterioles that are <500 to 1,000 μm in diameter (8). These vessels present with various combinations of medial hypertrophy, concentric or eccentric intimal fibrosis and more complex arteritis, plexiform or dilation lesions, with, in 30% of cases, in situ thrombosis (8). Both increased Pi and Pc′ in our patients suggest that these lesions are not associated with structural changes important enough to increase resistance of larger diameter pulmonary arteries. In addition, increased Pc′ at exercise appear entirely explained by exercise-induced vasoconstriction at the site of small resistive arteries. Previous histologic studies have also shown that 10% of patients with primary pulmonary hypertension present with pulmonary veno-occlusive disease (8). These patients are difficult to distinguish clinically from those with a precapillary pathologic process. In our series, a histologic examination of the lungs could be obtained in one of the female patients after a heart–lung transplantation. The examination disclosed no venous abnormalities in this patient whose Ppa/Q plots and Pc′ did not deviate from the average values of the group as a whole. In addition, because of the relative rarity of pulmonary veno-occlusive disease, we believe it unlikely that the increased Pc′ in the present study could have been explained by an increase in venous resistance.

Appetite suppressant drugs. Pulmonary hypertension in eight of our patients was associated with the intake of appetite suppressant drugs, mainly fenfluramines. The association between the intake of these drugs and primary pulmonary hypertension was recently established by a Western European case control study (24). The clinical course and histologic pattern in patients with fenfluramine-associated pulmonary hypertension do not appear different from those of the other patients with primary pulmonary hypertension (25). It is thus unlikely that Ppa/Q characteristics and Pc′ determinations in our patients would have been affected by previous intake of fenfluramines.

Conclusions. A recent study reported on the use of pulmonary artery pressure waveform analysis for the differential diagnosis of proximal versus distal obstruction of the pulmonary arterial tree in severe pulmonary hypertension (26). The present report shows that standard bedside hemodynamic evaluation with measurements at variable cardiac output and analysis of pulmonary artery occlusion pressure decay curves allow for an identification and quantification of increased distal small arteries and arterioles resistance.

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