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Original article

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## **In-depth hemodynamic phenotyping of pulmonary hypertension due to left heart disease**

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Take home message: Cpc-PH is characterized by pre-capillary pulmonary vascular disease and a positive response to inhaled nitric oxide

## **ABSTRACT**

The commonest cause of pulmonary hypertension (PH) is left heart disease (LHD). The current classification system for definitions of PH-LHD is under review. We therefore performed prospective in-depth invasive hemodynamic phenotyping in order to assess the site of increased pulmonary vascular resistance (PVR) in PH-LHD subsets.

Based on pulmonary artery occlusion waveforms yielding an estimate of the effective capillary pressure ( $P_c$ ), we partitioned PVR in larger arterial ( $R_{up}$ , upstream resistance) and small arterial plus venous components ( $R_{ds}$ , downstream resistance). In the case of small vessel disease,  $R_{up}$  decreases and  $R_{ds}$  increases. Inhaled nitric oxide (iNO) testing was used to assess acute vasoreactivity.

Right ventricular (RV) afterload (PVR, pulmonary arterial compliance and effective arterial elastance) was significantly higher in combined post- and pre-capillary PH (Cpc-PH, n=35) than in isolated post-capillary PH (Ipc-PH, n=20). RV afterload decreased during iNO in Cpc-PH and idiopathic pulmonary arterial hypertension (iPAH, n=31), but remained unchanged in Ipc-PH.  $R_{up}$  was similar in Cpc-PH ( $66.8\pm 10.8\%$ ) and iPAH ( $65.0\pm 12.2\%$ ,  $p=0.530$ ) suggesting small vessel disease, but significantly higher in Ipc-PH ( $96.5\pm 4.5\%$ ,  $p<0.001$ ) suggesting upstream transmission of elevated left atrial pressures (LAP).

RV afterload is driven by elevated LAP in Ipc-PH and is further increased by elevated small vessel resistance in Cpc-PH. Cpc-PH is responsive to iNO. Our data support current definitions of PH-LHD subsets.

Keywords: upstream resistance; pulmonary capillary pressure; diastolic pulmonary vascular pressure gradient; pulmonary vascular resistance; pulmonary arterial compliance; right ventricular afterload

## INTRODUCTION

The most common subset of pulmonary hypertension (PH) is PH due to left heart disease (LHD), resulting from left ventricular dysfunction (systolic and/or diastolic) and/or left-sided valvular heart disease [1]. PH-LHD is the consequence of an upstream transmission of elevated left atrial pressure (LAP). In 13% of cases with PH-LHD an increase in mean pulmonary artery pressure (mPAP) occurs that is disproportionate to LAP due to an additional contribution of “pre-capillary” pulmonary vascular disease, this results in decreased right ventricular-pulmonary vascular coupling and has been associated with increased mortality [2-5]. Such patients can be identified by an elevated diastolic pulmonary vascular pressure gradient (DPG)  $\geq 7$ mmHg. At present, the prognostic relevance of DPG has been both supported [5-11] and refuted [12-14]. Currently, PH-LHD is classified in the ESC/ERS guidelines as either (1) "isolated post-capillary PH" (Ipc-PH; DPG  $< 7$ mmHg and/or pulmonary vascular resistance (PVR)  $\leq 3$ WU) or (2) "combined post- and pre-capillary PH" (Cpc-PH; DPG  $\geq 7$ mmHg and/or PVR  $> 3$ WU) [15].

Based on the pulmonary artery pressure (PAP) decay curve after balloon occlusion the effective capillary pressure of the pulmonary circulation  $P_{c'}$  can be estimated (Figure 1) [16]. With  $P_{c'}$ , PVR can be partitioned into larger arterial (upstream,  $R_{up}$ ) and small arterial plus venous (downstream,  $R_{ds}$ ) components [16-19]. In healthy subjects PVR follows an almost equal distribution across the pulmonary circulation with  $\sim 60\%$   $R_{up}$  and  $\sim 40\%$   $R_{ds}$  [20]. In idiopathic pulmonary arterial hypertension (iPAH), there is a similar PVR partitioning pattern, yet a significant elevation in mPAP and  $P_{c'}$  has been described. This has been explained by the fact that  $P_{c'}$  is increased because small arterial remodelling extends to the capillary-venous compartment [16]. In chronic thromboembolic pulmonary hypertension (CTEPH) pulmonary artery occlusion waveform analysis has been employed to differentiate between central and

peripheral pulmonary vascular obstruction [21, 22]. We sought to partition PVR at baseline and after inhalation of nitric oxide in patients with PH-LHD.

## **METHODS**

### **Study population**

We prospectively enrolled 265 patients (Figure 2). The ethics committee of the Medical University of Vienna approved the study and all patients signed informed consents (#1496/2012). Patients underwent a first diagnostic right heart catheterization, vasoreactivity testing, pulmonary artery occlusion waveform analysis, and left heart catheterization including coronary angiography and left ventricular end-diastolic pressure measurement, as previously described [4, 23]. Catheterizations were performed for various indications, mostly for the diagnosis of elevated systolic PAP (sPAP) on echocardiography, in patients with chronic heart failure (HF) and/or in patients with suspected PH, but also prior to valve replacements, percutaneous interventions and surgical procedures. A diagnosis of HF was independently adjudicated according to the current HF guidelines of the European Society of Cardiology [24] and the American College of Cardiology Foundation/American Heart Association [25]. Patients with HF due to constrictive pericarditis, and due to infiltrative, restrictive, or hypertrophic cardiomyopathy were excluded. Patients were on specific and optimized HF treatments, at their physician's discretion, but none were taking PH specific drugs.

### **Hemodynamic assessment and vasoreactivity testing**

Hemodynamics were obtained at rest and during inhalation of 20ppm nitric oxide (iNO). For hemodynamic assessment, a 7F Swan-Ganz catheter (Edwards Lifesciences, Irvine, CA) was inserted from a femoral or jugular venous approach. Mean right atrial pressure, right ventricular pressure, systolic (sPAP), diastolic (dPAP) and mean PAP (mPAP), mean pulmonary arterial wedge pressure (mPAWP) and respective oxygen saturations, including inferior and superior vena cava saturations were measured. Left ventricular end-diastolic

pressure (LVEDP) was measured via femoral arterial access with a 7F pigtail catheter (Cordis, Bridgewater, NY). All pressures were recorded as averages of 8 time-pressure integral derivations during several respiratory cycles [26] using Sensis (Siemens AG, Berlin and Munich, Germany). Zero reference was at midthoracic level [26]. Cardiac output (CO) was assessed in triplicate by thermodilution. With the catheter in the pulmonary artery, patients were given 20ppm NO via a continuous positive airway pressure mask under continuous flow oxygen at 2L/min (Pulmonox-Mini, Messer-Griesheim, Vienna, Austria) for 5 minutes before a complete hemodynamic assessment was repeated. iNO administration was continued during these measurements. A positive classic response to iNO was defined as a reduction of mPAP  $\geq 10$ mmHg to an absolute value of mPAP  $\leq 40$ mmHg with increased or unchanged CO [15]. A non-classic response was defined as a reduction of mPAP  $\geq 10$ mmHg without a drop below an absolute mPAP value of 40mmHg [27].

### **Hemodynamic definitions**

Transpulmonary gradient (TPG) was calculated by subtracting mPAWP from mPAP. DPG was calculated as the difference between diastolic PAP (dPAP) and mPAWP [2, 28, 29]. PVR was calculated by dividing TPG by cardiac output (CO) and expressed in Wood units (WU; mmHg·min·L<sup>-1</sup>). C<sub>PA</sub> was defined as stroke volume (SV) divided by pulmonary pulse pressure (difference between systolic and diastolic PAP). The pulmonary vascular resistance-compliance time (RC-time; product of PVR and C<sub>PA</sub>) was estimated as previously described [30] and expressed in milliseconds. Effective arterial elastance (E<sub>a</sub>) was calculated as the ratio of mPAP to SV.

### **Partitioning of pulmonary vascular resistance**

Pulmonary artery occlusion waveforms were recorded at 250Hz during breath hold at end-expiration over ~8 seconds. Pressure signals were filtered using a 2-pole digital low-pass filter with a cutoff at 18Hz. Measurements were performed in triplicate with an average difference in  $R_{up}$  of  $4\pm 2\%$ . A bi-exponential fitting of the pressure decay curve between the moment of occlusion and mPAWP, with normalization to mPAP was performed in order to assess  $P_{c'}$  (a surrogate of zero flow pressure,  $P_{zf}$ ) [16, 31, 32] (Figure 1). Using  $P_{c'}$ , PVR was partitioned into larger arterial (upstream,  $R_{up}$ ) and small arterial plus venous (downstream,  $R_{ds}$ ) components.  $R_{up}$  was assessed as  $(mPAP - P_{c'}) / (mPAP - mPAWP) * 100$ . Pulmonary artery occlusion waveforms from patients with atrial fibrillation and other forms of arrhythmia at the time of hemodynamic assessment were excluded (n=19; Figure 2).

### **Pulmonary hypertension definitions and subset classification**

The pulmonary hypertension (PH) guidelines [15] distinguish the following hemodynamic definitions during measurements at rest, without iNO and oxygen: (1) “Non-PH” with mPAP <25mmHg, (2) pre-capillary PH with mPAP  $\geq 25$ mmHg and mPAWP  $\leq 15$ mmHg, and (3) post-capillary PH with mPAP  $\geq 25$ mmHg and mPAWP >15mmHg.

Post-capillary PH was classified as either (1) mPAP  $\geq 25$ mmHg, mPAWP >15mmHg, DPG <7mmHg and/or PVR  $\leq 3$ WU (isolated post-capillary PH, Ipc-PH), or (2) mPAP  $\geq 25$ mmHg, mPAWP >15mmHg, DPG  $\geq 7$ mmHg and PVR >3WU (combined post- and pre-capillary PH, Cpc-PH) [15, 33]. Moderate to severe and severe left sided echocardiographic ventricular and valvular heart disease were assessed as probable causes of PH.

Ventilation-perfusion lung scintigraphies, multidetector computed tomographies, lung function tests – including spirometry and diffusion capacity measurements – and pulmonary angiographies were performed to exclude CTEPH, chronic obstructive pulmonary disease



(COPD) and interstitial lung disease (ILD). PAH associated with congenital heart disease, connective tissue disease or portal hypertension as well as CTEPH or PH due to ILD (moderate to severe) and/or COPD (Global Initiative of Obstructive Lung Disease [GOLD] 3 or 4) and/or obstructive sleep apnea syndrome and simultaneous left heart disease were classified as “combinations of diagnoses” or “Multiple-PH”. Patients with “Multiple-PH”, PAH associated with congenital heart disease or connective tissue disease, PH due to lung diseases and/or hypoxia and CTEPH were excluded from the study (n=154; Figure 2).

### **Statistical analysis**

Adherence to a Gaussian distribution was determined using the Kolmogorov-Smirnov test. Normally distributed data were described as means  $\pm$  standard deviations and the independent samples student *t*-test was utilized to compare continuous variables between two groups, while the paired-sample *t*-test was used to compare differences within groups. In case of skewed distribution data were described as medians (25<sup>th</sup> and 75<sup>th</sup> percentiles). One-way analysis of variance (ANOVA) with correction for multiple pairwise comparisons using the Bonferroni method was applied to assess differences across several groups. Qualitative variables were described with counts and percentages. The strength of association between quantitative variables was measured with Spearman's rank correlation coefficient. Data were analyzed with SPSS Statistics (Version 21 for Mac). All p-values result from two-sided tests, with significance inferred at  $p < 0.05$ .

## RESULTS

### Patients

92 patients fulfilled the pre-specified study criteria (Figure 2). 6 subjects had normal pulmonary hemodynamics ("Non-PH"), 31 patients were diagnosed with iPAH and 55 were classified as having PH-LHD (Figure 2); 20 with Ipc-PH and 35 with Cpc-PH. Clinical characteristics are listed in Table 1. LVEDP was measured in all patients for validation of mPAWP. Bland-Altman analysis showed that LVEDP was on average 2.6mmHg lower than mPAWP with limits of agreement ranging from -7.6 to 2.4mmHg in patients with PH-LHD. Larger differences between mPAWP and LVEDP were found in patients with mitral valve disease (1 patient with severe mitral stenosis and 4 patients with mitral regurgitation).

### Right ventricular afterload

Hemodynamics of the whole study population at rest and after inhalation of NO are shown in Table 2. Despite similar mPAWP ( $25.3 \pm 8.2$ mmHg vs.  $21.1 \pm 3.4$ mmHg;  $p=0.064$ ), baseline RV afterload was significantly higher in Cpc-PH (PVR  $6.4 \pm 3.5$ WU;  $E_a$   $0.8 \pm 0.4$  mmHg/mL) compared with Ipc-PH (PVR  $3.1 \pm 1.3$ WU,  $p<0.001$ ;  $E_a$   $0.6 \pm 0.2$ mmHg/mL,  $p=0.031$ ). RV afterload was highest in iPAH (Table 2, Figure 3A-B).

### Estimates of small pulmonary artery and capillary pressure ( $P_{c'}$ )

$P_{c'}$  was significantly different between groups (ANOVA  $p<0.001$ ) and significantly higher in Cpc-PH ( $31.3 \pm 8.2$ mmHg) than in Ipc-PH ( $26.6 \pm 8.3$ mmHg,  $p=0.026$ ) and "Non-PH" ( $12.8 \pm 2.0$ mmHg,  $p<0.001$ ) but similar to values observed in iPAH ( $29.2 \pm 9.4$ mmHg,  $p=0.365$ ) (Table 2).  $P_{c'}$  was significantly higher than mPAWP in all groups. However,  $P_{c'}$  to mPAWP gradients were larger in iPAH (Mean, [95% CI]: 20.7mmHg [17.2;24.3],  $p<0.001$ ); and Cpc-PH (10.2mmHg [8.4;12.0],  $p<0.001$ ) than in "Non-PH" (3.2mmHg [2.2;8.3],  $p=0.009$ ). In

Ipc-PH, the difference between  $P_{c'}$  and mPAWP was small (1.3mmHg [0.7;1.9],  $p<0.001$ ).  $P_{c'}$  correlated significantly with mPAWP in all groups. The strongest correlations were found in Ipc-PH ( $r=0.989$ ,  $p<0.001$ ) and “Non-PH” ( $r=0.900$ ,  $p=0.037$ ). Correlations were weaker in Cpc-PH ( $r=0.787$ ,  $p<0.001$ ) and iPAH ( $r=0.496$ ,  $p=0.005$ ).

During NO inhalation, a significant decrease in  $P_{c'}$  was observed in Cpc-PH (-2.6mmHg [-5.0;-0.2],  $p=0.025$ ) and iPAH (-4.4mmHg [-6.9;-1.9],  $p=0.007$ ), while  $P_{c'}$  increased significantly in Ipc-PH (3.4mmHg [0.4;6.4],  $p=0.014$ ) and did not change in “Non-PH” (-1.4mmHg [-8.3;5.4],  $p=0.458$ ) (Table 2).

### **Upstream resistance**

$R_{up}$  in Cpc-PH was similar ( $66.8\pm 10.8\%$ ) to that seen in iPAH ( $65.0\pm 12.2\%$ ,  $p=0.530$ ) and “Non-PH” ( $62.4\pm 4.6\%$ ,  $p=0.385$ ). In contrast,  $R_{up}$  was significantly higher in Ipc-PH ( $96.5\pm 4.5\%$ ,  $p<0.001$ ) than in Cpc-PH (Table 2, Figure 3C).  $R_{up}$  correlated strongly with DPG ( $r=-0.797$ ,  $p<0.001$ , Figure 5A) in PH-LHD. Correlations between  $R_{up}$  and TPG ( $r=-0.467$ ,  $p<0.001$ ), PVR ( $r=-0.495$ ,  $p<0.001$ ) and  $C_{PA}$  ( $r=0.279$ ,  $p=0.039$ ) were only weak (Figure 5B-D).

During NO inhalation,  $R_{up}$  increased significantly in Cpc-PH (by 8.0% [2.2;13.8],  $p=0.032$ ) and in iPAH (by 6.4% [2.6;10.2],  $p=0.009$ ) indicating a decrease of distal vascular resistance (Table 2, Figure 4C). In contrast,  $R_{up}$  did not change in Ipc-PH (-0.9% [-4.0;2.3],  $p=0.534$ ) and “Non-PH” (0.4% [-3.1;3.9],  $p=0.974$ ) (Table 2, Figure 4C).

### **Response to inhaled nitric oxide**

Patients with Cpc-PH and iPAH showed significant improvements in CO, mPAP, PVR,  $C_{PA}$ , TPG and DPG during inhalation of NO (Table 2, Supplementary Tables A and B, Figure 4A

and B). In contrast, only an isolated increase of mPAWP occurred in Ipc-PH (Table 2). In “Non-PH”  $C_{PA}$  increased significantly during NO inhalation (Table 2). 3 iPAH patients (9.7%) and 3 Cpc-PH patients (8.6%) fulfilled classic “hemodynamic responder” criteria. In 9 patients with iPAH (29.0%), 5 patients with Cpc-PH (14.3%) and 1 patient with Ipc-PH (5.0%) mPAP dropped by  $\geq 10$ mmHg but not  $\leq 40$ mmHg (non-classic response). None of the patients with Ipc-PH and “Non-PH” fulfilled classic responder criteria.

Supplementary Tables A and B show relative changes from baseline under iNO in Ipc-PH, Cpc-PH and iPAH stratified by hemodynamic responder status. In classic responders with Cpc-PH (n=3), mPAP decreased by  $33 \pm 17\%$  (from  $43.7 \pm 6.8$ mmHg to  $30.0 \pm 11.4$ mmHg,  $p=0.036$ ), CO increased by  $33 \pm 18\%$  (from  $5.6 \pm 2.1$ L/min to  $7.0 \pm 1.9$ L/min,  $p=0.018$ ) and PVR decreased by  $55 \pm 8\%$  (from  $5.1 \pm 2.4$ WU to  $2.1 \pm 0.6$ WU,  $p=0.005$ ). In iPAH (n=3), mPAP decreased by  $42 \pm 5\%$  (from  $51.0 \pm 11.4$ mmHg to  $29.3 \pm 6.8$ mmHg,  $p=0.021$ ) and PVR decreased by  $53 \pm 9\%$  (from  $11.2 \pm 5.1$ WU to  $5.6 \pm 3.6$ WU,  $p=0.021$ ), while CO remained unchanged ( $3 \pm 5\%$ ; from  $5.6 \pm 2.1$ L/min to  $7.0 \pm 1.9$ L/min,  $p=0.423$ ).

In non-classic responders with Cpc-PH (n=5), mPAP decreased by  $4 \pm 13\%$  (from  $68.3 \pm 9.0$ mmHg to  $50.5 \pm 7.3$ mmHg,  $p=0.002$ ), PVR decreased by  $17 \pm 32\%$  (from  $11.9 \pm 4.8$ WU to  $5.7 \pm 3.2$ WU,  $p=0.007$ ), while CO remained unchanged ( $4 \pm 15\%$ ; from  $4.2 \pm 1.2$ L/min to  $4.4 \pm 1.4$ L/min,  $p=0.275$ ). In iPAH (n=9), mPAP decreased by  $7 \pm 9\%$  (from  $63.6 \pm 9.2$ mmHg to  $49.3 \pm 8.0$ mmHg,  $p<0.001$ ), CO increased by  $9 \pm 13\%$  (from  $4.8 \pm 0.9$ L/min to  $5.3 \pm 1.0$ L/min,  $p=0.016$ ) and PVR decreased by  $19 \pm 14\%$  (from  $11.4 \pm 2.0$ WU to  $7.5 \pm 2.1$ WU,  $p<0.001$ ).

In non-responders with Cpc-PH (n=27), PVR decreased by  $17 \pm 32\%$  (from  $5.3 \pm 2.3$ WU to  $4.3 \pm 2.1$ WU,  $p=0.011$ ), while CO remained unchanged ( $4 \pm 15\%$ ; from  $5.3 \pm 1.1$ L/min to  $5.5 \pm 1.2$ L/min,  $p=0.292$ ). The decrease in mPAP ( $4 \pm 13\%$ , from  $44.3 \pm 11.0$ mmHg to  $42.3 \pm 11.2$ mmHg,  $p=0.056$ ) did not reach statistical significance. In iPAH (n=19), mPAP decreased by  $6 \pm 9\%$  (from  $50.8 \pm 14.5$ mmHg to  $47.5 \pm 15.0$ mmHg,  $p=0.004$ ), CO increased by

9±12% (from 4.5±1.2L/min to 4.9±1.2L/min, p=0.007) and PVR decreased by 18±14% (from 10.3±5.3WU to 8.5±4.9WU, p=0.003).

## DISCUSSION

In this study, we examined detailed hemodynamics in PH-LHD patients and located the site of increased PVR by calculating  $R_{up}$  using the pulmonary artery occlusion technique. We also assessed changes in RV afterload during inhalation of NO in PH-LHD.  $R_{up}$  is significantly lower in Cpc-PH than in Ipc-PH but resembles that in iPAH, consistent with the presence of pre-capillary pulmonary vascular disease in Cpc-PH. In contrast, the increase in PVR and PAP in Ipc-PH is driven by elevated LAP.

$P_{c'}$  is widely thought to reflect the pressure in small pulmonary arteries and capillaries [16-18], and should not exceed 16mmHg in healthy subjects [20]. Values above 20mmHg have been associated with pulmonary edema [20]. Concordant with previous studies using mono-exponential [19] and bi-exponential fitting of the PAP decay curve after balloon occlusion [16], we found that  $P_{c'}$  was markedly increased in iPAH compared to “Non-PH”.  $P_{c'}$  was significantly higher in Cpc-PH than in Ipc-PH (Table 2). In Ipc-PH, the difference between  $P_{c'}$  and mPAWP was negligible with a difference of  $1.3 \pm 1.2$  mmHg, and an almost perfect linear relationship between mPAWP and  $P_{c'}$  ( $r=0.989$ ,  $p<0.001$ ) suggesting that  $P_{c'}$  and mPAP elevation are determined by mPAWP. In contrast, the correlation between  $P_{c'}$  and mPAWP was only moderate in Cpc-PH ( $r=0.787$ ,  $p<0.001$ ), similar to the findings in iPAH ( $r=0.496$ ,  $p<0.001$ ).  $P_{c'}$  was significantly higher than mPAWP in Cpc-PH suggesting an additional pre-capillary resistance component leading to an out-of-proportion increase in PAP (Figure 6).

We located the site of increased PVR in Cpc-PH by partitioning PVR into  $R_{up}$  and  $R_{ds}$  using the pulmonary artery occlusion technique. Cpc-PH showed the same pattern of PVR partitioning as iPAH (Figure 3C) with ~60%  $R_{up}$  and ~40%  $R_{ds}$ . The present findings are in agreement with histologic evidence of small vessel disease in Cpc-PH resembling iPAH [2]. Ipc-PH showed very high  $R_{up}$  (Figure 3C) indicating a passive increase in PVR and PAP driven by elevated left-sided filling pressures. To identify the best hemodynamic predictor of

increased downstream stiffness and pulmonary vascular disease in PH-LHD, we performed regression analyses including PVR,  $C_{PA}$ , TPG and DPG, and  $R_{up}$ . We found a strong negative correlation between DPG and  $R_{up}$ , while TPG, PVR and  $C_{PA}$  correlated only weakly with  $R_{up}$  (Figure 5). Interestingly,  $R_{up}$  was not different between Ipc-PH patients with DPG <7mmHg and PVR  $\leq 3$ WU (n=6;  $R_{up}$  96.9 $\pm$ 4.2%, p=0.479; Supplementary Figure A) and those with DPG <7mmHg and PVR >3WU (n=14;  $R_{up}$  95.3 $\pm$ 5.3%). These results suggest that DPG appears to be more sensitive than PVR and  $C_{PA}$  for the detection of changes in the downstream compartment and might therefore be more meaningful for the definition of pulmonary vascular disease in PH-LHD.

Vasoreactivity in HF has been studied in the past using systemic infusions of nitrates [11, 34-36] and prostaglandin E1 [37]. In a more recent study in HFrEF patients greater improvements in PVR, DPG and TPG could be observed in Cpc-PH compared to Ipc-PH. However, prostaglandin E1 and nitrates lower systemic blood pressure and increase CO. We performed selective pulmonary vasoreactivity testing using iNO. Patients with Cpc-PH showed significant improvements in RV afterload during NO inhalation (Table 2, Figure 5), but this was not the case in patients with Ipc-PH. The proportion of patients fulfilling classic hemodynamic responder criteria was similar in Cpc-PH (8.6%) and iPAH (9.7%). Interestingly, iNO led to significant improvements in RV afterload in Cpc-PH irrespective of hemodynamic responder status (Supplementary Table A). These findings may explain the significant hemodynamic response of Cpc-PH patients in the single positive randomized trial of sildenafil in PH-HF [38]. However, the study by Guazzi and colleagues was an exploratory trial with hemodynamic and echocardiographic endpoints and to date no positive randomized controlled trial with outcome data has been reported, in PH-LHD [39-41]. Furthermore, in the recent randomized controlled MELODY-1 study, Macitentan was associated with an increased incidence of significant fluid retention versus placebo in patients with Cpc-PH [42]. In addition, Macitentan resulted in no significant changes in NT-proBNP

and PVR.

### **Limitations**

The number of patients with iPAH and Cpc-PH in relation to Ipc-PH is overrepresented in this study, because the inclusion of patients with Ipc-PH was halted at a sample size of 20 patients, while inclusion of iPAH and Cpc-PH patients was continued. Data from vasoreactivity testing of classic responders should be interpreted with caution because only 3 Cpc-PH and 3 iPAH patients fulfilled the traditional hemodynamic responder criteria. Bi-exponential fitting of the decay curve may be affected by the presence of high v-waves in PAWP tracings in case of atrial fibrillation and mitral regurgitation. In addition, arrhythmia in atrial fibrillation may alter the time dependent algorithm for the derivation of  $P_c$ . Therefore, patients with atrial fibrillation and other forms of arrhythmia at the time of hemodynamic assessment were excluded from our analyses and only 1 Cpc-PH patient and 3 Ipc-PH patients had significant mitral regurgitation.

Another problem is that many hemodynamic parameters, such as TPG, pulmonary pulse pressure, ejection fraction and  $dP/dt_{max}$  etc, are load dependent. For PVR it has been shown that the relationship between pressure gradient and flow is linear. Furthermore, modulation of flow and pressure using dobutamine infusion in dogs had no effect on the partitioning of PVR [43]. Hence, change in loading conditions of the pulmonary vascular system does not seem to influence the evaluation of the upstream component of PVR. For TPG, a flow and LAP dependent increase has been described, while DPG has been shown to be rather insensitive to these hemodynamic variables [29].



## **Conclusion**

Our data show that increased RV afterload is driven by elevated LAP in Ipc-PH and aggravated by pulmonary small vessel disease in Cpc-PH. Cpc-PH is responsive to iNO. The easiest hemodynamic parameter to assess the presence of pulmonary vascular disease in PH-LHD is DPG, which may serve as a surrogate for  $R_{up}$ , while PVR should be used with caution. Taken together, our in-depth analysis provides physiologic support for current definitions of PH-LHD sub-types.

## **DISCLOSURES**

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PF received travel and accomodation support from Actelion to participate in scientific symposia.

AMP, NPK, JJ and DSC have no conflicts of interest to declare.

IML has relationships with drug companies including AOPOrphan Pharmaceuticals, Actelion, Bayer-Schering, Astra-Zeneca, Servier, Cordis, Medtronic, GSK, Novartis, Pfizer and United Therapeutics. In addition to being investigator in trials involving these companies, relationships include consultancy service, research grants, and membership of scientific advisory boards.

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## FIGURE LEGENDS

Figure 1. Pulmonary artery occlusion waveform.

Pressure decay curve between the moment of occlusion (vertical dashed line) and the recording of mean pulmonary arterial wedge pressure (mPAWP) for the assessment of pressure in pre-capillary small pulmonary arteries and pulmonary capillaries ( $P_c$ ), and pulmonary vascular resistance-compliance time (RC-time).

dPAP=diastolic pulmonary artery pressure; mPAP=mean pulmonary artery pressure;  
sPAP=systolic pulmonary artery pressure.

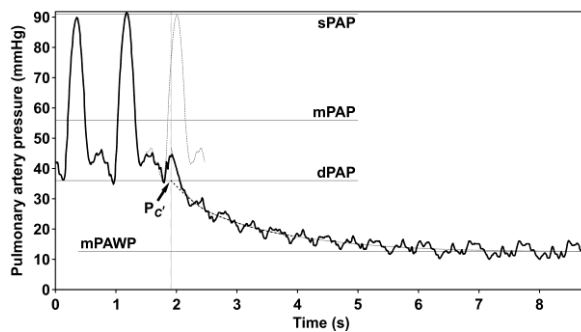


Figure 2. Patient disposition.

265 patients were prospectively enrolled in our study. Pulmonary artery occlusion waveform analysis was not possible in 19 patients because of atrial fibrillation/arrhythmia. 92 patients were available for final analyses. Of those, 6 subjects had normal pulmonary hemodynamics (“Non-PH”), 20 patients had isolated post-capillary pulmonary hypertension (Ipc-PH), 35 patients had combined post- and pre-capillary pulmonary hypertension (Cpc-PH) and 31 patients had idiopathic pulmonary arterial hypertension (iPAH).

PH=pulmonary hypertension; APAH-CHD=pulmonary arterial hypertension associated with congenital heart disease; APAH-CTD=pulmonary arterial hypertension associated with connective tissue disease; CTEPH=chronic thromboembolic pulmonary hypertension

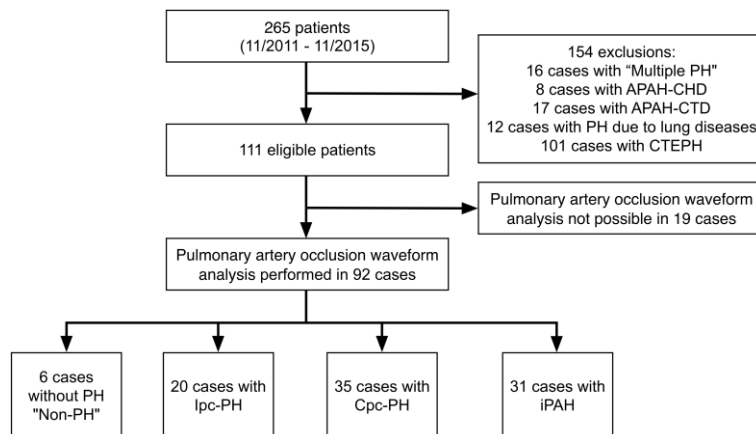


Figure 3. Right ventricular afterload and upstream resistance.

Pulmonary vascular resistance (PVR, Panel A), pulmonary arterial compliance ( $C_{PA}$ , Panel B) and upstream resistance ( $R_{up}$ , Panel C) in “Non-PH” (white bars), Ipc-PH (blue bars), Cpc-PH (purple bars) and iPAH (red bars). P-values are results of independent samples *t*-tests (\*) and one-way ANOVA with correction for multiple pairwise comparisons using the Bonferroni method (†), respectively.

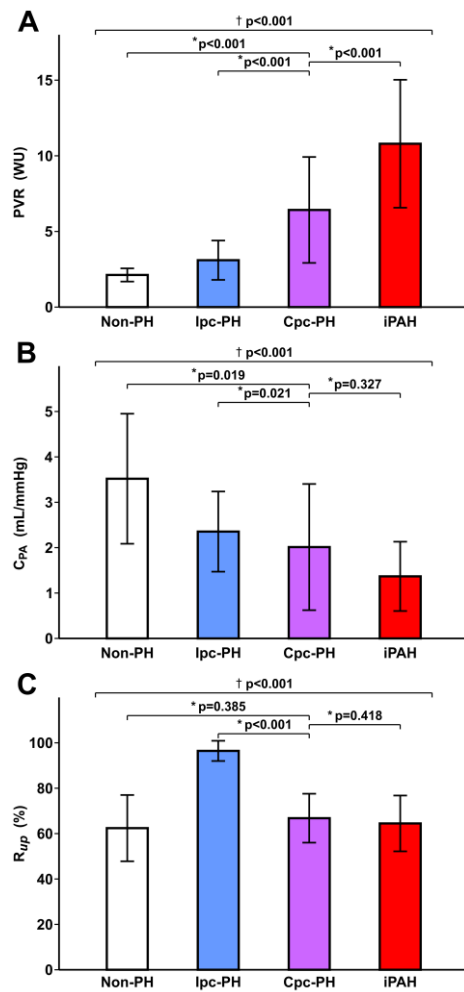


Figure 4. Effect of inhaled nitric oxide on right ventricular afterload.

Pulmonary vascular resistance (PVR, Panel A), pulmonary arterial compliance ( $C_{PA}$ , Panel B) and upstream resistance ( $R_{up}$ , Panel C) at baseline (solid bars) and after inhalation of nitric oxide (hatched bars) in “Non-PH” (white bars), Ipc-PH (blue bars), Cpc-PH (purple bars) and iPAH (red bars). P-values results from paired samples *t*-tests.

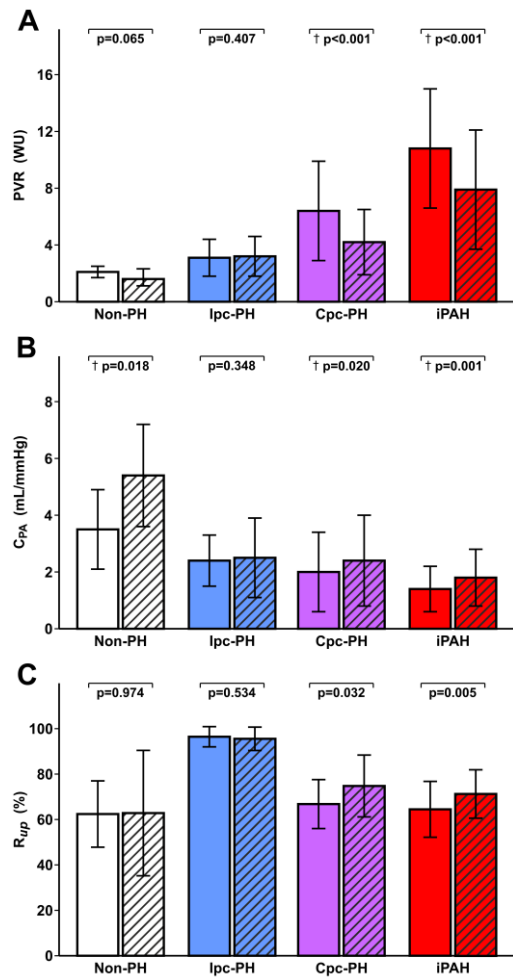


Figure 5. Relationship between upstream resistance and parameters of right ventricular afterload in pulmonary hypertension due to left heart disease.

Correlation between upstream resistance and diastolic pulmonary vascular pressure gradient (Panel A), transpulmonary gradient (Panel B), pulmonary vascular resistance (Panel C) and pulmonary arterial compliance (Panel D). Lines mark means and confidence intervals of the linear regression functions.

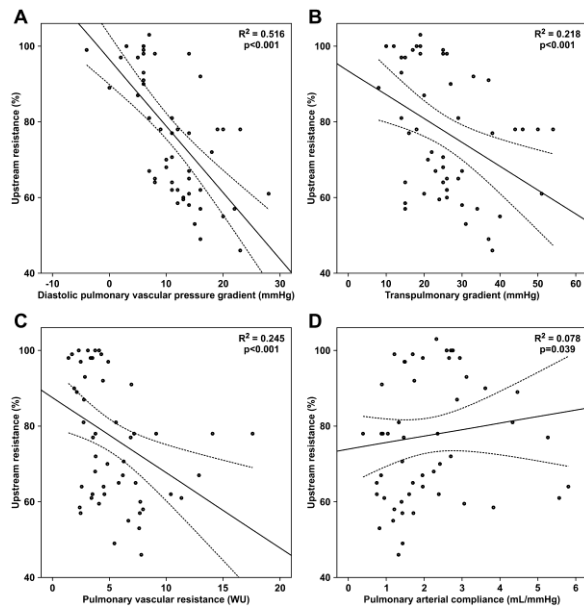
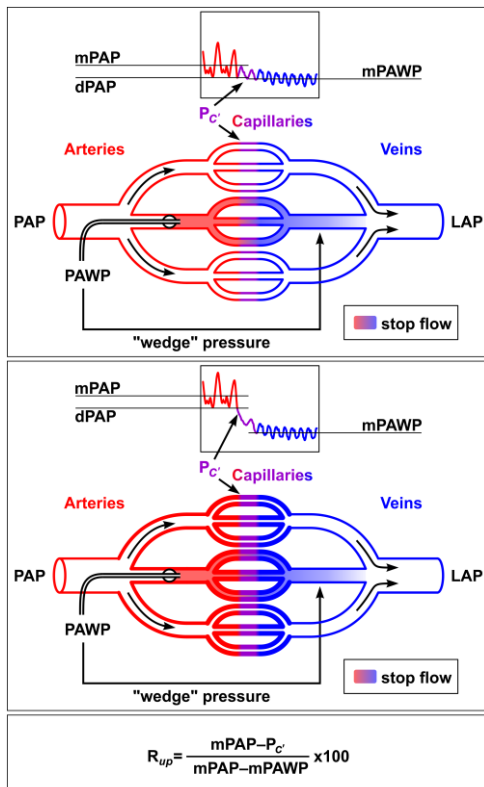


Figure 6. The pulmonary circulation in Ipc-PH and Cpc-PH.

Models of the pulmonary circulation with corresponding phenotypes of pressure decay curves in Ipc-PH (upper panel) and Cpc-PH (middle panel). In Ipc-PH, there is a rapid decay from pulmonary artery pressure (PAP) to pulmonary arterial wedge pressure (PAWP). The pressure in pre-capillary small pulmonary arteries and pulmonary capillaries ( $P_c$ ) is determined by left atrial pressure (LAP) and is at the same level as mPAWP. In contrast, the pressure decay from PAP to PAWP is slow in Cpc-PH.  $P_c$  is markedly elevated in comparison to mPAWP due to an additional component of pulmonary vascular disease at the level of small pulmonary arteries and capillaries. The bottom panel shows the formula for upstream resistance ( $R_{up}$ ).



## TABLES

**Table 1.** Clinical characteristics.

	Non-PH (n=6)	IpC-PH (n=20)	CpC-PH (n=35)	iPAH (n=31)
Age—years	67.9±16.9	65.3±12.8	66.3±11.2	46.9±17.9
Sex—no. (%)				
Female	3 (50.0)	14 (70.0)	16 (45.7)	21 (67.7)
Body-mass index—kg/m <sup>2</sup>	26.3±6.1	29.4±6.4	27.3±5.4	25.3±5.0
NYHA functional class—no. (%)				
I	2 (33.3)	0 (0)	1 (2.9)	4 (12.9)
II	2 (33.3)	6 (30.0)	6 (17.1)	5 (16.1)
III	2 (33.3)	11 (55.0)	15 (42.9)	13 (41.9)
IV	0 (0)	3 (15.0)	13 (37.1)	9 (29.0)
Drug therapy—no. (%)				



Thiazide diuretics	1 (16.7)	3 (15.0)	7 (20.0)	0 (0)
Loop diuretics	0 (0)	11 (55.0)	27 (77.1)	10 (32.3)
Mineralocorticoid receptor antagonists	1 (16.7)	10 (50.0)	23 (65.7)	13 (41.9)
ACEI/ARB	3 (50.0)	13 (65.0)	23 (65.7)	3 (9.7)
Digoxin	0 (0)	0 (0)	6 (17.1)	0 (0)
β-Blockers	2 (33.3)	11 (55.0)	23 (65.7)	9 (29.0)
Ca <sup>2+</sup> channel blockers	0 (0)	3 (15.0)	8 (22.9)	4 (12.9)
Heart failure—no. (%)				
Heart failure with preserved ejection fraction	0 (0)	14 (70.0)	26 (74.3)	0 (0)
Heart failure with reduced ejection fraction	0 (0)	3 (15.0)	6 (17.1)	0 (0)
Valvular heart disease—no. (%)*				
Mitral regurgitation	0 (0)	3 (15.0)	1 (2.9)	0 (0)
Mitral stenosis	0 (0)	0 (0)	1 (2.9)	0 (0)

Aortic regurgitation	0 (0)	0 (0)	1 (2.9)	0 (0)
Tricuspid regurgitation—no. (%)				
Moderate to severe	0 (0)	1 (5.0)	4 (11.4)	5 (16.1)
Severe	0 (0)	4 (20.0)	13 (37.1)	4 (12.9)
Arterial hypertension—no. (%)	6 (100.0)	14 (70.0)	27 (77.1)	8 (25.8)
Stable ischemic heart disease—no. (%)	1 (16.7)	4 (20.0)	11 (31.4)	0 (0)
Atrial fibrillation—no. (%)	1 (16.7)	9 (45.0)	19 (54.3)	1 (3.2)
COPD GOLD 1-2—no. (%)	2 (33.3)	4 (20.0)	8 (22.9)	0 (0)
ILD—no. (%)	0 (0)	0 (0)	0 (0)	0 (0)
Creatinine clearance <60mL/min—no. (%)	2 (33.3)	10 (50.0)	16 (45.7)	3 (9.7)
NT-proBNP—pg/mL*	389.4 (38.7;538.1)	1757.0 (326.4;4167.5)	1272.0 (788.3;5298.8)	822.0 (234.1;2197.5)

ACEI=angiotensin-converting-enzyme inhibitor; ARB=angiotensin receptor blocker; COPD=chronic obstructive pulmonary disease; Cpc-PH=combined post- and pre-capillary pulmonary hypertension; GOLD=Global Initiative for Chronic Obstructive Lung Disease; ILD=interstitial

lung disease; iPAH=idiopathic pulmonary arterial hypertension; Ipc-PH=isolated post-capillary pulmonary hypertension; NT-proBNP=N-terminal pro-hormone of brain natriuretic peptide; NYHA=New York Heart Association; PH=pulmonary hypertension.

\*Moderate to severe or severe valvular heart disease.

**Table 2.** Hemodynamic characteristics at baseline and after inhalation of nitric oxide.

Hemodynamic variable	"Non-PH" (n=6)		Ipc-PH (n=20)		Cpc-PH (n=35)		iPAH (n=31)	
	Baseline	iNO	Baseline	iNO	Baseline	iNO	Baseline	iNO
HR—bpm	72.4±14.7	61.7±8.8	75.7±12.9	77.4±4.3	75.6±14.8	75.6±16.4	79.4±14.2	76.1±15.7†
CO—L/min	5.9±1.0	6.0±1.0	5.6±2.2	5.4±1.4	5.0±1.3	5.5±1.4†	4.6±1.1	4.9±1.2†
SVR—WU	14.2±0.6*	14.2±3.7*	16.0±5.3	16.6±7.2	18.3±6.9	17.0±5.9	19.0±5.8	19.6±5.0
mRAP—mmHg	5.4±3.0*	7.2±1.9*	12.6±5.5*	12.9±7.8	15.8±4.9	15.9±7.6	9.5±4.7*	8.5±4.2*
mPAP—mmHg	21.3±2.2*	20.4±2.1*	38.9±11.6*	40.8±13.9	48.1±12.6	42.2±11.6†	54.9±13.6*	46.1±13.8†
mPAWP—mmHg	9.5±3.9*	11.0±2.9*	25.3±8.2	27.6±8.2†	21.1±3.4	22.6±3.9†	8.5±2.9*	9.5±4.0*†
LVEDP—mmHg	11.0±4.1*	8.0±2.6*	23.0±7.3	24.8±8.5†	19.1±5.5	20.2±3.9†	9.6±3.3*	9.3±8.2*
P <sub>c</sub> —mmHg	12.8±2.0*	13.0±2.8*	26.6±8.3*	29.4±8.6†	31.3±8.2	28.7±8.4†	29.2±9.4	24.6±9.1†
E <sub>a</sub> —mmHg/mL	0.3±0.1*	0.2±0.0*	0.6±0.2*	0.6±0.3	0.8±0.4	0.6±0.3†	1.0±0.4	0.8±0.4*†
PVR—WU	2.1±0.4*	1.6±0.6*	3.1±1.3*	3.2±1.4	6.4±3.5	4.2±2.3†	10.8±4.2*	7.9±4.2*†

C <sub>PA</sub> —mL/mmHg	3.5±1.4*	5.4±1.8*†	2.4±0.9*	2.5±1.4	2.0±1.4	2.4±1.6†	1.4±0.8*	1.8±1.0†
RC-time—ms	445±189*	493±204	405±152*	397±138	588±190	447±158†	764±331*	693±200*
R <sub>up</sub> —%	62.4±4.6	62.8±7.6	96.5±4.5*	95.6±5.1*	66.8±10.8	74.8±13.6†	64.5±12.3	71.3±10.7†
TPG—mmHg	12.5±3.5*	9.4±3.4*	18.0±7.5*	16.3±5.7*†	29.0±10.7	21.7±10.3†	46.5±13.7*	36.3±14.9*†
DPG—mmHg	3.5±3.9*	2.8±1.8*	3.9±2.2*	2.4±4.1*	14.2±4.9	7.4±8.0†	28.0±11.6*	20.7±11.5*†

CO=cardiac output; C<sub>PA</sub>=pulmonary arterial compliance; Cpc-PH=combined post- and pre-capillary PH; DPG=diastolic pulmonary vascular pressure gradient; E<sub>a</sub>=effective arterial elastance; HR=heart rate; Ipc-PH=isolated post-capillary PH; mPAP=mean pulmonary artery pressure; mPAWP=mean pulmonary arterial wedge pressure; mRAP=mean right atrial pressure; iNO=inhaled nitric oxide; PAH=pulmonary arterial hypertension; PH=pulmonary hypertension; PVR=pulmonary vascular resistance; R<sub>up</sub>=upstream resistance; SVR=systemic vascular resistance; TPG=transpulmonary gradient; WU=Wood units.

\*p<0.05, compared with values in Cpc-PH using independent samples *t*-test; †p<0.05, compared with baseline values within the same group using paired samples *t*-test.

**“Online Data Supplement”**

Table A. Response to inhaled nitric oxide in combined post- and pre-capillary pulmonary hypertension (Cpc-PH).

PH-LHD (n=55)					
	All Ipc-PH* (n=20)	All Cpc-PH (n=35)	Cpc-PH Classic responders (n=3)	Cpc-PH Non-classic responders (n=5)	Cp-PH Non-responders (n=27)
Relative change					
mPAP (%)	+2±13	<b>-10±16</b>	<b>-33±17</b>	<b>-4±13</b>	-4±13
CO (%)	+1±15	<b>+7±18</b>	<b>+33±18</b>	+4±15	+4±15
PVR (%)	-5±33	<b>-27±33</b>	<b>-55±8</b>	<b>-17±32</b>	<b>-17±32</b>
R <sub>up</sub> (%)	+1±4	<b>+10±15</b>	<b>+49±15</b>	+6±17	<b>+13±14</b>

CO=cardiac output; mPAP= mean pulmonary artery pressure; PVR=pulmonary vascular resistance; R<sub>up</sub>=upstream resistance.

Statistically significant (p<0.05) relative changes from baseline are highlighted in **bold**. \*1 patient with Ipc-PH fulfilled non-classic responder criteria.

Table B. Response to inhaled nitric oxide in idiopathic pulmonary arterial hypertension (iPAH).

	All iPAH	Classic responders	Non-classic responders	Non-responders
Relative change	(n=31)	(n=3)	(n=9)	(n=19)
mPAP (%)	<b>-14±14</b>	<b>-42±5</b>	<b>-7±9</b>	<b>-6±9</b>
CO (%)	<b>8±11</b>	3±5	<b>9±13</b>	<b>9±12</b>
PVR (%)	<b>-27±17</b>	<b>-53±9</b>	<b>-19±14</b>	<b>-18±14</b>
R <sub>up</sub> (%)	<b>10±17</b>	<b>49±15</b>	8±12	6±14

CO=cardiac output; mPAP= mean pulmonary artery pressure; PVR=22; R<sub>up</sub>=upstream resistance.

Statistically significant ( $p < 0.05$ ) relative changes from baseline are highlighted in **bold**.

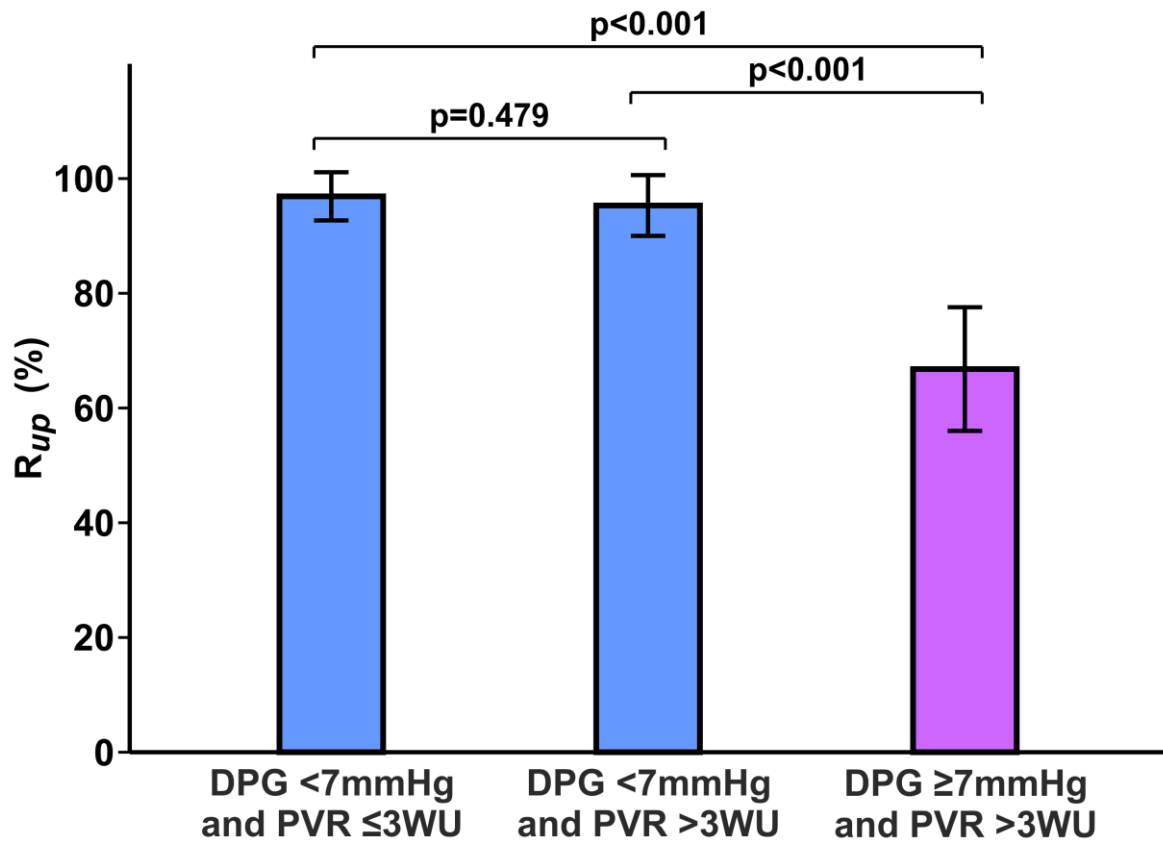


Figure A. Upstream resistance in pulmonary hypertension due to left heart disease.

Upstream resistance ( $R_{up}$ ) in pulmonary hypertension due to left heart disease with diastolic pulmonary vascular gradient (DPG) <7mmHg and pulmonary vascular resistance (PVR)  $\leq 3$ WU (n=6; left blue bar), DPG <7mmHg and PVR >3WU (n=14; right blue bar) and DPG  $\geq 7$ mmHg and PVR >3WU (n=35; purple bar). P-values are results of independent samples *t*-tests.