



## **Microvascular Disease in Chronic Thromboembolic Pulmonary Hypertension: Hemodynamic Phenotyping and Histomorphometric Assessment**

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# Microvascular Disease in Chronic Thromboembolic Pulmonary Hypertension

## Hemodynamic Phenotyping and Histomorphometric Assessment

**BACKGROUND:** Pulmonary endarterectomy (PEA) is the gold standard treatment for patients with operable chronic thromboembolic pulmonary hypertension. However, persistent pulmonary hypertension (PH) after PEA remains a major determinant of poor prognosis. A concomitant small-vessel arteriopathy in addition to major pulmonary artery obstruction has been suggested to play an important role in the development of persistent PH and survival after PEA. One of the greatest unmet needs in the current preoperative evaluation is to assess the presence and severity of small-vessel arteriopathy. Using the pulmonary artery occlusion technique, we sought to assess the presence and degree of small-vessel disease in patients with chronic thromboembolic pulmonary hypertension undergoing PEA to predict postoperative outcome before surgery.

**METHODS:** Based on pulmonary artery occlusion waveforms yielding an estimate of the effective capillary pressure, we partitioned pulmonary vascular resistance in larger arterial (upstream resistance [ $R_{up}$ ]) and small arterial plus venous components (downstream resistance) in 90 patients before PEA. For validation, lung wedge biopsies were taken from nonobstructed and obstructed lung territories during PEA in 49 cases. Biopsy sites were chosen according to the pulmonary angiogram still frames that were mounted in the operating room. All vessels per specimen were measured in each patient. Percent media (%MT; arteries) and intima thickness (%IT; arteries, veins, and indeterminate vessels) were calculated relative to external vessel diameter.

**RESULTS:** Decreased  $R_{up}$  was an independent predictor of persistent PH (odds ratio per 10%, 0.40 [95% CI, 0.23–0.69];  $P=0.001$ ) and survival (hazard ratio per 10%, 0.03 [95% CI, 0.00–0.33];  $p=0.004$ ). Arterial %MT and %IT of nonobstructed lung territories and venous %IT of obstructed lung territories were significantly increased in patients with persistent PH and nonsurvivors.  $R_{up}$  correlated inversely with %MT ( $r=-0.72$ ,  $P<0.001$ ) and %IT ( $r=-0.62$ ,  $P<0.001$ ) of arteries from nonobstructed lung territories and with %IT ( $r=-0.44$ ,  $P=0.024$ ) of veins from obstructed lung territories. Receiver operating characteristic analysis disclosed that  $R_{up} < 66\%$  predicted persistent PH after PEA, whereas  $R_{up} < 60\%$  identified patients with poor prognosis after PEA.

**CONCLUSIONS:** Pulmonary artery occlusion waveform analysis with estimation of  $R_{up}$  seems to be a valuable technique for assessing the degree of small-vessel disease and postoperative outcome after PEA in chronic thromboembolic pulmonary hypertension.

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**Key Words:** pulmonary hypertension  
■ pulmonary vascular resistance



## Clinical Perspective

### What Is New?

- Upstream resistance predicts postoperative survival and hemodynamic outcome of patients with chronic thromboembolic pulmonary hypertension (CTEPH) undergoing pulmonary endarterectomy.
- Patients with CTEPH with adverse outcome after pulmonary endarterectomy are characterized by remodeling of small arteries in nonoccluded lung territories and venous remodeling in occluded lung territories.
- Upstream resistance correlates with the degree of remodeling of small arteries and veins in CTEPH.

### What Are the Clinical Implications?

- Upstream resistance may be useful in identifying patients with CTEPH at high risk of postoperative death and persistent pulmonary hypertension.
- These findings may impact the preoperative assessment and treatment algorithm of patients with CTEPH.

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare, progressive pulmonary vascular disease characterized by chronic obstruction of major pulmonary arteries with persistent organized thrombi that is potentially curable by pulmonary endarterectomy (PEA). However, persistent or recurrent pulmonary hypertension (PH) after PEA, which can be observed in 17% to 51% of patients, remains a significant problem and is associated with high morbidity and mortality.<sup>1-4</sup> In addition to major pulmonary vascular obstruction, a concomitant small-vessel arteriopathy has been described.<sup>5</sup> The presence and degree of small-vessel arteriopathy have been suggested to play an important role in the development of persistent PH and survival after PEA.<sup>6,7</sup> However, the current standard preoperative assessment is unable to detect the presence of small-vessel disease, nor does it reliably predict the postoperative outcome.

The pulmonary artery occlusion technique has been developed to estimate effective pulmonary capillary pressure ( $P_c$ ). For this purpose, the pressure decay curve obtained during wedging of the Swan-Ganz catheter balloon for the assessment of pulmonary arterial wedge pressure is registered and analyzed. Based on this pulmonary artery pressure decay curve,  $P_c$  can be estimated.<sup>8</sup> Using  $P_c$ , pulmonary vascular resistance (PVR) can be partitioned into larger arterial (upstream,  $R_{up}$ ) and small arterial plus venous (downstream resistance) components.<sup>8-11</sup> In healthy subjects, PVR follows an almost equal distribution across the pulmonary circulation with ~60%  $R_{up}$  and ~40% downstream resistance.<sup>12</sup> In idiopathic pulmonary arterial hypertension, there is a similar

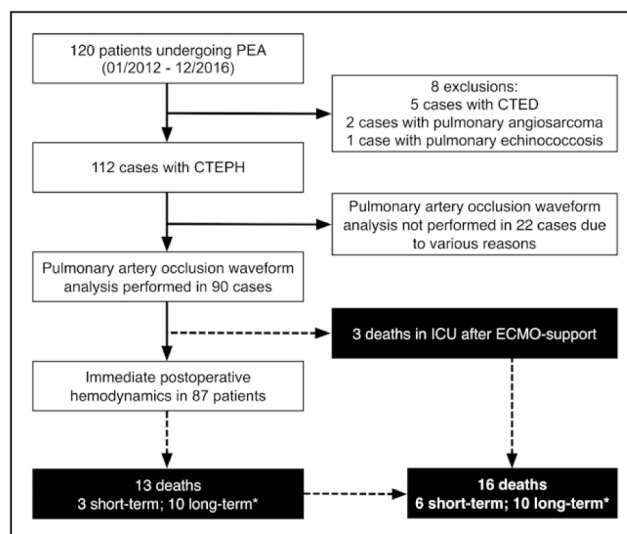
PVR partitioning pattern, yet with significant elevation of mean pulmonary artery pressure (mPAP) and  $P_c$ ,<sup>8,13</sup> which is increased as small arterial remodeling extends to the capillary-venous compartment.<sup>8</sup> Increased  $R_{up}$  values have been reported in CTEPH,<sup>8</sup> and in two relatively small studies, lower  $R_{up}$  was associated with more distal pulmonary vascular obstruction<sup>14</sup> and with worse postoperative outcomes in patients undergoing PEA.<sup>15</sup>

To assess feasibility and to validate the method, we sought to partition PVR in patients with CTEPH before PEA, correlate these findings with histomorphometric changes in lung biopsy samples obtained during PEA, and relate these data to outcomes.

## METHODS

### Study Population

The authors declare that supporting data will not be made available. Between January 2012 and August 2016, 120 patients underwent PEA at our institution (single-center study). Patients with chronic thromboembolic disease without PH, pulmonary angiosarcoma, pulmonary artery obstruction because of echinococcosis or arrhythmias at the time of hemodynamic assessment were excluded. A total of 90 consecutive patients with CTEPH were prospectively enrolled in this study (Figure 1). Immediate postoperative PVR and survival served as coprimary outcomes of the study.



**Figure 1. Patient disposition.**

A total of 120 patients underwent pulmonary endarterectomy (PEA) between January 2012 and December 2016 at our institution, which was performed a median of 3.0 (range: 1.0–45.5) days after diagnosis. Eight patients were excluded because of different underlying diseases (5 chronic thromboembolic disease [CTED], 2 pulmonary angiosarcoma, 1 pulmonary echinococcosis). A total of 112 cases had chronic thromboembolic pulmonary hypertension (CTEPH); of these, 22 patients were not included in the study for various reasons (atrial fibrillation, other arrhythmia, and right heart failure at the time of hemodynamic assessment). A total of 90 patients were included in the study, of whom 87 underwent immediate postoperative hemodynamic assessment; 3 patients required extracorporeal membrane oxygenation (ECMO) and died in the intensive care unit (ICU) before hemodynamic assessment. A total of 16 patients died after surgery (30-day in-hospital: 6; long-term: 10). Of the long-term deceased, 3 died from malignancies (\*) and were excluded from analysis of disease-specific survival.

The ethics committee of the Medical University of Vienna approved the study, and all patients signed informed consents before pulmonary artery occlusion waveform analyses (No. 1496/2012). A total of 55 patients agreed to undergo open lung biopsy during PEA and signed respective informed consent forms (No. 220/2008). Before PEA, patients underwent a first diagnostic right heart catheterization, pulmonary artery occlusion waveform analysis, digital-subtraction pulmonary angiography, and left heart catheterization including coronary angiography and left ventricular end-diastolic pressure measurement, as previously described.<sup>13,16–18</sup> Hemodynamics were reassessed within 4 days after PEA in the intensive care unit before removal of the intraoperative Swan-Ganz and left atrial catheters (“immediate postoperative”) when patients were off vasopressors. Mean pulmonary arterial wedge pressure (mPAWP) and mean left atrial pressure were measured for assessment of left ventricular filling pressures.

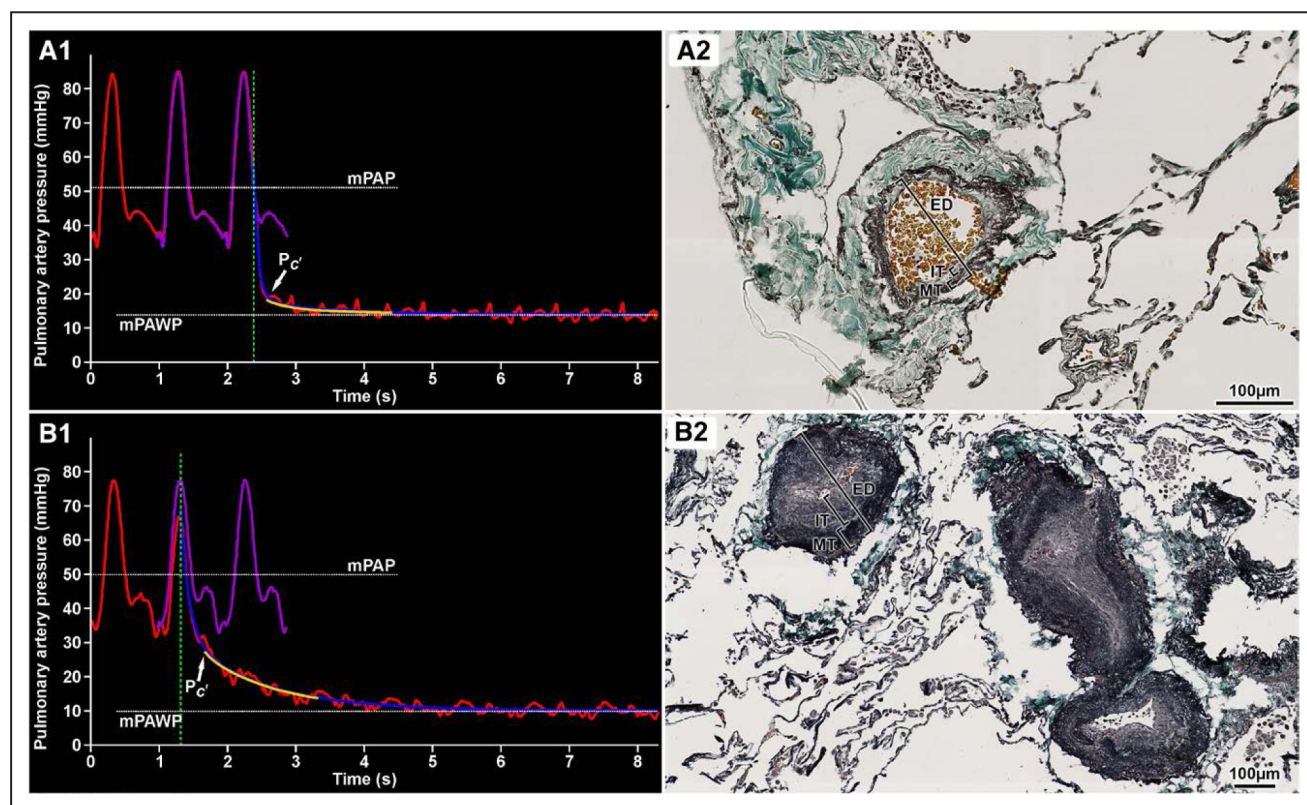
## Hemodynamic Definitions

PVR was calculated by dividing the difference between mPAP and mPAWP by cardiac output (CO) and expressed in Wood units (WU; mmHg·min·L<sup>-1</sup>). For immediate postoperative PVR, mean left atrial pressure was utilized for PVR

calculation. Pulmonary arterial compliance ( $C_{PA}$ ) was defined as stroke volume divided by pulmonary pulse pressure (difference between systolic and diastolic pulmonary artery pressure). Persistent PH after PEA was defined as immediate postoperative PVR  $\geq 5.3$  WU.<sup>4</sup>

## Partitioning of PVR

Pulmonary artery occlusion waveforms were recorded in triplicate at 250 Hz during breath hold at end-expiration over ~8 s. Three operators (I.M.L., C.G., and N.S.S.) performed the assessments, and after a learning curve minimized assessments to a total of 2 to 4 per patient on both sides of the lungs. Pressure signals were filtered using a 2-pole digital low-pass filter with a cutoff at 18 Hz. Pressure decay curves were analyzed by fitting the data between the moment of occlusion and stabilization of the pressure tracing at the level of pulmonary arterial wedge pressure with a biexponential equation, which includes a rapidly decreasing exponential (filling of the capillary compartment from the arterial compartment) and a slowly decreasing exponential (emptying of the capillary compartment into the venous compartment<sup>19</sup>; Figure 2).  $P_c$  was calculated with the exact solution for a 3-compartment model



**Figure 2. Pulmonary artery occlusion waveforms and lung histologies.**

Representative pulmonary occlusion waveforms (**A1** and **B1**) and trichrome stains of small pulmonary arteries (**A2** and **B2**). The vertical dashed lines in **A1** and **B1** mark the moment of occlusion on the pressure decay curve followed by the recording of mean pulmonary arterial wedge pressure (mPAWP) for the assessment of pressure in precapillary small pulmonary arteries and pulmonary capillaries ( $P_c$ ). Marks in **A2** and **B2** indicate where intimal and medial thicknesses in relation to the external vessel diameter were scored. **A**, Data from a long-term survivor with a preoperative upstream resistance ( $R_{up}$ ) of 92%, low relative intima (%IT) and media thickness (%MT), and immediate postoperative pulmonary vascular resistance (PVR) of 2.0 Wood units (WU). A rapid decay from pulmonary artery pressure (PAP) to pulmonary arterial wedge pressure (PAWP) can be observed with  $P_c$  at the same level as PAWP (**A1**). The histological sample in **A2** shows normal pulmonary vessels without evidence of pulmonary vascular disease. **B**, Data from a patient with a preoperative  $R_{up}$  of 57%, increased %IT and %MT, and an immediate postoperative PVR of 10.1 WU. This patient died 7 days after pulmonary endarterectomy in the intensive care unit. Note the slow pressure decay from PAP to PAWP and the markedly elevated  $P_c$  in comparison with mPAWP. **B2** shows pulmonary arteries with significant medial hypertrophy and intimal fibrosis. mPAP indicates mean pulmonary artery pressure.



of the pulmonary circulation formalized by Baconnier et al,<sup>19</sup> with a normalization procedure to mPAP as proposed by Pagnamenta et al.<sup>20</sup> Using  $P_{c,v}$ , PVR was partitioned into larger arterial (upstream,  $R_{up}$ ) and small arterial plus venous (downstream resistance) components.  $R_{up}$  was assessed as  $(mPAP - P_{c,v}) / (mPAP - mPAWP) \times 100$ .<sup>8</sup> Two observers analyzed the occlusion waveforms independently (C.G. and M.G.). Interobserver variability for  $R_{up}$  was  $1 \pm 2\%$ .

## Histomorphometry

Surgeons (S.T., B.M., and W.K.) performed 2 lung wedge biopsies each in 49 patients during PEA. In 6 patients, surgeons decided to not perform a biopsy for technical reasons and overall length and difficulty of PEA. It has been previously speculated that small-vessel arteriopathy may be confined to nonobstructed lung vessels with increased blood flow.<sup>5</sup> To study differences between nonobstructed and obstructed vascular territories, biopsies were taken in each patient from nonobstructed and obstructed lung as demarcated by pulmonary angiography. Freshly harvested specimens were fixed with formalin and embedded in paraffin. Several 2- $\mu$ m sections were stained using a modified Trichrome stain and scanned using TissueFAXS plus 8 (Tissue Gnostic) and the Tissue Quest Analysis software. Pulmonary arteries were distinguished from pulmonary veins by localization in relation to bronchi, and by structure. When position and structure of a vessel did not definitively identify it as an artery/arteriole or vein/venule (primarily small [ $<100 \mu$ m] vessels), the vessel was designated as an indeterminate vessel and was analyzed separately. All vessels suitable for analysis were measured in each patient. Percent medial thickness (%MT; arteries) and percent intimal thickness (%IT; arteries, veins, and indeterminate vessels) were calculated relative to external diameter as previously described.<sup>21,22</sup> For each vessel measured, intimal morphology was qualitatively categorized as eccentric, concentric, occlusion or luminal webs/recanalization.<sup>23</sup> Analyses were carried out by 2 observers (C.G. and R.F.) who were blinded to hemodynamics, and were validated by an independent experienced pathologist (P.D.). Interobserver variability for %MT and %IT was  $0.5 \pm 0.3\%$ .

## Statistical Analysis

Adherence to a Gaussian distribution was determined using the Kolmogorov-Smirnov test. Normally distributed data were described as means $\pm$ SDs, and the independent samples Student t test was utilized to compare continuous variables between 2 groups. Qualitative variables were described with counts and percentages. The strength of association between quantitative variables was measured with the Spearman rank correlation coefficient. Deaths were determined after a median of 51 (25th and 75th percentile: 43; 59) months. Overall survival was measured from the date of PEA to the date of death. The impact of hemodynamic parameters on long-term survival and PH recurrence was analyzed by Cox proportional hazard models and logistic regression models. Variables with a *P* value  $<0.150$  in the univariable models were included in the adjusted regression model. The proportional hazard assumption was tested using Schoenfeld residuals and was found to be

**Table 1. Preoperative Clinical and Hemodynamic Characteristics**

Clinical/Hemodynamic Variable	All (n=90)	Survivors (n=74)	Nonsurvivors* (n=13)
Clinical variable			
Age, y	54.9 $\pm$ 12.8	53.8 $\pm$ 12.2	59.9 $\pm$ 13.6
Sex, n (%)			
Male	59 (65.6)	45 (60.8)	11 (84.6)
Female	31 (34.4)	29 (39.2)	2 (15.4)
Body mass index, kg/m <sup>2</sup>	26.6 $\pm$ 4.7	26.9 $\pm$ 4.9	25.1 $\pm$ 4.0
History of venous thromboembolism, n (%)	70 (77.8)	56 (75.7)	11 (84.6)
Medical treatment before PEA, n (%)	19 (21.1)	15 (20.3)	4 (30.7)
WHO functional class, n (%)			
I	14 (18.9)	13 (17.6)	1 (7.6)
II	32 (35.6)	29 (39.2)	2 (15.4)
III	36 (40)	27 (36.5)	8 (61.5)
IV	8 (8.9)	5 (6.8)	2 (15.4)
Hemodynamic variable			
Heart rate, beats/min	78.1 $\pm$ 15.6	76.8 $\pm$ 14.7	80.0 $\pm$ 11.9
Cardiac output, L/min	4.9 $\pm$ 1.3	5.0 $\pm$ 1.4	4.3 $\pm$ 0.8
Cardiac index, L $\cdot$ min <sup>-1</sup> $\cdot$ m <sup>-2</sup>	2.5 $\pm$ 0.6	2.5 $\pm$ 0.6	2.4 $\pm$ 0.5
Mean right atrial pressure, mm Hg	11.2 $\pm$ 5.6	10.8 $\pm$ 5.6	13.5 $\pm$ 5.8
Pulmonary arterial systolic pressure, mm Hg	87.5 $\pm$ 21.4	87.2 $\pm$ 21.6	94.6 $\pm$ 16.5
Pulmonary arterial diastolic pressure, mm Hg	30.1 $\pm$ 9	29.8 $\pm$ 9.2	33.7 $\pm$ 7.3
Mean pulmonary arterial pressure, mm Hg	49.3 $\pm$ 12.1	50.0 $\pm$ 12.3	54.9 $\pm$ 9.0
Mean pulmonary arterial wedge pressure, mm Hg	9.6 $\pm$ 3.5	9.3 $\pm$ 3.5	11.1 $\pm$ 3.3
Effective capillary pressure, mm Hg	17.9 $\pm$ 9.3	15.8 $\pm$ 7.7	31.3 $\pm$ 4.9†
Pulmonary vascular resistance, WU	8.6 $\pm$ 3.2	8.5 $\pm$ 3.1	10.5 $\pm$ 3.3‡
Pulmonary arterial compliance, mL/mm Hg	1.2 $\pm$ 0.5	1.3 $\pm$ 0.5	0.9 $\pm$ 0.3‡
Upstream resistance, %	83.8 $\pm$ 14.9	88.4 $\pm$ 9.7	55.5 $\pm$ 2.6†

Values represented by means  $\pm$  standard deviations. PEA indicates pulmonary endarterectomy; WHO, World Health Organization; and WU, Wood units.

\*Three patients who died from malignancies were excluded; *P* values derived from independent-samples *t* test.

†*P* $<0.001$ .

‡*P* $<0.05$ .

valid. Receiver operating characteristic (ROC) analyses were performed to assess the predictive potential of  $R_{up}$  on persistent PH and survival. Cutoff values were determined by maximizing the Youden index, which is the sum of sensitivity and specificity minus 1. In addition, ROC analyses were performed to assess the predictive value of different models on persistent PH and survival. The method of DeLong et al<sup>24</sup> was used to compare areas under two ROC curves. Data were analyzed with SPSS Statistics (Version 21 for Mac) and SAS (version 9.2 for Windows). All *P* values result from 2-sided tests, with significance inferred at *P*  $<0.05$ .

**Table 2. Baseline and Immediate Postoperative Hemodynamics**

Hemodynamic Variable	Baseline n=90	Immediate Postoperative n=87
Cardiac output, L/min	4.9±1.3	5.7±1.5*
Mean pulmonary artery pressure, mm Hg	49.3±12.1	31.0±8.6*
Pulmonary vascular resistance, WU	8.6±3.2	3.5±1.9*
Pulmonary arterial compliance, mL/mm Hg	1.2±0.5	3.0±1.8*

Values represented by means ± standard deviations. WU indicates Wood units.

\* $P<0.001$ , compared with baseline values using paired samples t test.

## RESULTS

### Patients

A total of 112 patients with CTEPH underwent PEA between January 2012 and December 2016 at our institution, out of whom 90 were included in the study (Figure 1). A majority (66%) were male, and the mean age was  $55\pm13$  years. PEA was combined with coronary artery bypass graft surgery in 6 patients, with tricuspid valve replacement in 2 patients and with mitral valve replacement in 1 patient. One patient underwent re-PEA 6 years after successful PEA for recurrence of CTEPH because of inadequate anticoagulation. No complications occurred as a consequence of hemodynamic assessment or lung biopsies. Clinical

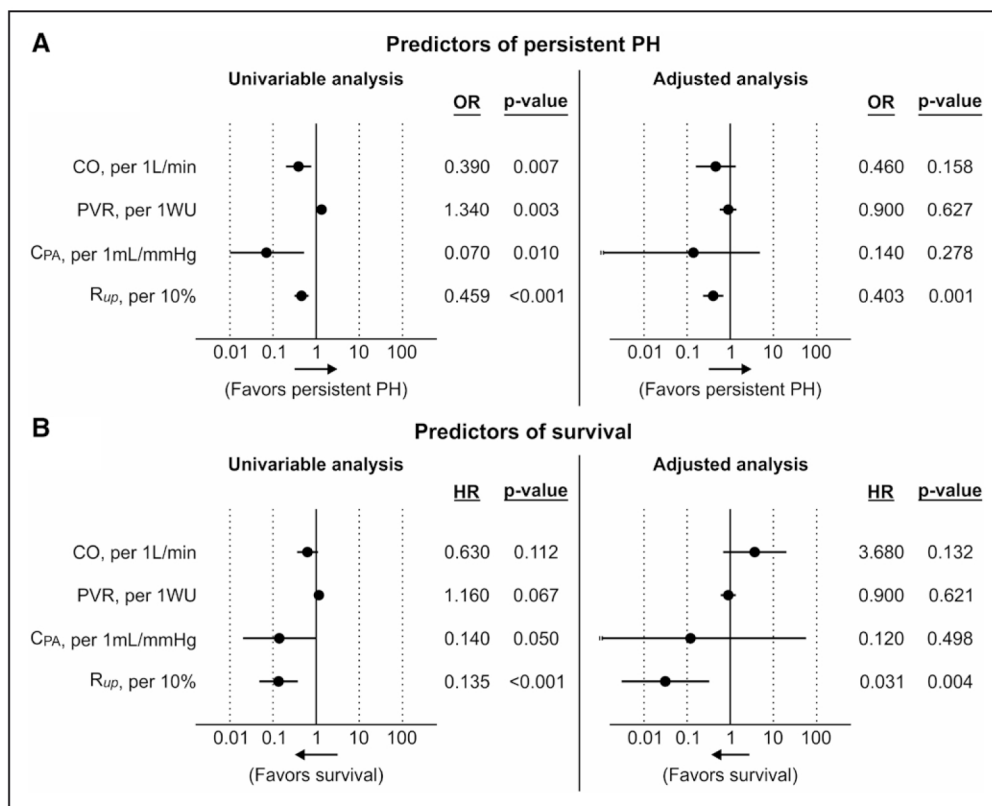
characteristics and preoperative hemodynamics are provided in Table 1. Key hemodynamics at baseline and after PEA are listed in Table 2.

### Hemodynamics

Baseline right ventricular afterload was higher in non-survivors (PVR,  $10.5\pm3.3$  WU,  $P=0.049$ ;  $C_{PA}$   $0.9\pm0.3$  mL/mm Hg,  $P=0.041$ ) compared with survivors (PVR  $8.5\pm3.1$  WU;  $C_{PA}$   $1.3\pm0.5$  mL/mm Hg). Despite similar mPAWP ( $9.3\pm3.5$  mm Hg vs  $11.1\pm3.3$  mm Hg;  $P=0.095$ ),  $P_c$  was significantly higher in nonsurvivors ( $31.3\pm4.9$  mm Hg vs  $15.8\pm7.7$  mm Hg,  $P<0.001$ ), resulting in a lower  $R_{up}$  in nonsurvivors ( $55.5\pm2.6\%$ ) compared with survivors ( $88.4\pm9.7\%$ ,  $P<0.001$ , Table 1). Representative pulmonary artery occlusion waveforms are shown in Figure 2. In a subgroup of 7 patients,  $R_{up}$  was assessed in multiple lung segments (Table 1 in the online-only Data Supplement) with an average difference of  $1.0\pm0.5\%$ .

### Predictors of Persistent PH

In a univariable logistic regression analysis, baseline CO, PVR,  $C_{PA}$ , and  $R_{up}$  were significant predictors of persistent PH after PEA. Adjusted analysis revealed that only baseline  $R_{up}$  remained an independent predictor of persistent PH (Figure 3A).

**Figure 3. Predictors of persistent pulmonary hypertension and survival.**

Forest plots illustrate univariable and adjusted analyses for (A) persistent pulmonary hypertension (PH) and (B) survival after pulmonary endarterectomy. Persistent PH was defined as a pulmonary vascular resistance (PVR)  $\geq 5.3$  Wood units (WU). Upstream resistance ( $R_{up}$ ) was the only predictor of persistent PH and survival at adjusted analysis. CO indicates cardiac output;  $C_{PA}$ , pulmonary arterial compliance; HR, hazard ratio; and OR, odds ratio.

ROC analysis identified a  $R_{up}$  cutoff at 66% as having the highest Youden index (0.51) for the prediction of persistent PH after PEA. This analysis identified an area under the curve of 0.761, and  $R_{up} < 66\%$  predicted persistent PH with a specificity of 58% and sensitivity of 93%. The area under the curve for a model including CO, PVR,  $C_{PA}$ , and  $R_{up}$  (0.895) was significantly larger than for a model including CO, PVR, and  $C_{PA}$  alone (0.783,  $P < 0.001$ ).

$R_{up}$  showed a strong inverse correlation with immediate postoperative PVR ( $r = -0.72$ ,  $P < 0.001$ , Figure 4A), whereas baseline PVR ( $r = 0.40$ ,  $P = 0.001$ ) and  $C_{PA}$  ( $r = -0.37$ ,  $P = 0.002$ ) showed only weak to moderate correlation with immediate postoperative PVR.  $R_{up}$  was also a significant predictor of relative change in PVR (from baseline to immediate postoperative) in linear regression analysis ( $r = -0.61$ ,  $P < 0.001$ , odds ratio,  $-0.01$  [95% CI,  $-0.12$  to  $-0.01$ ]).

## Predictors of Survival

Sixteen patients died in the perioperative period ( $n = 6$ , 5% in-hospital mortality) or during long-term follow-up ( $n = 10$ ). In univariable Cox regression analyses,  $R_{up}$  (hazard ratio per 10% change: 0.14 [95% CI, 0.05–0.38];  $P < 0.001$ ) was a significant predictor of survival, whereas  $C_{PA}$  approached statistical significance (hazard ratio, 0.14 [95% CI, 0.02–1.00];  $P = 0.05$ ). In an adjusted analysis including CO, PVR, and  $C_{PA}$ , only baseline  $R_{up}$  was an independent predictor of postoperative survival (hazard ratio per 10% change, 0.03 [95% CI, 0.00–0.33];  $P = 0.004$ ; Figure 3B).

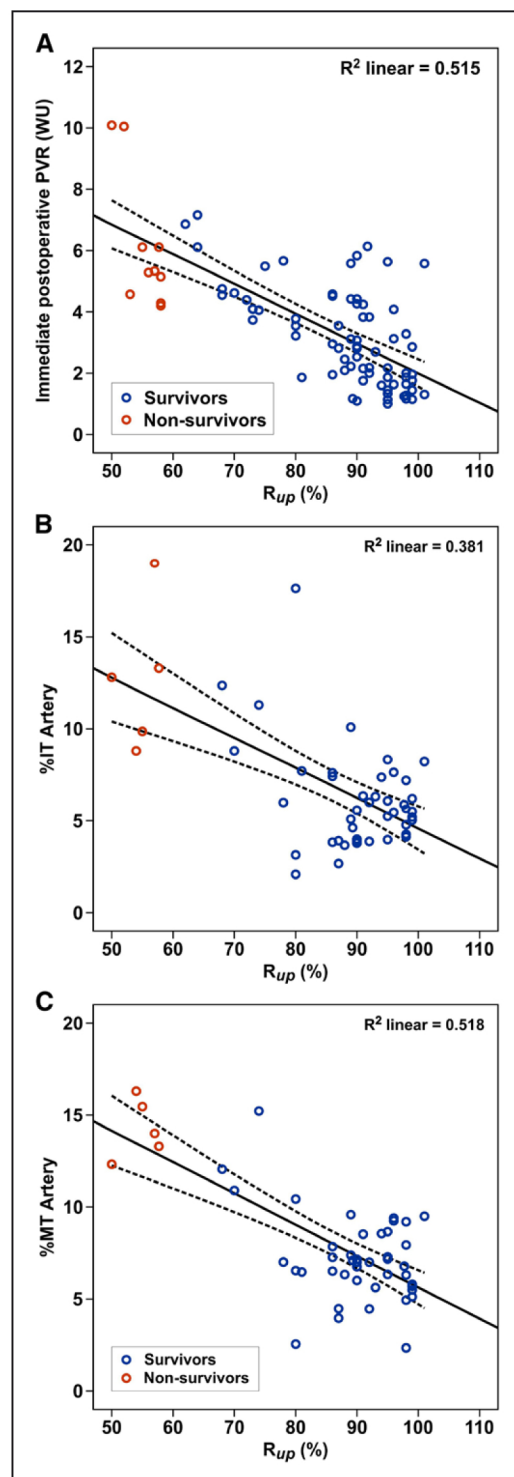
ROC analysis revealed a  $R_{up}$  cutoff at 60% as having the highest Youden index (0.813) for the prediction of survival versus nonsurvival after PEA. This cutoff led to an area under the curve of 0.854, a specificity of 81%, and sensitivity of 100% for the prediction of survival. Only patients with  $R_{up}$  values  $< 60\%$  died after surgery. The area under the curve for a model including CO, PVR,  $C_{PA}$ , and  $R_{up}$  (1.000) was significantly larger than for a model including CO, PVR, and  $C_{PA}$  alone (0.691,  $P < 0.001$ ).

## Histomorphometric Analysis of Pulmonary Vascular Remodeling

Overall, 4448 vessels were analyzed in 49 patients. On average,  $24.1 \pm 3.3$  arteries,  $40.2 \pm 5.3$  veins, and  $8.0 \pm 1.2$  indeterminate vessels per patient were analyzed. An overview of histomorphometric changes from obstructed and nonobstructed lung territories is given in Figure 5.

### Arteries

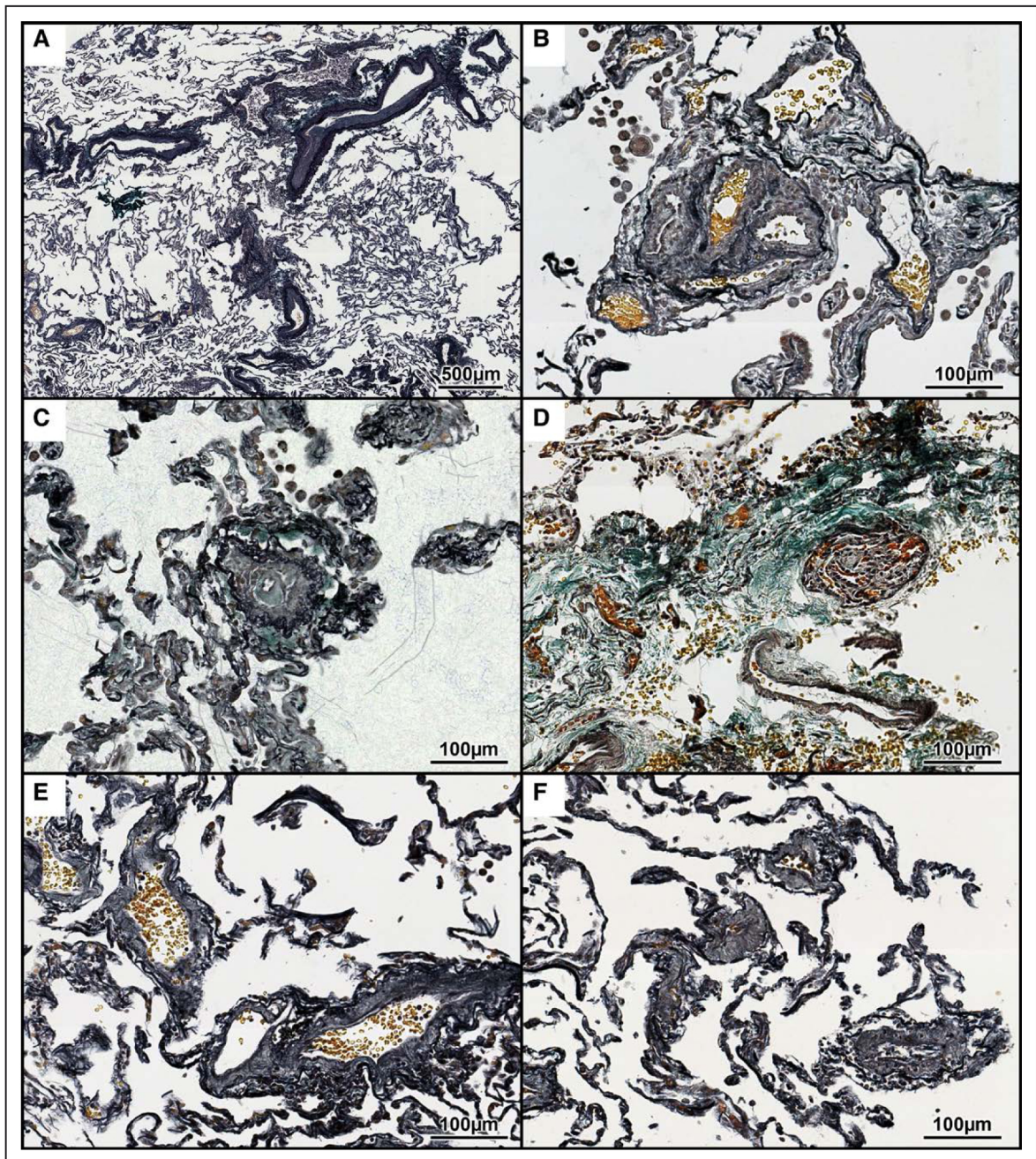
For arterial vessels, no significant differences were seen in %MT and %IT in nonobstructed versus obstructed lung territories. However, in patients with



**Figure 4.** Relationship between upstream resistance, immediate postoperative pulmonary vascular resistance, and histomorphometric data. Correlation between upstream resistance ( $R_{up}$ ), immediate postoperative pulmonary vascular resistance (PVR, **A**), relative intima thickness (%IT, **B**), and media thickness (%MT, **C**) in survivors (blue circles) and nonsurvivors (red circles). Lines mark means and CIs of the linear regression functions.  $R_{up}$  provides information on postoperative PVR and on presence and degree of small-vessel disease. WU indicates Wood unit.

persistent PH and in nonsurvivors, arterial %MT and arterial %IT were significantly higher in nonobstructed lung segments (Tables 3 and 4).





**Figure 5. Histopathology of pulmonary vessels in chronic thromboembolic pulmonary hypertension (CTEPH).**

Histological sections of lung biopsies taken from obstructed (A, B, E, and F) and nonobstructed (C and D) lung territories of patients suffering from CTEPH, stained with a modified Trichrome stain. A, Pulmonary arteries with mild to moderate intimal fibrosis and thrombotic lesions. B, Small occluded pulmonary artery with multiple secondary lumina (so-called colander-like lesion). C, Small pulmonary artery from a nonobstructed lung territory displaying medial hypertrophy, intimal fibrosis, and adventitial proliferation. D, Plexiform lesion from a nonobstructed lung territory close to the pleura. E, Pulmonary veins in an occluded lung territory showing mild intimal fibrosis. F, Pulmonary veins in an occluded lung territory showing moderate to severe intimal fibrosis.

In the morphology analysis, concentric intimal remodeling and intimal occlusion of arterial vessels in non-obstructed lung territories were more common in non-survivors (Table 4). Plexiform lesions were observed in 2 nonsurvivors.  $R_{up}$  was inversely correlated with arterial %MT ( $r=-0.72$ ,  $P<0.001$ ) and %IT ( $r=-0.62$ ,  $P<0.001$ ) in nonobstructed lung territories (Figure 4B and 4C, Table II in the online-only Data Supplement). PVR,  $C_{PA}$ , and mPAP did not correlate with histomorphometric

data of nonobstructed lung territories (Table II in the online-only Data Supplement).

### **Veins and Indeterminate Vessels**

For veins and indeterminate vessels, no significant differences were seen in %MT and %IT in nonobstructed versus obstructed lung territories. Diameter of venous vessels was comparable between nonobstructed ( $137\pm84$  µm) and obstructed lung territories ( $152\pm87$



**Table 3. Histomorphometric Data Stratified by Immediate Postoperative Pulmonary Vascular Resistance**

Variable	Nonobstructed Lung Segments				Obstructed Lung Segments			
	All n=49	PVR <5.3 WU n=40	PVR ≥5.3 WU n=9	P Value	All n=49	PVR <5.3 WU n=40	PVR ≥5.3 WU n=9	P Value
Arteries, %MT, %	7.9±3.1	7.1±2.4	11.3±3.8	<0.001	8.2±4.4	8.3±4.6	7.3±3.3*	0.541
Arteries, %IT, %	6.8±3.5	6.0±2.9	9.9±4.5	0.002	5.9±3.2	6.1±3.4	4.6±0.6*	0.197
Veins, %IT, %	5.0±3.0	4.9±3.0	5.3±3.4	0.765	5.0±3.2	4.3±1.3	11.8±3.4*	<0.001
Indeterminate vessels, %IT, %	6.7±2.5	6.8±2.6	6.4±2.4	0.679	6.8±2.8	6.3±2.2	11.4±3.8*	<0.001
Intimal morphology								
Arteries, n (%)								
Concentric	25 (51.0)	18 (45.0)	7 (77.8)	0.138	22 (44.9)	17 (42.5)	5 (55.6)	0.713
Occluded	7 (14.3)	4 (10.0)	3 (33.3)	0.105	0 (0)	0 (0)	0 (0)	1.000
Recanalized/webs/clots	0 (0)	0 (0)	0 (0)	1.000	12 (24.4)	11 (27.5)	1 (11.1)	0.420
Plexiform	2 (4.1)	0 (0)	2 (22.2)	0.031	0 (0)	0 (0)	0 (0)	1.000
Veins, n (%)								
Concentric	13 (26.5)	10 (25.0)	2 (22.2)	1.000	11 (22.4)	6 (15.0)	5 (55.6)	0.019
Occluded	0 (0)	0 (0)	0 (0)	1.000	0 (0)	0 (0)	0 (0)	1.000
Recanalized/webs/clots	0 (0)	0 (0)	0 (0)	1.000	0 (0)	0 (0)	0 (0)	1.000
Indeterminate vessels, n (%)								
Concentric	15 (30.6)	14 (35.0)	1 (11.1)	0.242	13 (26.5)	9 (22.5)	4 (44.4)	0.220
Occluded	0 (0)	0 (0)	0 (0)	1.000	0 (0)	0 (0)	0 (0)	1.000
Recanalized/webs/clots	0 (0)	0 (0)	0 (0)	1.000	0 (0)	0 (0)	0 (0)	1.000

P values listed in the table are results from comparisons between PVR <5.3 WU and PVR ≥5.3 WU. Quantitative data were analyzed using the independent-samples t test. The Fisher exact test was used for qualitative data. Values represented by means ± standard deviations. %IT indicates relative intima thickness; %MT, relative media thickness; PVR, pulmonary vascular resistance measured immediately postoperatively; and WU, Wood units.

\*P<0.05, paired-samples t test comparing obstructed and nonobstructed lung territories of patients with immediate postoperative PVR ≥5.3 WU.

μm,  $P=0.696$ ). However, in patients with persistent PH and in nonsurvivors, %IT of indeterminate vessels and veins were significantly higher in obstructed lung segments (Tables 3 and 4).

Concentric intimal remodeling of venous vessels in obstructed lung territories was more common in patients with persistent PH and nonsurvivors (Tables 3 and 4).  $R_{up}$  showed a moderate inverse correlation with venous %IT ( $r=-0.44$ ,  $P=0.024$ , [Table II in the online-only Data Supplement](#)) in obstructed lung territories. PVR,  $C_{PA}$ , and mPAP did not correlate with histomorphometric data of obstructed lung territories ([Table II in the online-only Data Supplement](#)).

## DISCUSSION

This is the largest prospective study assessing the association between preoperative  $R_{up}$  and (1) postoperative hemodynamic outcome, (2) long-term survival after PEA, and (3) small-vessel disease by lung histology. We found that (1)  $R_{up}$  is an independent predictor of persistent/recurrent PH; (2)  $R_{up} < 60\%$  identifies patients with a poor prognosis after PEA; and (3)  $R_{up}$  correlates inversely with the degree of microvascular remodeling.

A preoperative PVR >12.5 WU has previously been labeled as a marker of concomitant small-vessel

arteriopathy and predictor of poor prognosis with mortality rates of 10.1%.<sup>25</sup> However, preoperative PVR failed to predict survival as a continuous variable in multivariable analysis in both our current analysis and several previous studies.<sup>3,26</sup> More recent studies have identified postoperative PVR as an independent predictor of survival,<sup>3,4</sup> but robust preoperative hemodynamic markers of poor postoperative outcome (survival or persistent PH) and small-vessel arteriopathy have not been available.

The pulmonary artery occlusion technique is believed to provide information on the presence and degree of small artery and capillary-venous disease based on the assessment of  $P_{c'}$ .  $P_{c'}$  reflects the pressure in small pulmonary arteries and capillaries,<sup>8–10</sup> and is crucial for the partitioning of PVR in  $R_{up}$  and downstream resistance. Kim and colleagues previously identified a strong correlation between preoperative  $R_{up}$  and postoperative PVR.<sup>15</sup> They also observed that all 4 postoperative deaths occurred in patients with  $R_{up}$  values <60%.<sup>15</sup> However, because of the small sample size ( $n=26$ ) and short follow-up, a formal survival analysis was not possible.<sup>15</sup> We identified  $R_{up}$  as an independent predictor of persistent PH and survival after PEA, and found that a  $R_{up} < 66\%$  was the best predictor for persistent PH, whereas a  $R_{up} < 60\%$  best predicted mortality. Further,

**Table 4. Histomorphometric Data Stratified by Survival Status**

Variable	Nonobstructed Lung Segments				Obstructed Lung Segments			
	All n=49	Survivors n=44	Nonsurvivors n=5	P Value	All n=49	Survivors n=44	Nonsurvivors n=5	P Value
Arteries, %MT, %	7.9±3.1	7.2±2.4	14.3±1.6	<0.001	8.2±4.4	8.3±4.5	7.3±3.3*	0.633
Arteries, %IT, %	6.8±3.5	6.1±2.8	12.8±4.0	<0.001	5.9±3.2	6.0±3.3	4.6±0.6*	0.353
Veins, %IT, %	5.0±3.0	4.9±2.7	4.2±3.1	0.613	5.0±3.2	4.4±1.4	11.8±2.0*	<0.001
Indeterminate vessels, %IT, %	6.7±2.5	6.6±2.5	7.3±3.0	0.595	6.8±2.8	6.4±2.3	11.4±2.8*	<0.001
Intimal morphology								
Arteries, n (%)								
Concentric	25 (51.0)	20 (45.5)	5 (100.0)	0.049	22 (44.9)	20 (45.5)	2 (40.0)	0.075
Occluded	7 (14.3)	4 (9.1)	3 (60.0)	0.017	0 (0)	0 (0)	0 (0)	1.000
Recanalized/webs/clots	0 (0)	0 (0)	0 (0)	1.000	12 (24.4)	11 (25.0)	1 (20.0)	1.000
Plexiform	2 (4.1)	0 (0)	2 (40.0)	0.009	0 (0)	0 (0)	0 (0)	1.000
Veins, n (%)								
Concentric	13 (26.5)	12 (27.3)	1 (20.0)	1.000	11 (22.4)	7 (15.9)	4 (80.0)	0.007
Occluded	0 (0)	0 (0)	0 (0)	1.000	0 (0)	0 (0)	0 (0)	1.000
Recanalized/webs/clots	0 (0)	0 (0)	0 (0)	1.000	0 (0)	0 (0)	0 (0)	1.000
Indeterminate vessels, n (%)								
Concentric	15 (30.6)	14 (31.8)	1 (20.0)	1.000	13 (26.5)	9 (20.5)	4 (80.0)	0.014
Occluded	0 (0)	0 (0)	0 (0)	1.000	0 (0)	0 (0)	0 (0)	1.000
Recanalized/webs/clots	0 (0)	0 (0)	0 (0)	1.000	0 (0)	0 (0)	0 (0)	1.000

P values listed in the table are results from comparisons between survivors and nonsurvivors. Quantitative data were analyzed using the independent-samples *t* test. The Fisher exact test was used for qualitative data. Values represented by means ± standard deviations. %IT indicates relative intima thickness; and %MT, relative media thickness.

\**P*<0.05, paired-samples *t* test comparing obstructed and nonobstructed lung territories of nonsurvivors.

in the multivariable analysis,  $R_{up}$  was the only hemodynamic parameter that was able to predict postoperative outcome at baseline, before PEA.

The presence of a concomitant small-vessel arteriopathy has been suggested to play a critical role in the development of persistent PH and survival after PEA.<sup>6,7</sup> The first systematic description of small-vessel disease in CTEPH was provided in the early 1990s by Moser and Bloor.<sup>5</sup> In that study, lung biopsy specimens from 15 patients undergoing PEA and autopsy specimens from 16 patients who died after PEA were analyzed.<sup>5</sup> Examination disclosed pulmonary hypertensive lesions of small pulmonary arteries, including plexiform lesions.<sup>5</sup> However, type and extent of small-vessel arteriopathy did not appear to relate to preoperative hemodynamics or other patient characteristics.<sup>5</sup> Subsequently, in 2 relatively small studies, Jujo et al found an association between pulmonary vascular remodeling and both increased postoperative PVR and greater postoperative hypoxemia.<sup>27,28</sup> Lung biopsies were obtained during PEA, but they did not differentiate between obstructed and nonobstructed territories.

In the current study, we confirm that conventional preoperative hemodynamic values (mPAP, PVR, and  $C_{PA}$ ) do not correlate with the presence or degree of small-vessel arteriopathy. However, we found that  $R_{up}$  was strongly inversely correlated with %MT and %IT

of small pulmonary arteries in nonobstructed lung territories. Patients with persistent PH and nonsurvivors had significantly higher arterial %MT and %IT, whereas there were no differences of venous and indeterminate vessel %IT in nonobstructed lung territories (Tables 3 and 4).

Upper limits of normal for arterial %IT and %MT have been reported as 6.4% and 8.1%, respectively.<sup>23</sup> Based on these thresholds, 59% (n=29) of our patients did not have histological evidence of small-vessel disease. The remaining 41% of patients showed arterial remodeling of various degrees. Interestingly, venous %IT in obstructed lung territories was significantly increased in patients with persistent PH and nonsurvivors (Tables 3 and 4). This observation is in concordance with the previous description of venous remodeling in patients with CTEPH because of bronchopulmonary venous shunting.<sup>29</sup> In addition, we found that the average diameter of venous vessels was comparable between nonobstructed (137±84 μm) and obstructed lung territories (152±87 μm, *P*=0.696). This may further support the hypothesis of venous remodeling in obstructed lung territories caused by bronchopulmonary shunting.  $R_{up}$  correlated negatively with venous %IT of obstructed lung territories.

A previous study found that in 5 of 7 patients, variation was >10% between a flow-directed and

wire-directed approach of  $R_{up}$  assessment.<sup>14</sup> However, in the current study, we did not find relevant differences in  $R_{up}$  between different lung segments (Table 1 in the online-only Data Supplement). Although some have postulated the potential for heterogeneity in distal vascular disease across different lobes,<sup>14</sup> a recent study utilizing systematical lung tissue sampling demonstrated that microvascular disease in CTEPH is uniformly distributed across the whole lung.<sup>29</sup> We therefore hypothesize that  $R_{up}$  is uniformly distributed across the pulmonary circulation and may be independent of the site of occlusion, and that both arterial and venous changes may contribute to decreased  $R_{up}$ . The pathomechanism explaining the association between  $R_{up}$  and venous %IT remains not completely clear.

## Limitations

Lung biopsy specimens were not performed in all 90 patients, and were relatively small pieces of tissue. Furthermore, the sample size for the hemodynamic study (n=90) and for the histology substudy (n=49), and the number of nonsurvivors (n=13) were relatively low, such that both the overall results and, in particular,  $R_{up}$  cutoff values derived from ROC analysis need to be validated externally. In addition, arrhythmia including atrial fibrillation may alter the time-dependent algorithm for the derivation of  $P_c$ . Therefore, patients with atrial fibrillation and other forms of arrhythmia had to be excluded from our study before enrollment (n=5), and our findings and conclusions are theoretically not applicable to patients with CTEPH and atrial fibrillation. Finally, postoperative lung injury and hypoxia were not assessed systematically in our study. Therefore, we are not able to say whether lung injury after PEA may be predominantly attributed to venous changes of reopened vascular territories.

## Conclusions

Our data suggest that preoperative  $R_{up}$  is an independent predictor of persistent PH and survival in patients with CTEPH undergoing PEA.  $R_{up}$  correlated with histomorphometric indices (%IT and %MT) of small-vessel disease. A preoperative  $R_{up} < 66\%$  identified patients with persistent PH after PEA, and patients with a preoperative  $R_{up} < 60\%$  had the highest postoperative risk of death. Taken together, pulmonary artery occlusion waveform analysis providing estimates of  $R_{up}$  may provide a valuable and safe technique for assessing the degree of small-vessel disease and postoperative outcome after PEA in patients with CTEPH.

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