Pulmonary Vascular Reactivity and Prognosis in Patients With Chronic Thromboembolic Pulmonary Hypertension
A Pilot Study

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Background—Surgical pulmonary endarterectomy is the preferred treatment for chronic thromboembolic pulmonary hypertension. Persistent pulmonary hypertension after pulmonary endarterectomy has been recognized as a major determinant of poor outcome. We tested whether acute vasoreactivity identifies chronic thromboembolic pulmonary hypertension patients prone to develop persistent/recurrent pulmonary hypertension after pulmonary endarterectomy and whether the degree of acute vasoreactivity affects survival or freedom from lung transplantation.

Methods and Results—Right-sided heart catheterization at baseline and after inhalation of 40 ppm nitric oxide for 20 minutes was performed in 103 patients (56.3 ± 15.3 years old, 53 women). Reductions in mean pulmonary arterial pressure (ΔmPAP; $-8.8 \pm 12.6\%$; $P < 0.0001$) and pulmonary vascular resistance ($-16.1 \pm 18.1\%$; $P < 0.0001$) and an increase in mixed venous saturation during inhaled nitric oxide ($9.1 \pm 11.6\%$; $P < 0.0001$) were observed. Sixty-two patients underwent pulmonary endarterectomy after a median of 49 days (25th and 75th percentiles: 24 and 123 days). Operated patients were followed up for a median of 70.9 months (25th and 75th percentiles: 14 and 97 months). Change in mPAP during inhaled NO was identified as a predictor of persistent/recurrent pulmonary hypertension after pulmonary endarterectomy. Patients experiencing a reduction in mPAP >10.4% with nitric oxide inhalation had a better postoperative outcome. A significant correlation was found between ΔmPAP and immediate postoperative pulmonary vascular resistance ($r = 0.5$, $P < 0.0001$).

Conclusions—A total of 80 (77.7%) of 103 patients demonstrated acute pulmonary vascular reactivity of some degree. A decrease in mPAP >10.4% under inhaled nitric oxide is a predictor of long-term survival and freedom from lung transplantation in adult patients with chronic thromboembolic pulmonary hypertension who are undergoing pulmonary endarterectomy. (*Circulation*. 2009;119:298-305.)

Key Words: pulmonary heart disease ■ hypertension, pulmonary ■ thrombosis ■ endarterectomy ■ survival

Chronic thromboembolic pulmonary hypertension (CTEPH) is thought to result from single or recurrent pulmonary thromboemboli arising from sites of venous thrombosis.[1] For reasons still unclear, the lysis of blood clots does not occur in 0.1% to 3.8% of acute pulmonary thromboemboli,[2–5] which evolve to organized obstructions of the pulmonary artery. An increase in pulmonary vascular resistance (PVR) is followed by right ventricular overload, and eventually right ventricular failure. In patients with predominantly proximal disease, surgical pulmonary endarterectomy provides a potential cure of the disease.[6–10] Persistent or recurrent pulmonary hypertension (PH) after pulmonary endarterectomy is believed to result from concomitant small-vessel arteriopathy.[9,10] Post–pulmonary endarterectomy PH remains a critical and consistent determinant of perioperative risk and is associated with increased postoperative morbidity and mortality.[11,12] Although traditional diagnostic modalities are adequate in identifying the presence of proximal disease in CTEPH, assessments of pulmonary vascular microcirculatory dysfunction are experimental at this stage.[11]

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In idiopathic pulmonary arterial hypertension, the relative contribution of vascular tone in individual patients is assessed by acute administration of inhaled nitric oxide (iNO),[13–16] which has been labeled as a predictor of the response to calcium channel blockers and survival.[17] Because of the concept that CTEPH is primarily an obstructive major-vessel

disorder, vasoreactivity has not been included in guidelines for systematic preoperative assessment.[6]

The aim of the present study was to examine the degree of acute vasoreactivity to iNO in CTEPH patients. Furthermore, we tested the hypothesis that the degree of acute vasoreactivity predicts post–pulmonary endarterectomy PH, ie, persistent/recurrent PH, and affects long-term outcome.

Methods

Patient and Clinical Assessments

Patients were recruited at the Pulmonary Hypertension Unit, Vienna General Hospital, which is a national referral center for pulmonary endarterectomy in Austria. Patients were screened if they had CTEPH diagnosed between May 1994 and December 2006. Diagnosis of CTEPH was established by chest radiograph, transthoracic and transesophageal echocardiography with Doppler, pulmonary function tests including arterial blood gas analysis at rest and with exercise, right-sided heart catheterization (RHC), pulmonary angiography, ventilation-perfusion scan of the lungs, and multislice and high-resolution CT scans. A panel of cardiologists, pulmonologists, radiologists, and cardiothoracic surgeons reviewed each case.

Criteria for pulmonary endarterectomy at the Medical University of Vienna have been a resting mean pulmonary arterial pressure (mPAP) >25 mm Hg in the presence of a pulmonary capillary wedge pressure <15 mm Hg, plus surgical accessibility to thromboembolic lesions[6] according to the staff surgeon (WK) and his team. In CTEPH, no correlation exists between thrombus burden (percentage of vascular obstruction) and the degree of hemodynamic compromise.[18] Therefore, we have not made an attempt to quantify vascular obstruction; however, the surgical CTEPH type, which reflects the accessible amount of thrombus,[8] was documented systematically. CTEPH type was classified by the surgical specimen[7,19] as follows: type I, presence of a central thrombus; type II, thickened intima, fibrous webs, and bands within the lobar arteries; type III, occlusions in the segmental and subsegmental branches; or type IV, very distal thrombi. Currently, there exists no standardized definition for inoperability, although a disproportionately high PVR in relation to the most proximal location of thrombi, comorbidities and associated medical conditions, the patient's wishes, and the functional status of the affected pulmonary parenchyma contribute to the classification of an inoperable state. To avoid bias, we NO-tested all patients who were diagnosed with CTEPH before the assessment of operability was made; however, only operated patients were included in further analysis because of heterogeneity of drug treatments (ie, conventional therapy, prostacyclin analogues, endothelin receptor blockers, and phosphodiesterase inhibitors) in the unoperated group at follow-up and the uncertainty about how these treatments might affect hemodynamics at 1 year.

None of the patients in the present study had medical conditions that would pose a relative contraindication to vasodilator testing because of the possibility of systemic vasodilatation, such as that which occurs in severe coronary or cerebrovascular disease, preexisting systemic hypotension, or other life-threatening illnesses. Patients were excluded if they had received any PH-specific therapy or nitrates within the 6 months before enrollment. The Ethics Committee of the Medical University of Vienna approved the study, and patients provided written informed consent.

Hemodynamic Measurements and Acute Vasodilator Testing

RHC hemodynamic assessments were obtained on 4 occasions: (1) at baseline; (2) during iNO; (3) if patients underwent surgery, 12 to 24 hours after endarterectomy in the intensive care unit before removal of the intraoperative Swan-Ganz catheter; and (4) 1 year after pulmonary endarterectomy. Patients were off oxygen (O_2) at least 1 hour before undergoing RHC and acute vasodilator testing.

For RHC, a 7F Swan-Ganz catheter (Baxter, Irvine, Calif) was inserted from a femoral or jugular approach. Mean right atrial pressure (mRAP), mPAP, pulmonary arterial wedge pressure, and respective oxygen saturations, including the inferior and superior vena cava, were measured. Cardiac output was assessed both by thermodilution and by the Fick method. PVR was calculated with standard hemodynamic formulas.

With the catheter in the pulmonary artery, patients breathed 40 ppm NO (Pulmomix, Messer-Griesheim, Vienna, Austria) via a continuous positive airway pressure mask under constant flow of oxygen at 4 L/min (Messer-Griesheim Pulmonox-Mini) for 20 minutes before a complete hemodynamic measurement was repeated. NO application was continued during these measurements. A complete hemodynamic responder status was defined by a decrease in mPAP of at least 10 mm Hg and an absolute mPAP decrease below 40 mm Hg in the presence of a normal or increased cardiac output during iNO.[20]

Statistical Analysis

Continuous parameters are summarized as mean±SD or, in the case of a skewed distribution, as median (25th percentile–75th percentile). Discrete data are presented as counts. Changes in mPAP (ΔmPAP), PVR (ΔPVR), and mixed venous saturation (ΔMV$_{sat}$) were calculated as follows: (NO-mPAP/mPAP)−1, (NO-PVR/PVR)−1, and (NO-MV$_{sat}$/MV$_{sat}$)−1. For comparison of groups with regard to continuous parameters, the Wilcoxon rank sum test was used.

In the absence of a standardized definition and in accordance with available literature,[21,22] post–pulmonary endarterectomy PH was defined as mPAP ≥25 mm Hg and PVR ≥400 dyne · s · cm^{-5} measured at the 1-year follow-up RHC. The influence of mRAP, cardiac index, mPAP, ΔmPAP, CTEPH type, and duration of symptoms before diagnosis on post–pulmonary endarterectomy PH was investigated by multivariable logistic regression analysis. Furthermore, the influence of mRAP, cardiac index, mPAP, ΔmPAP, CTEPH type, and duration of symptoms before diagnosis on disease-specific survival was investigated by multivariable Cox regression analysis. Disease-specific survival was defined as freedom from lung transplantation or freedom from death due to right-sided heart failure. Patients who died of noncardiac causes were censored. Hemodynamic responsiveness to iNO was depicted by a receiver operator characteristic curve analysis. Cutoffs were chosen by maximizing the Youden index, which is the sum of sensitivity and specificity. The influence of ΔmPAP on survival above this cutoff was investigated by a Kaplan–Meier plot and the log-rank test. The influence of post–pulmonary endarterectomy PH on survival was investigated in the same way.

Pearson correlation coefficients and regression lines were calculated for immediate postoperative PVR and ΔmPAP, as well as for immediate postoperative PVR and PVR after 1 year. The influence of ΔmPAP, CTEPH type, cardiac index, mRAP, mPAP, and duration of symptoms on immediate postoperative PVR was investigated by multivariable linear analysis. Furthermore, the influence of the same factors on the likelihood of an immediate postoperative PVR ≥500 dyne · s · cm^{-5}[8] was investigated by a logistic regression analysis, and the influence of the cutoff ΔmPAP on survival was verified by log-rank tests.

In general, probability values below 0.05 were considered statistically significant; however, in the multivariable analyses, a Bonferroni-corrected level of 0.05/6=0.008 was used to account for multiplicity. The statistical R-software package was used.[23]

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patients

A total of 103 patients diagnosed with CTEPH provided written informed consent for the study (Figure 1). Hemodynamic parameters and patient baseline characteristics are summarized in Table 1. Fifty-three patients were female. At inclusion, 12 patients were in World Health Organization
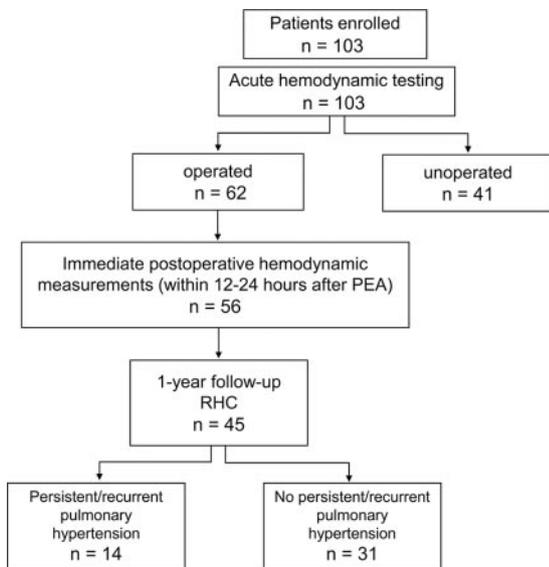
Figure 1. Patient disposition. PEA indicates pulmonary endarterectomy.

functional class II, 64 were in class III, and 27 were in functional class IV, according to diagnostic criteria defined by the World Health Organization.[24] The median duration of symptoms was 12 months (25th, 75th percentiles: 6, 32 months) in 62 patients.

Sixty-two patients (53.2 ± 15.4 years old, 32 women) fulfilled operability criteria and underwent pulmonary endarterectomy a median of 49 days (24, 123 days) after inclusion in the study. CTEPH types were type I in 15 patients (24%), type II in 33 patients (54%), type III in 10 patients (16%), and type IV in 4 patients (6%). Median follow-up of operated patients was 70.9 months (14, 97 months).

Hemodynamic Measurements Under iNO
Reductions in mPAP ($-8.8\pm12.6\%$; $P<0.0001$) and PVR ($-16.1\pm18.1\%$; $P<0.0001$) and an increase in MV_{sat}

Table 1. Baseline Patient Characteristics

	Patients Undergoing Pulmonary Endarterectomy (n=62)	Patients Not Undergoing Pulmonary Endarterectomy (n=41)
Age, y	53.2 ± 15.4	60.9 ± 13.9
mPAP, mm Hg	48.2 ± 12.3	49.7 ± 11.9
mRAP, mm Hg	8.1 ± 4.5	11.4 ± 6.3
PVR, dyne $\cdot$ s $\cdot$ cm^{-5}	746.6 ± 294.4	740.1 ± 294.3
Cardiac index, L $\cdot$ min^{-1} $\cdot$ m^{-2}	2.5 ± 0.6	2.3 ± 0.6
MVsat, %	62.2 ± 10.2	55.6 ± 11.4
Mean arterial blood pressure, mm Hg	103.9 ± 10.1	104.2 ± 10.7
WHO functional class, II/III/IV	4/42/16	8/22/11
Surgical CTEPH type, I/II/III/IV	15/33/10/4	NA

WHO indicates World Health Organization; NA, not applicable.

($9.1\pm11.6\%$; $P<0.0001$) after NO inhalation were found in the group as a whole. There was no significant difference in acute vasoreactivity to iNO between patients undergoing pulmonary endarterectomy and those not undergoing pulmonary endarterectomy.

Patients Who Did Not Undergo Pulmonary Endarterectomy
iNO was associated with a significant reduction in mPAP by 2.9 ± 4.9 mm Hg or $6\pm10\%$ ($P=0.005$) and in PVR by 105.4 ± 134.4 dyne $\cdot$ s $\cdot$ cm^{-5} or $15\pm21\%$ ($P<0.001$). iNO led to an increase in MV_{sat} by 5.3 ± 5.9 or $10.4\pm11.7\%$ ($P<0.001$). Among 41 patients not undergoing pulmonary endarterectomy, there were none who fulfilled the criteria for hemodynamic responder status.[20]

Patients Who Underwent Pulmonary Endarterectomy
Inhalation of NO was associated with a significant reduction in mPAP by 5.5 ± 6.2 mm Hg or $11\pm14\%$ ($P<0.001$) and in PVR by 109.3 ± 113 dyne $\cdot$ s $\cdot$ cm^{-5} or $17\pm14\%$ ($P<0.001$). iNO led to an increase in MV_{sat} by $4.5\pm4.4\%$ ($P<0.001$; Figure 2). Among 62 patients undergoing pulmonary endarterectomy, 8 patients (12.9%) fulfilled the criteria for complete hemodynamic responder status.[20]

Immediate Postoperative Hemodynamics
Immediate postoperative PVR measurements were collected from 56 patients; no data for the immediate postoperative period could be found for the remaining 6 patients (Figure 1). Mean immediate postoperative PVR was 382.6 ± 176 dyne $\cdot$ s $\cdot$ cm^{-5}. There was a significant difference between patients with recurrent/persistent PH after 1 year and patients with normal hemodynamics (551 ± 185 versus 296 ± 86 dyne $\cdot$ s $\cdot$ cm^{-5}; $P=0.0001$). A significant correlation was found between ΔmPAP and immediate postoperative PVR ($r=0.5$, $P<0.0001$; Figure 3). Furthermore, statistical analysis revealed a significant correlation between immediate postoperative PVR and PVR after 1 year ($r=0.6$, $P<0.0001$; Figure 4). The influence of ΔmPAP on immediate postoperative PVR was confirmed in the multivariable linear model (slope$=5.9$, 95% CI 2.24 to 9.5; $P=0.002$). Furthermore, this analysis indicated an influence of CTEPH types III and IV on immediate postoperative PVR (slope$=122.1$, 95% CI 24.4 to 219.8; $P=0.02$). ΔmPAP showed a significant influence on the likelihood of an immediate postoperative PVR ≥500 dyne $\cdot$ s $\cdot$ cm^{-5} (log OR$=0.19$, 95% CI 0.07 to 0.37; $P=0.012$).

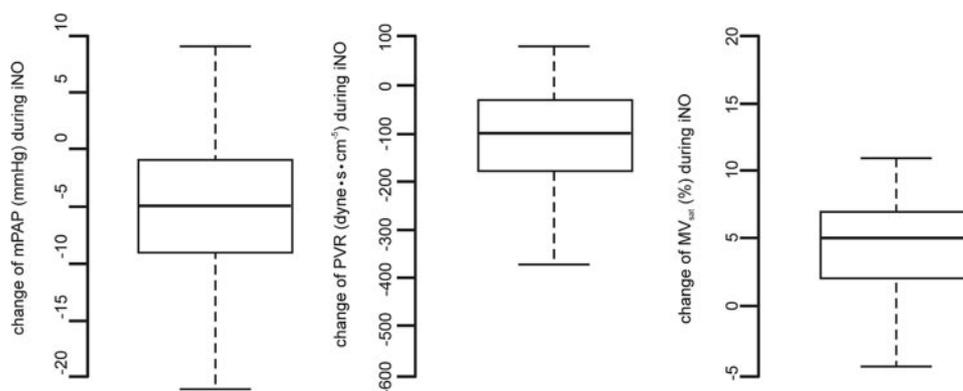## One-Year RHC and Post–Pulmonary Endarterectomy PH
At 1-year follow-up, 45 operated patients underwent repeated RHC. Six patients had died of right-sided heart failure before the 1-year follow-up, and 2 additional patients succumbed to noncardiac death in the first year after pulmonary endarterectomy. Nine patients refused to repeat RHC because of excellent clinical status. At 1 year, mPAP had changed by -17 ± 14.1 mm Hg ($P<0.0001$), mRAP by -1.9 ± 3.8 mm Hg ($P=0.001$), cardiac index by 0.34 ± 0.7 L $\cdot$ min^{-1} $\cdot$ m^{-2} ($P=0.002$), and PVR by -352 ± 337 dyne $\cdot$ s $\cdot$ cm^{-5} ($P<0.0001$).

Taken together, 14 patients experienced post–pulmonary endarterectomy PH, and 31 had normal hemodynamics at

Figure 2. Box plot of change in mPAP, PVR, and MV$_{sat}$ during NO inhalation in operated patients at baseline. iNO led to a reduction in mPAP by 5.5±6.2 mm Hg ($P<0.0001$), a reduction in PVR by 109.3±113 dyne · s · cm^{-5} ($P<0.0001$), and an increase in MV$_{sat}$ by 4.5±4.4% ($P<0.001$).

follow-up (Table 2). All hemodynamic responders showed a resting mPAP <25 mm Hg and a PVR <400 dyne · s · cm^{-5} at follow-up. There was a significant difference in duration of symptoms before diagnosis between patients who manifested postoperative PH and those who did not (24 [12, 60] versus 10 [4.25, 15.75] months, $P=0.02$).

Table 2 illustrates the comparison of hemodynamics (mPAP, PVR, and cardiac index) at baseline and 1-year follow-up between patients with and without post–pulmonary endarterectomy PH. Median ΔmPAP was −2±8% versus −17±11% in patients with post–pulmonary endarterectomy PH versus no post–pulmonary endarterectomy PH. Median ΔPVR was −10±14% in the post–pulmonary endarterectomy PH patient group and −22±16% in patients with no post–pulmonary endarterectomy PH. The magnitude of hemodynamic response to iNO appeared to correspond to surgical CTEPH type, with CTEPH type 1 showing a change in mPAP of −10±17%, type 2 showing a change of −14±13%, type 3 showing a change of −5±9%, and type 4 being associated with a ΔmPAP of 4±8%. Multivariable logistic regression analysis revealed ΔmPAP, CTEPH type,

and duration of symptoms as predictors of post–pulmonary endarterectomy PH (Table 3) at a statistical significance level of 0.05 but not at the Bonferroni-corrected level of 0.008.

Survival and Freedom From Lung Transplantation Among Operated Patients

During a median observation period of 70.9 (14, 97) months, 15 end points were reached, ie, 13 patients died and 2 underwent double lung transplantation. Among the 13 deceased patients, noncardiac death occurred in 2. These 2 patients died of malignancies and were excluded from further analysis. Perioperative in-hospital death occurred in 4 patients at 6±4 days after pulmonary endarterectomy. Autopsy revealed right-heart failure as the cause of death. These patients had demonstrated an increase in mPAP during iNO of 1.9±2.5% at baseline.

One- and 3- year cumulative rates of death and lung transplantation were 10.2%, and 13.6%, respectively, at 5 years. Multivariable Cox regression analysis revealed ΔmPAP and mRAP as predictors of survival and freedom from lung transplantation. In the present analysis, neither
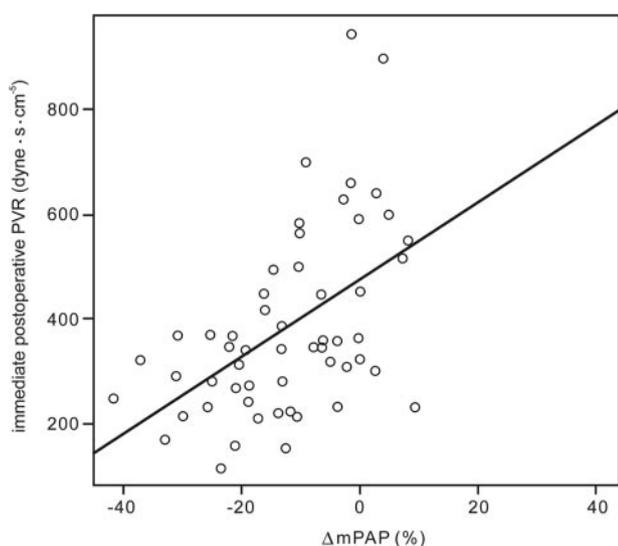
Figure 3. Scatterplot of immediate postoperative PVR against ΔmPAP under iNO. The least squares fit (immediate postoperative PVR=471.4+7.36×ΔmPAP [%]) is illustrated as a solid line.
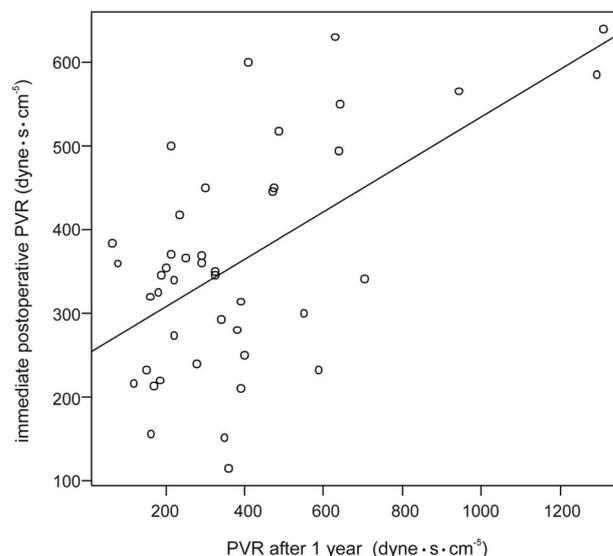
Figure 4. Scatterplot of immediate postoperative PVR against PVR after 1 year. The least squares fit (immediate postoperative PVR=250.7+0.3×PVR after 1 year) is illustrated as a solid line.

Table 2. Hemodynamic Variables Stratified by Definition of Postoperative PH, at Baseline and 1 Year After Pulmonary Endarterectomy

	Post–Pulmonary Endarterectomy PH (n=14)	No Post–Pulmonary Endarterectomy PH (n=31)
Baseline		
mPAP, mm Hg	46.5±13.4	47.1±10.5
ΔmPAP, %	−2±8	−17±11
Cardiac index, L · min^{-1} · m^{-2}	2.3±0.41	2.6±0.62
PVR, dyne · s · cm^{-5}	796.7±328.1	710.3±267
ΔPVR, %	−10±14	−22±16
After pulmonary endarterectomy		
WHO functional class (I/II/III/IV)	0/3/11/0	17/12/2/0
mPAP, mm Hg	40±5.2	25±7.3
Cardiac index, L · min^{-1} · m^{-2}	2.4±0.6	3±0.5
PVR, dyne · s · cm^{-5}	686.5±293	247.8±93.3

WHO indicates World Health Organization.

Post–pulmonary endarterectomy PH denotes mPAP ≥25 mm Hg and PVR ≥400 dyne · s · cm^{-5} at 1-year follow-up after pulmonary endarterectomy. No post–pulmonary endarterectomy PH indicates patients without PH according to this definition.

baseline cardiac index, duration of symptoms, CTEPH type, nor mPAP had a significant influence on survival (Table 4). Post–pulmonary endarterectomy PH showed a significant bivariate influence on survival ($P<0.0001$).

The change in mPAP under iNO can predict death or lung transplantation in patients undergoing pulmonary endarterectomy with a sensitivity of 71% (58%, 82%) and a specificity of 90% (81%, 97%) at a cutoff value of 10.4% (estimated area under the receiver operating characteristic curve 0.87 [0.78, 0.95]; Figure 5). Patients with ΔmPAP ≥10.4% had a better long-term outcome than those with ΔmPAP <10.4% ($P=0.002$; Figure 6).

Discussion

In the present study, reduction in mPAP by a minimum of 10.4% during iNO was associated with better long-term outcome (survival/freedom from lung transplantation) after pulmonary endarterectomy. The response to acute vasoreactivity testing predicted immediate postoperative PVR and PVR at 1 year. Significant and specific improvements in pulmonary hemodynamics after iNO suggest that although

Table 3. Multivariable Logistic Regression Analysis of Predictors of Post–Pulmonary Endarterectomy PH

|	Log OR	95% CI Limits	P
Cardiac index	−1.11	−3.07 to 0.33	0.18
ΔmPAP	0.27	0.12 to 0.52	0.006
mPAP	0.04	−0.05 to 0.15	0.4
CTEPH type	1.34	0.12 to 2.86	0.05
mRAP	0.05	−0.12 to 0.25	0.56
Duration of symptoms before diagnosis	0.07	0.02 to 0.15	0.02

CTEPH type was analyzed in a dichotomized manner comparing types I and II with types III and IV.

**Table 4. Multivariable Cox Regression Analysis of Predictors of Survival/Freedom From Lung Transplantation**

	Log Hazard Ratio	95% Hazard Ratio Confidence Limits	P
Cardiac index	0.19	−1.04 to 1.42	0.76
ΔmPAP	0.08	0.03 to 0.14	0.002
mPAP	0.03	−0.02 to 0.08	0.25
CTEPH type	−0.34	−1.14 to 0.45	0.4
mRAP	0.18	0.06 to 0.3	0.003
Duration of symptoms before diagnosis	0.004	−0.007 to 0.2	0.52

CTEPH is defined as an obstructive major-vessel pulmonary disease, an increased vascular tone is one of its features.

CTEPH is an important cause of PH. The disease is underdiagnosed, and its true prevalence is still unclear. It is characterized by major-vessel intraluminal thrombus organization and stenosis or complete obliteration of pulmonary arteries.[6] Pulmonary embolism, either as single or recurrent episodes, is thought to be the key initiating event.[9] Endarterectomy of organized pulmonary artery thrombus is the treatment of first choice for patients with CTEPH.[8] Criteria for operability are highly center-specific. For example, at our institution, ≈50% of patients are classified as not being candidates for surgery. Furthermore, approximately 10% to 24% of patients who undergo pulmonary endarterectomy obtain no relief and maintain a pulmonary hypertensive state,[25–27] likely owing to a concomitant small-vessel arteriopathy. Recent research has provided evidence suggesting that the mechanistic view of CTEPH as a disease caused solely by obliteration of central pulmonary arteries due to organized thrombi may have been too simplistic.[28,29] Vascu-
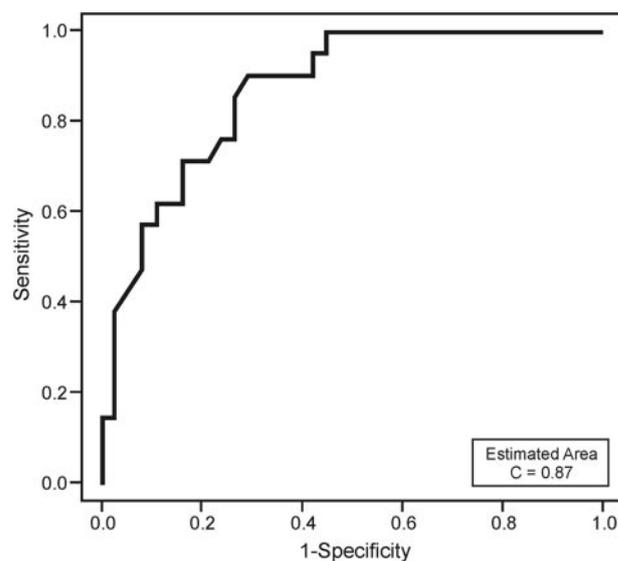
Figure 5. Receiver operating characteristic curve identifying ΔmPAP of 10.4% as the ΔmPAP level with the greatest area under the curve (estimated area). The change in mPAP under iNO can predict death or lung transplantation with a sensitivity of 71% and a specificity of 90% at a cutoff value of 10.4% (estimated area under the receiver operating characteristic curve 0.87) after pulmonary endarterectomy.
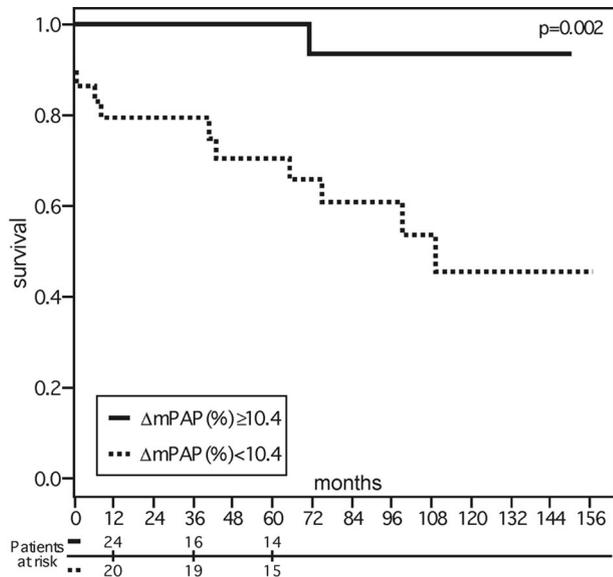
Figure 6. Kaplan–Meier survival curves in patients with operated CTEPH and ΔmPAP ≥10.4% compared with patients with ΔmPAP <10.4%. In patients with ΔmPAP ≥10.4% survival/freedom from lung transplantation was significantly better (*P*=0.002).

lar remodeling distal to the occluded major pulmonary artery may be an important contributor to PH and may affect vascular territories free of clot.[30] Small-vessel pulmonary arteriopathy of CTEPH is histologically indistinguishable from pulmonary arterial hypertension.[10]

Therefore, preoperative assessment of the degree of functionality of the resistance-vessel compartment or small-vessel disease is an important need. The exact site at which iNO exerts vasodilation is important. In an experimental model of acute microembolic pulmonary hypertension, 40 ppm of iNO affected the partitioning of PVR, which suggests small precapillary pulmonary arteries as the predominant site of action.[31] In isolated blood-perfused rat[32] and lamb[33] lungs, it was demonstrated that iNO decreased resistance in small arteries and veins, with no effect on larger-capacitance arteries and veins.[32] These observations suggest that iNO acts predominantly on resistance vessels, ie, arterioles and/or venules with a diameter <100 to 200 μm, that are at a short distance from alveoli.

In idiopathic pulmonary arterial hypertension, acute vasoreactivity testing with iNO can help identify patients in whom elevated tone is so significant that they must be managed with calcium channel blockers.[34] Acute hemodynamic responses have been reported for different subclasses of pulmonary arterial hypertension.[35] In CTEPH, it was expected that fixed thrombotic obstructions would not allow any vasoreactive response, yet more recent studies have provided evidence for a certain degree of vasoreactivity.[36,37]

In the present study, 8 (12.9%) of 62 operated patients fulfilled classic hemodynamic responder status criteria,[20] which seems higher than expected, albeit less common than in idiopathic pulmonary arterial hypertension patients.[16] Ulrich et al[37] showed no difference in acute vasoreactivity between 22 CTEPH patients and 35 patients with pulmonary arterial hypertension and no relation between the acute

vasodilator response to iNO and the change in World Health Organization functional class or exercise capacity 3 and 12 months after initiation of long-term vasodilator therapy; however, a possible relationship between acute vasoreactivity and outcome after surgery in CTEPH was not addressed in that study.

In the study by Suntharalingam et al,[36] 9 patients with surgically inaccessible distal disease and 9 patients with post–pulmonary endarterectomy PH were included. Subgroup analysis suggested that post–pulmonary endarterectomy PH patients were more responsive to both iNO and sildenafil than de novo patients. Only 1 of 18 patients fulfilled formal hemodynamic response criteria, which is in accordance with the present study, in which the magnitude of hemodynamic response to iNO was related to surgical CTEPH type, with the smallest response in CTEPH types III and IV. Survival and outcome were not followed. The authors concluded that acute hemodynamic responses may translate to improved clinical outcomes in this patient population. The strengths of the present study compared with the former studies are the larger patient population and the systematic follow-up over a period of several years.

The role of medical therapy in CTEPH, including choice of drugs and patient selection, remains unclear and is in need of further exploration.[25] By helping to identify those patients least likely to benefit from pulmonary endarterectomy, acute vasodilator testing may help define candidates for trials of medical therapy.[21,38–42] Regardless of alternative treatments, including the use of bosentan, it would be valuable to avoid surgery in high-risk cases in which there is little benefit. Whether acute vasoreactivity would also enable the prediction of outcome in unoperated patients is unknown, because off-label drug use in this desperate group of patients has prevented a systematic analysis.

Limitations of the present study include the small sample size, its single-center design, and the occurrence of relatively few events. Thus, additional studies are required to stimulate a change in current clinical practice. In the present pilot study, we have determined the cutoff value for ΔmPAP based on a limited sample size without a validation cohort.

Vasodilator testing can be performed easily. Limitations are the technical setup, relatively high costs and expertise, and a lack of data in patients undergoing chronic vasodilator treatment, for example, with bosentan. The combination of iNO and oxygen provides additive pulmonary vasodilation.[43] Although administration of oxygen alone did not cause significant changes in hemodynamics in CTEPH patients (data not shown), we used adjunctive oxygen to facilitate continuous NO delivery.

In summary, the present study demonstrates that despite the major-vessel obstructive nature of CTEPH, patients display significant acute vasoreactivity. Acute vasoreactivity testing may serve to predict immediate postoperative PVR and, subsequently, recurrent/persistent PH and survival.

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Disclosures

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CLINICAL PERSPECTIVE

Recent research suggests that chronic thromboembolic pulmonary hypertension is a combination of major vessel remodeling triggered by thrombus and a classic pulmonary arteriopathy. Approximately 10% to 24% of patients in whom significant amounts of thrombus are removed during surgical pulmonary endarterectomy obtain no persistent relief and maintain or develop a pulmonary hypertensive state, which is an important predictor of survival. Vascular remodeling distal to the occluded major pulmonary arteries may be an important contributor to pulmonary hypertension and may affect vascular territories free of clot. Inhaled nitric oxide acts predominantly on resistance vessels, that is, arterioles and/or venules with a diameter <100 to 200 μm, that are at short distances from alveoli. In our pilot study, we tested whether acute vasoreactivity to inhaled nitric oxide could identify patients with chronic thromboembolic pulmonary hypertension with small-vessel arteriopathy who were prone to manifest persistent/recurrent pulmonary hypertension after pulmonary endarterectomy and whether the degree of acute vasoreactivity affected survival and freedom from lung transplantation. In 62 consecutive patients undergoing surgery, change in mean pulmonary arterial pressure during inhaled nitric oxide was identified as a predictor of persistent or recurrent pulmonary hypertension after pulmonary endarterectomy. Patients experiencing a reduction in mean pulmonary arterial pressure $>10.4\%$ with nitric oxide inhalation had a better postoperative outcome. A significant correlation was found between the change in mean pulmonary arterial pressure and immediate postoperative pulmonary vascular resistance. In summary, the present study demonstrates that despite the major-vessel obstructive nature of chronic thromboembolic pulmonary hypertension, patients display significant acute vasoreactivity. Acute vasoreactivity testing may serve to predict immediate postoperative pulmonary vascular resistance, as well as recurrent or persistent pulmonary hypertension and survival long-term.

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