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Ratio of Pulmonary Vascular Resistance to Occluded Pulmonary Segments as an Indicator of Operability of Chronic Thromboembolic Pulmonary Hypertension Lesions

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Abstract

Objective: The operability evaluation for pulmonary thromboendarterectomy (PEA) in patients with chronic thromboembolic pulmonary hypertension (CTEPH) is always difficult. In this study, we aimed to identify a better indicator of operability in patients with surgically accessible CTEPH lesions.

Methods: Two-hundred-eight patients with surgically accessible CTEPH lesions who underwent PEA at Beijing Anzhen Hospital from March 2001 to February 2014 were retrospectively reviewed. The occluded pulmonary segments (OPS) were assessed by ventilation/perfusion scintigraphy, pulmonary vascular resistance (PVR) was measured by right heart catheterization and the PVR/OPS ratio was calculated.

Results: Seven (3.37%) early deaths occurred in the post-PEA period, six late deaths occurred during the mean follow-up period of 58.3 ± 39.7 months; the 5 year actuarial survival rate was 95.1% ± 3.5%. The PVR/OPS ratios of early and late death after PEA were significantly higher than those of early and late survival, respectively. A PVR/OPS ratio of <100 dyne·s·cm-5/OPS had much better specificity (88.7% *vs.* 69.2%) and sensitivity (92.3% *vs.* 38.5%) than did PVR alone in the prediction of early and late survival. The difference between the two areas under their receiver operating characteristic curves reached statistical significance (z test: Z=1.9917, P=0.046).

Conclusion: The PVR/OPS ratio is a better indicator of operability for surgically accessible CTEPH than is PVR alone. Patients with a PVR/OPS ratio of <100 dyne·s·cm-5/OPS have better early and long-term outcomes after PEA.

Keywords: Chronic thromboembolic pulmonary hypertension; Pulmonary thromboendarterectomy; Pulmonary vascular resistance; Occluded pulmonary segments

Introduction

Pulmonary thromboendarterectomy (PEA) is the treatment of choice for chronic thromboembolic pulmonary hypertension (CTEPH) [1,2]. The location and extent of the proximal thromboembolic obstruction is the most critical determinant of operability. Obstructions that originate more distally are not amenable to PEA with the current surgical techniques. The anatomic and hemodynamic findings must be interpreted in concert to fully evaluate the extent of the disease.

An acceptable postoperative hemodynamic outcome requires that the preoperative hemodynamic impairment be consistent with the magnitude of surgically accessible thromboembolic material as determined by imaging studies. This determination is critical. If the major component of the preoperative hemodynamic impairment is derived from surgically inaccessible disease or from resistance conferred by a secondary small-vessel arteriopathy, residual pulmonary hypertension will develop postoperatively. Depending on the extent of the postoperative pulmonary hypertension, this outcome may be associated with adverse short and long term consequences [3,4].

The most optimal method by which to define the inconsistency between preoperative hemodynamic impairment and surgically accessible CTEPH lesions has not yet been fully explored. Thus, there is no effective, objective parameter to serve as a classifier for CTEPH operability assessment. To identify indicative parameters that define the inconsistency between surgically assessable CTEPH lesions and pulmonary vascular resistance (PVR), we retrospectively analyzed the records of 208 patients with surgically accessible CTEPH who underwent PEA at Beijing Anzhen Hospital from March 2001 to February 2014.

Patients and Methods

Two hundred eight patients with surgically accessible CTEPH underwent PEA at Beijing Anzhen Hospital from March 2001 to February 2014. All patients were retrospectively reviewed. Their basic demographic data and risk factors are presented in Table 1. All patients underwent operability assessment before determination of the surgical treatment method.

Pulmonary angiography or pulmonary artery multislice computed tomography angiography (PACTA), pulmonary artery magnetic resonance imaging, isotope ventilation/perfusion scintigraphy (V/Q

scintigraphy) and echocardiography were performed to characterize the pathophysiological features of CTEPH. In 95% of patients, PACTA and V/Q scintigraphy were performed within 7 days before the surgical procedures.

Patient demographics and preoperative risk factors	**n=208**
Male (n, %)	129 (62.0)
Age (years)	47.8 ± 15.4
Disease course (years)	5.1. ± 2.5
6MWT(m)	273.9 ± 38.5
WHO functional class III, n(%)	112 (53.8)
WHO functional class IV, n(%)	96 (46.1)
Cyanosis (%)	156 (75)
Shunt across PFO, n(%)	59 (28.4)
Syncope, n(%)	73 (35.1)
Paradoxical organ embolism, n(%)	9 (4.3)
Severe Tricuspid regurgitation, n(%)	132 (63.5)
CTR	0.66 ± 0.15
EKG S1Q3T3 sign, n (%)	59 (28.4)
PaO_2 (mmHg)	65.4 ± 8.7
SaO_2 (%)	86.5 ± 4.2
SPAP (mmHg)	95.8 ± 26.7
PVR (dynes.s.cm-5)	880.4 ± 518
sPAP/sBP	0.93 ± 0.16
mPAP	68.53 ±15.4
Creatinine(umol/L)	96.7 ± 16.8
NT-proBNP (ng/dL)	931.5 ± 308.4
Preoperative San Diego Classification,n	
San DiegoType I	64
San DiegoType II	116
San Diego Type III	28
Ventilation/perfusion scan (defect segment, OPS)	10.7 ± 1.1

PFO: Patent Foramen Ovale; PVR: Pulmonary Vascular Resistance; sPAP: Systolic Pulmonary Artery Pressure; sPAP/sBP: Pulmonary to Systemic Systolic Artery Pressure Ratio; cRBBB: Complete Right Bundle Branch Block; CTR: Cardiac to Thoracic Ratio; mPAP: Mean Pulmonary Artery Pressure. The S1Q3T3 sign is the ECG manifestation of acute pressure and volume overload of the right ventricle and is exhibited as an S wave in lead I (signifying a complete or more often incomplete RBBB) and a Q wave, slight ST elevation, and inverted T wave in lead III.

Table 1: Basic demographic data and risk factors.

Nuclear medicine physicians performed V/Q scintigraphy to identify the occluded pulmonary segments (OPS). V/Q scintigraphy was performed using 99mTc-labeled macroaggregated albumin (99mTc-MAA) and 99mTc gas (99Tc). Images were acquired using a Precedence SPECT/CT g-camera (Royal Philips Electronics, Inc., The Netherlands). The perfusion images were acquired after intravenous administration of 100 MBq of 99mTc-MAA with the patient in the supine position.

The images were acquired in eight standard projections (anterior, posterior, right lateral, left lateral, right anterior oblique, left anterior oblique, right posterior oblique, and left posterior oblique) with a low-energy, general-purpose collimator. Ventilation images using 81mKr were acquired immediately after each perfusion view. 99mTc was

inhaled through a mouthpiece. The acquisition parameters were the same as those used for the perfusion study but the 20% window was centered on the energy peak of 99mTc (140 keV). Images were reported from a Hermes workstation (Nuclear Diagnostics Ltd., UK) by experienced nuclear medicine physicians.

Images were interpreted according to the modified Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) criteria [5,6]. The total OPS were obtained by counting the number of segments with perfusion defects on perfusion scintigraphy and comparing this number with that on ventilation scintigraphy in eight projections. If the perfusion segment was completely defected, it was counted as one OPS, and if the perfusion segment was only partially defected, it was counted according to the percentage of the defect relative to the whole segment.

Right heart catheterization was used to assess the hemodynamic status of all patients. Cardiac catheterization was completed under sedation and local anesthesia without intubation. Pulmonary artery pressure, mean pulmonary artery pressure and cardiac output (CO) were measured on room air. Hemodynamic parameters including the right atrial pressure, pulmonary artery pressure and pulmonary capillary wedge pressure were obtained by standard clinical methods. CO was measured using Fick's procedure (l/min) body surface area was calculated from height and weight and the cardiac output index was calculated from CO and body surface area.

The PVR/OPS ratio was also calculated. The decision to perform PEA was based on a careful preoperative assessment of each individual patient's hemodynamic status and pathophysiological conditions. The consistency between the surgically accessible lesions and PVR were thus determined. The Institutional Review Board of Beijing Anzhen Hospital approved this study. Written informed consent was obtained from each patient for the surgical procedure.

Therapeutic regimen

A total of 208 patients with surgically accessible CTEPH underwent standard PEA under general anesthesia with the support of cardiopulmonary bypass and deep hypothermia circulatory arrest. The operation was performed through a median sternotomy using techniques similar to those established by Jamieson and Kapelanski [7]. The cardiopulmonary bypass duration was 228.6 ± 31.2 min, the clamping time was 89.6 ± 27.5 min and the circulatory arrest time was 32.8 ± 15.3 min.

All surviving patients were on life-long warfarin administration and their international normalized ratios were maintained within the range of 2.0 to 3.0. Surgical survivors who had residual pulmonary hypertension received specific pulmonary vasodilative therapy including prostanoids, endothelin receptor antagonists, PDE 5-inhibitors or combination.

Statistical analysis

All statistical analyses were retrospectively performed with SAS version 8.2 for Windows (SAS, Cary, NC). Summary statistics for all continuous variables are presented as mean ± standard deviation.

Categorical data are summarized as frequencies and percentages. Cumulative event rates such as actuarial survival were estimated using the Kaplan-Meier method. Differences between the two groups were analyzed with the chi-square test, Fisher's exact test, the Wilcoxon rank sum test, or the log rank test as appropriate.

Results

Out of the 208 PEA procedures, seven early deaths occurred due to persistent pulmonary artery hypertension and right heart failure (surgical mortality, 3.37%) shown in Table 2. In total, 10.3 ± 1.2 OPS were confirmed by intraoperative assessment of the vasculature and 10.7 ± 1.1 OPS were confirmed through preoperative V/Q scintigraphy and pulmonary angiography/PACTA. The difference between these two methods did not reach statistical significance (t=1.9325, P=0.0542).

Early Deaths (before postoperative discharge)		
Deaths	**Postoperative interval**	**comments**
1	7 days	Persistent pulmonary hypertension and right heart failure
2	15 days	Persistent pulmonary hypertension and right heart failure
3	5 days	Persistent pulmonary hypertension and severe ischemia-reperfusion injury
4	5 days	Persistent pulmonary hypertension and right heart failure
5	8 days	Persistent pulmonary hypertension and right heart failure
6	11 days	Persistent pulmonary hypertension and right heart failure
7	13 days	Persistent pulmonary hypertension and right heart failure
Late Deaths (after postoperative discharge)		
Deaths	**Postoperative interval**	**comments**
8	11 months	Persistent pulmonary hypertension and right heart failure
9	3 years	Persistent pulmonary hypertension and copious hemoptysis

10	5 years	Persistent pulmonary hypertension and right heart failure
11	8 years	Persistent pulmonary hypertension and right heart failure
12	8 years	Persistent pulmonary hypertension and right heart failure
13	9 years	Persistent pulmonary hypertension and right heart failure

Table 2: Causes of early and late death after PEA.

The 201 surgical survivors were followed up from 1 to 157 months (58.3 ± 39.7 months); the cumulative follow-up time was 976.5 patient-years. During the follow-up, six patients died of persistent pulmonary artery hypertension and right heart failure 11 months to 9 years after the procedure.

The Kaplan-Meier actuarial survival curve showed a 5 year post-PEA actuarial survival rate of 95.1% ± 3.5%. The 201 surgical survivors underwent V/Q scintigraphy 3 months post-PEA and the OPS decreased from 10.7 ± 1.1 preoperatively to 2.4 ± 0.9 postoperatively; the difference reached statistical significance (t=31.5511, P=0.0001). As presented in Table 3, the PVR/OPS ratios for early and late death after PEA were significantly higher than those for early and late survival, respectively.

However, only the PVR of early death after PEA was significantly higher that of early survival; the difference in the PVR between late death and late survival did not reach statistical significance (Table 3).

Variables	Early death N=7	Early survival N=201	Late death N=6	Late survival N=195
PVR, dynes.s.cm-5	1191.0 ± 277.9 T=2.260, P=0.026	856.8 ± 251.4	863.7 ± 86.7 T=0.043, P=0.966	856.6 ± 255.4
PVR/OPS, dynes.s.cm-5/OPS	119.6 ± 11.6 T=3.567, P=0.001	79.5 ± 19.3	104.2 ± 7.7 T=2.288, P=0.025	78.6 ± 19.1

Table 3: Comparative results of PVR and PVR/OPS between early death and early survival and between late death and late survival.

As shown in Figure 1, receiver operating characteristic (ROC) curves were developed by plotting sensitivity against 1–specificity for PVR and PVR/OPS to predict death after PEA. To obtain a better balance between sensitivity and specificity, a PVR/OPS ratio of <100 dyne·s·cm-5/OPS and a PVR of <1000 dyne·s·cm-5 were chosen as the cut-off points for the operability criteria.

The predicative values for the two criteria are shown in Table 4. The results revealed that a PVR/OPS ratio of <100 dyne·s·cm-5/OPS had much better specificity (88.7% *vs.* 69.2%, respectively) and sensitivity (92.3% *vs.* 38.5%, respectively) than did PVR alone. The difference between the two areas under the ROC curves reached statistical significance (z test: Z=1.9917, P=0.046) (Figure 1 and Table 4).

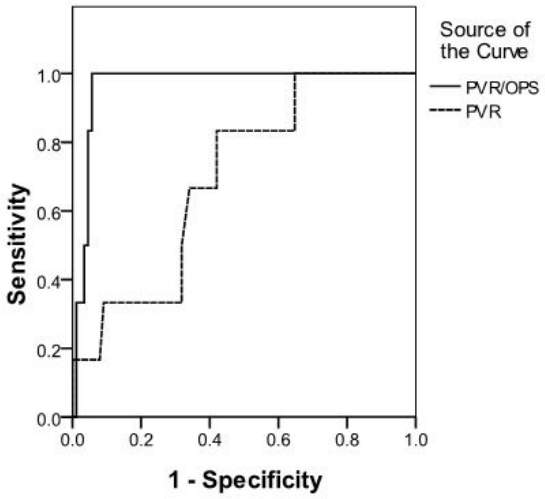

Figure 1: Receiver operating characteristic curves for PVR and PVR/OPS ratio as CTEPH operability indicators.

Parameters	PVR<1000 dynes.s.cm-5		PVR/ OPS <100 dynes.s.cm-5/ OPS	
	Death	Survival	Death	Survival
Above the value	5	60	12	22
Under the value	8	135	1	173
Sensitivity, %	38.5	-	92.3	-
Specificity, %	69.2	-	88.7	-
Accuracy, %	67.3	-	88.9	-
Positive Predictive Value, %	7.7	-	35.3	-

Negative Predictive Value, %	94.4	-	99.4	-
Area Under the Curve	0.700 ± 0.094 (0.516, 0.883)	-	0.966 ± 0.018 (0.928, 1.00)	-
P value	0.13		0	
The difference between the two curves Z test, **Z**=1.9917, **P**=0.046 *: (95% CI); CI: Confidence Interval.				

Table 4: PVR/OPS ratio and PVR as indicators of CTEPH operability.

Discussion

Fibrotic material is removed from the proximal pulmonary arteries during PEA [8]. A typical patient has a severely elevated PVR at rest, no significant comorbidities unrelated to right heart failure, and the presence of chronic thrombi on angiography consistent with the measured PVR. On the other hand, a lack of objective criteria serving as classifiers for CTEPH operability assessment often lead to the exclusion of patients who may otherwise benefit from surgical consideration [9]. The postoperative outcome after PEA for CTEPH is difficult to predict, and substantial efforts have been made to define operability classifiers. Some authors have analyzed specific angiographic findings in an attempt to predict the outcomes of PEA. Kunihara et al. [10] retrospectively reviewed pulmonary angiography findings in 90 patients who underwent PEA. They concluded that angiographic criteria can predict the success of PEA. Segments with obstruction but preservation of peripheral perfusion seemed to have a greater impact than did occluded segments on hemodynamic improvement. Reichelt et al. evaluated the role of 64-row CT in the diagnostic workup of patients with CTEPH using digital subtraction angiography as the method of diagnostic reference. They reported that the sensitivity and specificity of CT for detecting general CTEPH-related pathological changes were 98.3% and 94.8% at the main/lobar level and 94.1% and 92.9% at the segmental level, respectively. The sensitivity and specificity of CT regarding the different pathological criteria of CTEPH (complete obstruction, intimal irregularities, bands and webs and indirect signs) were 88.9% to 100.0% and 96.1% to 100.0% at the main/lobar level and 84.3% to 90.5% and 92.0% to 98.7% at the segmental level respectively, Reichelt et al. reported that CT is an accurate and reliable noninvasive alternative to conventional digital subtraction angiography in the diagnostic workup of patients with CTEPH [11]. The extent of central disease (CD) could be scored (i.e., the CD score) and a CD score of ≤ 1 was judged as relatively peripheral disease [12]. However, neither the CD score nor 64-row CT has the power to define inconsistencies between surgically accessible lesions and a high PVR [1].

Despite growing experience worldwide the approach to and criteria for patient selection remain variable and center or expert dependent. A significant proportion of patients with CTEPH may be unable to undergo PEA for a number of reasons most frequently because of concerns regarding distal or inaccessible disease. Although traditional preoperative testing and currently available tools can adequately identify the presence of proximal lesions in patients with CTEPH, they provide only limited information on the status of the microvasculature because persistent pulmonary hypertension is the most important determinant of the post-PEA outcome, preoperative identification of CTEPH patients with concomitant small-vessel disease and/or micro vascular disease is crucial. PVR is a useful parameter with which to identify concomitant small-vessel disease. Kim reported that by assessing the relative contribution of small vessels to the PVR the pulmonary artery occlusion technique represents a promising tool for determining the surgical risk in patients with a high PVR [13,14]. However, more information on the potential value or risk of preoperative medical therapies is required, and the pulmonary artery occlusion technique is relatively risky for patients with CTEPH.

In some patients, endarterectomy is not an option because of severe comorbidities or predominant involvement of the distal pulmonary arteries. As with any surgery, careful preoperative assessment is mandatory and the decision to perform PEA must be tailored to the individual patient. Once a diagnosis of CTEPH has been established, pulmonary angiography should be performed to determine the disease location. Patients with CTEPH with main-, lobar-, or proximal segmental-level defects have generally been characterized as having proximal lesions. The experience of the PEA team will however determine which lesions are considered to be surgically treatable. The presence of a surgically accessible lesion does not always mean that the CTEPH is treatable such as in cases of significant concomitant small-vessel disease. Additionally, accessibility is not solely dependent on the angiographic appearance but also on the skill and experience of the surgeon. Indeed, even obstruction within segmental or sub segmental branches depicted on high-quality angiograms can be removed by surgeons with adequate experience [15]. All of these factors impact the operability for any individual patient with CTEPH, and the operability evaluation protocol may be cardiac center- and/or surgeon-sensitive.

In addition to defining the degree of proximal disease another equally critical assessment is preoperative screening of micro vascular disease. Traditionally, this screening has focused on correlations between the hemodynamic and radiographic findings. This approach relies on expert opinion and remains subjective with criteria varying among centers and experts. The most useful objective parameter in assessing potential concomitant small-vessel disease is PVR. The preoperative PVR in patients with CTEPH is determined by the presence of chronic thromboembolic disease (either surgically accessible or inaccessible), concomitant small-vessel arteriopathy and right heart function (CO). A high PVR in the absence of substantial chronic thromboembolic disease on angiography suggests concomitant small-vessel disease which increases the risk of persistent postoperative arterial hypertension and is associated with increased short- and long-term mortality [16]. Several studies have found that a high preoperative PVR is associated with increased PEA mortality and poor hemodynamic outcomes [17]. Hartz et al. found that a PVR of >1100 dyne·s·cm-5 was associated with a PEA mortality rate of 41% *vs.* <6% in patients with a PVR of <1100 dynes·s·cm-5. This observation was supported by Dartevelle et al. who reported a high postoperative mortality rate of 10% in patients with a preoperative PVR of 900 to

1200 dyne·s·cm-5 that further increased to 20% with a PVR of >1200 dyne·s·cm-5. Similarly, in a large series of 500 patients with CTEPH who underwent PEA, Jamieson et al. reported that patients with a preoperative PVR of >1000 dyne·s·cm-5 had a significantly higher mortality rate than did those with a preoperative PVR of <1000 dyne·s·cm-5 (10.1% *vs.* 1.4%, respectively; P<0.0001) [18,19]. Although D'Armini et al. reported that PEA leads to hemodynamic recovery even in severely compromised patients with CTEPH; the balance of evidence indicates that a high preoperative PVR has an unfavorable effect on the outcome after PEA [20].

The predictive power of PVR in CTEPH operability assessment has not been previously examined. Based on our literature analysis and the present retrospective study, we sought to compare the relative predicative value of a PVR/OPS ratio of <100 dyne·s·cm-5/OPS *vs.* a PVR of <1000 dyne·s·cm-5 for CTEPH operability. Our results revealed that a PVR/OPS ratio of <100 dyne·s·cm-5/OPS has a much better specificity (88.7% *vs.* 69.2%) and sensitivity (92.3% *vs.* 38.5%) than does PVR alone. As shown in Figure 1, the difference between the two areas under their ROC curves reached statistical significance (z test: Z=1.9917, P=0.046). In other words, a PVR/OPS ratio of ≥ 100 dyne·s·cm-5/OPS indicates the presence of CTEPH with concomitant small-vessel disease and/or micro vascular disease.

Study Limitations

This was a retrospective analysis and some confounding factors may have hidden the presence of associations between the early and late prognoses of PEA and the PVR and PVR/OPS ratio. To further determine the efficacy of these two parameters in assessment of CTEPH operability further studies in a wider range are needed. The overall results of the present study are relatively inconclusive and very preliminary because of the limited sample size and lack of adjustment for other risk factors. Additional series reports would allow us to reduce significant bias. However, the present results may help to guide the development of surgical treatment of CTEPH.

Conclusion

To define the operability of surgically accessible CTEPH, the PVR/OPS ratio is a better indicator of operability than is the PVR alone. Patients with a PVR/OPS ratio of <100 dyne·s·cm-5/OPS have better early and late outcomes after PEA whereas a PVR/OPS ratio of ≥ 100 dyne·s·cm-5/OPS indicates the presence of CTEPH with concomitant small-vessel disease and/or micro vascular disease.

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Competing Interests

The authors have declared that no competing interests exist.

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