



Evaluating the efficacy of balloon pulmonary angioplasty using quantitative analysis of SPECT pulmonary ventilation/perfusion scintigraphy in patients with chronic thromboembolic pulmonary hypertension

Rong-Zheng Ma¹, Chao-Ling Jin¹, Sen Yang¹, Ping-Ping Han¹, Huan Li¹, Ji-Xiang Liu^{2,3,4,5}, Jin-Zhi Wang^{2,3,4,5}, Qiang Huang^{2,3,4,5}, Wan-Mu Xie^{2,3,4,5}, Pei-Ran Yang^{3,4,5,6}, Zhen-Guo Zhai^{2,3,4,5}, Li-Ping Fu¹

¹Department of Nuclear Medicine, China-Japan Friendship Hospital, Beijing, China; ²Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, Beijing, China; ³National Center for Respiratory Medicine, Beijing, China; ⁴Institute of Respiratory Medicine, Chinese Academy of Medical Sciences, Beijing, China; ⁵National Clinical Research Center for Respiratory Diseases, Beijing, China; ⁶State Key Laboratory of Medical Molecular Biology, Department of Physiology, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences and School of Basic Medicine, Peking Union Medical College, Beijing, China

Contributions: (I) Conception and design: RZ Ma, CL Jin, S Yang; (II) Administrative support: H Li, Q Huang, WM Xie, ZG Zhai, LP Fu; (III) Provision of study materials or patients: RZ Ma, PP Han; (IV) Collection and assembly of data: RZ Ma, CL Jin, JX Liu, JZ Wang, PR Yang; (V) Data analysis and interpretation: RZ Ma, S Yang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Li-Ping Fu, MD. Department of Nuclear Medicine, China-Japan Friendship Hospital, No. 2 of Yinghuayuan Road, Chaoyang District, Beijing 100029, China. Email: fulipjh@126.com; Zhen-Guo Zhai, MD. National Center for Respiratory Medicine, Beijing, China; Institute of Respiratory Medicine, Chinese Academy of Medical Sciences, Beijing, China; National Clinical Research Center for Respiratory Diseases, Beijing, China; Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, No. 2 of Yinghuayuan Road, Chaoyang District, Beijing 100029, China. Email: zhaizhguo235@outlook.com.

Background: Single-photon emission computed tomography (SPECT) ventilation perfusion imaging is the main imaging method for the diagnosis of pulmonary embolism, and its application in the diagnosis and efficacy evaluation of chronic thromboembolic pulmonary hypertension (CTEPH) has been paid more and more attention. In recent years, with the development of computer software technology, ventilation/perfusion (V/Q) imaging quantitative analysis technology has become more and more mature. The objective of this study was to investigate the utility of quantitative analysis of pulmonary V/Q scintigraphy in evaluating the efficacy of balloon pulmonary angioplasty (BPA) in patients with CTEPH.

Methods: In this retrospective analysis, we collected data of patients diagnosed with CTEPH who underwent BPA at the China-Japan Friendship Hospital from April 2018 to September 2020. The sample consisted of 23 males and 28 females, with an average age of 55.1 ± 12.7 years. All patients underwent V/Q scintigraphy within one week before surgery, and we reviewed the pulmonary angiography within 1–3 months following the last BPA procedure. We repeated V/Q scintigraphy within 1 week before or after the pulmonary angiography, at the time of collecting clinical and hemodynamic parameters of these patients. We divided the patients into two groups based on the presence of residual pulmonary hypertension post-surgery and compared the pre- and post-operative quantitative pulmonary perfusion defect percentage scores (PPDs%) using the *t*-test.

Results: In all, 102 V/Q scintigraphy scans were performed in 51 patients. The quantitative PPDs% were positively correlated with the hemodynamic indexes mean pulmonary arterial pressure (mPAP), pulmonary vascular resistance (PVR), and mean right ventricular pressure (RVP) ($r=0.605, 0.391, \text{ and } 0.464$, respectively, all $P<0.001$) and negatively correlated with the 6-minute walking distance (6MWD)

($r=-0.254$, $P=0.010$). The average preoperative quantitative PPDs% were $(49.0\pm 15.6)\%$ which significantly decreased to $(33.5\pm 13.9)\%$ after surgery ($t=11.249$, $P<0.001$). The preoperative quantitative PPDs% were $(54.7\pm 15.7)\%$ and $(44.0\pm 13.8)\%$ in the residual pulmonary hypertension group and the non-residual pulmonary hypertension group, respectively ($t=2.599$, $P=0.012$). The postoperative quantitative PPDs% were $(41.5\pm 12.5)\%$ and $(26.3\pm 11.0)\%$, in the residual pulmonary hypertension group and the non-residual pulmonary hypertension group, respectively ($t=4.647$, $P<0.001$).

Conclusions: In this study, we found that quantitative analysis of SPECT pulmonary V/Q scintigraphy adequately reflected the pulmonary artery pressure and clinical status in patients with CTEPH. Our results demonstrate its definite utility in predicting residual pulmonary hypertension and in evaluating the postoperative efficacy of BPA in patients with CTEPH.

Keywords: Chronic thromboembolic pulmonary hypertension (CTEPH); efficacy evaluation; quantitative analysis; single-photon emission computed tomography pulmonary ventilation/perfusion scintigraphy (SPECT pulmonary V/Q scintigraphy)

Submitted Aug 24, 2023. Accepted for publication Jan 17, 2024. Published online Mar 06, 2024.

doi: 10.21037/qims-23-1208

View this article at: <https://dx.doi.org/10.21037/qims-23-1208>

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by pulmonary thromboembolism (PTE) causing widespread obstruction of the pulmonary vascular bed. If untreated, progressive pulmonary vascular resistance (PVR) can lead to right-sided heart failure and worsen the patient's prognosis (1). Currently, pulmonary endarterectomy (PEA) is the gold standard in treatment for CTEPH (2). Balloon pulmonary angioplasty (BPA) is a percutaneous pulmonary artery interventional therapy developed in recent years. Several studies have demonstrated that BPA can significantly improve the pulmonary hemodynamic state and prognosis in patients with CTEPH (3,4) and offers a promising treatment modality for patients with CTEPH who are unable to undergo PEA.

At present, BPA is indicated as an option in the following cases: patients who cannot undergo PEA due to distal vascular occlusion; patients with less severe pulmonary vascular disease but significantly reduced blood flow or those with comorbidities that significantly increase the risk of surgery; patients with persistent hypertension or recurrent pulmonary hypertension (PH) after PEA; and patients requiring salvage angioplasty following early failure of PEA (5).

In single-photon emission computed tomography (SPECT) pulmonary ventilation/perfusion (V/Q) scintigraphy, a noninvasive imaging technique that continues to be used in the diagnosis of CTEPH, the diagnosis is

mainly based on mismatched V/Q scintigraphy due to impaired blood perfusion induced by thromboembolism (6). Furthermore, semi-quantitative measurement of the pulmonary perfusion defect percentage scores (PPDs%) can be used effectively for monitoring and evaluating treatment efficacy in CTEPH (7). There have been continued advances in the SPECT software in recent years. The image analysis software makes the quantitative assessment of pulmonary perfusion defects easier. Results can be generated more conveniently and the analysis can be more objective than semiquantitative measures of mismatch.

In this study, we explored the utility of quantitative analysis of V/Q scintigraphy in evaluating the efficacy of BPA in patients with CTEPH by comparing the percentage changes of preoperative and postoperative perfusion defects in patients who underwent BPA. Compared with the traditional semi-quantitative analysis based on visual analysis, quantitative analysis is more objective and reproducible, which is more conducive to the clinical application of V/Q imaging in the field of CTEPH. We present this article in accordance with the STROBE reporting checklist (available at <https://qims.amegroups.com/article/view/10.21037/qims-23-1208/rc>).

Methods

General information

We retrospectively collected V/Q scintigraphy data, clinical,

and hemodynamic parameters from patients diagnosed with CTEPH in the China-Japan Friendship Hospital between April 2018 and September 2020. Diagnosis was as per the guidelines of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) for the diagnosis and treatment of pulmonary hypertension published in 2022 (8).

Exclusion criteria: (I) a history of pulmonary surgery or diseases complicated with vasculitis or pulmonary artery tumor; (II) the time interval between any V/Q imaging before or after surgery and the corresponding right heart catheterization was more than 1 week; (III) the right heart catheterization details or clinical data were incomplete.

A total of 67 eligible patients were screened from April 2018 to September 2020, including 13 patients who only underwent perfusion and lacked ventilation imaging, and three patients who had poor quality of ventilation or perfusion images due to technical problems that affected the accuracy of quantitative analysis. The final analysis included 51 patients and we analyzed 102 pre- and post-operative V/Q images. This included 23 males and 28 females, aged between 27–77 years, with an average age of 55.1 ± 12.7 years.

All patients fulfilled the clinical diagnostic criteria for CTEPH [after at least 3 months of standardized anticoagulation therapy; the presence of chronic thrombosis confirmed by computed tomography (CT) pulmonary angiography, V/Q scintigraphy, or pulmonary angiography; right heart catheterization showed the mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg at rest] (1). All patients underwent V/Q SPECT scintigraphy within one week prior to surgery, and pulmonary angiography was performed within 1–3 months following surgery. V/Q SPECT scintigraphy was repeated within one week before or after the repeat pulmonary angiography. Among these, 46 patients underwent BPA more than once. The duration of follow-up was 12.0 ± 6.9 months.

General information about the patients and their pre- and post-operative clinical indicators were collected. Hemodynamic parameters were obtained using right heart catheterization. We divided patients into the residual pulmonary hypertension group and the non-residual pulmonary hypertension group based on the presence or absence of residual pulmonary hypertension (mPAP > 30 mmHg) after surgery, respectively (9). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was conducted with approval from the Ethics Committee of China-Japan Friendship

Hospital (No. 2022-KY-085). Written informed consent was obtained from all participants.

Imaging method

Images were acquired using the dual-head gamma camera (Siemens Symbia T16 True point SPECT-CT; Siemens Medical Solutions, USA), which is equipped with a low-energy, high-resolution collimator. The energy peak was set at 140 keV with a window of $\pm 10\%$. A disposable pulmonary ventilation introducer: ^{99m}Tc -technetium air ventilation device (VITA Medical Ltd., Australia), was used as the ventilation equipment. The V/Q scintigraphy was completed in one day.

Pulmonary ventilation tomography

An eluate of Technetium 99m pertechnetate ($^{99m}\text{TcO}_4^-$) (with a concentration of > 370 MBq/0.1 mL) was injected into the graphite tong pot of the technetium gas generator (VITA Medical Limited, Australia) and heated in the enclosed chamber filled with argon gas. Technetium was released when the $^{99m}\text{TcO}_4^-$ evaporated. The mask was attached to the tube, and the patient was asked to inhale the technetium gas for 1 min. The patient was positioned lying on the back on the examination table, with arms over the head, so that the detector was placed as close to the chest as possible. The two detectors were rotated by 180° , and each detector acquired 32 projections, with 20 s for each projection. There were 64 projections in total. The acquisition matrix was 128×128 , with a zoom factor of 1. The patient was instructed to breathe as normally as possible during the process of acquiring the images to minimize the influence of respiratory movements. The ordered subsets expectation maximization (OSEM) method was used to reconstruct the image (8 subsets, 2 iterations), and the coronal, sagittal, horizontal and 3D model images were obtained.

Pulmonary perfusion tomography

Before the start of the imaging procedure, the patient was instructed to inhale oxygen with a flow rate of 2–4 L/min and an inhalation period of 5–10 min. The patient was positioned on his/her back on the examination table, with arms raised over the head so that the detector was as close to the chest as possible. A total of 185–370 MBq ^{99m}Tc -labeled macroaggregated albumin (MAA) (Beijing Atomic Hi-Tech Co., Ltd., China; radiochemical purification $\geq 95\%$) was slowly administered intravenously. The acquisition

parameters were the same as for pulmonary ventilation scintigraphy. Perfusion count-rate exceeded ventilation count-rate by a factor of 3 or more.

Low-dose CT scan

A low-dose CT scan was performed after the pulmonary perfusion tomography, with the patient remaining positioned on the same bed. The tube voltage was 110 kV, and the tube current was 25 mAs. The slice thickness was 5 mm. The parameters were collected, and the images were taken during breath-holding at the end of inspiration.

Image analysis

Quantitative analysis of images

All raw SPECT data were imported into the HERMES workstation (HERMES Medical Solutions AB, Sweden), where the V/Q ratio software provided in the system was used to reconstruct the perfusion and ventilation SPECT images, utilizing the low-dose CT images for attenuation correction. After the reconstruction, 10% of the maximum perfusion and ventilation imaging counts were selected as the threshold and set as the pulmonary boundary. After the radioactivity counts of perfusion and ventilation imaging images being normalized and corrected respectively, the respective radioactivity counts of each voxel were obtained, and then the radioactivity count ratio of perfusion and ventilation imaging images were obtained by dividing them.

The reconstructed perfusion/ventilation SPECT and low-dose CT images were imported into the system using the Hybrid 3D software. The boundary contours of the left and right lungs and the whole lung were automatically sketched on the lung CT to obtain the volume of interest (VOI). Areas exhibiting reverse mismatch on V/Q scintigraphy were manually delineated and removed. After processing, the software automatically generated the anatomic volume of the left and right lung based on CT images, the perfusion function volume of the left and right lung based on perfusion images, the ventilation function volume of the left and right lung based on ventilation images, and the volume of V/Q mismatch.

Semi-quantitative analysis of images

The V/Q scintigraphy was evaluated by two experienced nuclear medicine physicians who were blinded to the assessment. The number of lung segments with lung perfusion defects was recorded, and a semi-quantitative

analysis of the pulmonary perfusion images was done using the Meyer method (10). The PPDs% was calculated. The normal functional volume percentage were as follows: 18% in the upper lobe of the right lung, 12% in the middle lobe of the right lung, and 25% in the lower lobe of the right lung; 13% in the intrinsic segment of the left upper lobe, 12% in the lingula segment of the left lung, and 20% in the lower lobe of the left lung. Each lobe was assigned a coefficient based on the severity of its perfusion defect. The degree of perfusion defect from mild to severe was rated as 0.75, 0.50, 0.25, and 0, respectively, with 1 representing completely normal pulmonary perfusion. The actual perfusion percentage for each lobe was obtained by multiplying the normal perfusion percentage and the coefficient of each lobe, and these were added to obtain the perfusion percentage for the whole lung. PPDs%, which reflected the severity of the pulmonary vascular perfusion defect, was calculated as 1 minus the pulmonary perfusion percentage.

Statistical analysis

IBM SPSS 19.0 software was used for statistical analysis. Quantitative data that conformed to the normal distribution were represented as $\bar{x} \pm s$, while those that did not conform to the normal distribution were represented as $M (P_{25}, P_{75})$. The correlation between V/Q scintigraphy quantitative parameters, semi-quantitative parameters, and the visual analysis of patients with CTEPH was conducted using Pearson's correlation analysis. Paired *t*-test was used to compare the parameters before and after BPA in patients with CTEPH. Independent samples *t*-test was used to compare the pre- and post-operative quantitative PPDs% in the residual pulmonary hypertension group and the non-residual pulmonary hypertension group. A receiver operator characteristic (ROC) curve was used to calculate the area under the curve (AUC), and the cut-off values for the post-operative quantitative PPDs% and PPDs% against the pulmonary hypertension group were analyzed. The DeLong approach was used to test the difference in the AUC between the qualitative and semi-quantitative methods (MedCalc). Binary logistic regression model was used to analyze the related variables of residual pulmonary hypertension, and factors with a P value of <0.05 in the univariate test were included in the multivariate analysis to determine the final influencing factors of residual pulmonary hypertension. A P value of <0.05 was considered

statistically significant, and all P value was a two-sided test.

Results

Clinical data

The sample for this study consisted of a total of 51 patients diagnosed with CTEPH who underwent BPA between April 2018 and September 2020 and the patient selection flowchart is shown in *Figure 1*. There were 23 males and 28 females. The patients were aged 27 to 77 years, with

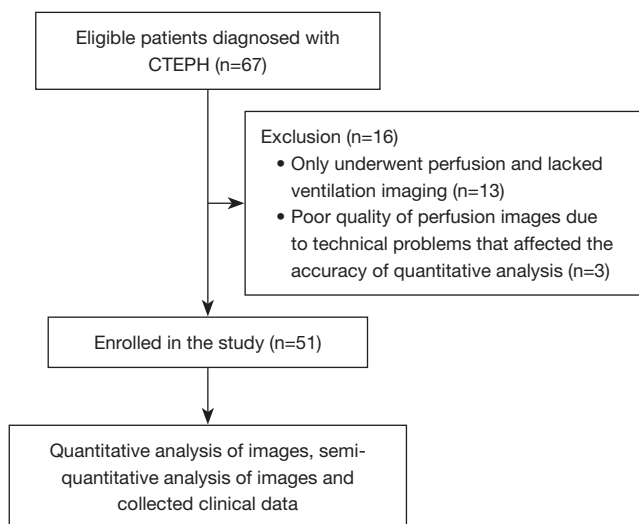


Figure 1 Patient selection flowchart. CTEPH, chronic thromboembolic pulmonary hypertension.

an average age of 55.1 ± 12.7 years. The average BMI was 24.2 ± 3.4 kg/m², and the average 6-minute walking distance (6MWD) was 379 ± 99 m. There were 7 patients with grade I cardiac function, 21 patients with grade II, 19 patients with grade III, and 4 patients with grade IV cardiac function as per the criteria of the New York Heart Association (NYHA) Functional Classification.

Among the 51 patients included in the study, 147 BPA treatments were performed and a total of 588 pulmonary arteries were treated, with an average of 4.0 pulmonary arteries treated per operation. Among them, 46 patients had BPA ≥ 2 times and were followed up for 12.0 ± 6.9 months. All patients with BPA were treated with anticoagulant therapy after the surgery. Among them, hemoptysis occurred in 8 cases (5.4%) after BPA, and reperfusion pulmonary edema (RPE) occurred in 4 cases (2.9%).

Correlation analysis of the quantitative and semi-quantitative results of pulmonary V/Q scintigraphy

Fifty-one patients underwent a total of 102 V/Q scintigraphy scans before and after surgery. The quantitative PPDs% were $(41.2 \pm 16.6)\%$, and the semi-quantitative PPDs% were $(35.4 \pm 16.0)\%$. The number of pulmonary segments with perfusion defects (NPSPDs) was 7.8 ± 2.6 . Correlation analysis showed a positive relationship between quantitative PPDs and semi-quantitative PPDs ($r=0.744$, $P<0.001$) and between quantitative PPDs and NPSPDs ($r=0.746$, $P<0.001$), as shown in *Figure 2*.

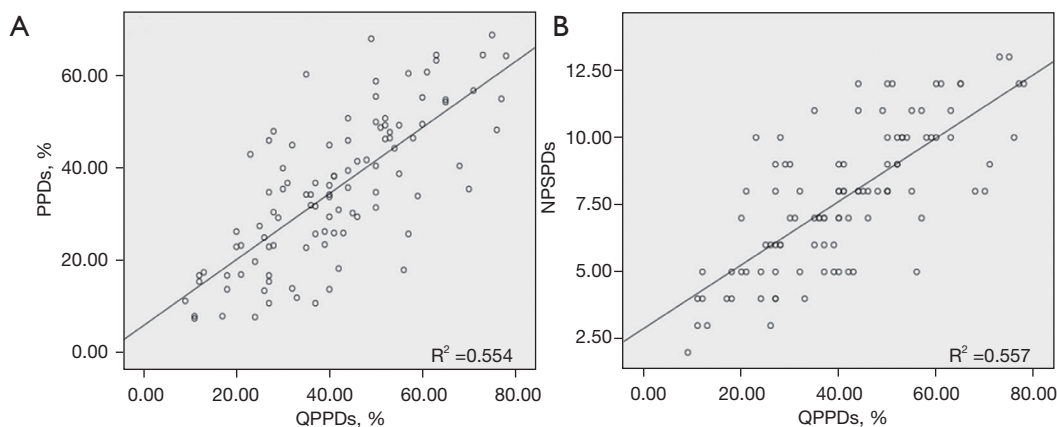


Figure 2 Correlation analysis of QPPDs% presented a positive correlation with PPDs% and NPSPDs (A: $r=0.744$, $P<0.001$; B: $r=0.746$, $P<0.001$). PPDs%, pulmonary perfusion defect percentage scores; NPSPDs, number of pulmonary segments with perfusion defects; QPPDs%, quantitative pulmonary perfusion defect percentage scores.

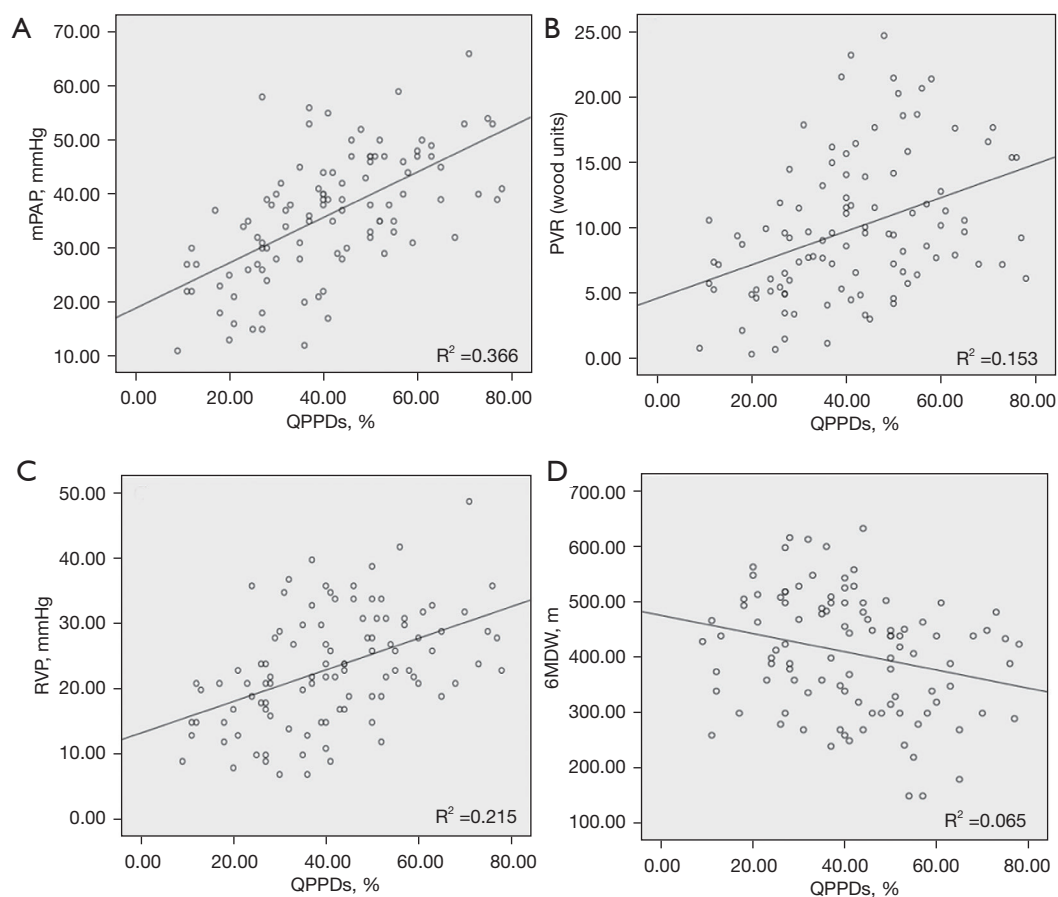


Figure 3 Correlation analysis of QPPDs% and hemodynamic indexes. PPDs% presented a positive correlation with mPAP, PVR, RVP (A: $r=0.605$, $P<0.001$; B: $r=0.391$, $P<0.001$; C: $r=0.464$, $P<0.001$), and a negative correlation with 6MWD (D: $r=-0.254$, $P=0.010$). QPPDs%, quantitative pulmonary perfusion defect percentage scores; PPDs%, pulmonary perfusion defect percentage scores; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; RVP, right ventricular pressure; 6MWD, 6-minute walking distance.

Correlation analysis of quantitative indexes of pulmonary V/Q scintigraphy and hemodynamic and clinical parameters

Based on the 102 V/Q scintigraphy data, right heart catheterization, and clinical parameters, the quantitative PPDs% was positively correlated with mPAP, PVR, and right ventricular pressure (RVP) ($r=0.605$, 0.391 , and 0.464 , respectively, all $P<0.001$) and negatively correlated with 6MWD ($r=-0.254$, $P=0.010$), as shown in *Figure 3*.

Comparison of preoperative and postoperative V/Q scintigraphy, clinical parameters, and hemodynamic parameters in patients with CTEPH

As seen in *Table 1*, the preoperative NPPDs, PPDs%, and

quantitative PPDs% were all decreased after the BPA (all $P<0.001$). Additionally, the preoperative value of 6MWD was 379 ± 99 m, which rose to 440 ± 108 m after the BPA ($t=-5.309$, $P<0.001$).

As shown in *Table 2*, all the pulmonary hemodynamic parameters of patients with CTEPH, including mPAP, PVR, and RVP after BPA, were significantly improved (all $P<0.001$).

Comparison of the quantitative parameters of V/Q scintigraphy patients with or without postoperative residual pulmonary hypertension

As shown in *Table 3*, out of the 51 patients with CTEPH, 27 had no residual pulmonary hypertension while the other 24 had residual pulmonary hypertension. The pre-

Table 1 Comparison of V/Q scintigraphy parameters and clinical parameters in CTEPH patients before and after BPA

Item	Before BPA	After BPA	t/Z value	P value
NPSPDs (n)	9.0±2.5	6.5±2.2	8.383	<0.001
PPDs%	43.1±15.4	27.6±12.5	7.898	<0.001
Quantitative PPDs (%)	49.0±15.6	33.5±13.9	11.249	<0.001
6MWD (m)	379±99	440±108	-5.309	<0.001
NT-proBNP (pg/mL)	503 [120–1,002]	226 [78–700]	-4.307	<0.001
Mixed venous oxygen saturation (%)	64.2±5.7	66.8±5.9	-3.644	0.001
Serum creatinine level (μmol/L)	77.1±16.2	77.1±15.2	-0.058	0.954
D-dimer (ng/mL)	0.55±0.64	0.42±0.45	1.79	0.08

Data are means ± SD or median [interquartile range]. V/Q, ventilation/perfusion; CTEPH, chronic thromboembolic pulmonary hypertension; BPA, balloon pulmonary angioplasty; NPSPDs, the number of pulmonary segments with perfusion defects; PPDs%, pulmonary perfusion defect percentage scores; 6MWD, 6-min walking distance; NT-proBNP, N-terminal pro B-type natriuretic peptide.

Table 2 Comparison of preoperative and postoperative hemodynamic parameters of BPA in patients with CTEPH

Item	Before BPA	After BPA	t/Z value	P value
mPAP (mmHg)	42.2±8.6	30.2±11.1	8.198	<0.001
PVR (Wood)	12.3±5.0	7.5±4.9	7.017	<0.001
RVP (mmHg)	26.8±8.0	19.9±8.1	6.499	<0.001
RAP (mmHg)	4.5±2.7	3.9±2.4	1.867	0.068
PAWP (mmHg)	9.1±2.8	9.5±2.6	-0.967	0.338

Data are mean ± standard deviation. 1 mmHg =0.133 kPa, 1 Wood =80 dns·s·cm⁻⁵. BPA, balloon pulmonary angioplasty; CTEPH, chronic thromboembolic pulmonary hypertension; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; RVP, right ventricular pressure; RAP, right atrial pressure; PAWP, pulmonary arteriole wedge pressure.

Table 3 Demographic and difference in quantitative PPDs% pre- and post-surgery after grouping based on whether there was residual pulmonary hypertension

Group	mPAP ≤30 mmHg (n=27)	mPAP >30 mmHg (n=24)	t/Z value	P value
Age (years)	51.9±14.6	58.8±9.2	2.031	0.048
Gender (male/female)	14/13	9/15		0.400
Quantitative PPDs% pre-surgery	44.0±13.8	54.7±15.7	2.599	0.012
Quantitative PPDs% post-surgery	26.3±11.0	41.5±12.5	4.647	<0.001

Data are means ± SD or numbers of subjects. PPDs%, quantitative pulmonary perfusion defect percentage scores; mPAP, mean pulmonary artery pressure.

and postoperative quantitative PPDs% in the residual pulmonary hypertension group were higher than those in the non-residual pulmonary hypertension group ($t=2.599$, $P=0.012$; $t=4.647$, $P<0.001$, respectively).

Difference in diagnostic efficacy of quantitative PPDs% and PPDs% in residual pulmonary hypertension

The cut-off values for the residual pulmonary hypertension group and the non-residual pulmonary hypertension group

Table 4 ROC curve analysis after residual pulmonary hypertension grouping

Item	Sensitivity (%)	Specificity (%)	Cut-off value	AUC (95% CI)	P value
QPPDs%	83.3	70.4	28.5	0.812 (0.697–0.927)	<0.001
PPDs%	62.5	81.5	31.0	0.754 (0.618–0.890)	0.002

There was no significant difference in the diagnostic efficacy between the quantitative PPDs% and PPDs% analyses (DeLong Z value =0.799, P=0.424). QPPDs%, quantitative pulmonary perfusion defect percentage scores; PPDs%, pulmonary perfusion defect percentage scores; ROC, receiver operating characteristic; AUC, areas under the curve; CI, confidence interval.

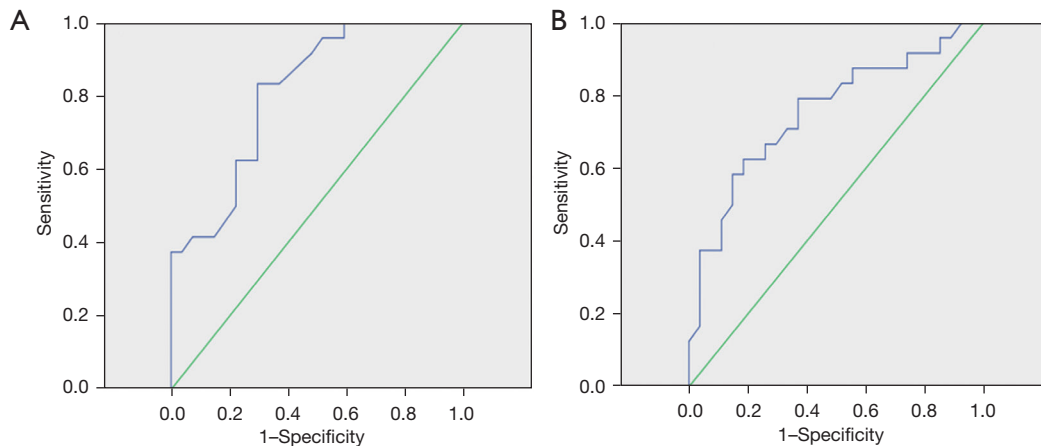


Figure 4 The ROC curves for QPPDs% and PPDs% diagnosis of residual pulmonary hypertension. The AUC were 0.812 (A) and 0.754 (B), respectively. The cut-off values of residual pulmonary hypertension evaluated by QPPDs% was 28.5% (A) and by PPDs% was 31.0% (B). There was no significant difference in the diagnostic efficacy between the quantitative PPDs% and PPDs% analyses (DeLong Z value =0.799, P=0.424). QPPDs%, quantitative pulmonary perfusion defect percentage scores; PPDs%, pulmonary perfusion defect percentage scores; ROC, receiver operating characteristic; AUC, areas under the curve.

were 28.5% and 31.0%, respectively. The sensitivity and specificity for the evaluation of quantitative PPDs% in residual pulmonary hypertension was 83.3% and 70.4%, respectively. The sensitivity and specificity for the evaluation of PPDs% in residual pulmonary hypertension was 62.5% and 81.5% respectively. There was no significant difference in the diagnostic efficacy between the quantitative PPDs% and PPDs% analyses (DeLong Z value =0.799, P=0.424; see Table 4 and Figure 4).

Analysis of factors influencing residual pulmonary hypertension after BPA

We analyzed gender, age, preoperative QPPDs%, BMI, 6WMD, cardiac function grade, mPAP, PVR, RVP, RAP, and other indicators using a single factor analysis. The results showed that preoperative QPPDs% (OR =1.052, 95% CI: 1.008–1.098, P=0.019), mPAP (OR =1.092, 95%

CI: 1.010–1.181, P=0.028), and RVP (OR =1.103, 95% CI: 1.011–1.203, P=0.027) were factors influencing residual pulmonary hypertension after BPA surgery. Multivariate regression analysis showed that QPPDs% was not a significant factor for residual pulmonary hypertension (OR =1.043, 95% CI: 0.995–1.094, P=0.079). See Figure 5 for typical patient images.

Discussion

Due to acute pulmonary embolism or repeated pulmonary artery thrombosis that cannot be completely dissolved, chronic inflammation, and thickening of the pulmonary artery intima, CTEPH eventually develops into chronic pulmonary embolism, culminating in pulmonary hypertension. The key findings of our study were as follows: (I) the quantitative analysis index QPPDs% of V/Q imaging correlated well with the traditional semi-

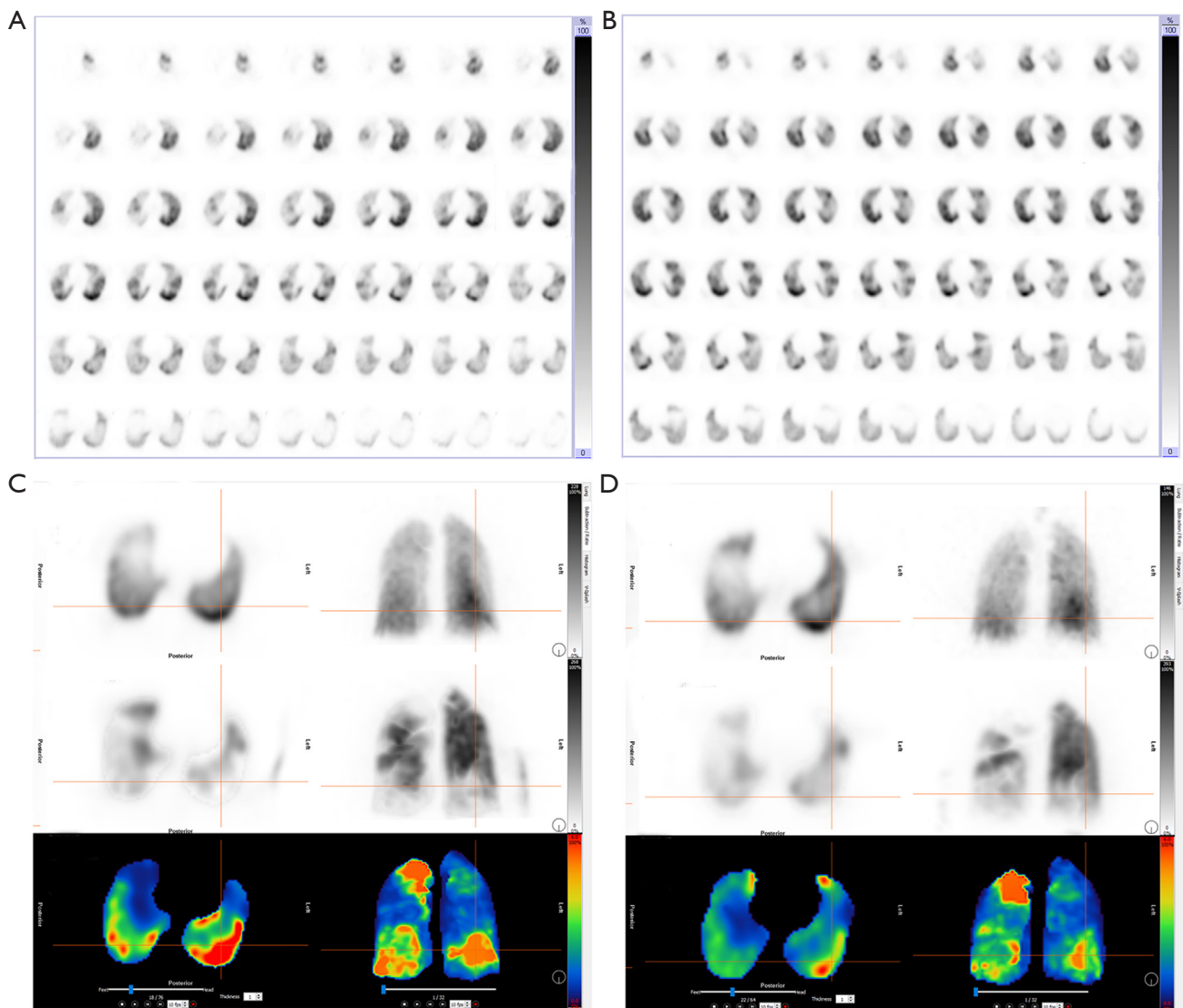


Figure 5 Preoperative and postoperative pulmonary perfusion tomography (A,B) images of a patient and 3D schematics (C,D) of preoperative and post-operative quantitative analysis software identifying areas of pulmonary ventilation/perfusion imaging mismatch. Comparison of pulmonary perfusion images at transverse position before and after balloon pulmonary angioplasty (A: before surgery; B: after surgery). The upper panel of (C) and (D) is the 3D display of the pulmonary ventilation scintigraphy, the middle panel of (C) and (D) is the 3D display of the pulmonary perfusion imaging, the lower panel of (C) and (D) is the 3D display of the perfusion/ventilation mismatch area automatically identified by HERMES software, and the red part in the image refers to the perfusion/ventilation mismatch area. The radioactivity distribution of the pulmonary ventilation scintigraphy is generally normal. Therefore, it is considered that the mismatch area is equivalent to the quantitative perfusion defects area in both lungs. It can be seen that the postoperative quantitative perfusion defects area (D) in both lungs is significantly smaller than that before surgery (C).

quantitative analysis for CTEPH image analysis, and quantitative analysis demonstrated obvious advantages because of its objectivity, simplicity of use, and high repeatability; (II) quantitative analysis index QPPDs% adequately reflected the pulmonary artery pressure and

clinical status of patients, and preoperative QPPDs% was found to be an independent risk factor for postoperative residual pulmonary hypertension. Quantitative analysis of V/Q imaging serves as a valuable indicator for predicting the prognosis and assessing the postoperative efficacy of

BPA in patients with CTEPH. Lack of timely diagnosis or treatment can result in delays, affect the prognosis, and eventually endanger life. Chronic thrombosis and increased pulmonary artery pressure lead to an imbalanced pulmonary ventilation and blood perfusion ratio, which is reflected in V/Q scintigraphy.

The guidelines for the diagnosis and treatment of pulmonary hypertension published by the ESC and the ERS in 2022 (8) recommend pulmonary V/Q scintigraphy as the preferred test for the diagnosis of CTEPH. The diagnosis of CTEPH can be safely ruled out with a negative V/Q scintigraphy result, with grade I recommendation and class C evidence. However, the conventional V/Q scintigraphy based on visual evaluation cannot be used for quantitative analysis as it lacks quantitative analysis indicators that can objectively reflect the severity of CTEPH. Furthermore, there are additional limitations in that it is inconvenient and challenging to standardize this method, making it difficult to establish an objective measure of the severity of CTEPH.

The quantitative PPDs% measured by SPECT/CT quantitative software can make up for these limitations and provide an effective method for quantitatively assessing the extent of disease involvement and severity of CTEPH in patients. The main advantages of quantitative analysis are its simplicity of operation, objectivity, and strong repeatability. Besides, subjective aspects such as the experience and personal ability of viewers have little impact on the results, giving it obvious advantages over semi-quantitative analyses.

In this study, we found that the quantitative analysis of PPDs% based on the software correlated well with the traditional semi-quantitative analysis of PPDs% and reflected pre- and post-operative hemodynamics and clinical status of patients with CTEPH, thereby demonstrating the feasibility of its use to analyze images in patients with CTEPH. The quantitative analysis indexes were more objective, reproducible, and not constrained by the professional competence of the reader, all of which contributed to their reliability. We found that the quantitative PPDs% was positively correlated with the hemodynamic indicators mPAP, PVR, and RVP and negatively correlated with 6MWD. Consistent with earlier research in China and elsewhere (11-13), the results showed that the quantitative analysis of V/Q scintigraphy could reflect the hemodynamics and clinical status of patients with CTEPH. Ultimately, patients will certainly benefit from the entire treatment process as the use of this non-invasive imaging means can reflect their postoperative hemodynamic status and thereby minimize the use of invasive pulmonary

angiography for routine reviews.

Drugs and surgery are currently the mainstays of treatment for CTEPH, with surgery being the only cure for the condition. The most common surgical treatments for CTEPH primarily include PEA, BPA, and lung transplantation or combined heart-lung transplantation. PEA surgery remains the preferred therapeutic choice for CTEPH at present. BPA is a percutaneous pulmonary artery interventional therapy developed in recent years, which can be considered for certain categories of patients such as some patients who are not eligible for PEA surgery or residual pulmonary hypertension after PEA surgery (13).

Currently, computed tomography pulmonary angiography (CTPA) and V/Q scintigraphy are the popular non-invasive imaging methods for evaluating the efficacy of BPA in patients with CTEPH. CTPA is a non-invasive approach with high resolution for accurately evaluating the patency of proximal pulmonary blood vessels. However, CTPA has a high radiation dosage and is therefore not suitable for repeated use. Due to its restricted capability in diagnosing peripheral small blood vessels, CTPA can often yield false negative results. Additionally, patients with a history of anaphylaxis, triggered by any allergen, face an elevated risk of hypersensitivity-type reactions to iodinated IV contrast.

In this study, the postoperative mPAP, PVR, RVP, N-terminal pro B-type natriuretic peptide (NT-proBNP), and mixed venous oxygen saturation substantially decreased compared with the preoperative levels, while the 6MWD was significantly higher than that before surgery. Our findings that BPA definitively improved the hemodynamic parameters and exercise tolerance in patients with CTEPH are in line with those of several previous studies (4,14-16).

A study conducted in 2021 revealed that the semi-quantitative PPDs% on V/Q scintigraphy correlated with hemodynamic measures after PEA. Further, preoperative PPDs% was identified as one of the main risk factors for residual pulmonary hypertension following PEA (7). Hashimoto *et al.* found that functional %volume of the lung calculated from the lung perfusion SPECT (FVL-LPSPECT) based on SPECT pulmonary perfusion imaging was significantly improved after BPA surgery, which, like the hemodynamic index, mPAP, and the clinical parameter, 6MWD, can reflect the postoperative improvement of patients (16). The authors of this study also found that the postoperative NPSPDs, PPDs%, and quantitative PPDs% after BPA measured using V/Q scintigraphy decreased as compared with the preoperative ones, indicating that

the semi-quantitative and quantitative parameters of V/Q scintigraphy both could effectively reflect the improvements that BPA surgery had on pulmonary blood perfusion. Our result pertaining to the evaluation of the postoperative efficacy of BPA is consistent with the findings of Wang *et al.* (14). On the basis of traditional semi-quantitative analysis, we found that among the hemodynamic measures, the quantitative PPDs% was predictive of post-BPA.

In this study, we further found that among 51 patients with CTEPH, 24 had residual pulmonary hypertension post-surgery, accounting for about 47.1% (24/51 cases), which is higher than the 25% incidence of postoperative residual pulmonary hypertension in patients with CTEPH reported in literature (17). A probable explanation is that all of the 51 patients with CTEPH included in this study were patients who underwent BPA surgery because they were found unsuitable for PEA. Most patients had distal vascular occlusion or were patients who have a low risk/benefit ratio for PEA treatment after evaluation, such as those with less severe pulmonary vascular disease but with significantly reduced blood flow or those with comorbidities that significantly increase the risk of surgery. The clinical profile of these patients is typically more complicated than that of patients who are candidates for PEA, resulting in a higher incidence of residual pulmonary hypertension (18). In one study, it was found that when the CT pulmonary angiography after PEA showed ≤ 2 residual pulmonary segments with perfusion defects, the proportion of residual pulmonary hypertension was significantly reduced (19).

In contrast to CTPA, which is premised on documenting obstruction of (larger) pulmonary vessels, V/Q scintigraphy is better suited to the identification of obstructive lesions in smaller, more peripheral blood vessels. In this study, the proportion of patients with preoperative quantitative PPDs% in the residual pulmonary hypertension group was significantly higher than that of the non-residual pulmonary hypertension group, indicating that the preoperative quantitative PPDs% could be a useful predictor of postoperative outcomes. As the preoperative quantitative PPDs% increases, the incidence of residual pulmonary hypertension after surgery is higher. In this study, the postoperative quantitative PPDs% in the residual pulmonary hypertension group was higher than that of the non-residual pulmonary hypertension group, indicating that the quantitative PPDs% in V/Q scintigraphy can objectively and non-invasively reflect the hemodynamic status in patients with CTEPH after BPA or can be used as an effective reference index to evaluate the efficacy of surgery.

There are some limitations to this study. This was a single-center retrospective study with a relatively small sample size. Further, multicenter studies with larger samples and prospective research data are needed to verify the utility of V/Q scintigraphy quantitative analysis in evaluating the efficacy of CTEPH in patients. Further studies are needed to explore the difference between quantitative analysis and conventional methods of analysis in the diagnosis of CTEPH, and to further validate its clinical utility. In addition, the measurement of quantitative analysis parameters of V/Q scintigraphy in this study was still at the level of the whole lungs and pulmonary lobes. In order to better address clinical needs, additional research is needed in the future to realize the quantitative analysis of V/Q scintigraphy at the lung segment level.

Conclusions

In this study, we found that it was possible to quantitatively assess the percentage of pulmonary V/Q mismatched defects in patients with CTEPH using SPECT pulmonary V/Q scintigraphy, and this quantification corresponded with the results of conventional visual analysis. Further, it adequately reflected the pulmonary artery pressure and clinical status in patients with CTEPH, indicating its definite utility in predicting residual pulmonary hypertension and evaluating the postoperative efficacy of BPA in patients with CTEPH.

Acknowledgments

The authors would like to acknowledge the hard and dedicated work of all the staff that implemented the intervention and evaluation components of the study.

Funding: This work was supported by the National Natural Science Foundation of China (Nos. 81970058 and 82241029), the Chinese Academy of Medical Sciences (CAMS) Innovation Fund for Medical Sciences (CIFMS) (Nos. 2021-I2M-1-049 and 2021-I2M-1-061), and the National High Level Hospital Clinical Research Funding (No. 2022-NHLHCRF-LX-01-01-02).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://qims.amegroups.com/article/view/10.21037/qims-23-1208/rc>

Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at <https://qims.amegroupp.com/article/view/10.21037/qims-23-1208/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was conducted with approval from the Ethics Committee of China-Japan Friendship Hospital (No. 2022-KY-085). Written informed consent was obtained from all participants.

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Cite this article as: Ma RZ, Jin CL, Yang S, Han PP, Li H, Liu JX, Wang JZ, Huang Q, Xie WM, Yang PR, Zhai ZG, Fu LP. Evaluating the efficacy of balloon pulmonary angioplasty using quantitative analysis of SPECT pulmonary ventilation/perfusion scintigraphy in patients with chronic thromboembolic pulmonary hypertension. *Quant Imaging Med Surg* 2024;14(3):2590-2602. doi: 10.21037/qims-23-1208