Original Article

Impact of pulmonary thromboendarterectomy on tricuspid regurgitation in patients with chronic thromboembolic pulmonary hypertension: a single-center prospective cohort experience

Yanan Zhen[1#], Jianbin Zhang[1#], Xiaopeng Liu[1], Guang Sun[1], Xia Zheng[1], Yongxin Han[1], Zhenguo Zhai[2], Aili Li[3], Fan Lin[1], Peng Liu[1]

[1]Department of Cardiovascular Surgery, [2]Department of Respiratory and Critical Care Medicine, Center of Respiratory Medicine, [3]Department of Ultrasonic Medicine, China-Japan Friendship Hospital, Beijing 100029, China

Contributions: (I) Conception and design: Y Zhen, J Zhang, P Liu; (II) Administrative support: P Liu; (III) Provision of study materials or patients: X Liu, G Sun; (IV) Collection and assembly of data: X Zheng, Y Han; (V) Data analysis and interpretation: Z Zhai, A Li; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Peng Liu. Department of Cardiovascular Surgery, China-Japan Friendship Hospital, Beijing 100029, China. Email: Liupeng6618@yeah.net.

Background: For patients with chronic thromboembolic pulmonary hypertension (CTEPH) and tricuspid regurgitation (TR) undergoing pulmonary thromboendarterectomy (PTE), whether concomitant tricuspid annuloplasty should be carried out is still controversial.

Methods: The study population consisted of 45 consecutive patients with CTEPH who were scheduled to undergo PTE. All PTE surgeries were conducted with a median sternotomy and deep hypothermia circulatory arrest (DHCA). We collected and analyzed the demographics, surgical details, echocardiographic parameters, and right heart catheterization (RHC) results of these patients.

Results: Moderate to severe TR was documented in 48.9% (22/45) of the patients pre-operatively and 4.4% (2/45) of the patients post-operatively. In patients with grade 4 TR, severity decreased to grade 2 in 8 and to grade 1 in 1. In patients with grade 3 TR, severity decreased to grade 2 in 9, to grade 1 in 3, and 1 remained unchanged. In patients with grade 2 TR, severity decreased to grade 1 in 8, and 15 remained unchanged. The post-operative TR velocity was decreased significantly (431.9±53.4 *vs.* 196.5±154.0, $P<0.001$). Pulmonary artery systolic pressure was 84±17 mmHg pre-operatively and decreased to 38±14 mmHg post-operatively ($P<0.001$). The pre and post-operative pulmonary diastolic pressure was 29±9 and 17±7 mmHg, respectively ($P<0.001$). The pre and post-operative mean pulmonary pressure was 48±10 and 24±9 mmHg, respectively ($P<0.001$). The pulmonary vascular resistance (PVR) (1,025.4±465.0 *vs.* 476.6±181.2 dynes·sec·cm^{-5}, $P<0.001$) and pulmonary artery wedge pressure (PAWP) (9±4 *vs.* 5±2 mmHg, $P<0.001$) decreased significantly after operation. The cardiac index (CI) increased significantly (1.9±0.5 *vs.* 2.3±0.4, $P=0.003$) after operation.

Conclusions: In conclusion, functional TR could be alleviated after PTE even in patients with high PVR. However, the long-term results need to be further investigated.

Keywords: Pulmonary thromboendarterectomy (PTE); chronic thromboembolic pulmonary hypertension (CTEPH); tricuspid regurgitation (TR)

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) develops in 0.56–3.8% of acute pulmonary embolism patients (1,2), and is characterized by intraluminal thrombus organization, fibrosis, and subsequent unobstructed small vessel remodeling (3). These characterizations result in pulmonary hypertension and progressive right heart failure (4).

Sustained pulmonary hypertension may lead to persistent right ventricle pressure overload, tricuspid annular dilatation, and regurgitation. Such functional tricuspid regurgitation (TR) also occurs in advanced mitral valve disease. For patients with severe functional TR caused by mitral valve disease and pulmonary hypertension, mitral valve surgery with simultaneous tricuspid annuloplasty is safe, effective, and associated with better long-term right-sided remodeling (5). However, for severe functional TR caused by CTEPH, some studies have shown there to be a significant improvement of tricuspid valve function after pulmonary thromboendarterectomy (PTE) without simultaneous tricuspid annuloplasty (6,7). But the enrolled patients were not very severe, the pulmonary vascular resistance (PVR) was relatively not very high. In China, most of the patients undergoing PTE surgery were advanced-stage CTEPH with >1,000 dynes·sec·cm^{-5} PVR, maybe because the awareness and understanding for the disease is still lacking.

For patients with relatively advanced-stage CTEPH and TR who undergo PTE, whether or not tricuspid annuloplasty should simultaneously be conducted is still controversial. Our study aimed to review our data of PTE without simultaneous tricuspid annuloplasty and evaluate the impacts on the changes in pulmonary artery pressure, TR, and right heart function.

Methods

Study population

The study population consisted of 45 consecutive patients with CTEPH who were scheduled to undergo PTE between December 2016 and June 2019 at our hospital. Patients who did not undergo echocardiography pre-operatively or within one month post-operatively were excluded. We collected and analyzed the demographics, surgical details, echocardiographic parameters, and right heart catheterization (RHC) results of these patients. The study procedures followed institutional guidelines and was approved by the institutional review board of our hospital. The enrolled patients have signed the informed consent for the use of the data. All of the data was collected prospectively. The report of this study followed Strengthening the Reporting of Cohort Studies (STROCSS) criteria.

Surgical procedure

All PTE surgeries were conducted with a median sternotomy and deep hypothermia circulatory arrest (DHCA). The technique of the procedure was in accordance with that reported by the university of California San Diego Health Center (8). Circulatory arrest time was strictly limited to 20 minutes; when more time was needed, we restarted the cardiopulmonary bypass (CPB) for 10 minutes, and then PTE was continued with a second circulatory arrest. After complete thromboendarterectomy, we sutured the pulmonary artery. We then rewarmed the patients, stopped CPB, and closed the incision. Patients were transferred to the intensive care unit (ICU) after the procedure.

Transthoracic echocardiographic parameters

Patients underwent transthoracic echocardiography before and within one month after PTE surgery. All echocardiograms were performed with the commercially available machine, EPIQ 7C (Philips, USA), with a 1.0–5.0 MHz linear array transducer S5-1. Patients were in left-lateral position, and II lead electrocardiogram was monitored.

Pulmonary artery diameter (PAD), pulmonary artery velocity (PAV), transverse diameter of right atrium (TDRA), transverse diameter of right ventricular basal segment, and transverse diameter of left ventricle were measured. The area of TR was determined in the apical four-chamber view according to the following criteria: grade 1 (trivial or no TR, 0< jet area <2 cm^2), grade 2 (mild TR, 2< jet area <4 cm^2), grade 3 (moderate TR, 4< jet area <10 cm^2), and grade 4 (severe TR, jet area >10 cm^2). All data was stored digitally for further analysis. Two independent investigators did the analysis and the investigators were blinded to whether the images were from before or after surgery. All measurements were in accordance with the guidelines for echocardiographic assessment (9).

RHC

RHC was performed for the included patients using

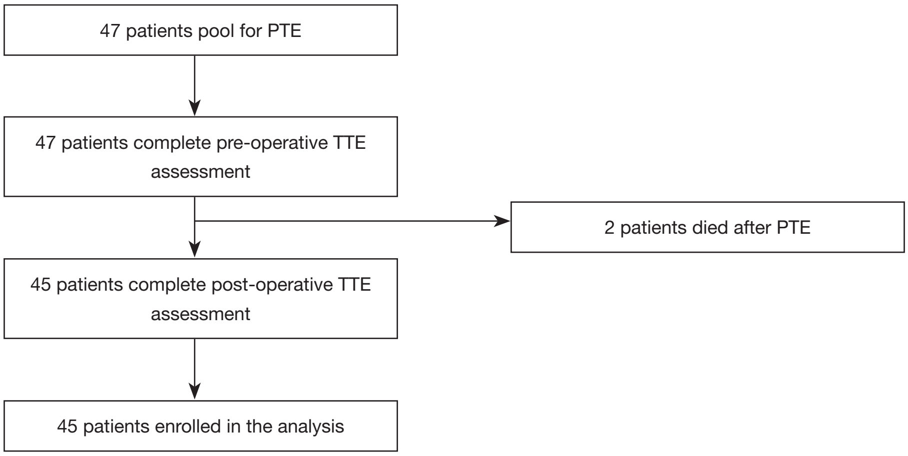

Figure 1 Flow diagram of the study. PTE, pulmonary thromboendarterectomy; TTE, transthoracic echocardiography.

a Swan-Ganz catheter through a femoral vein access. Pulmonary artery pressure (systolic, diastolic, and mean), PVR, pulmonary artery wedge pressure (PAWP), and cardiac index (CI) were measured with the commercially available machine Vigileo (Edward, USA).

Statistical analyses

Continuous variables were presented as mean ± SD, and discrete variables were presented as numbers and percentages. A two-sided paired student *t*-test was performed for continuous variables, and the chi-square test or Fisher's exact test was used to analyze discrete variables. Multivariate stepwise logistic regression analysis was applied to detect independent predictors of significant TR. The pre-operative and post-operative TR grade comparison was conducted using Wilcoxon rank-sum test. Spearman's correlation coefficient was used to evaluate the correlation between pre-operative, post-operative TR, and other variables. Data analysis was performed using SPSS version 23 (SPSS Inc., Chicago, IL, USA). A P value of <0.05 was considered statistically significant.

Table 1 Demographics and clinical features

Characteristics	No.
Age (years)	49±12
Gender (men/women)	28/17
BMI	23.7±3.7
Duration of symptomatic pulmonary hypertension (years)	5.0±4.6
NYHA classification (n)	
2	10
3	24
4	11
Commodities (n)	
Coronary artery disease	1
Deep venous thrombosis	20
Antiphospholipid syndrome	6
Hyperhomocysteinemia	6
Hereditary antithrombin III deficiency	1

BMI, body mass index; NYHA, New York Heart Association.

Results

Baseline characteristics

Finally, we enrolled 45 CTEPH patients (28 males; mean age 49±12 years) who received PTE surgery with DHCA (*Figure 1*). The duration of symptomatic pulmonary hypertension was 5.0±4.6 years. New York Heart Association (NYHA) functional classification was recorded for every patient. The demographics and clinical features are shown in *Table 1*.

RHC

The results of pre-operative and post-operative RHC are shown in *Table 2*. Pulmonary artery systolic pressure was 84±17 mmHg pre-operatively and decreased to 38±14

Table 2 The results of pre-operative and post-operative right heart catheterization

Variable	Pre-operative	Post-operative	P value
sPAP (mmHg)	84±17	38±14	<0.001
dPAP (mmHg)	29±9	17±7	<0.001
mPAP (mmHg)	48±10	24±9	<0.001
CI [L/(min·m^2)]	1.9±0.5	2.3±0.4	0.003
PVR (dynes·sec·cm^{-5})	1,025.4±465.0	476.6±181.2	<0.001
PAWP (mmHg)	9±4	5±2	<0.001

sPAP, systolic pulmonary artery pressure; dPAP, diastolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; CI, cardiac index; PVR, pulmonary vascular resistance; PAWP, pulmonary artery wedge pressure.

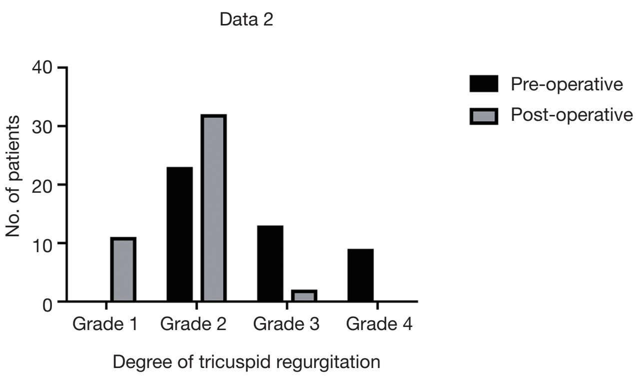

Figure 2 The pre-operative and post-operative severity of tricuspid regurgitation.

mmHg post-operatively (P<0.001). The pre and post-operative pulmonary diastolic pressure was 29±9 and 17±7 mmHg, respectively (P<0.001). The pre-operative and post-operative mean pulmonary pressure was 48±10 and 24±9 mmHg, respectively (P<0.001). The PVR (1,025.4±465.0 *vs.* 476.6±181.2 dynes·sec·cm^{-5}, P<0.001) and PAWP (9±4 *vs.* 5±2 mmHg, P<0.001) was decreased significantly after operation. CI was increased significantly [1.9±0.5 *vs.* 2.3±0.4 L/(min·m^2), P=0.003] after operation.

Severity of TR

Moderate to severe TR was documented in 48.9% (22/45) of patients pre-operatively and in 4.4% (2/45) of patients post-operatively (*Figure 2*). In patients with grade 4 TR, severity decreased to grade 2 in 8 and to grade 1 in 1. In patients with grade 3 TR, severity decreased to grade 2 in 9, to grade 1 in 3, and 1 remained unchanged. In patients with grade 2 TR, severity decreased to grade 1 in 8, and 15 remained unchanged. The post-operative TR velocity was decreased significantly (431.9±53.4 *vs.* 196.5±154.0 cm/sec, P<0.001).

Right ventricular and tricuspid morphology

The results of pre-operative and post-operative cardiac ultrasonography are shown in *Table 3*. The pre-operative PAD was 33.7±5.2 mm and decreased to 29.1±6.1 mm post-operatively (P=0.003). The pre-operative and post-operative PAV were 94.3±69.3 and 92.0±30.0 cm/sec, respectively (P=0.840). The TDRA was decreased from 50.4±9.1 to 41.4±6.5 mm (P<0.001).

Correlation of pre-operative, post-operative TR, and other variables

Pre-operative TR was correlated with mPAP (r=0.340, P=0.029), PVR (r=0.392, P=0.018), and TDRA (r=0.758, P<0.001). Post-operative TR has reversed correlation with post-operative CI (r=-0.298, P=0.047).

Discussion

CTEPH is a progressive pulmonary vascular disease. This disease is characterized by a direct organized embolic occlusion and the remodeling of larger pulmonary arteries. Later, small vessel disease is caused by unresolved thrombotic materials (10). Persistent pulmonary hypertension and right ventricle overload cause right ventricular hypertrophy, accompanied by tricuspid annular dilatation and subsequent functional TR (11). Menzel *et al.* (12) reported 89.7% CTEPH patients have moderate to severe TR while Thistlethwaite *et al.* (13) reported a mean TR of 3+ (TR jet filling more than 66% of the

Table 3 The results of pre-operative and post-operative cardiac ultrasonography

Variable	Pre-operative	Post-operative	P value
TR grade			<0.01
Grade 1	0	11	
Grade 2	23	32	
Grade 3	13	2	
Grade 4	9	0	
TR velocity (cm/sec)	431.9±53.4	196.5±154.0	<0.001
PAD (mm)	33.7±5.2	29.1±6.1	0.003
PAV (cm/sec)	94.3±69.3	92.0±30.0	0.840
TDRA (mm)	50.4±9.1	41.4±6.5	<0.001

TR, tricuspid regurgitation; PAD, pulmonary artery diameter; PAV, pulmonary artery velocity; TDRA, transverse diameter of the right atrium.

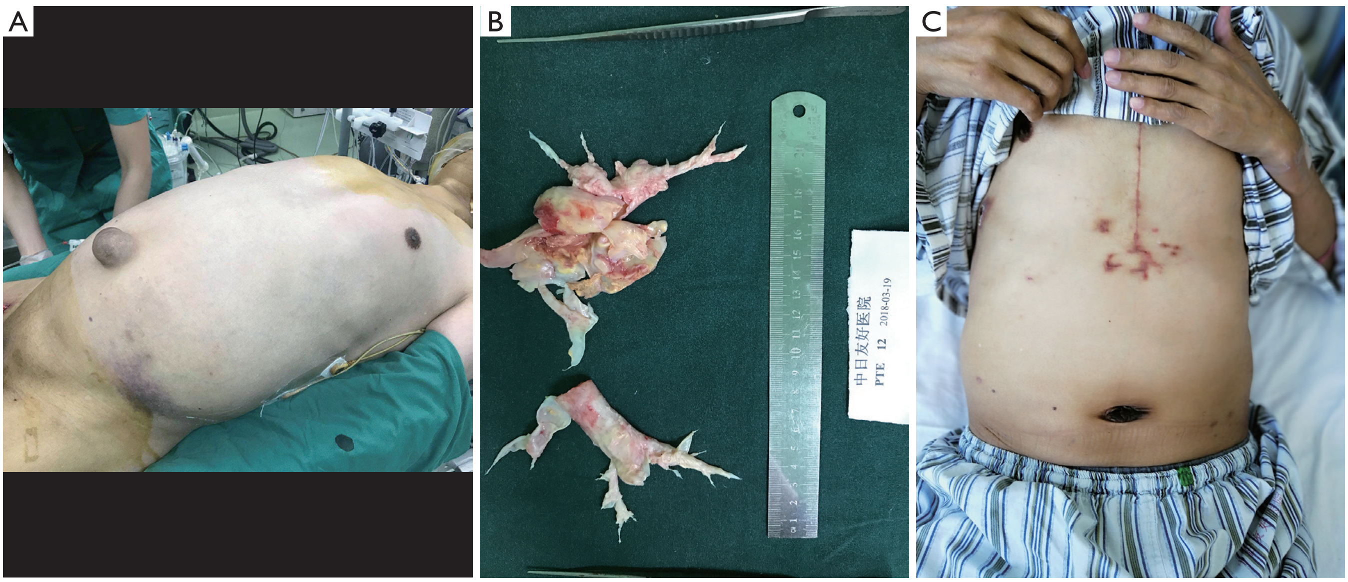

Figure 3 A typical case of CTEPH patient underwent PTE surgery. (A) Abdominal bulging in a patient with end-stage pulmonary hypertension; (B) thickened intima and organized thrombus in the pulmonary artery; (C) abdominal bulging was relieved after the operation. CTEPH, chronic thromboembolic pulmonary hypertension; PTE, pulmonary thromboendarterectomy.

right atrium). In our study, all patients presented with echocardiography that was proven as TR, among whom 22 were classified as moderate or severe. As reported, in end-stage CTEPH, hepatosplenomegaly and ascites may occur due to severe TR and right heart failure (*Figure 3*).

Functional TR was defined as the failure of leaflet coaptation without evidence of leaflet or subvalvular apparatus abnormalities (7), usually secondary to long-lasting pulmonary hypertension. Severe functional TR also usually develops in patients with left-sided valvular disease. In the past, surgeons have been conservative in performing tricuspid annuloplasty because TR could be reduced after left-sided surgery alone (14). However, more studies have shown that simultaneous tricuspid annuloplasty and left-sided heart surgery are associated with better right ventricle remodeling and long-term results (5,15-17). As for TR associated with CTEPH, there is a limited amount of data that has been published to illustrate whether simultaneous tricuspid annuloplasty should be performed in PTE surgery.

Sadeghi *et al.* (6) reported that 70% of patients showed a marked decrease in severe TR even without annuloplasty of a dilated tricuspid annulus, and the resolution of severe TR is related to the reduction of pulmonary hypertension. Menzel *et al.* (12) reported that 82.8% of moderate to severe TR in CTEPH patients could be alleviated after PTE without added tricuspid repair. Although the research did not specifically focus on whether tricuspid annuloplasty should be performed simultaneously, Li *et al.* (18) reported there to be a significant improvement in right ventricular dysfunction, including TR velocity and TR grade in patients receiving PTE after 2-year follow-up. Type 1 and type 2 CTEPH may be associated with better improvement of TR after PTE, in which the lesion location is more proximal (7,13). Different inspection modalities have demonstrated right ventricular reverse remodeling after PTE, and the improvement of TR and pulmonary artery compliance (19-23). Thistlethwaite *et al.* (24) reported three simultaneous PTE and tricuspid annuloplasty for patients with structural abnormality of tricuspid valve leaflet or chordae. They suggested that tricuspid valve repair should be performed for organic TR.

The largest case series was reported by Madani (8), the mean PVR of the patients in the study was 719 and 861.2 dynes·sec·cm^{-5} relatively. Maybe because the awareness and understanding of CTEPH is still lacking in China. Most of the patients received PTE were advanced-stage CTEPH with PVR >1,000 dynes·sec·cm^{-5}. In our study series, the mean PVR was 1,025.4 dynes·sec·cm^{-5}, all patients were functional TR. We did not conduct tricuspid annuloplasty even for severe TR. The results showed that the most severe TR could be quickly alleviated solely after PTE surgery. The current data suggested that tricuspid valve surgery need not be performed routinely in patients with CTEPH and secondary functional TR. However, long-term follow-up should be conducted to evaluate the right ventricular and tricuspid function.

There are several limitations to our study. First, the sample size is small, and it is only our preliminary experience. Second, the follow-up time is short; whether the improvement of TR will last should be further investigated.

Conclusions

In conclusion, functional TR could be alleviated after PTE even in patients with high PVR. However, the long-term results need to be further investigated.

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Footnote

Conflicts of Interest: 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 procedures followed institutional guidelines and was approved by the institutional review board of our hospital. The enrolled patients have signed the informed consent for the use of the data.

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