Percutaneous Transluminal Pulmonary Angioplasty for Takayasu's Arteritis-associated Pulmonary Hypertension: A Pilot Study

BRIEF TITLE: PTPA for TA-PH

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ABSTRACT

BACKGROUND Percutaneous transluminal pulmonary angioplasty (PTPA) is a treatment modality for chronic thromboembolic pulmonary hypertension, but whether it can be applied to Takayasu's arteritis-associated pulmonary hypertension (TA-PH), another chronic obstructive pulmonary vascular disease, remains unclear.

OBJECTIVES To investigate the efficacy and safety of PTPA for TA-PH.

METHODS Between January 1st, 2016 and December 31st, 2019, a total of 50 patients with TA-PH who completed the PTPA procedure (the PTPA group) and 21 patients who refused the PTPA procedure (the non-PTPA group) were prospectively enrolled in this cohort study. The primary outcome was all-cause mortality. The safety outcomes included PTPA procedure-related complications.

RESULTS Baseline characteristics and medical therapies were similar between the PTPA group and the non-PTPA group. During a mean follow-up time of 37 ± 14 months, deaths occurred in 3 patients (6.0%) in the PTPA group and 6 patients (28.6%) in the non-PTPA group, contributing to the 3-year survival rate of 93.7% in the PTPA group and 76.2% in the non-PTPA group ($p = 0.0096$ for log-rank test). The Cox regression model showed that PTPA was associated with a significantly reduced hazard of all-cause mortality in TA-PH patients (hazard ratio [95% CI], 0.18 [0.05 to 0.73]; $p = 0.017$). No peri-procedural death occurred. Severe complications requiring noninvasive positive pressure ventilation only occurred in 1 of total 150 sessions (0.7%).

CONCLUSIONS PTPA tended to be associated with a reduced risk of all-cause mortality with acceptable safety profiles and seemed to be a promising therapeutic option for TA-PH patients.

CONDENSED ABSTRACT

A total of 50 patients with TA-PH who completed the PTPA procedure (the PTPA group) and 21 patients who refused the PTPA procedure (the non-PTPA group) were enrolled. PTPA was associated with a significantly reduced hazard of all-cause mortality in TA-PH patients (hazard ratio [95% CI], 0.18 [0.05 to 0.73]; p = 0.017). No peri-procedural death occurred. Severe complications related to PTPA procedure requiring noninvasive positive pressure ventilation only occurred in 1 of total 150 sessions (0.7%). All these findings suggest that PTPA appears to be a promising therapeutic option for TA-PH patients.

KEY WORDS Takayasu's arteritis, pulmonary hypertension, percutaneous transluminal pulmonary angioplasty, efficacy, safety.

ABBREVIATIONS

6MWD = six-minute walking distance

CRP = C-reactive protein

ESR = erythrocyte sedimentation rate

PAP = pulmonary arterial pressure

PH = pulmonary hypertension

TA = Takayasu's arteritis

PTPA = percutaneous transluminal pulmonary angioplasty

PVR = pulmonary vascular resistance

RHC = right heart catheterization

INTRODUCTION

Takayasu's arteritis (TA) is a chronic inflammatory disease, predominantly affecting young women, characterized by granulomatous pan-arteritis of the aorta, its main branches and pulmonary arteries (1). The inflammatory process initially leads to thickening of the arterial wall and may result in stenosis, occlusion, dilation or aneurysm formation. Although TA is thought to have a worldwide distribution, it is more common in Asian and North African populations than in European or North American populations (2).

Pulmonary TA has been recognized as a subgroup of TA, characterized by the involvement of pulmonary arteries and pulmonary hypertension (PH) which can lead to right heart failure and premature death. Pulmonary artery involvement has been reported in 14% to 86% of TA patients (3-6), mimicking chronic thromboembolic pulmonary hypertension (CTEPH) and usually combined with systemic artery involvement (7-8). TA-associated PH (TA-PH) is now classified within group 4 PH (CTEPH and other pulmonary artery obstructions) in recent ESC guidelines (9). However, no specific treatment guidance for TA-PH is mentioned. In our recently reported nationwide registry (10), patients with TA-PH presented with female predominance and had severely compromised hemodynamics. The 1-, 3- and 5-year survival rates were 94.0%, 83.2% and 77.2%, worse than that in overall TA (11).

In recent years, percutaneous transluminal pulmonary angioplasty (PTPA) has emerged as an important treatment option for selective CTEPH patients who are not candidates for pulmonary endarterectomy surgery (12-13). Interventional experience with PTPA in patients with TA-PH has been limited to small case series (14-17). Despite variations in the interventional techniques described in these prior reports, the hemodynamic results found in these early reports were promising.

The aim of this study was to evaluate the potential efficacy and safety of the PTPA technique in a large cohort of consecutive patients with TA-PH.

METHODS

Study Population

From January 1st, 2016 to December 31st, 2019, all consecutive patients with definite diagnosis of TA-PH in our center were prospectively enrolled in this cohort study. Patients with TA-PH were diagnosed according to clinical presentations, serological tests (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP] levels), imaging features (transcatheter pulmonary angiography and CT aorta angiography) and invasive hemodynamic assessment (fulfilling the hemodynamic criteria for pre-capillary PH with mean pulmonary arterial pressure [PAP] ≥ 25 mm Hg, pulmonary artery wedge pressure [PAWP] ≤ 15 mm Hg and pulmonary vascular resistance [PVR] > 3 Wood U measured by right heart catheterization [RHC]). The diagnosis of TA was made according to the Ishikawa criteria modified by Sharma (18) and/or the 1990 American College of Rheumatology (19). Typical pulmonary artery impairment included stenosis, occlusion, luminal irregularity, or aneurysm on transcatheter pulmonary angiography. Other diseases causing pulmonary artery stenosis, including CTEPH, pulmonary sarcoidosis, fibrosing mediastinitis, pulmonary angiosarcoma, and congenital pulmonary artery stenosis, were excluded.

As an explorative treatment strategy for TA-PH, PTPA was recommended for all TA-PH patients in our center. Patients who completed the PTPA procedure (those still undergoing the PTPA procedure were excluded from analysis) were included as a PTPA group. Patients who refused the PTPA procedure were included as a non-PTPA group. Furthermore, we also included all TA patients without pulmonary artery involvement diagnosed at the same period in our hospital (the non-pulmonary artery involvement group) in the secondary analysis. The Ethics Committee of Peking Union Medical College Hospital approved the study (Approval number: JS-1233). Written informed consent was obtained from all patients in the PTPA group and the non-PTPA group. The data in the non-pulmonary artery involvement group were

retrospectively reviewed and anonymously presented, and the informed consent was therefore waived.

Data Collection

To reduce the influence of inflammation status on baseline hemodynamic and functional parameters, all baseline parameters in the PTPA group and the non-PTPA group were collected in the stable phase of TA. If patients were still in the acute phase of TA at the in-hospital assessment identified by sustained fever, elevated ESR or CRP levels, they would be treated under the guidance of experienced rheumatologists with glucocorticoids and immunosuppressants for at least 3 months prior to data collection. Hemodynamic parameters at baseline and re-evaluation were measured by RHC (Supplemental Methods). Other important clinical parameters, including WHO functional class, six-minute walking distance (6MWD) and N-terminal pro-brain natriuretic peptide (NT-proBNP), were collected at baseline and re-evaluation.

PTPA Procedure and Strategy

Pulmonary angiography was performed to identify the target vessels before the first PTPA session. In selected lesions, optical coherence tomography (OCT, C7 Dragonfly, St. Jude Medical, MA, USA) was used to visualize the intra-luminal morphology of the target vessels to optimize the interventional procedure (Supplemental Figure 1). The PTPA procedure is detailed in Supplemental Methods.

In order to restore pulmonary artery flow as much as possible, both proximal (pulmonary trunk, lobar and segmental branches) and distal lesions (sub-segmental branches) were treated. For proximal lesions, if balloon dilation could not achieve a satisfied pulmonary flow grade (= 3) and distal mean PAP (Pd) to proximal mean PAP (Pa) ratio measured by a pressure wire (PrimeWire Certus, St. Jude Medical, MA, USA) across the targeted lesion (Pd/Pa > 0.7), stent

implantation (Express LD, Express SD or Carotid WALLSTENT, Boston Scientific, MA, USA) would be evaluated and considered.

Medical Treatment

Anti-inflammatory therapies (glucocorticoids and immunosuppressants) and pulmonary arterial hypertension medications (endothelin receptor antagonists, phosphodiesterase type-5 inhibitors, and prostacyclin derivatives) were prescribed based on the judgement of a multidisciplinary clinic including specialists in rheumatology, cardiology, and interventional cardiology. PTPA procedures were performed in the stable phase of TA. If patients were in the acute phase of TA, they were treated with glucocorticoids and immunosuppressants for at least 3 months prior to PTPA consideration. After the PTPA procedure, all patients, regardless of ESR and CRP levels, were administrated with small sustained doses of glucocorticoids. For those patients underwent stent implantation, dual antiplatelet therapy (aspirin and clopidogrel) was prescribed for at least 6 months.

Outcomes and Definitions

Follow-up was performed until April 30th, 2021 at regular intervals. The primary outcome was all-cause mortality. The key secondary outcomes were changes from baseline to re-evaluation in PVR and 6MWD. Other secondary outcomes included changes from baseline to re-evaluation in mean PAP, mean right arterial pressure (RAP), cardiac index, WHO functional class, NT-proBNP and oxygen saturation. The safety outcomes were procedure-related complications, including pulmonary artery injury (defined as pooling or extravasation of contrast at the target lesion for PTPA caused by wire perforation, balloon over-dilation and high-pressure contrast injection), hemoptysis, lung injury (presence of lung opacities on chest radiograph and/or CT scan with/without hemoptysis, with/without hypoxemia), contrast induced nephropathy (defined as a peak increase in serum creatinine concentration of either ≥

25% or ≥ 0.5 mg/dl [44.2 μmol/l] over baseline during the first 72 hours post-procedure), and peri-procedural death (defined as death that occurred within 30 days of the procedure).

Statistical Analysis

The primary analysis was based on 71 patients to assess the differences in the primary and secondary outcomes between the PTPA group and the non-PTPA group whereas the secondary analysis was based on 394 patients to compare the PTPA group and the non-PTPA group against the non-pulmonary artery involvement group. The survival time was from diagnosis to the date of death, or to the censored date of April 30th, 2021. The survival rates were estimated with the Kaplan-Meier method and compared by log-rank test. Furthermore, two Cox regression models were constructed to calculate the unadjusted and adjusted hazard ratio of all-cause death: Model 1 had group as the only study variable and Model 2 was the Model 1 plus age and gender.

Continuous variables were expressed as mean with standard deviation (SD) and tested using the independent Student t-test or as median with interquartile range (IQR) and tested using the Mann-Whitney U test. Linear regression models were used to analyze the changes in continuous efficacy variables from baseline to re-evaluation, including mean PAP, mean RAP, PVR, cardiac index, arterial oxygen saturation (SaO_2), mixed venous oxygen saturation (SvO_2), NT-proBNP and 6MWD. The linear models included the group as the study variable, the baseline value of the efficacy variable, and age and sex as covariates, from which the adjusted least-squares mean differences between two groups and adjusted least-squares mean changes from baseline together with their 95% confidence intervals (CIs) were calculated. Binary variables were expressed as number with percentage and tested using the Chi-square test. The comparisons of efficacy differences between the PTPA group and the non-PTPA group in WHO functional class was performed using logistic regression model with the group as the

study variable and baseline value, age and sex as covariates, from which adjusted odds ratio of having an event between the PTPA group and the non-PTPA group with 95% CI was calculated.

All statistical analyses were performed using SPSS version 20 (SPSS Inc., Chicago, Illinois, USA) and the level of statistical significance was set at $p < 0.05$.

RESULTS

Study Population and Baseline Characteristics

From January 1st, 2016 to December 31st, 2019, a total of 562 patients were diagnosed as TA. Of the 490 TA patients who underwent CT pulmonary angiography, pulmonary artery involvement was excluded in 323 patients (the non-pulmonary artery involvement group). Of the 167 patients with pulmonary artery involvement, 82 patients were diagnosed as TA-PH. Among them, 61 patients received PTPA treatment and the other 21 refused PTPA treatment (the non-PTPA group). Of the 61 patients that received PTPA treatment, 50 patients who completed the PTPA procedure (including those patients who had severe complications and stopped the procedure) were included for further analysis (the PTPA group) (Figure 1). Baseline characteristics in the PTPA group and the non-PTPA group are shown in Table 1. A total of 14 patients, including 9 in the PTPA group and 5 in the non-PTPA group had elevated ESR and/or CRP at the first in-hospital assessment (Supplemental Table 1) and all were normal after anti-inflammatory therapies prior to baseline data collection. There were no significant differences in baseline characteristics and medical therapies between the PTPA group and the non-PTPA group. The baseline characteristics of patients in the non-pulmonary artery involvement group are shown in Supplemental Table 1.

PTPA Procedures

In the 150 PTPA sessions of those 50 patients in the PTPA group, a total of 360 lesions were treated. The mean number of PTPA sessions per patient, dilated lesions per session and dilated lesions per patient were 3.0 ± 1.2 sessions, 3.4 ± 1.8 lesions and 7.2 ± 4.1 lesions,

respectively. Locations and types of treated lesions were shown in Table 2. In proximal lesions, 14 stents were implanted in 10 patients. Detailed information on the location, size, efficacy and outcome of stents is shown in Supplemental Table 2. Representative images of PTPA efficacy are presented in Figure 2.

Primary Outcome

During the mean follow-up time of 37 ± 14 months (38 ± 12 months in the PTPA group and 35 ± 17 months in the non-PTPA group, p = 0.314), 3 patients (6.0%) in the PTPA group and 6 patients (28.6%) in the non-PTPA group died. In the PTPA group, one patient responded well to PTPA treatment and the PVR decreased from 9.8 to 4.9 Wood U after two PTPA sessions. However, she died of refractory respiratory failure after massive hemoptysis and secondary pulmonary infection 11 months after the second PTPA session. Another patient died of aggressive right heart failure 18 months after only one session of PTPA treatment due to poor pulmonary artery status (only occlusive and tortuous lesions, and a lack of good target vessels). The last patient had in-stent restenosis in both stents implanted in her fourth PTPA session. Although treated by repeated dilation with larger balloons at her fifth PTPA session, she died of aggressive right heart failure 6 months later. In the non-PTPA group, all 6 patients died of progressive right heart failure.

Although the demographic parameters, baseline hemodynamic parameters, exercise capacity and medical therapies were comparable between the PTPA group and the non-PTPA group, the 3-year survival rates were 93.7% (95% CI, 81.7 to 97.9) in the PTPA group, better than 76.2% (95% CI, 52.0 to 90.0) in the non-PTPA group (p = 0.0096 for log-rank test) (Figure 3). Furthermore, the Cox regression analysis (Model 2) showed that PTPA was associated with a significantly reduced hazard of all-cause mortality in TA-PH patients (hazard ratio [95% CI], 0.18 [0.05 to 0.73]; p = 0.017) (Table 3).

For patients in the non-pulmonary artery involvement group, 15 (4.6%) patients were lost to follow-up and 14 patients died during a mean follow-up time of 43 ± 17 months. The 1- and 3-year survival rates were 97.8% (95% CI, 95.5 to 98.9) and 96.5% (95% CI, 93.7 to 98.1) (Supplemental Figure 2). The Cox regression models revealed that patients in the non-PTPA group had a higher hazard of all-cause death than those in the non-pulmonary artery involvement group (hazard ratio [95% CI], 7.71 [2.93 to 20.27]; $p < 0.001$), and the hazards of the mortality were similar between the PTPA group and the non-pulmonary artery involvement group (hazard ratio [95% CI], 1.62 [0.45 to 5.83]; $p = 0.463$) (Supplemental Table 3).

Secondary Outcomes

Parameters at re-evaluation were not available in 5 patients in the non-PTPA group. Thus, efficacy analysis was conducted in all 50 patients in the PTPA group and 16 patients in the non-PTPA group, respectively. Duration from baseline to re-evaluation was 14 ± 10 months in the PTPA group and 12 ± 12 months in the non-PTPA group ($p = 0.497$). Detailed information of efficacy analysis is shown in Table 4. The adjusted least-squares mean difference between the PTPA group and the non-PTPA group was -3.4 Wood U (95% CI, -5.1 to -1.7; $p < 0.001$) in PVR and 83 meters (95% CI, 45 to 119; $p < 0.001$) in 6MWD. Furthermore, the adjusted odds of patients having WHO functional class III/IV significantly decreased in the PTPA group compared with the non-PTPA group (Odds Ratio [95% CI], 0.12 [0.02 to 0.71]; $p = 0.021$). Parameters at baseline and re-evaluation in both groups are shown in Supplemental Table 4.

Safety Outcomes

No peri-procedural deaths occurred in the current study. In total, PTPA procedure-related complications occurred in 28 of 150 PTPA sessions (18.7%). Pulmonary artery injury was the most common complication with an incidence of 18.0%. Among them, mild to moderate hemoptysis was observed in 8 (5.3%) sessions. All hemoptysis ceased after the procedure was temporarily stopped and additional oxygen therapy was supplied. Follow-up pulmonary

angiography at least one month later demonstrated spontaneous recovery (Figure 4) in 26 out of 27 (96.3%) vessels except for the one occurrence of restenosis after re-canalization of totally occluded right pulmonary artery. Lung injury occurred in 6 (4.0%) sessions and all were after the occurrence of hemoptysis during the procedure. Of them, only one patient was treated by noninvasive positive pressure ventilation therapy for 2 days. The other 5 patients were only treated with supplemental oxygen therapy (nasal cannula or venturi mask). All 6 patients with lung injury fully recovered in hospital. PTPA procedure-related complications are presented in Table 5.

Restenosis of Treated Lesions

Five cases of obvious vessel restenosis (5 out of 360 lesions, 1.4%) were found in 4 patients (4 out of 50 patients, 8.0%). Two patients experienced in-stent restenosis in 3 stents which were all treated by repeated dilation with a larger balloon. One patient developed restenosis of the right pulmonary artery 3 months after the first PTPA session. At the first session, the totally occluded right pulmonary artery was successfully re-canalized but with a dissection. The last patient experienced actively recurrent TA with an elevated ESR and level of CRP after she stopped the anti-inflammatory therapy due to pregnancy.

DISCUSSION

In this largest prospective cohort study of PTPA for the treatment of TA-PH with a long follow-up period, we revealed that PTPA tended to be associated with a reduced risk of all-cause mortality with acceptable safety profiles (Central Illustration). We also preliminarily investigated the PTPA strategy of treating not only the proximal lesions but also the distal lesions, and the combination of balloon dilation and stent implantation, in patients with TA-PH.

Strategy of PTPA in TA-PH Patients

The interventional strategies described in previous studies included balloon dilation alone or in combination with stent implantation. Furthermore, most studies predominantly focused on proximal stenosis lesions. In 2014, Dong et al. reported on the interventional therapy for 14 TA-PH patients (14). Out of the total 22 treated proximal lesions, 18 lesions were only dilated by balloon catheters and the other 4 lesions were treated with self-expandable stent implantation. More recently, Yanagisawa et al. first utilized the step-by-step strategy in 4 TA patients and 7 periphery pulmonary stenosis patients (15). A remarkable hemodynamic improvement was also noted. In the current study, the PTPA strategy combined stent implantation in proximal lesions and balloon dilation in distal lesions. A total of 14 balloon dilated stents ranging from 6 mm to 9 mm in diameter were implanted in 10 patients. Stent selection was dependent on the diameter, length, and morphology of the target lesion. Notably, to minimize the occurrence rate of in-stent restenosis, only proximal lesions should be considered and antiplatelet therapy after the procedure should be standardized. However, the strategy of stent implantation in TA-PH needs to be investigated in the further researches.

Efficacy of PTPA in TA-PH Patients

Although it is still controversial whether pulmonary arterial hypertension medications in patients with TA-PH are effective (9), they are empirically prescribed by physicians in the "real world" due to the lack of therapeutic options. Recently, a nationwide registry with 140 patients with TA-PH, diagnosed by RHC, observed significant improvement in hemodynamics after medications approved for PAH. However, no improvement in exercise capacity was observed (10). Thus, to reduce the confounding factors of medical therapies in efficacy analysis, we included a current control group, in which patients refused PTPA treatment and only received medical therapy. We firstly revealed that PTPA tended to be associated with a reduced all-cause mortality in patients with TA-PH. We also included TA patients without pulmonary artery involvement diagnosed at the same period, in which, the survival rates were similar with

previously reported studies on overall TA patients (20-21). Notably, the relatively high prevalence of pulmonary artery involvement (34.1%) and PH (16.7%) in our group might be owed to that our center is the national PH referral center in China with high volume of PH patients. Interestingly, our study revealed that although those TA patients combining with pulmonary artery involvement had a higher all-cause mortality than those in the non-pulmonary artery involvement group, these patients could benefit from PTPA and had a near similar mortality compared with those without pulmonary artery involvement. Although the patients were not randomized in our study, they were consecutively enrolled and the baseline characteristics and medical therapies were comparable between the PTPA group and the non-PTPA group, which contributed to the relative low confounding effects. Further randomized controlled trials are needed to confirm the finding.

However, the average hemodynamic improvements of PTPA observed in TA-PH patients (12 mm Hg decrease of mean PAP and 5.0 Wood U decrease of PVR) were less comparable to that shown in CTEPH patients (22) (19 mm Hg decrease of mean PAP and 6.2 Wood U decrease of PVR). The most important reason was that near all of our patients had some vessels left untreated because of technical difficulty. Occlusion lesions are common in TA-PH patients and contribute to extensive perfusion defects. As a result, it was difficult to normalize the pulmonary artery pressure in our PTPA group. On the other side, although we could not treat all lesions, especially for those complete occlusion lesions with no proximal stump, these patients might also benefit from successful treatment of other stenosis lesions, even if a small amount in some patients. Another reason was the limited dilation effects due to the hard and sometimes long stenosis in patients with TA-PH. The phenomenon of “balloon waist” during dilation was common and a Pd/Pa > 0.8 could only be achieved in minority vessels despite sufficient diameter balloons and high dilated pressure being used.

PTPA Procedure-related Complications in TA-PH Patients

The peri-procedural complications varied in different studies with different interventional strategies. In this study, pulmonary artery injury was the most common complication with an incidence of 18.0%, similar to the results in a previous Japanese case series (15). However, the incidence of pulmonary artery injury was much higher than that in patients with CTEPH treated with PTPA (12,23-25). Interestingly, the majority (23 out of 27, 85.2%) of pulmonary artery injuries occurred when dealing with occlusion lesions. It was hence thought that the most important reason for high frequency of pulmonary artery injury was due to a higher number of occlusion lesions in TA-PH compared to that in CTEPH. However, except for the mild to moderate hemoptysis with/without lung injury occurring in 8 sessions, most (70.4%) pulmonary artery injuries were asymptomatic and without further clinical sequelae. Pulmonary angiography during follow-up revealed complete self-healing (Figure 4) in most vessels. All of these findings suggested that pulmonary artery injury was the most frequent but not serious complication.

Restenosis of Treated Vessels

Restenosis of the treated vessels was another important concern which needed to be considered in patients with TA-PH. The incidence of restenosis after PTPA in patients with TA-PH was not well documented and still controversial. An early study reported 4 adult patients with multiple intralobar pulmonary arterial stenosis, 2 of whom experienced restenosis after balloon dilation and were then treated with stent implantation. One of the 4 patients had an elevated ESR and was treated by prednisone and methotrexate. However, she still developed restenosis after balloon dilation followed by stent neointima formation identified by later pathologic examination after lung transplantation (17). However, in a recent study, no restenosis was found after PTPA in 14 patients with TA (14). All patients in that study received glucocorticoids and immunosuppressants during the perioperative and follow-up. Additionally, the balloon dilation and stent implantation were only performed in proximal large vessels. In

the current study, we recorded only 5 restenosis events in 4 patients, including three in-stent restenosis. The potential explanations for the relative low restenosis rate in our cohort might be as following: First, previous studies have reported that interventional procedures performed at the stable stage and post-procedure anti-inflammatory therapies were significantly associated with a lower restenosis rate (26-27). In our study, all procedures were performed in the stable phase of TA and small sustained doses of glucocorticoids were administrated after procedure, regardless of ESR and CRP levels. Second, the vessels of aortic branches and pulmonary arteries were completely different. Although patients in our cohort presented with elevated pulmonary arterial pressure, the level of pressure was significantly lower than that in systemic circulation. Third, to reduce in-stent restenosis rate, stent implantation was only considered in those proximal lesions, which could not be fully dilated by balloons.

Study Limitations

The study has several limitations. First, patients in the PTPA group and the non-PTPA group were not randomized. However, the patients were consecutively enrolled, and the baseline characteristics and medical therapies were similar between the two groups, which contributed to the relatively low confounding effects. Further randomized controlled trials are needed to confirm the findings from this study. Second, this is a single cohort study, and the observed differences may be subject to possible confounders. Third, the follow-up time was not long enough to detect any late vessel restenosis and TA relapse.

CONCLUSIONS

PTPA tended to be associated with a reduced risk of all-cause mortality with acceptable safety profiles and seemed to be a promising therapeutic option for TA-PH patients. These findings need to be confirmed by randomized controlled trials.

CLINICAL PERSPECTIVES

CLINICAL COMPETENCIES: This is the largest prospective cohort study of PTPA for the treatment of TA-PH with a long follow-up period. The results suggested that PTPA tended to be associated with a reduced risk of all-cause mortality with acceptable safety profiles in patients with TA-PH.

TRANSLATIONAL OUTLOOK: Further randomized controlled trials are needed to confirm the findings from this study.

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FIGURE LEGENDS

FIGURE 1. Flow Chart.

Among the 562 diagnosed TA patients, 50 patients in the PTPA group and 21 patients in the non-PTPA group were included for the primary analysis and 323 patients in the non-pulmonary artery involvement group were included for the secondary analysis. PAI = pulmonary artery involvement; PAP = pulmonary arterial pressure; PH = pulmonary hypertension; PTPA = percutaneous transluminal pulmonary angioplasty; TA = Takayasu's arteritis.

FIGURE 2. Representative Images of PTPA Efficacy for Occlusion Lesions.

(A)(B) Case 1: (A) Occlusion in right pulmonary trunk and (B) recanalized. (C)(D) Case 2: (C) Occlusion in left pulmonary trunk and (D) recanalized. (E)(F) Case 3: (E) Occlusion in right pulmonary trunk and (F) recanalized. (G)(H) Case 4: (G) Occlusion in right pulmonary trunk and (H) recanalized. (I)(J) Case 5: (I) Occlusion in left lower lobe and (J) recanalized. (K)(L) Case 6: (K) Occlusion in left lower lobe and (L) recanalized. (M)(N) Case 7: (M) Occlusion in left lower lobe and (N) recanalized. (O)(P) Case 8: (O) Occlusion in right lower lobe and (P) recanalized. White arrows indicated occlusions before PTPA. Red arrowheads indicated recanalization after PTPA. PTPA = percutaneous transluminal pulmonary angioplasty.

FIGURE 3. Survival of TA-PH Patients in PTPA Group and Non-PTPA Group.

Three-year survival rates were 93.7% and 76.2% in the PTPA group and the non-PTPA group, respectively. The survival rate was significantly better in the PTPA group compared with the non-PTPA group. PTPA = percutaneous transluminal pulmonary angioplasty.

FIGURE 4. Representative Images of Pulmonary Artery Injury during PTPA.

(A) The occlusion lesion before PTPA (not visualized indicated by white arrow). (B) A partial dissection at the target lesion (indicated by red arrowheads) caused by the guide wire and selective angiography during re-canalizing of the occlusion lesion. (C) The re-canalized vessel in the dissection plane 6 months after first treatment of the vessel. (D) The re-canalized vessel after 2 additional PTPA sessions.

CENTRAL ILLUSTRATION. Overview of the Study Design and Main Result.

The consecutively diagnosed TA-PH patients received either PTPA plus medical therapy or medical therapy only. Baseline characteristics and medical therapy were similar between the PTPA group and the non-PTPA group. PTPA was associated with a significantly reduced all-cause mortality. PTPA = percutaneous transluminal pulmonary angioplasty; TA-PH = Takayasu's arteritis-associated pulmonary hypertension.

TABLE 1. Baseline Characteristics in the PTPA Group and Non-PTPA Group.

Characteristics	PTPA group (n = 50)	Non-PTPA group (n = 21)	p
Age at diagnosis, yrs	40 ± 14	40 ± 16	0.841
Female	41 (82.0)	15 (71.4)	0.498
History of tuberculosis infection	12 (24.0)	6 (28.6)	0.686
Systemic artery involvement			
Carotid artery	17 (34.0)	6 (28.6)	0.656
Subclavian artery	14 (28.0)	7 (33.3)	0.653
Aorta	16 (32.0)	11 (52.4)	0.106
Renal artery	8 (16.0)	6 (28.6)	0.374
Clinical parameters			
Erythrocyte sedimentation rate, mm/h	6 (3-11)	4 (2-9)	0.422
C-reactive protein, mg/l	3 (2-6)	4 (2-7)	0.071
NT-proBNP, pg/ml	704 (184-2886)	1313 (1053-1597)	0.510
WHO functional class III/IV	24 (48.0)	9 (42.9)	0.692
6MWD, meters	381 ± 126	402 ± 101	0.532
Hemodynamic parameters			
Mean RAP, mm Hg	8 ± 5	8 ± 5	0.923
Mean PAP, mm Hg	51 ± 13	54 ± 14	0.345
PAWP, mm Hg	10 ± 3	10 ± 4	0.966
Cardiac index, l/min/m^2	2.7 ± 0.8	2.7 ± 0.7	0.790

PVR, Wood U	10.3 ± 5.4	11.2 ± 6.4	0.584
SaO_2, %	89.6 ± 6.5	90.6 ± 4.6	0.541
SvO_2, %	62.2 ± 10.4	63.8 ± 7.6	0.551
Medical therapy			
PAH medications			0.814
Monotherapy	9 (18.0)	5 (23.8)	
Combination therapy	41 (82.0)	16 (76.2)	
Glucocorticoids	34 (68.0)	14 (66.7)	0.913
Immunosuppressants	14 (28.0)	5 (23.8)	0.716

Values are n (%), mean ± SD, or median (IQR). 6MWD = six-minute walking distance; NT-proBNP = N-terminal fragment of pro-brain natriuretic peptide; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PTPA = percutaneous transluminal pulmonary angioplasty; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SaO_2 = arterial oxygen saturation; SvO_2 = mixed venous oxygen saturation.

TABLE 2. PTPA Procedures.

	Total lesions	Treated lesions	Success rate, %
Number of lesions[a]	478	360	75.3
Location of lesions			
Pulmonary trunk	18 (3.8)	15 (4.2)	83.3
Lobar branches	51 (10.7)	42 (11.7)	82.4
Segmental branches	256 (53.5)	183 (50.8)	71.5
Sub-segmental branches	153 (32.0)	120 (33.3)	78.4
Type of lesions			
Occlusion lesions	178 (37.2)	72 (20.0)	40.4
Stenosis lesions	300 (62.8)	288 (80.0)	96.0

Values are n (%). PTPA = percutaneous transluminal pulmonary angioplasty. [a]Data are presented as count (n).

TABLE 3. Cox Regression Models for the Effect of PTPA on All-cause Mortality.

	HR (95% CI)	p
Model 1		
PTPA	0.19 (0.05-0.78)	0.021
Model 2		
PTPA	0.18 (0.05-0.73)	0.017
Age at diagnosis, yrs	1.02 (0.98-1.07)	0.404
Female	1.05 (0.21-5.22)	0.948

CI = confidential interval; HR = hazard ratio; PTPA = percutaneous transluminal pulmonary angioplasty.

TABLE 4. Summary Statistics and Results from Linear Regression Model Analysis of Changes from Baseline in Continuous Outcomes.

Parameters	Summary statistics		Linear regression model analysis[b]					
			Within group comparison				Between group comparison	
	Changes from baseline		Re-evaluation vs. Baseline in PTPA group		Re-evaluation vs. Baseline in non-PTPA group		PTPA group vs. non-PTPA group	
	PTPA group (n = 50)	Non-PTPA group (n = 16)	Adjusted difference (95% CI)	p	Adjusted difference (95% CI)	p	Adjusted difference (95% CI)	p
PVR, Wood U	-5.0 ± 5.0	-1.9 ± 3.4	-5.0 (-5.8,-4.1)	< 0.001	-1.6 (-3.2,0)	0.055	-3.4 (-5.1,-1.7)	< 0.001
6MWD, meters	94 ± 74	8 ± 44	94 (75,112)	< 0.001	11 (-22,44)	0.492	83 (45,119)	< 0.001
Mean PAP, mm Hg	-13 ± 15	2 ± 10	-12 (-16,-8)	< 0.001	0 (-7,7)	0.968	-12 (-19,-4)	0.003
Mean RAP, mm Hg	-1 ± 4	1 ± 3	0 (-1,1)	0.838	1 (-1,3)	0.188	-1 (-3,1)	0.178
Cardiac index, l/min/m^2	0.4 ± 0.7	0.2 ± 0.7	0.4 (0.2,0.6)	< 0.001	0 (-0.4,0.4)	0.976	0.4 (0.01,0.8)	0.047
SaO_2, %	3.5 ± 7.0	0 ± 2.9	3.5 (2.4,4.7)	< 0.001	2.9 (0.8,5.0)	0.008	0.6 (-1.6,2.9)	0.582

SvO_2, %	7.7 ± 8.1	1.6 ± 3.5	8.2 (6.6,9.8)	< 0.001	3.5 (0.3,6.7)	0.034	4.7 (1.5,8.1)	0.007
NT-proBNP, pg/ml[a]	-1.3 ± 1.3	-1.2 ± 1.3	-1.3 (-1.7,-0.9)	< 0.001	-1.0 (-1.6,-0.4)	0.002	-0.3 (-1.0,0.3)	0.328

Values are mean ± SD. 6MWD = six-minute walking distance; NT-proBNP = N-terminal fragment of pro-brain natriuretic peptide; PAP = pulmonary arterial pressure; PTPA = percutaneous transluminal pulmonary angioplasty; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SaO_2 = arterial oxygen saturation; SvO_2 = mixed venous oxygen saturation. [a]NT-proBNP was log-transformed. [b]Baseline value, age and gender were introduced as covariates in the linear regression models.

TABLE 5. PTPA Procedure-related Complications.	
Complications	Total PTPA sessions (n = 150)
Overall complications	28 (18.7)
Peri-procedural death	0 (0)
Pulmonary artery injury	27 (18.0)
Without hemoptysis	19 (12.7)
With hemoptysis	8 (5.3)
Lung injury	6 (4.0)
Non-invasive positive pressure ventilation	1 (0.7)
Contrast induced nephropathy	1 (0.7)
Allergic reaction to contrast	0 (0)
Values are n (%). PTPA = percutaneous transluminal pulmonary angioplasty.	