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RESEARCH ARTICLE

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Better efficacy of sequential combination with balloon pulmonary angioplasty after long-term riociguat for patients with inoperable chronic thromboembolic pulmonary hypertension

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Abstract

The present study aimed to evaluate the efficacy of long-term riociguat sequentially combined with balloon pulmonary angioplasty (BPA) for patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH). Eight inoperable CTEPH patients were enrolled in this study, who have been administrated riociguat 2.5 mg three times daily for about 8 years, then underwent several sessions of BPA procedures. Data are prospectively collected to evaluate clinical outcomes, hemodynamics, exercise capacity, and right heart size and function by echocardiography at baseline, 8 years after riociguat, and 3 months after the final BPA. Eight patients (mean age 54.9 ± 11.4 years) were treated with riociguat 2.5 mg three times daily for 95.0 ± 10.7 months. Cardiac index (CI) (1.5 ± 0.5 L/min/m^2 to 2.4 ± 0.6 L/min/m^2, $p = 0.005$), 6 min walking distance (6MWD) (329.6 ± 87.5 m to 418.1 ± 75.8 m, $p = 0.016$), and pulmonary vascular resistance (PVR) (1336.9 ± 320.2 dyn·s·cm^{-5} to 815.4 ± 195.6 dyn·s·cm^{-5}, $p = 0.008$) were significant improvement after riociguat treatment. Mean 4.1 ± 1.6 additional combinational BPA sessions and mean 18.8 ± 8.1 balloon dilations were performed. Mean pulmonary artery pressure (54.1 ± 11.1 mmHg to 33.6 ± 7.7 mmHg, $p = 0.002$) and PVR (815.4 ± 195.6 dyn·s·cm^{-5} to 428.3 ± 151.2 dyn·s·cm^{-5}, $p < 0.001$) were further decreased. CI (2.4 ± 0.6 L/min/m^2 to 2.7 ± 0.7 L/min/m^2, $p = 0.028$) and 6MWD (418.1 ± 75.8 m to 455.7 ± 100.0 m, $p = 0.038$) were increased significantly. After long-term riociguat

Abbreviations: 6MWD, 6 min walking distance; BPA, balloon pulmonary angioplasty; CI, cardiac index; CO, cardiac output; CTEPH, chronic thromboembolic pulmonary hypertension; FC, functional class; IVC, inferior vena cava; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; MPAD, main pulmonary artery diameter; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RA, right atrial; RV, right ventricular; RV FAC, right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion; TRPD, tricuspid regurgitation pressure difference; WHO, World Health Organization.

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treatment, sequential combination with BPA delivered considerably incremental benefits on exercise capacity and pulmonary hemodynamics, as well as right heart size and function of technically inoperable CTEPH patients.

KEYWORDS
balloon pulmonary angioplasty, chronic thromboembolic pulmonary hypertension, echocardiography, pulmonary hypertension, riociguat

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH), as the fourth group of pulmonary hypertension (PH), is characterized by organized thrombi, pulmonary arteries remodeling resulting in stenosis or occlusion, progressive pulmonary pressure, and finally leading to right heart failure, and carries a poor prognosis.[1] According to the 2015 ERS/ESC PH Guidelines, pulmonary endarterectomy (PEA) is a potentially curative surgical treatment option for the majority of patients, and has become the preferred therapeutic strategy for CTEPH.[2] However, PEA is only suitable for those patients whose lesions mainly located in the main, lobar and segmental pulmonary arteries.[3] Approximately 40% of CTEPH patients with peripheral pulmonary arteries obstruction and those with comorbidities have been deemed unfavorable risk/benefit ratio are not amenable to the PEA. Moreover, studies have found that there is up to 35% residual PH after PEA.[4]

Microvascular arteriopathy in CTEPH provides a theoretical basis for the application of PH-targeted medications. Several clinical trials have justified the efficacy of PH-targeted medical therapy in CTEPH with patients who are technically inoperable or postoperative persistent PH or have an unacceptable risk/benefit ratio for PEA.[5-8] Riociguat, a stimulator of soluble guanylate cyclase, which was shown to significantly improve patient's exercise capacity, pulmonary vascular resistance (PVR), the N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) levels, and had an estimated 1-year survival of 97% in the CHEST trials, is the first drug approved for inoperable CTEPH or persistent/recurrent CTEPH after PEA.[9-10]

Balloon pulmonary angioplasty (BPA), also known as percutaneous transluminal pulmonary angioplasty, is a currently established alternative therapy for inoperable patients with CTEPH. It was first covered in a case report in 1988, which showed positive results in mean pulmonary artery pressure (mPAP) and pulmonary perfusion scan.[11] It wasn't until 2012 that BPA was shown to safety and efficacy with a refined approach using smaller size balloon for fewer lobes per procedure for nonoperable CTEPH patients.[12] With growing worldwide experience with BPA, its role in CTEPH treatment have evolved at a rapid pace, and will be updated in the next guidelines as the intervention.[13] The 2015 European Guideline recommends that riociguat or BPA is considered in patients who have been classified as persistent/recurrent CTEPH after PEA or who are technically nonoperable or carry an unfavorable risk:benefits ratio for PEA.[2] The use of targeted-PH medicine to decrease PH before BPA procedure is common. However, there is little data to show further benefit for the CTEPH patients who take long-term riociguat undergoing BPA procedures.

Therefore, the present study aimed to evaluate the efficacy of long-term riociguat and sequential combination with BPA procedure for the inoperable CTEPH patients, and to discover whether BPA had an additional benefit for CTEPH patients who were administrated long-term riociguat. Our PH center has been participated in the multicenter international CHEST study. Several participants have been taking riociguat for about 8 years, which creating conditions for the implementation of the study.

METHODS

Patient selection

This is a single-center, observational study. Eight patients, who participated in the international multicenter CHEST study from September 2009 to May 2020, were enrolled in the study. All these patients, who were technically inoperable CTEPH, have been receiving long-term riociguat of 2.5 mg three times daily for almost 8 years and sequentially combined with at least two BPA procedures at our center. The study was approved by the ethics committee of Beijing Chaoyang Hospital, Capital Medical University (NO.2019-KE-377). All the patients provided their written informed consents. The study is registered on ClinicalTrials.gov (NCT04326777).

Data collection

Data were collected at three time points: before riociguat (baseline), before the first BPA, and at least 3 months

after the final BPA, including medical history, age, gender, body mass index, comorbidities, NT-proBNP, WHO FC, 6MWD, and hemodynamic parameters measured by Swan-Ganz right heart catheterization and echocardiographic parameters. In terms of BPA, the frequency of BPA procedures, the number of dilated vessels and complications were documented.

Targeted medical therapy

Patients enrolled in the international CHEST study, were administrated riociguat adjusted from a starting dose of 1 mg three times daily up to a maximum of 2.5 mg three times daily before BPA depending on the patient's systolic blood pressure, side-effects and progressive CTEPH. The dose was not changed throughout the study.

BPA

BPA was step-wise performed by two skilled interventional radiologists. A conventional femoral venipuncture was made. A 6 F JR- or JL-guided catheter (Launcher, Cordis) was introduced to the target vessel by a guidewire. A 2-mm balloon was used for the first vascular expansion. Then the balloon was gradually inflated to a size no larger than the target vessel. In case of complications during the BPA procedure, the treatment was immediately made, including seal of the injury using a balloon catheter, bioabsorbable gelatin or metallic coil and the insertion of covered stents. Patients were discharged at least 1 day after each BPA session to observe refusion pulmonary edema and contrast kidney injury. Warfarin was routinely used at time of diagnosis of CTEPH and during all courses, the international normalized ratio was maintained between 2.0 and 3.0. Diuretics and vasoactive agents were given according to preoperative right heart function. For patients with estimated Glomerular Filtration Rate < 60 mL/(min*1.73 m^2), 0.9% sodium chloride injection was provided to hydrate at the rate of 0.5−1 mL/kg/h before BPA procedure to avoid the occurrence of postoperative acute contrast kidney injury. Most patients need several series of BPA procedures and each series of procedure includes two sessions. The odd-numbered intervals between the BPA sessions were no less than 1 month, and the even-numbered intervals were no less than 2 weeks. The number of BPA sessions, the total number of dilated vessels (sub-segmental level), and number of dilated vessels per session were collected. The treatment endpoint of this study is no less than 20% decrease in PVR level compared to before BPA procedures.

Statistical analysis

Continuous variables are expressed as mean ± SD or as median and interquartile range. Categorical variables are documented as numbers and percentages. Friedman test is used for variables not conforming to normal distribution or categorical variables. The data measured at the different time points are compared using one-way repeated measure analysis of variance. All statistical tests were performed with SPSS software version 24.0 (SPSS Inc.). All charts were made using GraphPad Prism 8.0 (GraphPad Software). $p < 0.05$ was considered to be statistically significant.

RESULTS

Patient characteristics

All the eight patients are technically inoperable CTEPH, the characteristics of the patients' baseline data are demonstrated in Table 1. From September 2009 to May 2020, 8 patients (mean age 54.9 ± 11.4 years, 7 women, 1 man) who enrolled in CHEST-1 and CHEST-2 have been administrated riociguat 2.5 mg three times daily for 95.0 ± 10.7 months. The

TABLE 1 Patients' Characteristics at Baseline.

Variables	Baseline
Subjects (*n*)	8
Age (years)	54.9 ± 11.4
Female, *n* (%)	7 (87.5)
BMI (kg/m^2)	25.9 ± 2.6
Previous VTE, *n* (%)	5 (62.5)
Period from symptoms to CTEPH diagnosis (months)	15.0 (12.0-36.0)
Period of riociguat used (months)	95.0 ± 10.7
Vitamin K antagonist	8 (100)
Comorbidities, *n* (%)	5 (62.5)
Hypertension	2 (25.0)
Hyperlipidemia	1 (12.5)
Type 2 diabetes	1 (12.5)
Gynecological disease	1 (12.5)
Lower limb vascular disease	1 (12.5)

Note: Data are expressed as mean ± SD or number(percentage) or median with first and third quartiles (Q1:Q3).

Abbreviations: BMI, body mass index; BPA, balloon pulmonary angioplasty; CTEPH, chronic thromboembolic pulmonary hypertension; VTE, venous thrombus embolism.

period from the first symptoms to diagnosis of CTEPH was 15.0 months (Q1-Q3: 12.0–36.0 months, $n = 8$). All patients have been on warfarin to maintain anticoagulant therapy. During the CHEST-2 study, sequential combination with BPA procedures were implemented. The distribution of chronic thromboembolic materials did not change at baseline and pre-BPA by pulmonary angiography after effective anticoagulants.

The outcomes of targeted medicine and BPA procedure

The exercise capacity, hemodynamics, serum NT-proBNP level at baseline, before BPA (riociguat treatment) and after final BPA (BPA treatment) are presented in Table 2 and Figures 1a–f. There were improvements in 6WMD (329.6 ± 87.5 m to 455.7 ± 100.0 m, $p = 0.003$), WHO FC (improvement in seven patients) and NT-proBNP level (1650.0 ± 1136.3 pg/mL to 169.5 (49.25–603.0) pg/mL, $p = 0.003$). The hemodynamics showed improvements in mPAP (51.9 ± 6.3 mmHg to 33.6 ± 7.7 mmHg, $p = 0.011$), CO (2.8 ± 0.9 L/min to 4.6 ± 1.3 L/min, $p = 0.008$), CI (1.5 ± 0.5 L/min/m^2 to 2.7 ± 0.7 L/min/m^2, $p = 0.005$), PVR (1336.9 ± 320.2 dyn·s·cm^{-5} to 428.3 ± 51.2 dyn·s·cm^{-5}, $p = 0.001$), SvO_2 ($55.6 \pm 11.7\%$ to $65.3 \pm 3.6\%$, $p = 0.056$). Certain parameters indicating right heart size and function by echocardiography are shown in Table 3, comparison with these data at baseline were also improved.

The study illuminates that PH-targeted medical therapy has positive benefits on CTEPH patients. There are increases in 6MWD of almost 100 m (329.6 ± 87.5 m to 418.1 ± 75.8 m, $p = 0.016$). WHO FC are improved by one class in 6 of 8 patients and two classes in 1 of 8 patients ($p = 0.011$). NT-proBNP values are noted from 1650.0 ± 1136.3 pg/mL to 440.5(257.5-1522.75) pg/mL, but no statistical different. Hemodynamics assessment showed significant improvement in CO of 1.3 L/min (2.8 ± 0.9 L/min to 4.1 ± 1.1 L/min, $p = 0.015$), and in CI of 0.9 L/min/m^2 (1.5 ± 0.5 L/min/m^2 to 2.4 ± 0.6 L/min/m^2, $p = 0.005$). Meanwhile, riociguat administration makes the decline of PVR by 521.5 dyn·s·cm^{-5} (1336.9 ± 320.2 dyn·s·cm^{-5} to 815.4 ± 195.6 dyn·s·cm^{-5}, $p = 0.008$). The CTEPH patients who received riociguat achieve not only significant improvements in 6MWD、CO、CI but also a significant reduction in PVR. However, the pulmonary

TABLE 2 Functional capacity, hemodynamics at baseline, before BPA and after BPA.

Variables ($n = 8$)	Baseline	Before BPA	After BPA	p
Exercise capacity				
WHO FC (n)				
I/II/III/IV	0/2/6/0	3/4/1/0	4/3/1/0	0.761
6MWD (m)	329.6 ± 87.5	418.1 ± 75.8*	455.7 ± 100.0**	<0.001
NT-proBNP(pg/mL)	1650.0 ± 1136.3	440.5 (257.5-1522.75)	169.5 (49.25-603.0)	0.005
Hemodynamics				
RAP, mmHg	10.0 ± 5.5	8.8 ± 2.8	6.9 ± 2.3	0.169
sPAP, mmHg	92.6 ± 11.4	90.8 ± 19.0	54.3 ± 12.6**	0.001
dPAP, mmHg	31.8 ± 5.2	35.6 ± 8.6	22.9 ± 5.3**	0.001
mPAP, mmHg	51.9 ± 6.3	54.1 ± 11.1	33.6 ± 7.7**	0.001
PAWP, mmHg	8.8 ± 2.0	12.9 ± 6.4	9.7 ± 2.1	0.371
CO, L/min	2.8 ± 0.9	4.1 ± 1.1*	4.6 ± 1.3	0.001
CI, L/min/m^2	1.5 ± 0.5	2.4 ± 0.6*	2.7 ± 0.7	<0.001
PVR, dyn·s·cm^{-5}	1336.9 ± 320.2	815.4 ± 195.6*	428.3 ± 151.2**	<0.001
SvO_2, %	55.6 ± 11.7	55.4 ± 8.2	65.3 ± 3.6**	0.027
SaO_2, %	NA	87.3 ± 7.0	91.4 ± 5.2	0.160

Note: Data are expressed as mean ± SD or number(percentage) or median with first and third quartiles (Q1: Q3).

Abbreviations: 6MWD, 6 min walking distance; BPA, balloon pulmonary angioplasty; CI, cardiac index; CO, cardiac output; dPAP, diastolic pulmonary arterial pressure; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; sPAP, systolic pulmonary arterial pressure; SvO_2, mixed venous oxygen saturation; WHO FC, world health organization functional class.

*p indicates the parameters before BPA compared with baseline, $p < 0.05$; **p indicates the parameters after BPA compared with before BPA, $p < 0.05$.

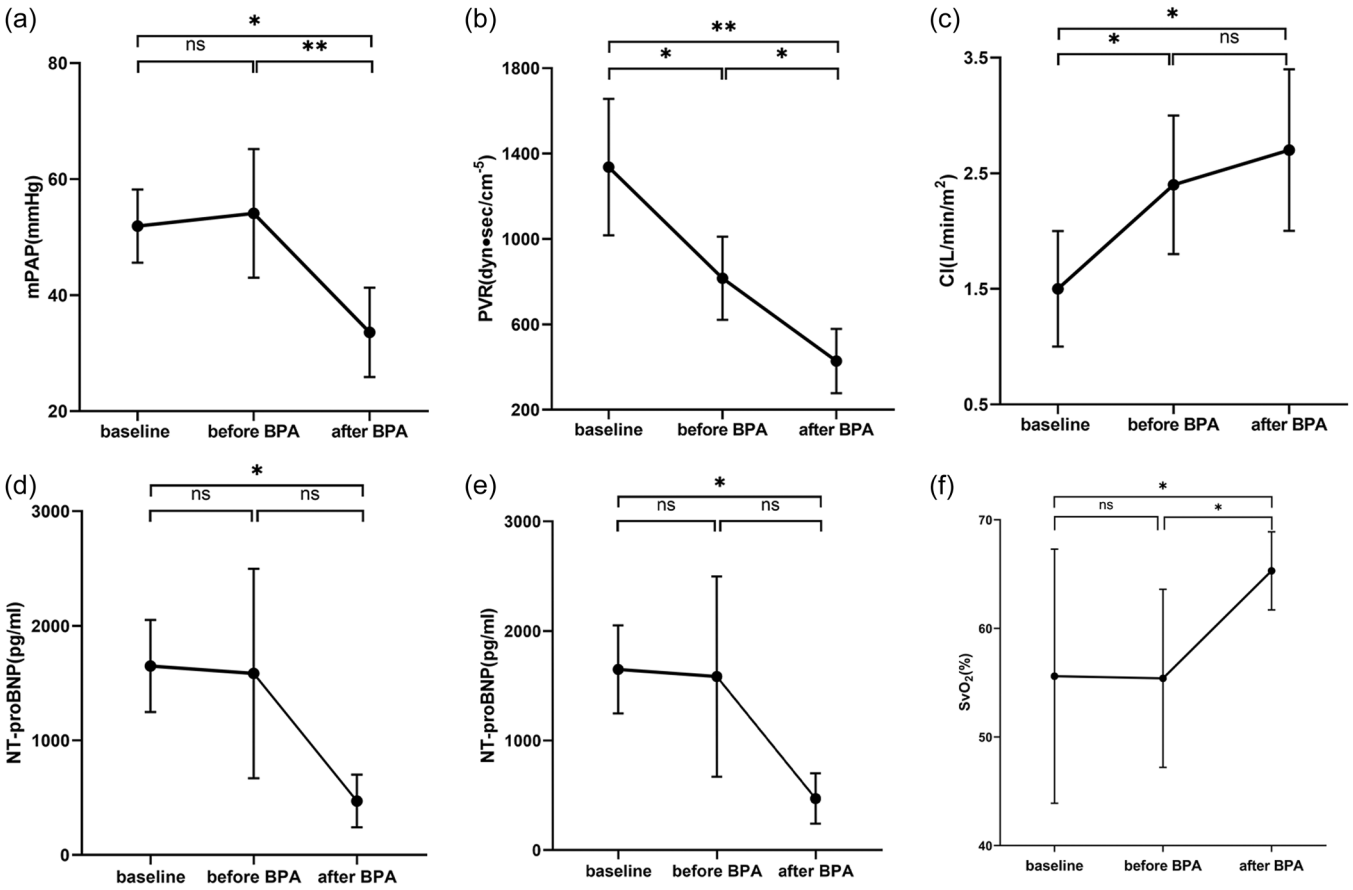

FIGURE 1 Effects of riociguat and combination BPA on hemodynamics and exercise capacity. (a), mPAP; (b), PVR; (c), CI; (d), NT-proBNP; (e), 6MWD; (f), SvO_2. ns indicates no significance, $*p < 0.05$,$**p < 0.01$. 6MWD, 6-min walk distance; BPA, balloon pulmonary angioplasty; CI= cardiac index; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PVR, pulmonary vascular resistance; SvO_2, mixed venous oxygen saturation.

TABLE 3 Echocardiographic parameters at baseline, before BPA and after BPA.

Echocardiographic data ($n = 8$)	Baseline	Before BPA	After BPA	*p*
LVEDD, mm	36.0 (28.4-37.5)	40.0 ± 4.1	46.3 ± 3.2	<0.001
RV basal diameter, mm	47.3 ± 7.6	49.0 (46.0−51.0)	41.3 ± 5.5	0.115
RV/LV diameter ratio	1.6 ± 0.5	1.2 ± 0.2	1.1 ± 0.1	0.028
RV free wall thickness, mm	6.4 ± 1.3	7.0 ± 1.8	6.3 ± 0.9	0.374
MPAD, mm	30.0 ± 4.5	39.9 ± 12.3	37.8 ± 12.6	0.089
RA minor dimension, mm	49.3 ± 8.8	52.0 (48.8−53.3)	46.6 ± 8.9	0.419
TRPD, mmHg	84.8 ± 10.5	91.1 ± 24.5	56.2 ± 16.5	0.013
TAPSE, mm	NA	16.7 ± 3.0	17.1 ± 3.7	0.500
IVC diameter, mm	NA	24.3 ± 6.0	19.0 ± 4.8	0.040
RV FAC, %	NA	33.0 ± 8.7	39.2 ± 15.6	0.310

Note: Data are expressed as mean ± SD or number (percentage) or median with first and third quartiles (Q1:Q3).

Abbreviations: IVC, inferior vena cava; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; MPAD, main pulmonary artery diameter; RA, right atrial; RV, right ventricular; RV FAC, right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion; TRPD, tricuspid regurgitation pressure difference.

arterial pressure slightly elevated, and SvO_2 remains almost similar. The echocardiographic indicators are demonstrated in Table 3. There is only an improvement in LVEDD (36.0 (28.4−37.5 mm) to 40.0 ± 4.1 mm, $p = 0.24$) and RV/LV diameter (1.6 ± 0.5 to 1.2 ± 0.2, $p = 0.23$), while no statistical differences. Furthermore, other parameters show that right heart structure continue to deterioration.

After 8 years riociguat administration, the eight patients were treated with a total of 33 sequential combination BPA sessions (mean 4.1 ± 1.6) and 150 balloon dilations (mean 18.8 ± 8.1). Pulmonary arterial pressure indicators significantly decrease in sPAP (90.8 ± 19.0 mmHg to 54.3 ± 12.6 mmHg, $p = 0.001$), dPAP (35.6 ± 8.6 mmHg to 22.9 ± 5.3 mmHg, $p = 0.003$), mPAP (54.1 ± 11.1 mmHg to 33.6 ± 7.7 mmHg, $p = 0.002$), respectively. Based on riociguat administration, CO and CI are further increased from 4.1 ± 1.1 L/min to 4.6 ± 1.3 L/min, 2.4 ± 0.6 L/min/m^2 to 2.7 ± 0.7 L/min/m^2 after several BPA sessions, respectively. SvO_2 also statistically improves from 55.4 ± 8.2% to 65.3 ± 3.6% ($p = 0.038$). PVR declines further from 815.4 ± 195.6 dyn·s·cm^{-5} to 428.3 ± 151.2 dyn·s·cm^{-5} ($p < 0.001$). NT-proBNP are further lessened from 440.5 (257.5−1522.75) pg/mL to 169.5 (49.25−603.0) pg/mL. In the aspect of exercise capacity, 6MWD is significantly improved from 418.1 ± 75.8 m to 455.7 ± 100.0 m ($p = 0.038$). No statistically significant difference is noted in WHO FC, but improvement comparing with values before BPA procedures. The echocardiographic parameters show that RV basal diameters, RV/LV basal diameter, RV free wall thickness, right atrial dimension, IVC diameter, TAPSE and RV FAC are improved to some extent, compared with indicators at baseline and after riociguat. Although those parameters show no statistical difference, it still shows a reduction in right heart size and an improvement in right heart function. Representative echocardiograms are shown in Figure 2 and 3.

Complications of BPA

There were seven procedures related complications of the total 33 interventions (21.2% of all interventions). There were 6 procedures caused by wire perforation of the pulmonary vasculature, with mild hemoptysis in five BPA sessions. There was asymptomatic, only observed a bit contrast effusion during one BPA session. One patient developed reperfusion edema with deteriorated dyspnea and desaturation during the postprocedural period of 24 h. There was no contrast-induced acute kidney injury. Noninvasive ventilation was used to oxygen therapy. No procedure-related death occurred.

DISCUSSION

With the recognition of CTEPH, the therapy strategies are updated gradually, including the preferred PEA, targeted medicine and emerging interventional treatment. According to the guidelines, riociguat is the first medication recommened for persistent/recurrent PH after PEA or inoperable CTEPH. In 2012, Janpanese investigators refined the BPA procedure to make it an alternative therapeutic approch for patients with inoperable CTEPH. However, it is not clear whether patients who receive long-term riociguat still benefit from BPA procedures. Our current study demonstrates the exercise tolerance and hemodynamics are further improved after long-term riociguat and sequential combination with BPA procdures for the inoperable CTEPH. The main findings of the present study are that[1] long-term riociguat improves exercise capacity and indicators reflecting right heart function of CO, CI, and NT-proBNP, decreases the PVR at the same time; [2] the combination of riociguat and sequential BPA procedures

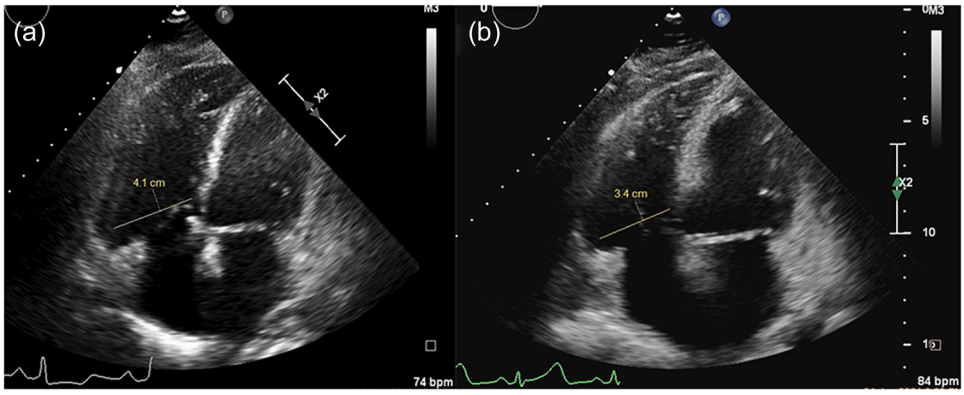

FIGURE 2 RV basal diameter. Measurements of RV size were made in dedicated RV views. This image illustrates measurements of RV diameter at the time of before BPA (a) and follow-up after treatment with BPA (b). BPA, balloon pulmonary angioplasty; RV, right ventricular.

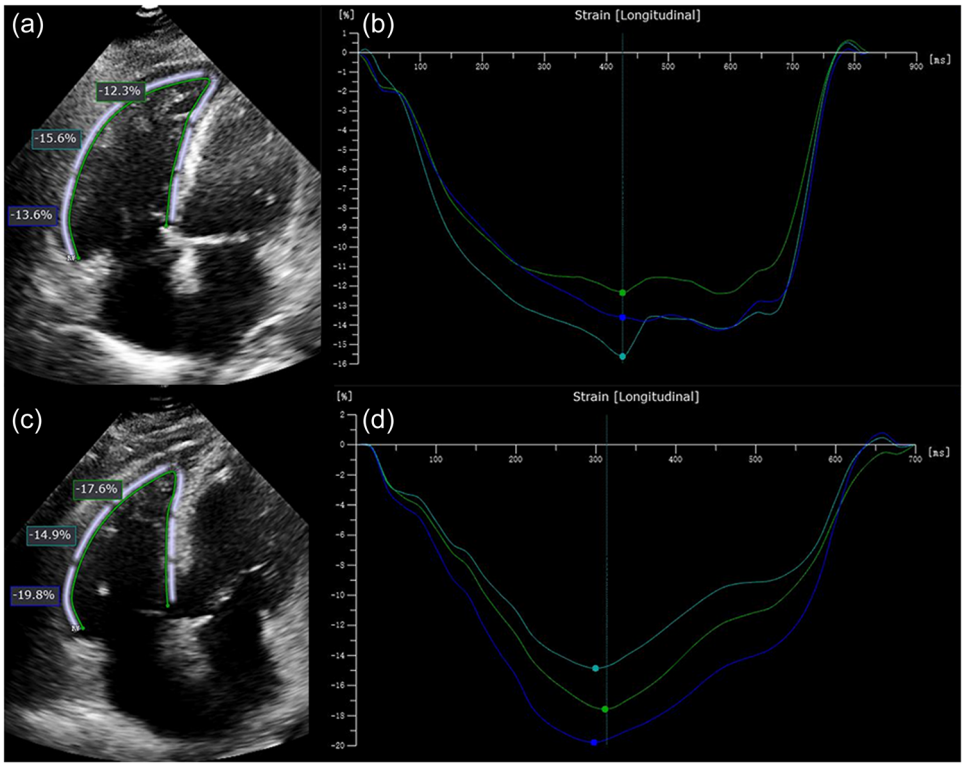

FIGURE 3 Analysis of RV longitudinal strain using speckle-tracking imaging. RV strain from the same representative patient before (upper panel) and after (lower panel) treatment with BPA. Before treatment, there is severe RV dysfunction. After BPA, systolic function is improved in base and apex segments of RV free wall (green and blue traces). Analysis of was performed from 3 segments (base, mid, and apex segments of RV free wall before (a) and after (c) BPA. Representative traces of RV strain curves before (b) and after (d) BPA. BPA, balloon pulmonary angioplasty; RV, right ventricular.

generates further improvement in CO, CI, PVR, 6WMD and NT-proBNP, in addition to decreasing the mPAP; [3] BPA can reverse RV remodeling and improve RV function. These findings suggest that BPA can further increase the beneficial effects on inoperable CTEPH patients who take long-term riociguat.

In the CHEST-1 study, there were significant improvements in the 6MWD by 39 ± 79 m, the NT-proBNP level by -291 ± 1717 pg/mL and WHO function class by 33%, the CO by 0.8 ± 1.1 L/min, as well as a mean reduction in PVR of 226 dyn·s·cm^{-5}.[10] In a 1-year open-label extension trial (CHEST-2), improvements in 6MWD and WHO FC were maintained, with a survival rate of 97% and a rate of clinical worsening-free survival of 88% at 1 year.[9] Nevertheless, long-term outcomes beyond 1 year has not been shown in the CHEST study. In our present cohort, exercise capacity and hemodynamics parameters have improved for up to 8 years after riociguat treatment and further improvements after BPA. Based on the results of several previous studies, exercise capacity and hemodynamics were associated with prognosis and overall survival among patients with CTEPH.[14,15] Hence, our findings clearly suggest the benefits of the sequential combinational treatment with riociguat and BPA.

However, right heart size and function assessed by echocardiography have no significant changes during long-term treatment with riociguat, and even tend to deteriorate. The present result contradicts previous data showing that patients under long-term treatment with riociguat demonstrated significantly reduced right heart size and improved RV function in PAH and CTEPH.[16] In the previous long-term riociguat study, the duration of administration was just 12 months, while our present study lasts 8 years whereby the results were beneficial, attesting to the long-term efficacy of riociguat. However, the study also shows an increased in mPAP, over-sized right heart and clinical worsening in some patients. As we know, CTEPH is a progressive condition. The CHEST study has shown that riociguat is not a curable treatment. Therefore, it is not surprising that patients who are technically inoperable or postoperative persistent PH or have an unacceptable risk/benefit ratio for PEA, treated with riociguat, whose pulmonary hemodynamic/RV size and function may deteriorate over time. These findings suggest that riociguat alone is insufficient for the

treatment of inoperable CTPEH patients. The riociguat therapy can only improve the function of right heart, nevertheless, the structure of right heart and pulmonary artery still gradually deteriorate due to the persistent PH.

Since Japanese investigators refining the BPA procedure in 2012, it has rapidly spread around the world due to its dramatically improved efficacy and safety. Published data from different countries have shown significant improvements in hemodynamics, exercise capacity and markers of heart failure such as BNP or NT-proBNP level.[17–19] Currently, BPA carries a class IIb recommendation for the treatment of inoperable CTEPH in the European guidelines.[2] PH-targeted medical therapy is common in CTEPH patients before treatment with BPA procedure, however, the further benefits of this approach remain unclear. In a small randomized controlled study by Sugimura et al., patients with inoperable CTEPH were treated with medical therapy before BPA for 1-3 months, which resulted in improved CO/CI, and PVR, but little change in mPAP and 6MWD,[20] which demonstrated that BPA combined with conventional vasodilator treatment was quite effective in terms of improving the pulmonary hemodynamics and short-term prognosis in patients with distal-type CTEPH. In another study of 36 patients by Wiedenroth et al, patients with inoperable CTEPH were given riociguat before BPA for mean 5 months, which suggested that the combination of riociguat and BPA was an effective treatment for patients with inoperable CTEPH, leading to significant improvements in physical capacity and pulmonary hemodynamics.[21] These findings illuminated that the short-term use of targeted-PH agents before BPA, which contributed to the improvements of right heart function and hemodynamics of the inoperable CTEPH patients, may guarantee the safety of BPA procedure by reducing the incidence of reperfusion pulmonary edema. Kaspar Broch et al. reported a significant improvement in RV functional parameters by echocardiography after BPA in 2015, which indicated credibility to this form of treatment in patients with CTEPH who undergo BPA.[22] In our current study, the changes of exercise capacity and hemodynamics as well as right heart size and function by echocardiography after BPA procedure are in line with these previous data. Thus, our study also supports the viewpoint that BPA procedure can reverse the remodeling of right heart structure and function.

Our results demonstrated that long-term riociguat and sequential combination with BPA is an effective treatment for patients with inoperable CTEPH. However, riociguat regulates the NO-sGC-cGMP pathway to prevent the development of PH, the use of anticoagulants for inoperable CTEPH patients merely prevent new thrombosis and reduce pulmonary arteries block. Therefore, medical therapy has limited effect, even long-term medication cannot avoid the aggravation of the disease. BPA procedure improves CTEPH patients' hemodynamics and exercise tolerance through several mechanisms. Firstly, an overall vessel expansion induced by the stretching of the arterial wall leads to lumen enlargement immediately after BPA.[23] Secondly, the BPA relieves hemodynamic stress towards the non-BPA-side lung and subsequently decreases the non-BPA-side PVR in patients with CTEPH, which plays a significant role in suppression or possibly regression of small-vessel arteriopathy in these patients.[24] Last but not least, BPA procedure improves total pulmonary artery compliance in proportion to a decrease in PVR.[25] Therefore, the BPA procedure directly opens the mechanical obstruction vessels through the above mechanisms to reduce PVR and pulmonary artery pressure, thereby decreasing the right cardiac load, significantly reversing remodeling of the RV structure as well as the improvement of RV function, and further improving the prognosis of patients.

Some limitations to this study must be considered. First, this is a single-center observational study. In addition, the number of patients enrolled was small. Furthermore, we have no matched control group. The PH itself is a rare disease. Moreover, the included cases were all from the CHEST study in our PH center in China, the CHEST study enrolled the subjects not only CTEPH but PAH. Our center is the largest patient number in China for CHEST study. The number of enrolled CTEPH subjects is relatively small. However, our research has its advantages. Namely, we selected patients from the CHEST study in China and our results derived from clinical real observational data. Those patients enrolled in study have taken riociguat for almost 8 years, but their mPAP, right heart size and function did not improve significantly, even some patients were clinically worse. Given this, we tried to practice sessions of BPA procedures for them, which led to a decrease in mPAP, further enhancement in CO/CI, PVR, especially in right heart size and function by echocardiography. We confirmed not only the long-term efficacy of riociguat in patients with inoperable CTEPH, but also further benefits from BPA procedure.

CONCLUSION

The study suggests that medical therapy combination with BPA is more effective than medical therapy alone. From this we can infer that the patients who do not normalize pulmonary hemodynamics with medical therapy should be offered BPA if appropriate, even

though long-term medication. This will be confirmed in our future larger prospective study.

AUTHOR CONTRIBUTIONS

Conception and design: Yuanhua Yang. *Administrative support*: Suqiao Yang and Yuanhua Yang. *Provision of study material or patients*: Juanni Gong and Tuguang Kuang. *Collection and assembly of data*: Wei Wang, Yidan Li, Qiang Huang and Jianfeng Wang. *Data analysis and interpretation*: Wei Wang and Yuanhua Yang. Manuscript writing: All authors. Final approval of manuscript: All authors.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Patient clinical data, RHC and BPA procedures as well as echocardiographic data are fully available in the original format for data transparency. The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS 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 approved by the ethics committee of Beijing Chaoyang Hospital, Capital Medical University (NO.2019-KE-377). All the patients provided their written informed consents.

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