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Balloon pulmonary angioplasty for the treatment of residual or recurrent pulmonary hypertension after pulmonary endarterectomy

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ABSTRACT

Background: Pulmonary endarterectomy (PEA) is the treatment of choice for chronic thromboembolic pulmonary hypertension (CTEPH). However, persistent pulmonary hypertension continues in 5–35% of patients after PEA. Recently, balloon pulmonary angioplasty (BPA) showed promise as a strategy for patients with non-operable CTEPH. Therefore, we investigated the usefulness of BPA for residual pulmonary hypertension after PEA.
Methods: Fifteen patients with residual pulmonary hypertension after PEA received 71 BPA sessions (4.7 ± 1.4 sessions/patient). The mean time between the PEA and the first BPA session was 28.1 ± 25.8 months. All patients underwent a comprehensive diagnostic work-up, including right heart catheterization, functional and laboratory tests, before, and 6–4 weeks after the BPA sessions.
Results: After BPA, the mean pulmonary arterial pressure decreased from 44.7 ± 6.4 to 30.8 ± 7.5 mm Hg (31% decline; $p < 0.001$). Pulmonary vascular resistance decreased from 551.9 ± 185.2 to 343.8 ± 123.8 dyn∗s/cm^{-5} (38% decline; $p < 0.001$). The 6-min walking distance increased from 383 ± 104 to 476 ± 107 m (mean change +93 m; $p < 0.001$). In two sessions (2.8%), serious periprocedural complications occurred. During a mean follow-up of 18 ± 14.3 months, one patient died two months after the last BPA session. Fourteen patients survived.
Conclusions: BPA could be a promising therapeutic strategy for persistent pulmonary hypertension after PEA in patients with CTEPH.

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a disease caused by persistent obstruction of pulmonary arteries as a result of organized residual pulmonary emboli and followed by development of progressive secondary arteriopathy in small pre-capillary pulmonary vessels and subsequent right ventricular function deterioration [1–3]. This disease develops in up to 4% of pulmonary embolism survivors and if left untreated, it is associated with a poor outcome [4,5]. Pulmonary endarterectomy (PEA) is the "gold standard" treatment for CTEPH. This complex surgical procedure is often curative; post-operatively, pulmonary haemodynamic parameters are often normalized, and can be accomplished with relatively low risk to patients, when performed in experienced centres [6–8]. However, as many as 5–35% of patients experience persistent or recurrent pulmonary hypertension after PEA [8–12]. Patients with residual mean pulmonary artery pressure >38 mm Hg or pulmonary vascular resistance >450 dyn∗s/cm^{-5} after PEA have significantly worse prognoses compared to patients with normalized pulmonary pressures [10–12]. Medical therapy has shown only limited effectiveness in treating this condition [13–16].

In the last couple of years, balloon pulmonary angioplasty (BPA) was developed as a promising strategy for patients with non-operable CTEPH [17]. Promising haemodynamic and clinical results have been achieved, particularly in Japanese centres, where significant improvements have been made in the technique originally described by Feinstein et al. [18–20]. Although there are clear therapeutic algorithms in the current guidelines with the key role of PEA in the treatment of operable CTEPH and only supplementary role of BPA, it has been well recognised, that there are important differences in the approach to qualification to surgery as well procedural experiences and results between

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European and Japanese CTEPH centres [21,22]. In Europe and the US, treatments for CTEPH are mainly based on PEA; whereas in Japan, CTEPH is predominantly treated with BPA [22]. Japanese experiences have indicated that BPA might be effective not only in patients with distal segmental or sub-segmental lesions, but even in patients with proximal disease, as well as in patients that experienced ineffective PEA [23,24]. However, clinical evidence remains limited on the effect of BPA on residual pulmonary hypertension after PEA, particularly data from European centres are lacking. We sought to assess whether sequential BPA might be a safe and effective treatment in patients that displayed residual or recurrent pulmonary hypertension after PEA, in two European reference centres.

2. Materials and methods

2.1. Patient selection

Between January 2010 and January 2017, 94 patients with confirmed CTEPH that were referred from two centres received PEAs, performed by an experienced PEA surgeon (AB). CTEPH was diagnosed on the basis of perfusion defects revealed with pulmonary scintigraphy and computed tomography scans. CTEPH diagnoses were confirmed with haemodynamic measurements during right-heart catheterization (RHC) and pulmonary angiography. All the patients were referred to PEA after evaluation in multidisciplinary CTEPH conference. Of the 94 patients treated, 88 survived the perioperative period. In 15 patients (17%), a RHC, performed 3 to 6 months after the procedure, revealed residual pulmonary hypertension, defined as a mean pulmonary artery hypertension (mPAP) ≥25 mm Hg, a pulmonary arterial wedge pressure (PCWP) <15 mm Hg, and pulmonary vascular resistance (PVR) ≥300 dyn/s∗cm^{-5} and World Heart Organisation (WHO) functional class ≥II. All 15 patients who met the criteria for residual pulmonary hypertension, were discussed with PEA surgeon to consider Re-Do-PEA. Eventually, all patients were included in the present study, and underwent staged BPA procedures.

The study protocol was approved by institutional Ethics Committees in both participating centres. All patients provided written informed consent for the procedure and for participation in the study.

2.2. Study protocol

Clinical parameters included the World Health Organization (WHO) functional class, which reflected subjective symptoms; a 6-min walking distance test (6-MWT); haemodynamic parameters measured during RHC; arterial oxygen saturation (SaO_2); mixed venous SaO_2; and N-terminal pro B-type natriuretic peptide (NT-proBNP) levels. These parameters were examined at four time points: first, at baseline, before PEA; then, 3–6 months after PEA; before the BPA series, and finally, at follow-up, 4–6 weeks after the final BPA procedure.

Right atrial pressure (RAP), pulmonary arterial pressure (PAP), and pulmonary arterial wedge pressure (PAWP) were measured during RHC with a Swan-Ganz catheter, according to current guidelines [25]. Cardiac output (CO) was determined with the thermodilution method. Pulmonary vascular resistance (PVR) was calculated by subtracting the PAWP from the mean PAP and dividing by the CO.

2.3. Balloon pulmonary angioplasty

BPA was performed in both centres, according to the same protocol, as a series of staged procedures. At 24 h before the procedure, patients discontinued chronic antithrombotic treatments with vitamin K antagonists or new oral anticoagulants. Both participating centres used similar procedural techniques. In most cases, access was achieved in the right femoral vein. An intravenous bolus of unfractionated heparin (2000–5000 units) was given at the beginning of the procedure. Then, heparin doses of 1000–2000 units were injected after each hour of the procedure. An MP, JR4, JL4, or AL1 6-F guiding catheter (Launcher; Medtronic, Minneapolis, MN, USA) was inserted into the right or left pulmonary artery with a 90-cm 6F vascular sheath (Flexor; Cook, Bloomington, IN, USA) to achieve a good selective approach to the target vessel. Then, 0.014-inch guidewires (Cruiser; Biotronik, Bülach, Switzerland; Whisper MS; Abbott Vascular, Santa Clara, CA, USA, Sion Blue, Asahi, Japan) were passed through the lesions and inserted distally in the subsegmental artery. Subsequently, the target branches were dilated with multiple balloon inflations using semi-compliant balloon catheters with a size between 1.25 and 10 mm. The balloon diameter and length were adjusted to the type of lesion and the degree of stenosis in the pulmonary artery observed with angiography, having regard to the undersizing strategy at the initial phase of treatment and 1:1 sizing at the optimization phase.

After deflation of the balloon, contrast was injected into the treated vessel in order to evaluate the angiographic effect of the procedure or to detect possible vessel injury.

In special cases, when the nature or significance of a lesion was unclear, additional diagnostic tools were applied, such as intravascular ultrasound or optical coherence tomography (Suppl. 1). Moreover, a pressure gradient was sometimes applied across the evaluated lesion and a pressure wire was used to assess the lesion [26,27]. After completing the procedure, each patient was transferred to the cardiac intensive care unit to monitor vital functions and potential complications for 48 h.

Periprocedural complications, including pulmonary artery injury (perforation, dissection) or pulmonary reperfusion oedema, were classified according to the classification proposed by Inami et al. [28]. BPA treatment was terminated when there were no treatable lesions in the pulmonary arteries or when the mPAP was <25 mm Hg.

2.4. Targeted medical therapy

Before 2014 patients received targeted medical therapy with sildenafil (25 mg TID) (3 patients), prostanoids (1 patient) or both (combined therapy - sildenafil and treprostinil in 1 patient). From January 2014 all treated patients received riociguat (10 patients). In three patients sildenafil was discontinued and riociguat was then administered. The initial dose was 1 mg three times daily, which was increased to the maximally tolerated dose (up to 2.5 mg three times daily) within 4–6 weeks. In all patients targeted medical therapy was initiated before the first BPA procedure.

2.5. Statistical analysis

Categorical variables are expressed as numbers (n) and percentages (%). Continuous variables are expressed as the mean ± SD, unless indicated otherwise. Comparisons between groups were performed with the unpaired Student's *t*-test or Mann–Whitney *U* test, for continuous variables, and with the Chi-square or Fisher's exact test, for categorical variables. A value of $p < 0.05$ was considered statistically significant.

3. Results

A total of 71 BPA sessions were performed in 15 patients (9 male, 6 female, 4.7 ± 1.4 sessions per patient) with residual/recurrent pulmonary hypertension after PEA. The clinical and procedural characteristics of the study group, including medical treatment before BPA, are shown in Table 1. The mean time from PEA to the first BPA session was 28.1 ± 25.8 months.

A total of 391 segmental or subsegmental arteries in 147 segments were dilated. The median number of pulmonary segments per patient targeted in all interventions was 10 (range 7–13). The procedural details are presented in Table 2. The target vessels were distributed as follows: right upper lobe: $n = 58$, right middle lobe: $n = 68$, right lower lobe: $n = 81$, left upper lobe: $n = 55$, lingular segment: $n = 51$, and left lower lobe: $n = 78$. Optical coherence tomography was used in 4 sessions (5.6%); intravascular ultrasound was used in 6 sessions (8.5%); and a pressure wire was used in 5 sessions (7%).

Table 1
Clinical and procedural characteristics of the study group.

Characteristic	Patients, $N = 15$
Male/Female	9/6
Age (years)	50.4 ± 13.5
Systemic hypertension	6 (40)
Diabetes	2 (13.3)
Angina pectoris	2 (13.3)
Hyperlipidaemia	4 (26.7)
C.O.P.D.	1 (6.7)
Chronic kidney disease	2 (13.3)
Vena Cava filter	4 (26.7)
Deep vein thrombosis	6 (40)
History of pulmonary embolism	11 (73.3)
Medical treatment before BPA:	
PDE-5 inhibitors	3 (20)
Soluble guanylate cyclase stimulator (riociguat)	10 (66.7)
Prostanoids	1 (6.7)
Endothelin-1 inhibitors	0 (0)
Combined therapy	1 (6.7)
Total number of BPA sessions	71
Number of sessions per patient	4.7 ± 1.3 (3–7)
Total number of treated vessels	391
Number of treated vessels per session	5.5 ± 1.2
Mean number of treated segments per patient	9.8 ± 2 (7–13)
Amount of contrast per session [ml]	297.6 ± 49.9
Mean radiation dose per patient [mGy]	4021 ± 1402
Time from PEA to first BPA session [months]	28.13 ± 25.8

Values are the number of patients (%) or the mean ± SD, as indicated. Values are means ± SD (range) BPA – balloon pulmonary angioplasty; C.O.P.D. – chronic obstructive pulmonary disease; PEA – pulmonary endarterectomy; PDE-5 – phosphodiesterase-5.

Table 2
Haemodynamic and clinical parameters at four time points: before PEA and after PEA, and before and after BPA.

	Before PEA	After PEA	Before BPA	After BPA
mRAP (mm Hg)	9.5 ± 4.9	7.9 ± 5.1	9.3 ± 4.4	5.2 ± 3.5 **, ***
mPAP (mm Hg)	48.5 ± 9.6	44.6 ± 7.8	44.7 ± 6.4	30.8 ± 7.54**, ***
CO (l/min)	4.6 ± 0.9	5.0 ± 1.2	5.34 ± 1.4	5.27 ± 1.23***
CI (l/min/m^2)	2.5 ± 0.6	2.7 ± 0.6	2.9 ± 0.74*&	2.9 ± 0.9***
PVR (dyn∗s/cm^{-5})	700.6 ± 207.7	583.1 ± 181.5#	551.9 ± 185.2*	343.8 ± 123.8**, ***
PVR (Wood U)	8.8 ± 2.6	7.3 ± 2.3#	6.9 ± 2.3*	4.35 ± 1.57**, ***
6-MWD (m)	348.7 ± 112.7	402.6 ± 109.8	382.7 ± 104.3	476 ± 106.8**, ***
NT-proBNP (pg/dl)	1489.3 ± 1577	2102.9 ± 3218	1554.8 ± 1541.3	537 ± 642.6**, ***
SaO_2 mv (%)	65.7 ± 5.8	64.9 ± 6.6	63.2 ± 6.4	69.4 ± 7.6
SaO_2 a (%)	93.1 ± 3.4	94.5 ± 3.2	95 ± 2.3*	95.25 ± 4.5

Values are presented as means ± SD; BPA – balloon pulmonary angioplasty. CO – cardiac output; CI – cardiac index; mRAP – mean right atrial pressure; mPAP – mean pulmonary artery pressure; 6-MWD – 6-minute walking distance; NT-proBNP – N-terminal-pro Brain-like Natriuretic Protein. PEA – pulmonary endarterectomy, PVR – pulmonary vascular resistance; SaO_2 a – arterial oxygen saturation; SaO_2 mv – mixed venous oxygen saturation.
* $p < 0.05$ before PEA vs pre-BPA.
** $p < 0.05$ pre-BPA vs post-BPA.
*** $p < 0.05$ before PEA vs post-BPA.
\# $p < 0.05$ before PEA vs after PEA.
& $p < 0.05$ after PEA vs before BPA.

3.1. Haemodynamic parameters

Before PEA, the studied patients had a mean pulmonary artery pressure (mPAP) of 48.5 ± 9.6 mm Hg, a mRAP of 9.5 ± 4.9 mm Hg, a mean CO of 4.6 ± 0.9 l/min, a mean cardiac index (CI) of 2.5 ± 0.6 l/min/m^2, and a mean PVR of 700.6 ± 207.7 dyn∗s/cm^{-5}. 6–12 months after the procedure we observed no significant improvements in the mPAP (44.7 ± 7.8 mm Hg; $p = 0.3$) or the mRAP (7.9 ±

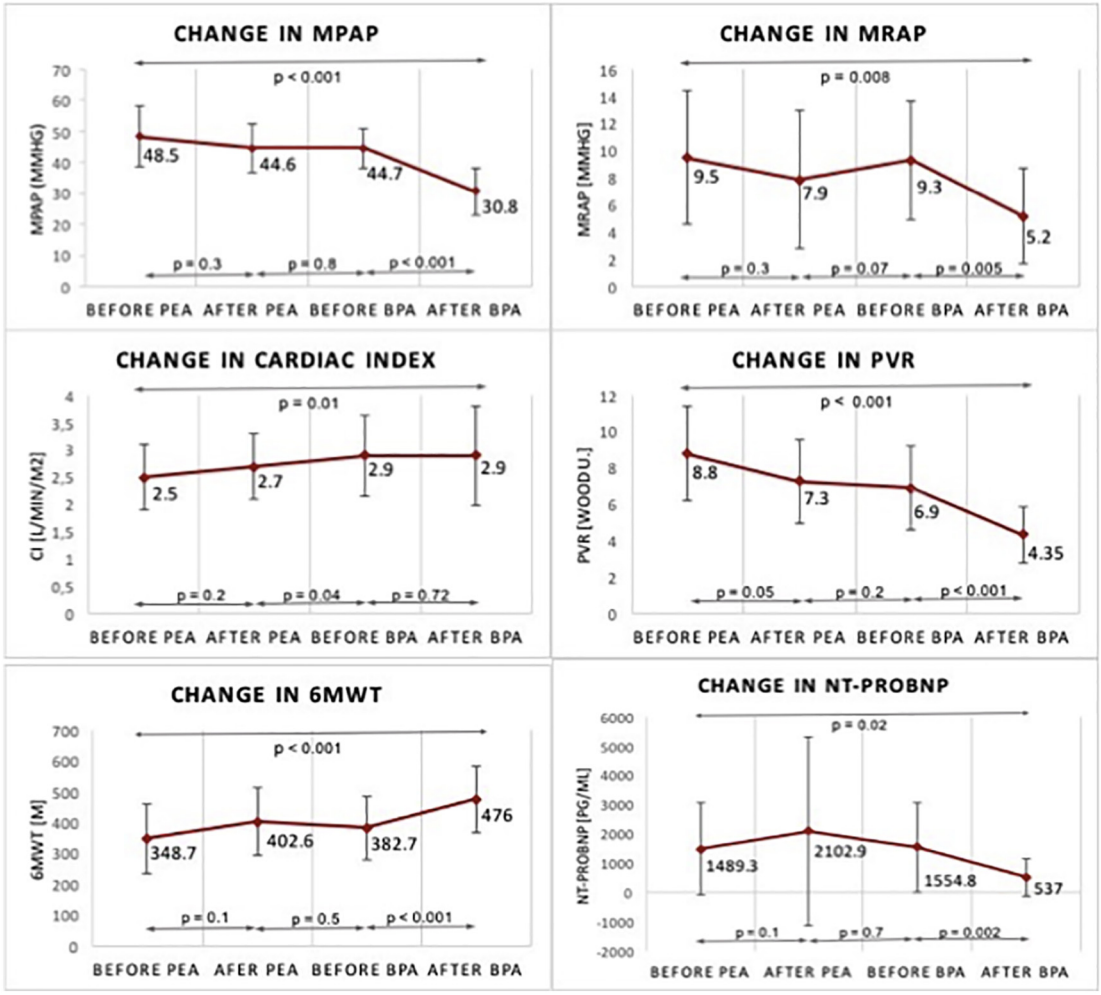

Fig. 1. Changes in haemodynamic and clinical parameters in patients with persistent pulmonary hypertension after a pulmonary endarterectomy (PEA). Parameters were measured before and after the PEA, and then, before and after treatment with supplemental balloon pulmonary angioplasty (BPA). Data are expressed as the mean ± SD. CI – cardiac index, PAP – pulmonary artery pressure, PVR – pulmonary vascular resistance, RAP – right atrial pressure, 6MWT - 6-min walking test, NT-proBNP - N-terminal pro B-type natriuretic peptide concentrations.

5.1 mm Hg; $p = 0.3$), CO (5.0 ± 1.2 l/min, $p = 0.2$) and CI (2.7 ± 0.6 l/min∗m^2, $p = 0.2$). However, mean PVR was significantly decreased (583.9 ± 181.5 dyn∗s/cm^{-5}, $p < 0.05$).

Before BPA we observed no significant changes in the haemodynamic parameters comparing to the values obtained after PEA, except for CI which increased from 2.7 ± 0.6 to 2.9 ± 0.74, ($p = 0.04$).

Compared to before the BPA, after the BPA, we observed significant improvements in the mPAP (30.8 ± 7.5 mm Hg; $p = 0.0007$), the mRAP (5.2 ± 3.5 mm Hg; $p = 0.005$), and the mean PVR (343.8 ± 123.8 dyn∗s/cm^{-5}; $p < 0.0001$). The mean CO (5.27 ± 1.2 l/min) and the mean CI (2.9 ± 0.9 l/min/m^2) did not improve compared to pre-BPA measurements ($p = 0.9$ and $p = 0.72$, respectively).

All haemodynamic measurements are shown in Table 2 and Fig. 1.

3.2. Laboratory and functional parameters

At baseline, the mean NT-pro BNP concentration in the study group was 1489.3 ± 1577 pg/dl, which was not significantly different from the post-PEA period (2102.9 ± 3218 pg/dl, $p = 0.9$).

Before BPA NT-pro BNP concentration was 1554.8 ± 1541.3 pg/dl. However, the mean NT-pro BNP changed significantly after BPA (537 ± 642.6 pg/dl, $p = 0.002$; Table 1 and Fig. 1).

Before PEA, the mean mixed venous SaO_2 was 65.7 ± 5.8%; after PEA it was 64.9 ± 6.6% ($p = 0.7$), before BPA it was 63.2 ± 6.4% ($p = 0.7$), and after BPA, it reached 69.4 ± 7.6%, with borderline statistical significance (vs before BPA, $p = 0.05$). In contrast, the mean arterial SaO_2 was 93.1 ± 3.4 before PEA, 94.5 ± 3.2% after PEA ($p = 0.15$), 95 ± 2.3% before BPA ($p = 0.009$), and 95.3 ± 2.5% after BPA ($p = 0.9$).

Before PEA, the mean 6-MWT was 348.7 ± 112.7 m, and did not improve significantly after the PEA procedure (402.6 ± 109.8 m, $p = 0.1$). Before BPA it was 382.7 ± 104.3 m ($p = 0.5$). After BPA the mean 6-MWT had improved significantly compared to pre-BPA (476 m ± 106.8, $p = 0.0004$; Table 1 and Fig. 1).

The WHO functional class developed, as follows: before PEA, 4 patients were in class IV, 10 were in class III; and 1 was in class II. After PEA 2 patients were in class I, 5 patients in class II, 5 patients in class III and 3 patients in class IV ($p = 0.02$ in comparison to before PEA). Before BPA, 1 patient was in class IV, 8 were in class III, and 6 were in class II. After BPA, no patient was in class IV, 2 patients were in class III, 11 were in class II, and 2 were in class I ($p = 0.03$ pre-BPA vs. post-BPA; Fig. 2).

3.3. Complications

No patient died during the periprocedural period. Out of 71 BPA sessions, complications were noted in 15 procedures (21.1%). However, serious complications were observed in only two sessions (2.8%). In one patient, a vessel rupture, associated with severe haemoptysis, required a covered stent implantation to stop the bleeding.

Other patients (6 sessions) experienced vessel perforations, but they did not require salvage methods, except short-term (5–10 min) balloon inflations, and there were no further clinical sequelae. The frequency of vessel injuries was 9.8% (7 of 71 sessions). We observed reperfusion pulmonary oedema in 7 sessions (9.8%), but only one patient (1.4%) had grade 3 severity, according to the Inami et al. scoring system and treatment required non-invasive pressure ventilation. The reperfusion pulmonary oedema was grade 2 in two patients (2.8% sessions) and grade 1 in the remaining four patients (5.6%). All these episodes were treated with supplemental oxygen flow (3–4 l/min) for one or two days. In one patient, an allergic reaction (urticaria and Quincke oedema) was observed during the procedure.

3.4. Follow-up

During a mean follow-up period of 18 ± 14.3 months, one patient died (sudden cardiac death of unknown reason) two months after the last BPA session. The remaining 14 patients survived and presented at the end of clinical follow-up WHO functional class as follows: 1 patient was in class III, 10 were in class II, and 3 were in class I. ($p = 0.7$ in comparison to "after BPA" time point).

4. Discussion

The present study demonstrated that BPA was a safe, effective treatment for patients with persistent pulmonary hypertension after PEA. We showed that the "sequential" complex approach, which combined PEA with additional elective BPA, had a beneficial impact.

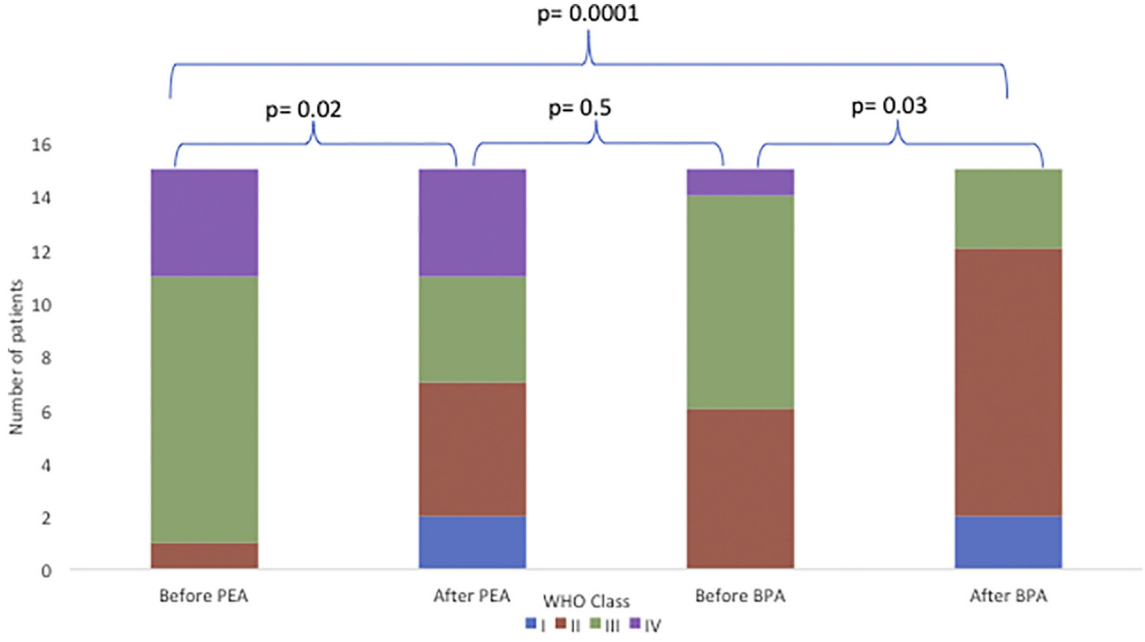

Fig. 2. Changes in World Health Organization (WHO) functional classes in patients treated with supplemental balloon pulmonary angioplasty (BPA) after a pulmonary endarterectomy (PEA).

Although PEA remains the most effective treatment for patients with CTEPH, as many as 5–35% patients have exhibited persistent or recurrent pulmonary hypertension [10–12]. Moreover, those patients have significantly worse prognoses compared to patients without persistent/recurrent pulmonary hypertension. Cannon et al. demonstrated that patients with residual mean pulmonary pressures >38 mm Hg and PVRs >450 dyn∗s/cm^{-5} after PEA had experienced significantly higher mortality during the observation period [11]. In our group, 15 out of 86 people that survived the PEA operation (18%) exhibited persistent/residual pulmonary hypertension, consistent with the rates reported in previous studies. Of them as many as 13 patients (86.7%) met the criteria of poor prognosis described by Cannon et al. Moreover, in our study group almost no haemodynamic improvement after PEA was achieved. The cause of residual, recurrent, or progressive pulmonary hypertension after PEA is unknown. It may result from ineffective removal of organized thrombotic material from distal, and sometimes proximal, segments of the pulmonary arteries [11]. Further, it may result from deep remodelling of pulmonary microcirculation, similar to that observed in idiopathic pulmonary arterial hypertension; however, in this case, it could not be cured after removing thrombi from the pulmonary vessels [12,29,30]. In addition, the progressive vascular disease associated with CTEPH might at least partially explain the failure of PEA surgery. Moreover, the pulmonary vasculature might exhibit recurrent thrombosis, due to ineffective anticoagulant therapy or recurrent pulmonary embolism, despite anticoagulant therapy, which might require individualized concepts [1,2,21,29].

Modern drugs, such as the soluble guanylate cyclase stimulator, riociguat, can reduce PVR by 25% in patients with persistent CTEPH after PEA and is approved by current guidelines in the treatment of inoperable CTEPH including residual/recurrent pulmonary hypertension after PEA [16,21]. Due to the fact that one potential cause of pulmonary hypertension relapse is the progressive development of pulmonary vascular disease, the use of targeted medical therapy might be justified in this group of patients. In our study, all patients received specific medical treatment before and during BPA therapy. Ten patients were treated with riociguat, and one patient received combination therapy (sildenafil and treprostinil). In three patients sildenafil was discontinued and riociguat therapy was started. The therapy was initiated before first BPA session to maximally decrease pulmonary pressure and protect microcirculation during BPA. We continued riociguat therapy after the completion of BPA in 13 of 15 patients to maintain the effects of the therapy.

BPA is an emerging interventional treatment for non-operable CTEPH. It involves staged sessions, during which lesions in targeted vessels are dilated with balloon catheters [19,20]. The efficacy of BPA in improving haemodynamic and functional parameters has been demonstrated in a number of previous studies [31–34]. The most recent studies on BPA included small subgroups of patients with recurrent pulmonary hypertension after PEA. However, only one systematic analysis was conducted to date, by Shimura et al. [24]. They studied nine patients with persistent pulmonary hypertension after PEA (23% of 39 patients that underwent PEA in their centre) [24]. Those authors demonstrated that the haemodynamics and symptoms after PEA were greatly improved with supplemental BPA. That finding suggested that BPA could be an efficacious therapeutic strategy, with great potential for patients with residual or recurrent pulmonary hypertension after PEA. Of note, they observed a low rate of serious complications. Only one serious vessel dissection occurred, which required a covered stent implantation, but no periprocedural deaths occurred. Shimura et al. suggested that the sequential hybrid therapy of PEA and BPA might be a safe, effective treatment option for patients with persistent pulmonary hypertension and also for patients with a mixed-pattern disease (i.e., proximal lesions more suitable for surgery mixed with distal lesions more suitable for BPA) [24].

It remains an open question whether Japanese results will be applicable to European practice, where PEA is more frequently performed. Indeed, in European specialized high-volume centres, PEA has produced excellent results [10–12]. In contrast, in Japan, most patients with CTEPH receive BPA as a primary invasive treatment [22].

A hybrid approach might be particularly effective in patients with very high PVR before PEA, which puts them at high perioperative risk. Wiedenroth et al. studied a group of patients treated with a hybrid procedure, where BPA was performed simultaneously with PEA [35]. Those authors concluded that the combination of surgical PEA and interventional BPA represented a new treatment option for highly selected patients at high-risk of CTEPH. However, a multidisciplinary team with substantial expertise in CTEPH would be required for that complex approach [35].

To our knowledge, the present study was the largest to date to evaluate supplemental BPA in patients with residual thromboembolic pulmonary hypertension after a previous PEA treatment. We found satisfactory results that demonstrated the effectiveness of such an approach. However, although our results showed improvement in haemodynamic parameters, the improvement was not as substantial as that reported in the previously mentioned study conducted at a Japanese centre. We did not observe complete normalization of the haemodynamic parameters. Moreover, the effectiveness of BPA therapy has appeared to be somewhat worse in European centres, compared to that observed in experienced Japanese centres [32–34]. The reasons for these differences were analysed previously, but the increasing experience in European BPA operators has provided increasingly better results, with moderate rates of periprocedural complications. Thus, in the near future, European BPA operators are likely to develop the same levels of experience and techniques as those held by Japanese operators [36].

The technical aspects of BPA in patients after PEA surgery also merit attention. When PEA is ineffective, the remaining lesions are often proximal, very hard, fibrotic occlusions (Suppl. 2). These lesions are very difficult to dilate, and dilation is often associated with elastic recoil, which results in reocclusion. Dilatation of fibrous ring-like lesions, particularly with oversized balloons, can lead to dangerous dissections and perforations, as observed in one of our patients and in one of the patients described by Shimura et al. Sometimes, after a PEA, the vessel wall is weakened; thus, when high pulmonary pressure coexists, aneurysmatic dilatation can occur in large pulmonary arteries. These conditions make it extremely difficult to navigate with the catheter in the vessel. All these factors contribute to making it more difficult to achieve complete haemodynamic normalization with BPA in patients that first received PEA, compared to patients that did not receive PEA for CTEPH.

There were some limitations in present study. First, it was retrospective in design; thus, the patients were included after BPA was completed. Second, although this study was the largest to date to consider a group of patients with persistent pulmonary hypertension, the number of participating patients was relatively low. Third, the precise aetiological mechanisms underlying the worsening haemodynamics and symptoms in our patients remain unknown, and might be different in different patients. Fourth, the range of time intervals between the PEA and BPA were significantly different between particular patients. Some had been treated with PEA in 2010, when BPA was not available as a therapeutic option; those patients might have been treated invasively up to three years after recognizing recurrent/persistent pulmonary hypertension. In contrast, other patients were treated as soon as six months after the PEA. Fifth, this was a relatively short-term study. Thus, the long-term efficacy of BPA for patients with residual pulmonary hypertension after PEA remains unknown.

In conclusion, supplemental BPA could be a promising therapeutic strategy for residual pulmonary hypertension after PEA in patients with CTEPH. The periprocedural complication rate was relatively low, despite the fact that intervention seemed to be more difficult. Future collaborative studies are needed to definitively establish the role of supplemental BPA in treating persistent pulmonary hypertension after PEA.

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Conflict of interest statement

The authors have no conflicts of interests to declare.

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