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CLINICAL RESEARCH
Pulmonary circulation

Comprehensive evaluation of the effectiveness and safety of balloon pulmonary angioplasty for inoperable chronic thrombo-embolic pulmonary hypertension: long-term effects and procedure-related complications

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Aims Although balloon pulmonary angioplasty (BPA) improves haemodynamics and short-term prognosis in patients with inoperable chronic thrombo-embolic pulmonary hypertension (CTEPH), the long-term effects of BPA, and procedure-related complications remain to be fully elucidated.

Methods and results From July 2009 to October 2016, we performed a total of 424 BPA sessions in 84 consecutive patients with inoperable CTEPH. We used 3D reconstructed computed tomography to determine target lesions of pulmonary arteries and optical computed tomography to select balloon size, if needed. In 77 patients (92%) who completed the BPA treatment [65 ± 14 (SD) years-old, male/female 14/63], haemodynamics and exercise capacity were examined at 6 months after last BPA and in the chronic phase [>12 months after first BPA, 31 (20, 41) months]. The BPA treatment significantly improved mean pulmonary arterial pressure (38 ± 10 to 25 ± 6 mmHg), pulmonary vascular resistance (7.3 ± 3.2 to 3.8 ± 1.0 Wood units), and 6-minute walk distance (380 ± 138 to 486 ± 112 m) (all $P < 0.01$), and the improvements persisted throughout the follow-up period (43 ± 27 months) ($N = 53$). In the 424 sessions, haemoptysis was noted in 60 sessions (14%), and non-invasive positive pressure ventilation (NPPV) was used to treat haemoptysis and/or hypoxemia in 33 sessions (8%). Furthermore, 5-year survival was 98.4% (only one patient died of colon cancer) with no peri-procedural death.

Conclusion These results indicate that BPA improves haemodynamics and exercise capacity in inoperable CTEPH patients with acceptable complication rate and that the beneficial haemodynamic effects of BPA persist for years with resultant good long-term prognosis.

Keywords Chronic thrombo-embolic pulmonary hypertension • Balloon pulmonary angioplasty • Long-term effects • Prognosis

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Introduction

Chronic thrombo-embolic pulmonary hypertension (CTEPH) is characterized by persistent pulmonary arterial obstruction due to organized thrombus and fibrous tissue.[1–4] Although pulmonary hypertension (PH)-targeted drugs have been developed in the last decade, CTEPH still remains a serious disease with poor prognosis.[5]

While pulmonary thromboendarterectomy (PEA) is an established treatment for CTEPH,[6–8] feasible and effective therapeutic strategy for inoperable CTEPH remains to be developed. In 2001, Feinstein *et al.*[9] reported for the first time the possible effectiveness of balloon pulmonary angioplasty (BPA) for 17 patients with inoperable CTEPH, which was defined as either distal pulmonary vascular lesions ($n = 7$) or severe comorbidities that made PEA difficult to perform ($n = 8$). However, they also reported the frequent adverse effects of the procedures, including haemoptysis due to re-perfusion injury that required oral intubation.[9] In the last decade, we and others reported that BPA improves haemodynamics, cardiac function, and exercise capacity of inoperable CTEPH without severe complications.[10–15] Pulmonary thromboendarterectomy is an established method as a treatment for CTEPH patients, and in experimental centre, both the short-term and the long-term effects of PEA on haemodynamics and prognosis have been already reported to be excellent.[16,17] Follow-up right heart catheterization (RHC) after PEA revealed that improvement of pulmonary vascular resistance persisted for 1 year after PEA.[16] It was also demonstrated that PEA significantly improved haemodynamics and exercise capacity, which lasted for 4 years after PEA.[17] Although we previously reported that BPA improved haemodynamics and short-term prognosis (2-year survival) compared with historical controls,[10] the long-term effects of BPA on haemodynamics and prognosis remain to be fully elucidated.

Regarding the complications of BPA procedures,[9] we have modified BPA strategies, using 3D reconstructed computed tomography (CT) to determine target lesions of the pulmonary arteries and optical computed tomography (OCT) to select appropriate balloon size, if needed. However, the details of complications with the recent BPA strategies also remain to be elucidated.

In the present study, we thus aimed to comprehensively examine the long-term haemodynamic and prognostic effects of BPA and the procedure-related complications.

Methods

The protocols of the present study were approved by the institutional review board of the Tohoku University Hospital (No. 2014-1-875). We obtained a written consent for participation from all patients.

Patients

We enrolled 84 consecutive patients with CTEPH who underwent BPA in our hospital from July 2009 to October 2016 (*Figure 1*). They were diagnosed as having inoperable CTEPH based on the standard criteria.[2,3] All patients had symptoms of World Health Organization functional class II or more. We performed a total of 424 BPA sessions (5.0 ± 2.5 procedures/patient) in 84 patients, in which we examined the occurrences of complications related to the procedures. Before we started BPA treatment, all patients had been treated with appropriate combination therapy with vasodilators and warfarin. In 77 patients (92%) who completed the BPA treatment, we examined haemodynamics parameters, exercise capacity, and serum levels of brain natriuretic peptide (BNP) and compared the data before first BPA session and those at 6 months after last BPA session (*Figure 1*). Since the BPA treatment was still ongoing in seven patients, they were excluded from the final analysis. Moreover, in 53 patients (63%), we examined the same parameters in the chronic phase (at the time of >12 months after last BPA sessions, *Figure 1*). Among 77 patients, 24 were excluded from the analysis in the chronic phase for the following reasons; last BPA procedure was performed within 12 months of the end of study period in 13, and no agreement was obtained for follow-up RHC in the remaining 11. At these four points (see Supplementary material online, *Figure S1*), information about medications including vasodilators and anticoagulation was collected based on the clinical charts (*Figure 1*).

Furthermore, we also retrospectively examined 20 patients with inoperable CTEPH who were diagnosed during 1992–2008 without BPA or PEA (historical control group). In this period, 35 inoperable CTEPH patients were referred to our hospital, 15 underwent BPA, and the remaining 20 were defined as the historical control group without BPA or PEA.

Balloon pulmonary angioplasty

We performed BPA via the right femoral vein to treat pulmonary arterial branches.[10,18] As we previously described, we selected vessels that were appropriate for ballooning on the basis of comprehensive findings, including webs, bands, abrupt narrowing, and complete obstructions, obtained by pulmonary angiography,[19] 3D-reconstructed CT[20] and intravascular

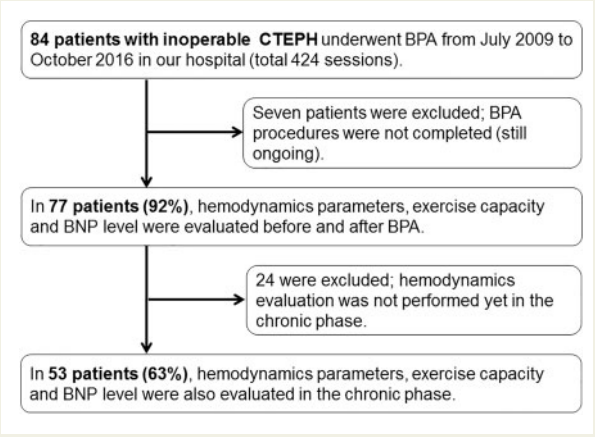

Figure 1 Study flow chart. We performed a total of 424 BPA sessions in 84 consecutive patients with chronic thrombo-embolic pulmonary hypertension in our hospital from July 2009 to October 2016. In 77 patients (92%) who completed the balloon pulmonary angioplasty (BPA) therapy, haemodynamics parameters, exercise capacity, and serum level of brain natriuretic peptide were examined at first right heart catheterization (RHC) in our hospital (i), before first BPA session (ii), and at 6 months after last BPA session (iii). In 53 patients (63%), the same parameters were again examined in the chronic phase (iv) (at the time of > 12 months after last BPA sessions). Among the 84 patients, 7 were excluded from the analysis since the BPA treatment was still ongoing. Among 77 patients, 24 were excluded from the analysis in the chronic phase for the following reasons; in 13 patients, last BPA procedure was performed within 12 months of the end of study period, and the remaining 11 did not agree with follow-up RHC.

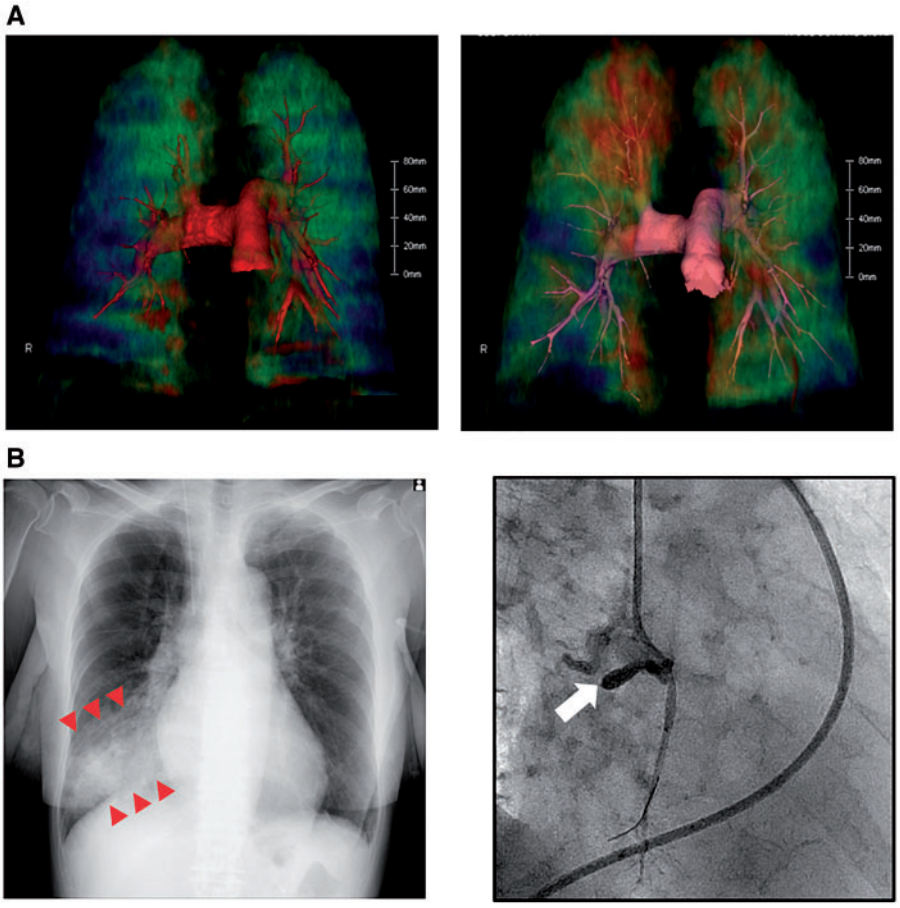

Figure 2 Representative images of major complications of BPA. (*A*) Fusion images of 3D-reconstructed pulmonary angiography and pulmonary perfusion images derived from dual-energy computed tomography in a chronic thrombo-embolic pulmonary hypertension patient before (left) and after (right) balloon pulmonary angioplasty (BPA). Lung field in blue and red indicates low and normal pulmonary perfusion area, respectively. In this patient, mean pulmonary arterial pressure was decreased from 43 mmHg to 19 mmHg after four sessions of BPA. (*B*) (Left) Chest X-ray on the day of BPA showing segmental pulmonary oedema at the right lower lung field (red arrowheads). In this patient, BPA was performed to the pulmonary artery of the right lower lobe. (Right) Selective pulmonary angiography showing pulmonary arterial dissection at the pulmonary artery segment of the left lower lobe after BPA (white arrow).

imaging modalities including OCT.[4,21,22] Fusion images of 3D-reconstructed pulmonary angiography and pulmonary perfusion images derived from dual-energy CT were used to select target lesion, where pulmonary lesions including stenosis and/or occlusion and low-perfusion area were noted (*Figure 2A*).[20] Under continuous intravenous infusion of heparin (400 U/h), we used soft-tipped 0.035-inch wire (Large Focus®, Terumo, Tokyo, Japan) to selectively engage a 6-Fr guiding catheter (Heartrail®, Terumo) to targeted vessels with a 6-Fr long sheath (Large Focus Introducer®, Terumo). Appropriate guiding catheters (JR4 or MP) were selected to suit the morphology of targeted vessels. During BPA procedures, oxygen was given at a flow rate of 5 L/min in all of the patients. We selected a balloon size based on a targeted vessel diameter measured by angiography and/or intravascular imaging modalities including OCT (St. Jude Medical, St. Paul, MN, USA) or optical frequency domain imaging (OFDI) (Terumo). After crossing a 0.014-inch guide wire (Chevalier®, Cordis, CA, USA) through the lesion, we carefully inflated a balloon (IKAZUCHI® for the lesion of 1.5–3.5 mm in diameter, and Bandicoot® for the lesion of 4.0–6.0 mm in diameter, KANEKA, Osaka, Japan).[10,18] Prompt visualization of pulmonary venous flow through targeted pulmonary arteries was defined as successful ballooning.[13] The BPA procedures were repeated at an interval of 4–8 weeks in all patients, and additional BPA was repeated until mean PAP was decreased below 30 mmHg[23,24] and/or no more treatable lesions were found.[10]

Measurements

Before BPA procedures, we performed RHC with a 6-Fr Swan-Ganz catheter (Edwards Life Science, Irvine, CA, USA) in supine position. Haemodynamic parameters, including mean pulmonary arterial pressure (mPAP), pulmonary arterial wedge pressure (PAWP), right atrial pressure (RAP), cardiac output, and pulmonary vascular resistance (PVR), were evaluated at the four points described above (see Supplementary material online, *Figure S1*). PAWP and RAP were measured at end-expiration, and mPAP was calculated using average systolic and diastolic PAP of consecutive 10 beats. Cardiac output was determined by the indirect Fick method and corrected for body surface area (cardiac index, CI). Cardiac index was also determined by thermodilution at the timing of first RHC, post-BPA, and chronic phase. SaO_2 was compared in 45 patients in whom

oxygenation was evaluated in room air. At the time of first RHC, intra-cardiac shunt was evaluated by dye dilution curves,[25] confirming that none of them had intra-cardiac shunt. Before haemodynamics study, exercise capacity was evaluated by 6-minute walk distance (6MWD), and serum levels of BNP were measured at each point.

Balloon pulmonary angioplasty procedure-related complications

In the present study, BPA procedure-related complications were defined as haemoptysis, pulmonary oedema, use of non-invasive positive pressure ventilation (NPPV), oral intubation and mechanical ventilation, pulmonary arterial dissection, and peri-procedural death.[26] Haemoptysis during or on the day of the procedure was defined as procedure related. Pulmonary oedema was defined as X-ray opacity in the lung segment treated with BPA on the day or next day of the procedure (*Figure 2*B). Non-invasive positive pressure ventilation (NPPV) or mechanical ventilation with oral intubation for haemoptysis or pulmonary oedema was performed by operators' decisions, if needed. Pulmonary arterial dissection was defined as a pooling of contrast media at a target lesion for BPA caused by a guiding catheter, guide wire, and/or balloon catheter (*Figure 2*B). Peri-procedural death was defined as death that occurred within 30 days of the procedure.

Statistical analysis

Continuous variables are expressed as mean ± SD or median [inter-quartile range (IQR)]. Change in each parameter was compared using the paired *t*-test or the Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical data, as appropriate. Cochran–Armitage trend test was used to evaluate temporal change in complication rate of the BAP procedure. Five-year survival was estimated with Kaplan–Meier method and was compared between the BPA and the historical control groups with log-rank test. Furthermore, to reduce the confounding effects related to differences in background between the two groups, we used the propensity score (PS) methods. For calculation of PS, we used a logistic regression model in which the treatment status (historical control vs. BPA) was regressed for the following 8 baseline characteristics including established risk factors[27]; age, mPAP, CI, PAWP, RAP, PVR, WHO functional class, and PH-specific therapy. Also, we conducted two analyses to adjust the difference in patient characteristics between the two groups; PS matching and the inverse probability of treatment weighted (IPTW) method with Cox regression modelling. A *P*-value <0.05 was considered to be statistically significant. All analyses were performed using JMP 12.2 (SAS Institute, Cary, NC, USA) and R 3.2.3 (R Foundation for Statistical Computing, Vienna; http://www.R-project.org/).

Results

Patient characteristics

We enrolled 84 consecutive patients in the present study, and 77 (92%) who completed the BPA procedures were selected for evaluation of the effects of BPA (*Figure 1*). Their baseline characteristics before first BPA are shown in *Table 1*. Mean age was 65 ± 14 year-old, and 63 of them (82%) were female. Median follow-up period from first RHC to last haemodynamic evaluation was 38 (24, 56) months. Mean values of mPAP, PVR, and CI and median BNP levels were 38 ± 10 mmHg, 7.3 ± 3.2 Wood units, WU, 2.7 ± 0.7 L/min/m^2, and 108 (43, 198) pg/dL, respectively. Mean 6MWD was 380 ± 138 m. They had symptoms of WHO functional class II or more [II/III/IV, 52/18/7 (68/23/5%), respectively]. Pulmonary vasodilators were administrated in almost all patients (74/77, 96%), and all patients received anticoagulant therapy with warfarin. Epoprostenol was used in 12 patients (12/77, 16%) and oxygen therapy in 64 patients (64/77, 83%).

Table 1 Patient characteristics before BPA

	N = 77
Age (years)	65 ± 14
Female (%)	63 (82%)
Median follow-up period (months)	38 (24, 56)
Number of BPA procedures	5.0 ± 2.5/patient
Total session number	424 (*N* = 84)[a]400 (*N* = 77)[b]
Haemodynamics	
mPAP (mmHg)	38 ± 10
PAWP (mmHg)	10 ± 4
RAP (mmHg)	6 ± 3
CI (L/min/m^2)	2.7 ± 0.7
PVR (WU)	7.3 ± 3.2
BNP (pg/dL)	55.8 (24.9, 220)
Exercise capacity	
6MWD (min)	380 ± 138
WHO functional class (II/III/IV, %)	52/18/7 (68/23/5)
Medications (%)	
Pulmonary vasodilators	74 (96)
PDE5i	56 (73)
ERA	13 (17)
Oral PGI_2	34 (44)
Epoprostenol	12 (16)
sGC	13 (17)
Diuretics	39 (51)
Anticoagulants	77 (100)
Oxygen therapy (%)	64 (83)

Continuous variables are expressed as mean ± SD. BNP level was expressed as median [inter-quartile range (IQR)] due to its non-normal distribution.
BNP, brain natriuretic peptide; CI, cardiac index; ERA, endothelin receptor antagonists; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PDE5i, phosphodiesterase-5 inhibitors; PVR, pulmonary vascular resistance; RAP, right atrial pressure; sGC, soluble guanylate cyclase; 6MWD, 6-minute walk distance, BPA, balloon pulmonary angioplasty; WHO, World Health Organization, SD, standard deviation.
[a]Total number of BPA procedures performed in the study period (patient number = 84).
[b]The number of BPA procedures performed for 77 patients with haemodynamics and prognosis data.

Balloon pulmonary angioplasty procedures

In a total of 424 BPA sessions, 1536 lesions were treated. The treated lesions were located in lobar branches (7 lesions, 0.4%), segmental branches (323 lesions, 21%), and sub-segmental branches (1206 lesions, 78.5%). Ring-like lesions, occluded lesions, and web lesions were noted in 73 (5%), 132 (9%), and 1331 lesions (86%), respectively. Average number of opened lesions per session was 3.7 ± 1.7, and 2.5 ± 1.0 segments were treated per session. Average time of the procedures including RHC and BPA was 170 ± 46 min per session (*N* = 260 sessions, from 2013 to 2016), and average volume of

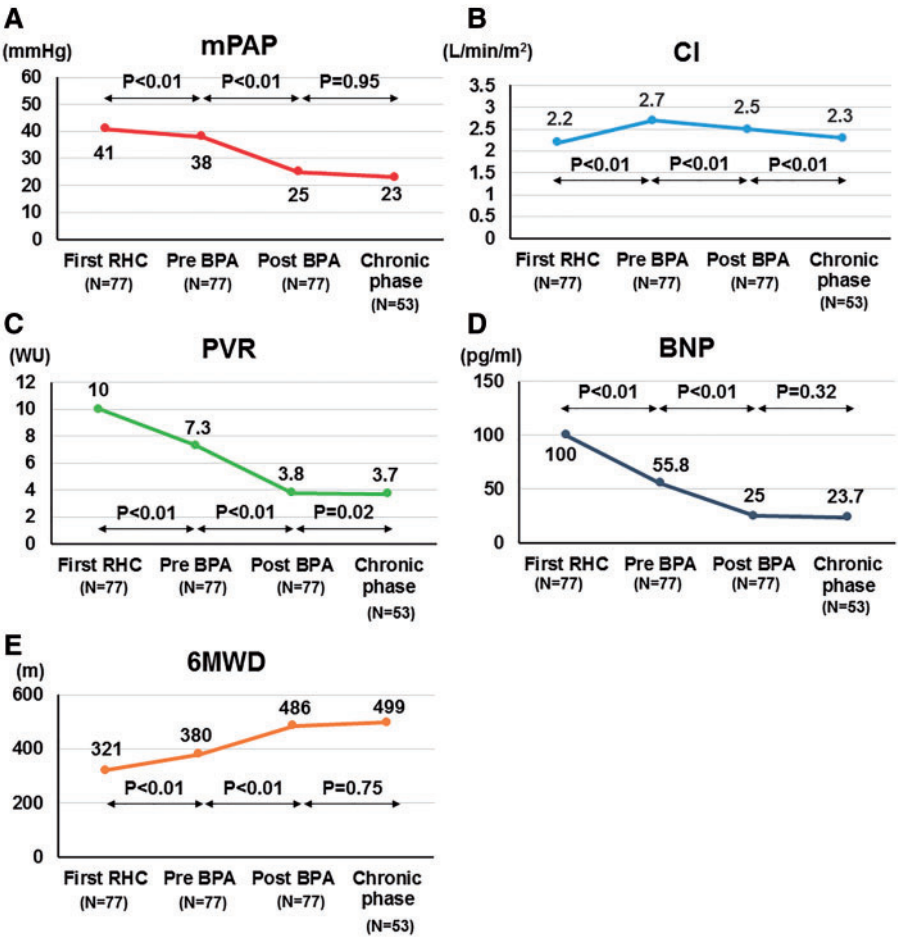

Figure 3 Changes in haemodynamics, exercise capacity, and BNP before and after balloon pulmonary angioplasty (BPA) therapy. (*A*) Mean pulmonary arterial pressure (mPAP). (*B*) Cardiac index (CI). (*C*) Pulmonary vascular resistance (PVR). (*D*) Brain natriuretic peptide (BNP). (*E*) 6-minute walk distance (6MWD). Haemodynamics, exercise capacity, and serum BNP levels were examined at the following four points; at first right heart catheterization (RHC) ($N = 77$), just before first BPA after medication ($N = 77$), at 6 months after last BPA ($N = 77$), and in the chronic phase (at the time of > 12 months after last BPA sessions, $N = 53$).

contrast media used was 192 ± 52 mL per session ($N = 260$ sessions, from 2013 to 2016). Radiation dose and fluoroscopy time were 723 ± 440 mGy and 79 ± 25 min per session, respectively ($N = 260$ sessions, from 2013 to 2016). No patients had radiation-induced dermatitis in the present study.

Short-term effects of balloon pulmonary angioplasty

Medical therapy alone significantly improved mPAP (41 ± 10 to 38 mmHg), CI (2.2 ± 0.6 to 2.7 ± 0.7 L/min/m^2), PVR (10 ± 4.6 to 7.3 ± 3.2 WU), BNP [100 (34, 244) to 55.8 (24.9, 220) pg/dL], and 6MWD (321 ± 136 to 380 ± 138 m) (all $P < 0.01$) (*Figure 3A–E*). When comparing these parameters between before first BPA (pre-BPA) and 6 months after last BPA (post-BPA), BPA showed significant additional improvement except for CI [mPAP, 38 ± 10 to 25 ± 6 mmHg; PVR, 7.3 ± 3.2 to 3.8 ± 1.0 WU; BNP 55.8 (24.9, 220) to 25 (16.1, 50) pg/dL; 6MWD 380 ± 138 to 486 ± 112 m] (all $P < 0.01$) (*Figure 3A, C–E*). Even after BPA, CI was slightly but significantly decreased (2.7 ± 0.7 to 2.5 ± 0.5 L/min/m^2, $P < 0.01$) (*Figure 3B*). Compared with CI at first RHC, CI post-BPA determined by both indirect Fick and thermodilution methods was significantly improved (see Supplementary material online, *Table S1*). After BPA, heart rate was significantly decreased from 74 ± 13/min to 62 ± 10/min, resulting in significant increase in stroke volume index after BPA (37 ± 8 mL/min/m^2 to 40 ± 8 mL/min/m^2, $P < 0.01$) (see Supplementary material online, *Table S1*). At 6 months after last BPA, the number of patients who received any vasodilators was significantly decreased from 96% (74/77) to 68% (52/77) ($P < 0.01$) (*Table 2*). Similarly, the number of patients who required oxygen therapy was significantly decreased from 83% (64/77) to 49% (41/77) ($P < 0.01$) (*Table 2*). Importantly, all 12 patients who had received intravenous epoprostenol before BPA were able to discontinue it after BPA (*Table 2*).

Table 2 Change in medications before and after BPA

	First RHC (*N* = 77)	Pre-BPA (*N* = 77)	Post-BPA (*N* = 77)	Chronic phase (*N* = 53)
Any vasodilators (%)	39 (51)	74 (96)	52 (68)[a]	22 (41)*†
Single (%)	18 (23)	39 (51)	22 (29)	10 (19)
Double (%)	18 (23)	28 (34)	22 (29)	9 (17)
Triple (%)	3 (4)	7 (9)	8 (10)	3 (4)
PGI2 iv (%)	6 (8)	12 (16)	0 (0)	0 (0)
Oxygen therapy (%)	43 (56)	64 (83)	41 (53)*	26 (49)

BPA, balloon pulmonary angioplasty; RHC, right heart catheterization.
*$P < 0.01$ vs. pre-BPA,
†$P < 0.01$ vs. post-BPA.

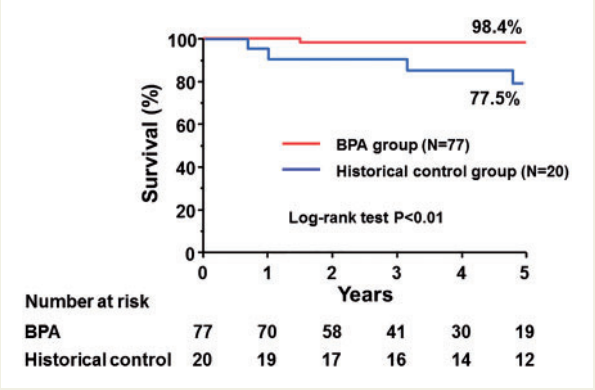

Figure 4 Five-year survival in inoperable chronic thromboembolic pulmonary hypertension (CTEPH) patients who completed balloon pulmonary angioplasty (BPA) therapy. Five-year survival in inoperable CTEPH patients who completed BPA therapy was 98.4%. Only one patient died of colon cancer at 13 months after last BPA session. The long-term prognosis of CTEPH patients was significantly better in the BPA group compared with the historical control group without BPA.

Long-term effects of balloon pulmonary angioplasty

In 53 patients (69%), we repeated haemodynamic evaluation in the chronic phase. Among them, median follow-up period from last BPA to last haemodynamic evaluation was 31 (20, 41) months. Importantly, the improvements of haemodynamics, exercise capacity, and plasma BNP levels lasted during the study period (*Figure 3A–E*). Among the 77 patients who completed BPA treatment, 5-year survival rate was excellent (98.4%) and only one patient died of colon cancer at 13 months after last BPA (*Figure 4*). Although haemodynamic variables and exercise capacity were comparable between the BPA and the historical control groups (see Supplementary material online, *Table S2*), 5-year survival was significantly better in the BPA group than in the historical control group (*Figure 4*). Although, the patient characteristics was comparable between the two groups after PS matching (see Supplemental material online, *Table S3*), 5-year survival was significantly better in the BPA group than in the historical control group (see Supplementary material online, *Figure S2*).

Table 3 Complications of BPA

Complications (%)	*N* = 424[a]
Pulmonary arterial dissection	30 (7)
Haemoptysis	60 (14)
Pulmonary oedema	4 (1)
Use of NPPV	33 (8)
Oral intubation	1 (<1)
Peri-procedural death	0 (0)

NPPV, non-invasive positive pressure ventilation.
[a]Total number of BPA procedures performed in the study period (patient number = 84).

Furthermore, Cox regression model with IPTW method also showed that BPA significantly reduced all-cause mortality (HR 0.02, 95% confidential interval 0.00 to 0.14, $P < 0.01$). The number of patients with any vasodilators in the chronic phase was significantly decreased from 6 months after BPA [68% (52/77) to 42% (20/53), $P < 0.01$] (*Table 2*). In contrast, the number of patients who required oxygen therapy was comparable between 6 months after BPA and the chronic phase [49% (26/53) vs. 53% (41/77), $P = 0.64$] (*Table 2*).

Balloon pulmonary angioplasty procedure-related complications

To examine the BPA procedure-related complications, all 424 sessions in 84 patients were reviewed (*Table 3*). Pulmonary angioplasty dissection and haemoptysis were noted in 30 (7%) and 60 sessions (14%), respectively. Haemoptysis was noted in 45 sessions during BPA procedures and in 15 sessions after the procedure. None of the patients with PA dissection showed haemoptysis or needed any additional transcatheter or surgical procedures or NPPV. Non-invasive positive pressure ventilation was used in 33 sessions (8%); 29 for haemoptysis, and 4 for segmental pulmonary oedema. Non-invasive positive pressure ventilation was used for haemostasis except for four cases with segmental pulmonary oedema and hypoxemia requiring oxygen therapy. Only one patient with haemoptysis subsequently required oral intubation and mechanical ventilation due to aspiration pneumonia. In 25 of the 29 sessions where NPPV was used for haemostasis, we succeeded in archiving haemostasis with NPPV alone,

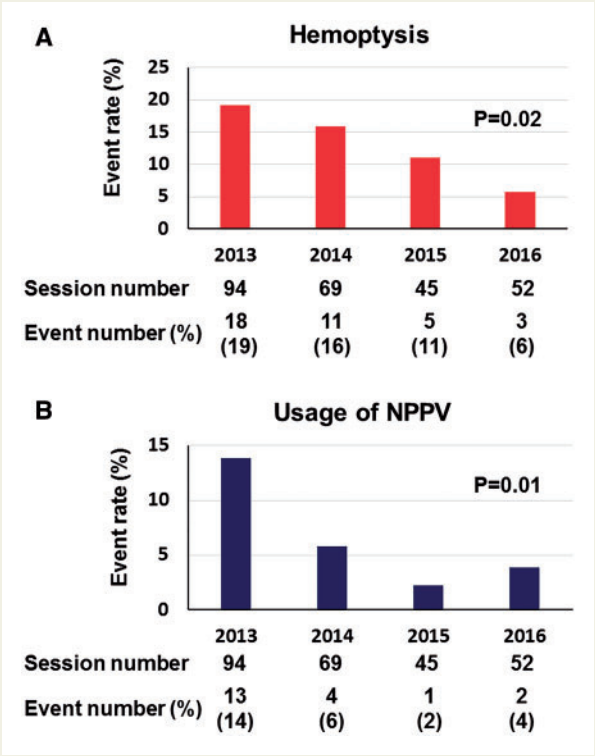

Figure 5 Major complications of balloon pulmonary angioplasty (BPA). (*A*) Occurrence of haemoptysis during or after BPA procedure was significantly decreased for the last 4 years. (*B*) Similarly, the use of non-invasive positive pressure ventilation was significantly decreased in the same period.

and in the remaining 4 sessions, where extravasation of contrast media was noted, additional procedures for haemostasis were required, including long balloon inflation at the proximal of bleeding site for 5–10 min in 3 sessions, and embolization with haemostatic absorbable gelatin sponge (SPONGEL®, GENCO Tibbi Cihazlar SAN. TIC. LTD. STI, Turkey) in one session. Importantly, there was no peri-procedural death. In the last 4 years, the occurrence of haemoptysis and the use of NPPV were significantly decreased (*Figure 5A and B*). Haemoptysis was noted in 37 sessions in 22 patients in the last 4 years. Among the 22 patients, 15 (68%) had haemoptysis only once (15/36 sessions, 40%), whereas the remaining 7 (32%) repeated haemoptysis two to four times (22/37 sessions, 60%).

Discussion

The novel findings of the present study were as follows: (i) in patients with inoperable CTEPH, BPA significantly improved haemodynamics and exercise capacity and plasma BNP levels on the top of optimal medical therapy, (ii) the improvements of these parameters by BPA lasted during the study period, (iii) long-term prognosis was excellent in the patients who completed BPA, and (iv) the procedure-related complications were noted at acceptable level. Although we and others previously demonstrated that BPA improved haemodynamics and short-term prognosis,[10,11,19] long-term effects of BPA remained to be elucidated. To the best of our knowledge, this is the first study that comprehensively demonstrates the long-term effects of BPA on haemodynamics, exercise capacity, and prognosis in patients with inoperable CTEPH.

Long-term effects of balloon pulmonary angioplasty

Recent study reported that inoperable CTEPH patients had poorer prognosis compared with CTEPH patients who underwent PEA.[27] Furthermore, medical therapy improved haemodynamics but not prognosis in those patients.[27] In the present study, a half of the patients had already received vasodilators when referred to our hospital. Since we started or added vasodilators and/or diuretics before BPA to stabilize haemodynamics, almost all patients (96%) received vasodilators at the time of first BPA (*Table 1*). This medical therapy caused significant improvement of haemodynamics and exercise capacity, and BPA further improved these parameters (*Figure 3*). At 6 months after BPA, some patients discontinued medications based on the decision by attending doctors. Although CI was slightly but significantly reduced after BPA, it remained within the normal range and was associated with significant improvement of arterial O_2 saturation (SaO_2) and reduction in heart rate (see Supplementary material online, *Table S1*). Thus, we consider that the slight reduction in CI associated with improvement of SaO_2 actually reflects the effect of the BPA therapy. Furthermore, we have previously reported that BPA improves RVEF as evaluated by MRI.[15] In the present study, 6MWD was also dramatically improved after BPA despite the reduction in CI (see Supplementary material online, *Table S1*). These findings indicate that BPA actually improves exercise response of cardiac output. Although it was repeatedly reported that haemodynamic improvement by PEA lasted for 4 years,[16,17,27] only one study showed that haemodynamic improvement by BPA lasted for 1 year.[19] In the present study, we were able to demonstrate for the first time that haemodynamic improvement by BPA lasted for 3 years.

We also have recently demonstrated that haemodynamic improvement by BPA results in significant improvement of glucose tolerance, renal and vascular functions, and nutritional status.[28] Importantly, there were positive correlations between the extents of haemodynamic improvements and those of other improvements.[28] Furthermore, we have recently demonstrated that BPA improves oxygenation through decrease in intra-pulmonary shunt.[29] Also, we have recently demonstrated with cardiac magnetic resonance that BPA improves biventricular functions in CTEPH patients.[15] We consider that these multiple haemodynamic beneficial effects of BPA may improve systemic metabolic dysfunctions in those patients. In the present study, only one patient died of colon cancer at 13 months after last BPA, and the 5-year survival was excellent (98.4%). Although in the historical control group, current PH-specific medications were unavailable, the long-term prognosis was significantly better in the BPA group than in the historical control group. We consider that these persistent improvements of haemodynamics, exercise capacity, and metabolic status should improve the long-term prognosis of CTEPH patients. In the present study, 12 patients had residual pulmonary hypertension (mPAP > 30 mmHg) after BPA treatment, which could be caused by residual occlusion of small pulmonary arteries.[30] It has been recently demonstrated that diastolic

PAP is associated with residual pulmonary hypertension,[31] suggesting that residual small pulmonary artery lesions could attenuate haemodynamics effects of BPA. In addition, lesion type of CTEPH evaluated by OCT may affect the outcome of BPA, where web lesions are most suitable for BPA.[32]

Balloon pulmonary angioplasty procedure-related complications

In the first pioneering study of BPA for CTEPH patients, although significant improvements of haemodynamics and exercise capacity were achieved, high incidence of procedure-related complications was also noted; among a total of 18 patients treated, 11 developed reperfusion pulmonary oedema, 3 of them required mechanical ventilation, and one patient died from reperfusion pulmonary oedema.[9] In this study, wire perforation was noted in one case, but the incidence of haemoptysis was not reported.[9] A recent study in Japan reported that the incidence of haemoptysis was 15.6% in all BPA procedures (from November 2004 to October 2010), but has been recently improved to 10.2% (from November 2010 to September 2011).[19] The incidence of haemoptysis in the present study was similar to this study, and has been significantly decreased in the last 4 years, suggesting that there could be a learning curve to safely perform BPA. We consider that BPA should be performed by operators who are well trained in BPA procedures and have experiences on diagnosis and treatment of PH in general and CTEPH in particular. In Japan, 11 institutes including us have been certified for BPA therapy by the Japanese Circulation Society (Japanese population is approximately 120 millions).

Haemoptysis may be caused not only by pulmonary re-perfusion injury but also by guide wire perforation. Indeed, in the present study, among the 60 cases with haemoptysis, only 3 showed segmental pulmonary oedema after BPA, and remaining 57 showed no typical X-ray opacity. In the first study of BPA for CTEPH, 0.035-inch guide wire was used for the procedure.[9] Since 0.014-inch guide wire is currently used for BPA in Japan, procedure-related complications should be decreased. As described in the Results section, the patients who had haemoptysis may repeat haemoptysis. Lesion type of CTEPH evaluated by angiography may affect complication rate, where higher complication rate is noted in web lesions in highly tortuous small vessels.[26]

In the present study, NPPV was used for haemostasis except for four patients with segmental pulmonary oedema. Although only one patient with haemoptysis subsequently required mechanical ventilation due to aspiration pneumonia, NPPV worked effectively in all the remaining cases. We usually prepare NPPV in advance for haemoptysis during BPA procedures. Pulmonary arterial dissection was another major complication of BPA, however, it has never caused bleeding or use of NPPV. We consider that reduction in complications may be associated with improved BPA procedures with 3D reconstructed CT and OCT and improvement of operator's skills for the procedure.

Study limitations

Several limitations should be mentioned for the present study. First, the present study is a single-centre study with a relatively small number of patients. Therefore, the present findings need to be confirmed in future multi-centre studies with a large number of patients. Second, when compared with a recent study,[27] the patients in the present study had relatively less severe symptoms and haemodynamic conditions, which might have been associated with good prognosis. Also, in contrast to the international registries,[27,33] the prevalence of CTEPH is higher in females than in males in Japan, where sex difference in the positive rate of HLA-B 5201 may be involved.[34] Although no sex differences were noted in terms of haemodynamics or efficacy of BPA in the present study (date not shown), caution should be taken in generalizing the results to Western populations. Third, some patients showed residual pulmonary hypertension even after completion of BPA therapy. This is probably because of the involvement of small pulmonary arteries,[30] for which new therapeutic strategy needs to be developed. Fourth, in the present study, not all patients were examined in the chronic phase of BPA. The patient selection might have affected the long-term effects of BPA on haemodynamics and exercise capacity in CTEPH patients. Fifth, we perform BPA for inoperable CTEPH patients with distal pulmonary arterial lesions and/or high-risk conditions including high age, several comorbidities, or frailty. In the present study, out of the 1536 lesions treated with BPA, 323 (21%) were segmental lesions, suggesting that some of them might be potential candidates for PEA. Finally, although BPA improved haemodynamics on the top of medical therapy (*Figure 3*), PH-specific medical therapy was heterogeneous, depending on the decisions of each attending doctor. Thus, further studies are needed to demonstrate the efficacy of the combination of medical therapy and BPA or superiority of BPA to PH-specific drug therapy.

Conclusions

Balloon pulmonary angioplasty improves haemodynamics and exercise capacity in inoperable CTEPH patients with acceptable complication risk. Although, the beneficial effects of BPA last for years with resultant good long-term prognosis of those patients, multicentre studies with a large number of patients are needed.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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