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French experience of balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension

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Abstract

Aims: To evaluate safety and efficacy of balloon pulmonary angioplasty (BPA) in a large cohort of patients with chronic thromboembolic pulmonary hypertension (CTEPH).

Methods and results: From 2014 to 2017, 184 inoperable CTEPH patients underwent 1006 BPA sessions. Safety and efficacy during the first 21 months (initial period) were compared with those of the last 21 months (recent period). A total of 154 patients had a full evaluation after a median duration of 6.1 months. Overall, there was a significant improvement in NYHA functional class, 6-min walk distance (mean change, +45 m), and a significant decrease in mean pulmonary artery pressure (PAP) and in pulmonary vascular resistance (PVR) by 26% and 43%, respectively. The percentage decrease of mean PAP and PVR were 22% and 37% in the initial period versus 30% and 49% in the recent period, respectively ($p<0.05$). The main

complications included lung injury (LI) which occurred in 9.1% of 1006 sessions (13.3% in the initial period versus 5.9% in the recent period, p<0.001). Per-patient multivariate analysis revealed that baseline mean PAP and the period during which BPA procedure was performed (recent versus initial period) were the strongest factors related to the occurrence of LI. Three-year survival was 95.1%.

Conclusion: This study confirms that a refined BPA strategy improves short-term symptoms, exercise capacity and hemodynamics in inoperable CTEPH patients with an acceptable risk-benefit ratio. Safety and efficacy improve over time, underscoring the unavoidable learning curve for this procedure.

Keywords: chronic thromboembolic pulmonary hypertension; balloon pulmonary angioplasty; lung injury

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is caused by the obstruction of the pulmonary arteries with non-resolving, organized fibrotic clots leading to elevated pulmonary vascular resistance (PVR), severe pulmonary hypertension (PH), right heart failure, and ultimately death (1-5).

Pulmonary endarterectomy (PEA) remains the recommended treatment for patients with operable CTEPH (6-12). However, about 40% of CTEPH patients are non-eligible for surgery

due to distal lesions or the presence of comorbidities (10). Today, balloon pulmonary angioplasty (BPA), an endovascular procedure to widen narrowed -or obstructed pulmonary arteries, is an emerging treatment option for patients with inoperable CTEPH (12, 13). This technique was first developed for treating congenital stenosis of pulmonary arteries (14). In CTEPH, Feinstein *et al.* reported in 2001, a first case series of 18 patients with a modest efficacy on pulmonary hemodynamics and a high rate of severe complications potentially lethal (15).

Over the last years, with refinements in the technique, several limited cases series, mainly from Japan, have reported major improvement in the safety and efficacy of BPA (16-24). These encouraging results have been recently confirmed in a multicenter registry of 308 patients with CTEPH treated with BPA in 7 centers in Japan between 2004 and 2013. This study demonstrated favorable effect of BPA on hemodynamics with a decrease in PVR of more than 50%. However, the complications rate remained elevated and mainly included non-severe lung injury (LI) which occurred in 17.8% of cases (25).

In Europe, over the recent years, the number of centers starting a BPA program is growing rapidly. A first series of 56 CTEPH patients, who underwent BPA in Germany, has been recently reported and demonstrated a significant hemodynamic improvement associated with a mortality rate of 1.8% (26).

We report the experience of BPA at the French reference center for Pulmonary Hypertension

(Paris-Sud University, Hospital Bicetre and Hospital Marie Lannelongue) where a BPA program was initiated in 2014.

METHODS

Patient Selection

All patients referred to Paris-Sud University for suspicion of CTEPH were evaluated during a multidisciplinary meeting including experienced surgeons for PEA, interventional radiologists/cardiologists, radiologists experienced in pulmonary vascular imaging and pulmonologists with expertise in pulmonary hypertension, as recommended by current guidelines (12). Patients underwent a complete workup including medical history and comorbidities assessment, ventilation/perfusion lung scan, spiral computed tomography (CT) scan with mandatory bi-planar reconstructions, digital subtraction pulmonary angiography and right heart catheterization. Eligibility for BPA was decided on the basis of a consensus among the multidisciplinary team. All the patients were informed about the potential risks and benefits of this interventional procedure and provided written informed consent.

Patient evaluation before and after BPA

All patients underwent a comprehensive clinical evaluation before the first BPA (baseline), before each BPA session and 3 to 6 months after the last BPA. Assessment at baseline and at

the last evaluation included New York Heart Association (NYHA) functional class, 6-minute walk distance (6MWD), blood gases on room air, serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) and complete right heart catheterization. Assessment before each new BPA session included NYHA functional class, laboratory studies and measurement of pulmonary artery pressure.

BPA technique

Four experienced operators (two interventional cardiologists and two interventional radiologists) performed the BPA procedures. All operators had more than 10 years of practice in endovascular treatment. BPA was performed using techniques similar to those previously described (16, 18). We approached the pulmonary arteries through the right femoral vein using peripheral guiding sheath (6 French Destination 65 cm; Terumo, Tokyo, Japan. 7 French ArrowFlex 80 cm; Teleflex, Durham, NC), with anticoagulation continued with a dosage of vitamin K antagonist to maintain an INR~3.0. A right-heart catheterization was performed at the beginning of the procedure to measure mean pulmonary artery pressure (mPAP) and cardiac output (CO) by thermodilution. A 6 French guide catheter (Launcher, Multipurpose, Judkins right and left 4.0, Amplatz right and left; Medtronic, MN) was inserted through the peripheral guiding sheath and was advanced to the target vessels. A dose of heparin (2000-3000 units) was then administered. Based on selective pulmonary angiography,

a 0.014-inch guide wire (Whisper MS; or Pilot 50-150; Abbott Vascular, Santa Clara, CA; PT2; Boston Scientific, Marlborough, MA) was passed across the target lesion. While selecting the target vessels, the lower lobe lesions were preferentially dilated because the pulmonary blood flow at this site is relatively high, thus lowering mPAP. Ring-like stenosis, web and subtotal lesions were targeted in priority. Tortuous lesions were exceptionally targeted and total occlusion lesions were rarely targeted. To approach total occlusion lesions, balloon support or medium tip weight wires (tip load 2.5-2.9g) were used. Furthermore, in cases of severe stenosis, abrupt narrowing, or complete obstruction, a 2.0-mm balloon catheter was initially used to dilate the lesions. Subsequently, the lesions were dilated to an appropriate size using 2.0-mm to 9.0-mm balloon catheters depending on vessel diameter (NC TREK; or Viatrac 14 Plus; Abbott Vascular, Santa Clara, CA; Ryujin Terumo, Tokyo, Japan). We treated 2 to 10 segmental or sub-segmental arteries in each procedure session according to patient severity, time of procedure (< 2 hours) and amount of contrast media given. Two BPA sessions were performed at 2 or 3 days intervals during one hospital admission. Catheterization was repeated at an interval of 3 to 4 weeks and additional BPA sessions were performed until mPAP below 30mmHg was achieved, and/or when we considered that we have treated all accessible lesions.

Definition of complications related to BPA

During the 6th world symposium on pulmonary hypertension, the task force on CTEPH has proposed a definition and classification of complications related to BPA procedures which have been recently published in a specific issue of the *European Respiratory Journal*. In that publication, LI appears to be the most common complication and is characterized by lung opacities in chest X-ray or CT scan with or without hypoxaemia and associated or not with hemoptysis (27). The cause of LI had been thought of reperfusion edema, as well as that of PEA, however recent insight has shown that the main underlying cause was hemorrhage complication due to distal vascular injury which was provoked by iatrogenic wire injury or over dilation of the lesion (13, 21, 27-29).

In our study, complications related to BPA were defined as follows: (1) LI (presence of lung opacities on chest radiograph and/or CT scan with or without hypoxemia and with or without hemoptysis). The severity of LI was considered as, mild (no treatment), moderate (requiring supplemental oxygenation) or severe (requiring mechanical ventilation and/or extracorporeal membrane oxygenation); (2) Hemoptysis; (3) Pulmonary artery perforation; (4) Pulmonary artery dissection; (5) Renal dysfunction.

We analyzed safety and efficacy of BPA for the overall population. We also compared the safety and efficacy results of BPA during the initial period of the program, defined by patients who underwent BPA during the first 21 months (between February 2014 and October 2015)

versus the recent period, defined by the last 21 months (between November 2015 and July 2017).

Statistical analysis

Data were stored in a personal computer-based data spreadsheet. All statistical analyses were performed using GraphPad Prism version 5 (GraphPad Software, La Jolla, CA, USA) and SPSS Statistics 17.0 (IBM, Armonk, NY, USA). Continuous variables are expressed as mean ± standard deviation or median and interquartile range according to variable distribution. Differences in continuous variables, such as patients' age, 6MWD, and hemodynamic characteristics, were compared using the independent Student's *t*-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. Categorical variables, such as gender, NYHA functional class and use of pulmonary arterial hypertension (PAH) targeted therapy or incidence of complications were expressed as number and percentage and were compared using the χ^2 test for independence or Fisher's exact test. Per-patient logistic regression analysis was used to evaluate the predictive variables for LI. The variables with a p-value <0.2 were included in the multivariate analysis.

The Kaplan–Meier method was used to estimate overall survival. For the survival analysis, the date of first BPA session was used as the start point to determine length of survival. The cut-off date was December 31, 2017. Patients who underwent lung transplantation were

censored at the date of transplantation.

For all analyses, the level of statistical significance was set at $p < 0.05$.

RESULTS

Patient characteristics and BPA procedures

Between February 2014 and July 2017 (42 months), 212 patients were considered as eligible for BPA. Twenty eight patients were excluded from the overall analysis because included in the ongoing randomized controlled trial comparing balloon pulmonaRy angioplasty versus riociguAt for the treatment of non-operable Chronic thromboembolic pulmonary hypertEnsion (RACE study, NCT 02634203). Thus, 184 patients were analyzed for safety. As second right heart catheterization after the last BPA has not yet been performed in 30 patients at time of cut-off date, the efficacy analysis was evaluated in 154 patients (**Figure 1**).

Baseline characteristics of the overall population (n=184) are depicted in **Table 1**.

The mean age of the patients was 63±14 years and 51% were male. A history of acute venous thromboembolism was reported in 135 patients (73%). At the time of BPA, 50 patients (27%) had medical conditions increasing the risk of CTEPH and including cardiac pacemaker or indwelling catheter (n=22), splenectomy (n=18), antiphospholipid syndrome (n=7) and myeloproliferative disorder (n=3). Pre-BPA, 94% of patients were in NYHA functional class II or III and 62% were receiving at least one PAH-targeted therapy for at least 3 months.

The main indications for BPA were clot inaccessibility to PEA (81%) and persistent or recurrent PH after surgery (8%). For patients who have been previously operated, the period from PEA to BPA was 68 ± 51 months. During the study period, the 184 patients underwent a total of 1006 sessions with a mean of 5.2 ± 2.4 sessions per patient during the initial period and 5.7 ± 2.1 during the recent period (NS). The median number of treated segments in each patient was 14.0 (range, 10.0-20.0) during the initial period and 16.0 (range, 12.0-21.0) during the recent period (p=0.076).

The fluoroscopy time was 44.4 ± 14.9 min/procedure in the initial period and 42.1 ± 12.3 in the recent period, respectively (p= 0.023). The median duration from first BPA to re-evaluation was 6.1 months (interquartile range: 4.5– 7.5).

Effects of BPA

In the 154 patients who underwent a complete clinical and hemodynamic evaluation after the last BPA procedure, a significant improvement in NYHA functional class, 6MWD and arterial partial pressure of oxygen (PaO_2) was observed. Hemodynamic parameters including right atrial pressure, mPAP, cardiac index and pulmonary vascular resistance (PVR) were also significantly improved. The percentage decrease in mPAP and PVR were 22% and 37% in the initial period compared to 30% and 49% in the recent period, respectively. This greater improvement in mPAP and PVR during the recent period was statistically significant (p=

0.017 and 0.006, respectively). **Table 2** shows the effects of BPA on symptoms, exercise capacity and hemodynamics in the initial and recent periods.

Complications of BPA

Complications related to BPA occurred in 113 of 1006 sessions (11.2% of all sessions and 46% of all patients) and included LI (9.1% of all sessions and 34% of all patients), hemoptysis (7.1% of all sessions), pulmonary artery perforation (2.8% of all sessions), pulmonary artery dissection (1.9% of all sessions) and renal dysfunction (0.2% of all sessions). The vast majority of LI occurred during the first 24 hours. Only 4 patients developed documented LI after 24 hours. Complications per session are summarized in **Table 3**. The rate of complications was reduced from 15.8% of sessions in the initial period to 7.7% in the recent period, respectively ($p< 0.001$). Similarly, the percentage of severe LI decreased from 10.4% of sessions during the initial period to 1.8% during the recent period, respectively ($p< 0.001$). Severe complications requiring non-invasive positive pressure ventilation were observed in 34.1% of patients and 9% of sessions during the initial period and in 5.1% of patients and 1.6% of sessions during the recent period, respectively ($p<0.001$). Four patients required intubation with mechanical ventilation (3 during the initial period and 1 during the recent period; $p=0.34$). Among those patients, 3 also required extracorporeal membrane oxygenation support (all during the initial period). Furthermore, a total of 6 stents has been

implanted in 5 patients in the setting of pulmonary artery dissection.

Predictive variables for LI

A comparison of baseline clinical characteristics, hemodynamic variables and PAH therapy between patients with or without LI is shown in **Table 4.** Patients who experienced LI had significantly higher baseline mPAP and PVR and poorer exercise capacity (6MWD). Factors associated with the occurrence of LI after BPA were analysed and are depicted in **Table 5**. Per-patient multivariate analysis revealed that baseline mPAP (Odds Ratio [OR], 1.08; 95% Confidence Interval [CI], 1.039-1.130; $p<0.001$) and the period during which BPA procedure was performed (recent versus initial period; OR, 0.367; 95% CI, 0.175-0.771; $p=0.008$) were the most significant factors related to LI.

Survival

In total, 7 deaths occurred among the 184 patients (3.8%). There were 4 peri-procedural deaths (within 30 days after BPA; 2.2%) which were related to severe LI. Three additional deaths occurred during the follow-up period. Two patients died from right heart failure at 15 and 22 months and 1 from cancer at 4 months after the first BPA.

Overall survival at 1 and 3 years was 97.3% and 95.1%, respectively (95% CI, 94.9-99.6% and 91.4-98.9%, respectively) (**Figure 2**).

DISCUSSION

In the present study, we report a large series of patients with inoperable CTEPH treated by balloon pulmonary angioplasty at the French reference center for pulmonary hypertension. In this high volume center, the program of pulmonary endarterectomy for CTEPH was launched in 1996 and today near 2000 patients have undergone surgery (30). Following the more recent publications on refined BPA and multiple contacts with experienced BPA Japanese centers during the year 2013, we started a BPA program for CTEPH in February 2014. For all patients, eligibility for BPA was decided on the basis of a consensus among the CTEPH team during a multidisciplinary meeting.

Our results confirm that BPA is an effective treatment for patients with inoperable CTEPH. Overall, we observed a statistically significant improvement in NYHA functional class, 6MWD, PaO_2 and hemodynamics. Complications related to BPA were observed in 11.2% of all sessions and 46% of all patients. As reported in previous studies, LI was the most frequent one (9.1% of all sessions and 34% of patients) and 20.7% of patients required non-invasive or invasive mechanical ventilation. Four patients (2.2%) died within 30 days after BPA (peri-procedural period) and 3 additional patients died during the follow-up, resulting in a mortality rate of 3.8%.

The average improvement in pulmonary hemodynamics was less pronounced in our study than in the recently reported Japanese registry with a 43% and 58% decrease in PVR,

respectively (25). This difference could be attributed to greater experience in BPA in Japan. However, it cannot be excluded that other factors may also contribute, including differences between French and Japanese patients. Indeed, the Japanese registry included a majority of female patients (80%) whereas there was no sex difference in our cohort of patients. Furthermore, previous episodes of venous thromboembolism were less frequently found in Japanese patients as compared with our cohort of patients (34.7 % and 73%, respectively). Finally, fewer Japanese patients were also diagnosed with associated medical conditions increasing the risk of CTEPH. Interestingly, the magnitude of hemodynamic improvement observed in our study was correlated with treatment period. Indeed, the decrease in PVR has improved over time and was significantly greater during the recent period (decrease by 48%) than during the initial period (decrease by 37%), which is very encouraging. This improvement is mainly due to the experience acquired over time. Thus, over the years, we increased the total number of treated segments in each patient (14.0 during the initial period versus 16 during the recent period) without increasing significantly the number of sessions per patient (5.2 during the initial period versus 5.7 during the recent period). The number of procedures per patient was, however, slightly higher in our study (median of 5) than in the Japanese registry (median of 4) (25).

As mentioned previously, complications related to BPA were not rare since they occurred in 113 of 1006 sessions (11.2% of all sessions and 46% of all patients). The observed rate of LI

was lower in our series compared to the Japanese registry (9.1% versus 17.8% of all sessions) (25). Interestingly, the rate of complications recorded in our patient population was also correlated to the treatment period. The frequency of LI was reduced from 13.3 % of sessions in the initial period to 5.9% in the recent period, respectively. Per-patient multivariate analysis evaluating variables associated with LI showed that baseline mPAP and the period of BPA procedure (recent versus initial period) were the most significant factors related to LI. Thus, patients with a high mPAP at baseline were at increased risk of developing LI after BPA. By contrast, those undergoing BPA in the recent period were at lower risk of LI. This significant decrease of LI during the recent period is due to the use of a refined BPA strategy developed over time to improve the safety of the procedure. In a recent study, Ejiri et al. showed that BPA-related vascular injury was the main cause and the strongest predictor of LI after BPA. In this study, the authors also found that high mPAP before BPA and BPA-related vascular injury were independent risk factors for severe LI requiring mechanical ventilation (29). Insofar as the leading cause of complications is distal vascular injury caused by the tip of the wire, we improved the wiring approach by using the knuckle wire technique to reduce the risk of vascular injury. We also used undersized balloons during the first sessions to prevent balloon injury and once hemodynamics was improved we treated target lesions with adequate diameter balloons. Furthermore, from June 2015, we have begun using a pressure-wire-guided technique during the first sessions for monitoring distal perfusion pressure in patients with

crossable lesions and baseline mPAP≥45 mmHg. This technique allows a measure of the mPAP at proximal and distal to the target lesions and two studies from Japan have shown that the use of pressure-wire-guided technique may reduce the risk of LI (20, 31).

Other factors might also contribute, including a better approach of target lesions. In 2016, Kawakami et al. proposed an angiographic classification of CTEPH lesions and assessed the rate of BPA-related complications according to the type of lesions. Five types of lesions were described as follows: ring-like stenosis lesion, web lesion, subtotal lesion, total occlusions lesion and tortuous lesion. In this study, the authors showed that complication rate was highly dependent on the lesion characteristics. The vascular complication rate was lower in ring-like stenosis and web lesions and was higher with tortuous lesions (32). The type of lesions was not recorded in our study because the initial period was completed before Kawakami's lesion distribution was published. However, our group targeted in priority ring-like stenosis, web and subtotal lesions and this careful approach has not changed during the initial and recent periods. Furthermore, in the study published by Ejiri et al. in 2018, the authors did not find any correlation between the angiographic type of treated lesion and the occurrence of LI (29). Therefore, all these findings suggest that the operators' experience together with the refinement of BPA technique both played a key role in decreasing the risk of BPA-related complications.

The observed mortality of 3.8% in our series is similar to the Japanese registry that reported a

mortality of 3.9% (25). In these two studies, the majority of deaths were observed during the peri-procedural period. In our series, peri-procedural mortality rate was lower in the recent period than in the initial period (1% versus 3.5%) and no peri-procedural death occurred over the last year of the study. Several factors may have contributed to improve survival, including better selection of candidates for BPA, careful wiring approach, use of pressure-wire-guided technique and undersized balloons during the first sessions, and better use of PAH-targeted therapy before BPA.

Our study has several limitations. Firstly, it is a monocentric study. Secondly, there is no control group only receiving medical therapy during the same period. Thirdly, as previously reported in other studies, a high proportion of our patients (62%) were receiving at least one PAH-targeted therapy for at least 3 months before the first BPA session (16-20, 22-26). One could assume that the use of medical therapy before BPA may have an impact on post-procedural outcome. Our study, unfortunately, does not allow any answers to be given to this issue. Indeed, our patients were not randomly assigned to receive either PAH-targeted drugs or no PAH-targeted drugs before BPA. Lastly, we don't have results of long-term follow-up of more than 3 years. Therefore, there might be cases of PH worsening after this period.

CONCLUSIONS

We report here the largest monocentric experience of BPA outside Japan, the pioneer country for this interventional technique. Our results confirm that a refined BPA significantly improves short-term symptoms, oxygenation, exercise capacity and hemodynamics in inoperable CTEPH patients. We observed that LI was the main peri-procedural complication and we demonstrated that high mPAP before BPA was a risk factor for LI. In our series, safety and efficacy have improved over time underscoring the unavoidable learning curve period for this complex procedure even in a high volume and experienced CTEPH center with a multidisciplinary approach. However, although peri-procedural mortality is acceptable, the rate of complications remains high and safety of the procedure can be further improved. In addition, long-term effects of BPA need to be properly evaluated in a prospective, multicenter study.

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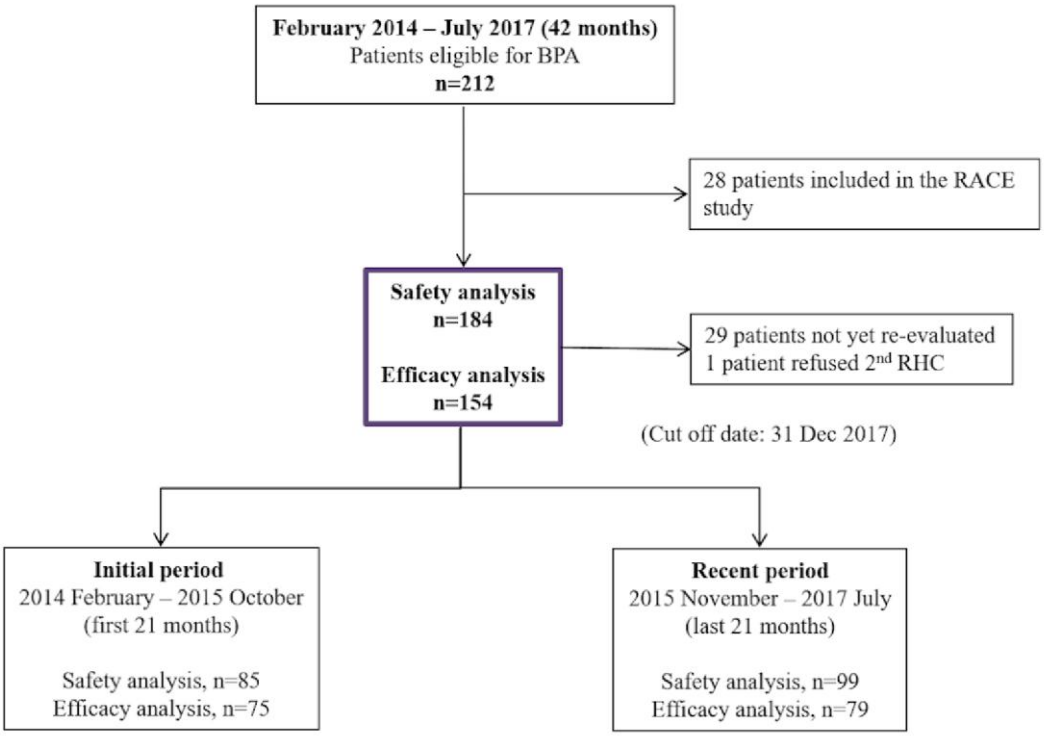
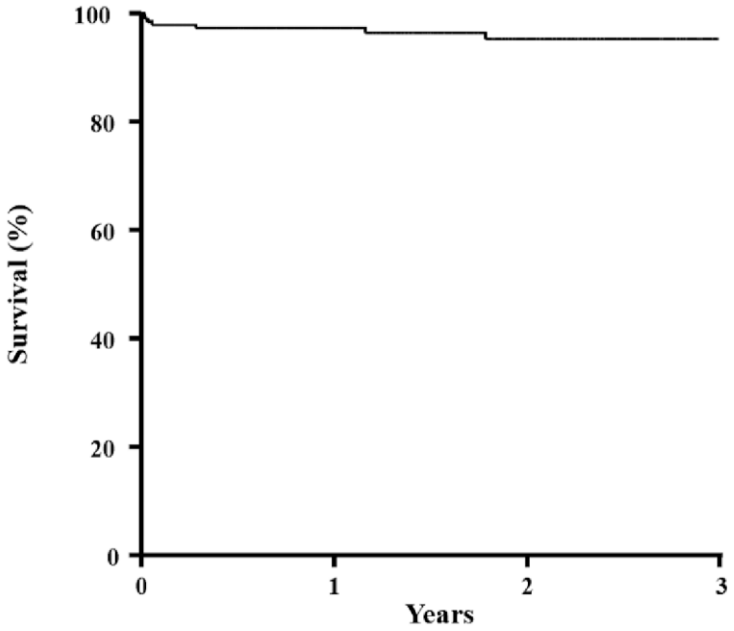
Figure legends

Figure 1. Flow chart of the study population

Abbreviations: BPA= balloon pulmonary angioplasty, RHC= right heart catheterization.

Figure 2. Survival from first balloon pulmonary angioplasty session (n=184)





Patients at risk	184	126	65	17

Table 1. Clinical Characteristics and Hemodynamic Data at baseline

Variable	N=184
Characteristics	
Age (years)	63 ± 14
Male (n, %)	94 (51)
NYHA FC I/II/III/IV (%)	1.1 / 35.0 / 59.0 / 4.9
6MWD (m)	397 ± 117
History of VTE (n, %)	135 (73)
Associated medical conditions	
Splenectomy (n, %)	18 (9.8)
Pacemaker / Indwelling catheter (n, %)	22 (12.0)
Myeloproliferative disorder (n, %)	3 (1.6)
APS (n, %)	7 (3.8)
Lung function tests	
TLC (% pred)	90.7 ± 15.2
FVC (% pred)	99.7 ± 21.9
FEV_1 (% pred)	89.1 ± 20.1
DLCO (% pred)	61.2 ± 13.6
Hemodynamics	
Systolic PAP (mmHg)	75.6 ± 17.5
Diastolic PAP (mmHg)	24.5 ± 7.4
Mean PAP (mmHg)	44.1 ± 9.8
Mean RAP (mmHg)	8.3 ± 4.0
PAWP (mmHg)	9.6 ± 3.5
Cardiac output (L/min)	4.89 ± 1.30
Cardiac index ($L/min/m^2$)	2.71 ± 0.64
PVR ($dynes.s.cm^{-5}$)	610 ± 255

SvO_2 (%)	62.2 ± 7.2
PAH therapy	
sGC stimulator (n, %)	59 (32.1)
ERA (n, %)	73 (39.7)
PDE5-I (n, %)	47 (25.5)
Prostacyclin analog (n, %)	13 (7.1)
Number of medications (none/single/double/triple) (%)	38.0 / 26.6 / 28.3 / 7.1
Indication for BPA	
Clot inaccessibility (n, %)	149 (81.0)
Unfavorable risk/benefit ratio for PEA (n, %)	16 (8.7)
Refusal of PEA (n, %)	4 (2.2)
Post-PEA (n, %)	15 (8.2)

Continuous variables are presented as mean ± SD. NYHA FC: New York Heart Association functional class; 6MWD: 6-minute walk distance; PEA: pulmonary endarterectomy; VTE: venous thromboembolism; APS: antiphospholipid syndrome; TLC: total lung capacity; % pred: % predicted; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1.0 second; DLCO: diffusing capacity for carbon monoxide; PAP: pulmonary artery pressure; RAP: right atrial pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; SvO_2: mixed venous oxygen saturation; sGC: soluble guanylate cyclase; ERA: endothelin receptor antagonist; PDE5-I: phosphodiesterase-5 inhibitor; PAH: pulmonary arterial hypertension; BPA: balloon pulmonary angioplasty.

Table 2. Clinical and Hemodynamic Data Before and After BPA

Variables	Total (n=154)			Initial period (n=75)			Recent period (n=79)			*P value
	Before	p value	After	Before	p value	After	Before	p value	After	
Characteristics										
NYHA FC (I,II / III,IV) (%)	35.3 / 64.7	< 0.001	78.7 / 21.3	25.3 / 74.7	< 0.001	65.3 / 34.7	44.9 / 55.1	< 0.001	92.0 / 8.0	< 0.001
6MWD (m)	396 ± 120	< 0.001	441 ± 104	383 ± 137	< 0.001	434 ± 119	407 ± 103	< 0.001	449 ± 86	0.411
PaO2 (mmHg)	65.0 ± 9.0	< 0.001	73.3 ± 12.0	65.0 ± 9.9	0.001	73.2 ± 12.9	65.1 ± 7.9	0.008	73.6 ± 10.5	0.901
Hemodynamics										
Systolic PAP (mmHg)	75.7 ± 17.0	< 0.001	53.0 ± 16.9	75.4 ± 16.9	< 0.001	57.4 ± 18.2	75.9 ± 17.2	< 0.001	48.9 ± 14.7	0.002
Diastolic PAP (mmHg)	24.2 ± 7.0	< 0.001	18.4 ± 6.4	24.6 ± 7.4	< 0.001	20.0 ± 6.8	23.9 ± 6.6	< 0.001	17.0 ± 5.6	0.003
Mean PAP (mmHg)	43.9 ± 9.5	< 0.001	31.6 ± 9.0	44.3 ± 9.8	< 0.001	33.8 ± 9.8	43.6 ± 9.1	< 0.001	29.5 ± 7.7	0.003
Mean RAP (mmHg)	8.1 ± 3.8	< 0.001	6.3 ± 2.8	8.0 ± 3.7	0.010	6.6 ± 2.9	8.2 ± 3.8	< 0.001	6.0 ± 2.7	0.149
PAWP (mmHg)	9.6 ± 3.4	0.050	10.3 ± 3.5	9.8 ± 3.5	0.176	10.4 ± 3.8	9.4 ± 3.2	0.160	10.1 ± 3.3	0.524
Cardiac Output (L/min)	4.86 ± 1.22	< 0.001	5.56 ± 1.35	4.88 ± 1.27	< 0.001	5.47 ± 1.47	4.85 ± 1.18	< 0.001	5.65 ± 1.23	0.400
Cardiac Index (L/min/m^2)	2.68 ± 0.60	< 0.001	3.07 ± 0.75	2.62 ± 0.58	< 0.001	2.96 ± 0.80	2.73 ± 0.62	< 0.001	3.18 ± 0.68	0.062
PVR (dynes.s.cm^{-5})	604 ± 226	< 0.001	329 ± 177	607 ± 218	< 0.001	371 ± 188	601 ± 236	< 0.001	289 ± 157	0.004
SvO2 (%)	62.6 ± 7.4	< 0.001	67.9 ± 7.3	62.9 ± 7.5	< 0.001	67.3 ± 8.1	62.4 ± 7.3	< 0.001	68.5 ± 6.4	0.353
Absolute change of mean PAP (mmHg)			-12.4 ± 10.6			-10.5 ± 10.4			-14.1 ± 10.5	0.038

% decrease of mean PAP (%)	-26.1 ± 21.3	-21.9 ± 21.5	-30.1 ± 20.4	0.017
% decrease of PVR (%)	-42.7 ± 27.4	-36.5 ± 29.1	-48.6 ± 24.5	0.006

Continuous variables are expressed as mean ± SD.

NYHA FC: New York Heart Association functional class; 6MWD: 6-minute walk distance; PaO2: arterial partial pressure of oxygen; RAP: right atrial pressure; PAP: pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; SvO_2: mixed venous oxygen saturation.

*Comparison between initial and recent periods.

Table 3. Complications per session

Overall complications (n, %)	113 (11.2)	70 (15.8)	43 (7.7)	< 0.001
Lung injury (n, %)	92 (9.1)	59 (13.3)	33 (5.9)	< 0.001
Mild / Moderate	36 (3.6)	13 (2.9)	23 (4.1)	0.394
Severe	56 (5.6)	46 (10.4)	10 (1.8)	< 0.001
Hemoptysis (n, %)	71 (7.1)	36 (8.1)	35 (6.2)	0.266
Pulmonary artery perforation (n, %)	28 (2.8)	16 (3.6)	12 (2.1)	0.179
Pulmonary artery dissection (n, %)	19 (1.9)	9 (2.0)	10 (1.8)	0.774
NPPV (n, %)	49 (4.9)	40 (9.0)	9 (1.6)	< 0.001
Intubation (n, %)	4 (0.4)	3 (0.7)	1 (0.2)	0.327
ECMO support (n, %)	3 (0.3)	3 (0.7)	0 (0)	0.086
Renal dysfunction (n, %)	2 (0.2)	2 (0.5)	0 (0.0)	0.195

NPPV: non-invasive positive pressure ventilation; ECMO: extracorporeal membrane oxygenation.

*Comparison between Initial and Recent periods.

Table 4. Comparison of characteristics and hemodynamic data between patients with and without lung injury after BPA

Variables	Lung injury (+) (n=63)	Lung injury (-) (n=121)	p value*
Baseline characteristics			
Age (years)	62.3 ± 14.8	64.0 ± 13.3	0.422
Male (n, %)	34 (54.0)	60 (49.6)	0.573
NYHA FC (I,II / III,IV) (%)	28.6 / 71.4	40.0 / 60.0	0.126
6MWD (m)	359 ± 131	417 ± 106	0.003
Baseline hemodynamics			
Mean RAP (mmHg)	8.7 ± 3.9	8.1 ± 4.0	0.415
Mean PAP (mmHg)	48.6 ± 9.7	41.7 ± 9.0	<0.001
Cardiac index (L/min/m^2)	2.55 ± 0.48	2.79 ± 0.70	0.014
PVR (dynes.s.cm^{-5})	727 ± 261	549 ± 231	<0.001
PAH therapy at baseline			
No treatment /monotherapy /combination therapy (%)	32 / 25 / 43	41 / 27 / 32	0.274

Continuous variables are presented as mean ± SD. BPA: balloon pulmonary angioplasty; NYHA FC: New York Heart Association functional class; 6MWD: 6-minute walk distance; RAP: right atrial pressure; PAP: pulmonary artery pressure; PVR: pulmonary vascular resistance; PAH: pulmonary arterial hypertension.

Table 5. Univariate and multivariate logistic regression analysis of predictive variables of lung injury

	Univariate			Multivariate		
Variable	**OR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Baseline characteristics						
Age (years)	0.991	0.970 – 1.013	0.420			
Male	1.192	0.647 – 2.194	0.573			
NYHA FC (I-II vs III-IV)	1.667	0.864 – 3.216	0.128			
6MWD (m)	0.996	0.993 – 0.999	0.005	0.996	0.993 – 0.999	0.022
Baseline hemodynamics						
Mean RAP (mmHg)	1.032	0.957 – 1.114	0.413			
Mean PAP (mmHg)	1.086	1.045 – 1.128	<0.001	1.083	1.039 – 1.130	<0.001
Cardiac index ($L/min/m^2$)	0.508	0.292 – 0.882	0.016			
PVR ($dynes.s.cm^{-5}$)	1.003	1.002 – 1.005	<0.001			
Other covariate						
Period of BPA procedure (recent vs. initial period)	0.340	0.181 – 0.640	0.001	0.367	0.175 – 0.771	0.008

OR: odds ratio; CI: confidence interval; NYHA FC: New York Heart Association functional class; 6MWD: 6-minute walk distance; RAP: right atrial pressure; PAP: pulmonary artery pressure; PVR: pulmonary vascular resistance; BPA: balloon pulmonary angioplasty.