Flow Grade-Based Success Rates, Complication Rates, and Balloon Pulmonary Angioplasty Patency for Total Occlusions

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ABSTRACT

Background: The number of successfully re-canalised total occlusions impacts haemodynamic improvement after balloon pulmonary angioplasty (BPA) in patients with chronic thromboembolic pulmonary hypertension (CTEPH). We aimed to clarify the current efficacy, patency, and success rate of BPA for total occlusions.

Methods: Between April 2016 and August 2021, 178 BPAs were performed in 100 patients with CTEPH and total occlusions. The primary success and subsequent patency rates immediately before the second BPA procedure (follow-up) were compared between the segmental and sub-segmental groups based on the flow grade, which was defined as follows: 0, no reperfusion; 1, minimal reperfusion; 2, partial reperfusion; and 3, complete reperfusion.

Results: Total occlusions were mainly located in the right lung (70%), and lower lobes (48%). The primary success rate was 88%, with significant improvements in oxygenation, haemodynamic parameters, and 6-minute walk test. The primary flow grade did not differ between groups. However, the proportion of lesions with a flow grade of 2 or 3 at follow-up was significantly higher in the sub-segmental group than in the segmental group (84% vs. 45%, respectively; \( P < 0.01 \)). In multivariate analysis, flow grade in the acute phase (odds ratio, 46.9 [95% confidence interval: 12.54–176.78]; \( P < 0.01 \)) and sub-segmental lesions (odds ratio, 13.8 [95% confidence interval: 3.24–58.94]; \( P < 0.01 \)) were independently associated with better patency (flow grade of 2 or 3) at follow-up.

Conclusions: Total occlusions can be safely and effectively treated with BPA. BPA for total occlusions may be preferable for sub-segmental over segmental lesions.
INTRODUCTION

In the latest guidelines, balloon pulmonary angioplasty (BPA) is recommended as a treatment option for inoperable patients with chronic thromboembolic pulmonary hypertension (CTEPH). Although the safety and efficacy of BPA have improved, the outcomes of BPA are still not equivalent to those of pulmonary endarterectomy (PEA). Complete resection of thromboembolic materials is the greatest advantage of PEA, enabling it as a potentially curative treatment for patients with CTEPH. In BPA, the number of successfully treated lesions correlates with changes in mean pulmonary artery pressure (PAP) after BPA. Therefore, to achieve similar therapeutic effects in BPA as in PEA, it is essential to treat all lesions from proximal to distal, as well as all angiographic lesion types, including total occlusions.

We previously reported the success and complication rates of BPA, according to the morphology of thromboembolic lesions: type A, ring-like stenosis; type B, web lesions; type C, sub-total lesions; type D, total occlusions; and type E, tortuous lesions. The success rate of BPA for total occlusions was 52.2%, which was the lowest among all lesion types. Gorges et al. reported that the number of successfully re-canalised total occlusions strongly affects haemodynamic improvement after BPA. Hence, improving BPA success rates for total occlusions is crucial to achieve further symptomatic and haemodynamic improvements after BPA.

PEA is suitable for proximal lesions in the main, lobar, and segmental pulmonary arteries, whereas BPA primarily targets distal lesions in the segmental and sub-segmental pulmonary arteries. We previously reported that haemodynamic improvement after BPA differed between surgically accessible proximal and inaccessible distal lesions. The outcome of BPA for total occlusions may also differ between segmental and sub-segmental lesions.
This novel study aimed to investigate the current success, patency, and complication rates of BPA for total occlusions between the segmental and sub-segmental pulmonary arteries, based on our experience, as well as its determinants, to maintain better patency in the chronic phase.

**MATERIAL AND METHODS**

**Study population**

This single-centre, retrospective, observational study was approved by the Institutional Review Board of the National Hospital Organization of Okayama Medical Center, Okayama, Japan (approval number: H29-RINKEN-017). This study complied with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.11 We analysed 1,195 BPAs performed in 499 patients with CTEPH between 16 April 2016 and 7 August 2021. Patients with at least one or more total occlusions in the segmental or sub-segmental pulmonary arteries treated with BPA were included in this study, irrespective of the initial BPA procedure. Patients with proximal total occlusions in the main or lobar pulmonary arteries were excluded. Written informed consent was obtained from each patient before the BPA procedure. All patients were diagnosed as inoperable by a multidisciplinary team comprising PEA surgeons, cardiologists experienced in pulmonary hypertension pharmacotherapy, interventionists experienced in BPA, and radiologists. The final PEA eligibility was judged considering every aspect, including the PEA risk defined by the presence of co-morbidities, patient age and frailty, the severity of haemodynamic impairment, and patient wishes.
Previous reports\textsuperscript{3,4,12,13} indicate general BPA procedures and peri-operative management. A biplane angiographic system (Allura Xper FD10/10; Philips Electronics, Amsterdam, The Netherlands) was used. A 9Fr in-dwelling sheath was placed in the internal jugular (13\%) and femoral (87\%) veins. A 6 or 7Fr sheath was inserted into the main pulmonary trunk via a 9Fr sheath using a 0.035-inch wire. Selective pulmonary angiography was performed before BPA to confirm the location of the lesion and evaluate the thromboembolic lesion type. Guiding catheters included a Mach1 peripheral MP catheter (Boston Scientific, Natick, MA, USA) for the right lung and an EXTRACK AL1 catheter (Medikit Corporation, Tokyo, Japan) for the left lung. If the guiding catheter was difficult to engage, or a stronger back-up force was required, a Judkins Right 4.0 guiding catheter (Boston Scientific), Judkins Left 4.0 guiding catheter (Boston Scientific), or Mach1 Coronary Q-Curve guiding catheter (Boston Scientific) were selected, as appropriate. Selective pulmonary angiography and a series of BPA procedures were performed using 8-inch images. Total occlusions (defined as lesions where the vessel was occluded with the distal part invisible) were divided into two groups based on anatomic location: the segmental group (Figure 1A) and the sub-segmental group (Figure 1B). The segmental group included lesions in the second and third branches of the pulmonary artery tree (vessel diameter 4–6 mm), which were directly separated from lobar pulmonary arteries. The sub-segmental group included lesions in the fourth or more distal branches of the pulmonary artery tree (vessel diameter < 4 mm), which were distal to segmental pulmonary arteries.

Regarding the technical information of guidewires for total occlusions, the wire escalation method in coronary re-vascularisation was employed.\textsuperscript{14} We gradually up-graded the selection of 0.014-inch conventional guidewires from B-pahm 0.6 (Japan Lifeline Co. Ltd., Tokyo,
Japan) to jacketed hydrophilic wires (Chevalier Floppy; Cordis/Johnson & Johnson, New Brunswick, NJ, USA). When conventional guidewires failed to pass through total occlusions, hard-tip guidewires (tip load ≥ 3 g) (Gladius: ASAHI INTECC, Aichi, Japan; Jupitar MAX: Boston Scientific; Chevalier PL-X: Cordis/Johnson & Johnson; Naveed 4 Tapered 1/Naveed 4 Tapered 10/Naveed 4 Hard 50: TERUMO, Tokyo, Japan) or high-penetration power guidewires (Astato XS; ASAHI INTECC) were selected with or without micro-catheter support (Corsair PV/Corsair Armaet: ASAHI INTECC; Prominent: Tokai Medical, Aichi, Japan; MIZUKI: Kaneka, Osaka, Japan). The use of micro-catheters was determined based on lesion stiffness and tortuosity. Total occlusions were classified into two types (soft and hard) according to the tip load required for the guidewire to penetrate the occlusion site. Soft lesions were defined as lesions penetrable by a conventional guidewire. Hard lesions were defined as lesions that could only be penetrated by a guidewire with a tip load ≥ 3 g. After successful guidewire penetration, intra-vascular ultrasound (IVUS) (Eagle Eye Platinum; Volcano, San Diego, CA, USA) was performed beyond the occlusion site to confirm whether the guidewire tip was in the true lumen. After confirmation, the lesion was dilated using an appropriately sized balloon catheter. Total occlusions were treated sequentially in stages via two separate BPA procedures: first, a balloon with a diameter smaller than that of the vessel was selected at the initial stage of BPA to reduce the risk of pulmonary vessel injury; second, the lesions were dilated again, if necessary, using the angiographically appropriate balloon size (Sapphire 2 Pro: OrbusNeich, Tokyo, Japan; SHIDEN: Kaneka, Osaka, Japan; IKAZUCHI PAD: Kaneka, Osaka, Japan [1–4 mm]; Angiosculpt: Philips Electronics; Crosspandar: Japan Lifeline Co. Ltd.; NSE PTA Rx: Nipro, Osaka, Japan; SHIDEN: Kaneka; Bandicoot RX: St. Jude Medical, St. Paul, MN, USA; Aviator Plus: Cordis/Johnson & Johnson [5–7 mm]; Sterling Monorail: Boston Scientific; Makaira: Kaneka [8 mm]) to
optimise the lumen diameter. Other lesion types (ring-like stenosis, web lesions, and sub-total occlusions) were also treated with each BPA procedure, to prioritise treatment efficacy.

**Definition of BPA success and pulmonary artery flow-grade**

The procedural success of the BPA for total occlusions was defined as the presence of a guidewire in the true lumen beyond the occluded lesion, confirmed by IVUS. Based on reports of acute myocardial infarction, the pulmonary artery flow grade of selective pulmonary angiography was categorised as follows: 0, no reperfusion; 1, minimal reperfusion; 2, partial reperfusion; and 3, complete reperfusion (Table 1). Flow grade videos are included in the Data Supplement.

**Data collection**

Data on medical history, medication use, and co-morbidities were obtained from medical records. The initial success rate of BPA, and changes in flow grade immediately after the initial BPA procedure to immediately before the second BPA procedure (follow-up) were analysed. Additionally, we compared the outcomes of BPA for total occlusions with those for segmental and sub-segmental lesions. Brain natriuretic peptide, the 6-minute walk test, haemodynamic parameters (systolic, diastolic, and mean PAP), cardiac index obtained by the thermal dilution method, pulmonary vascular resistance, percutaneous oxygen saturation, and partial pressure of arterial oxygen during blood gas analysis were also measured before the initial BPA procedure for total occlusions and follow-up. The location of the treated lesions, total number of treated lesions besides total occlusions, total procedure time, total radiation exposure time, and total volume of contrast medium were also analysed.

**BPA-related complications**
Complications related to the BPA procedures were defined as clinical symptoms (cough, bloody sputum, and significant hypoxia [percutaneous oxygen saturation decrease ≥ 5% during BPA]), BPA-related vascular injury (BRVI), and lung injury (LI). The incidences of BPA-related complications were compared between the segmental and sub-segmental groups. BRVI was defined as angiographic extravasation of contrast medium with or without clinical symptoms. LI was determined by comparing radiological images (computed tomography or X-ray) before and immediately after BPA based on the presence of newly appearing ground-glass opacities, consolidation, and pleural effusion. BRVI and LI were diagnosed by two independent physicians who were blinded to the BPA procedures and their results.

Statistical analyses

Continuous variables were presented as mean ± SD, or median (inter-quartile range), depending on the distribution of the data, whereas categorical variables were presented as number (percentage). The Mann–Whitney U, Pearson’s chi-square, or Fisher’s exact test was used for comparison between the groups for continuous and categorical variables, as appropriate. Differences between variables measured before and after BPA for total occlusions were evaluated using the paired t-test or Wilcoxon signed-rank test for continuous variables. Univariate and multivariate logistic regression analyses assessed independent associations with lesions achieving a flow grade of 2 or 3 immediately before the second BPA procedure. Multivariate analysis included age, male sex, mean PAP, cardiac index, pulmonary vascular resistance, penetration wire-tip load, maximum balloon size, flow grade immediately after the first BPA procedure, and sub-segmental lesions. Odds ratios (ORs) were estimated using a logistic regression model and presented as 95% confidence intervals (CIs) and P-values. Statistical significance was set at P < 0.05. All statistical analyses were conducted using SPSS software (version 25.0; IBM Corporation, Armonk, NY, USA).
RESULTS

Baseline characteristics and haemodynamic changes before and after BPA

A total of 178 BPA procedures in 100 patients with CTEPH who had at least one total occlusion were included in this study. All patients were considered inoperable because of lesion location (n = 52), patient refusal (n = 15), co-morbidities (n = 11), advanced age (≥ 79 years; n = 10), and severe haemodynamic impairment (pulmonary vascular resistance > 15 WU; n = 1). Eleven patients had previously received PEA. Baseline characteristics and haemodynamic changes before the initial BPA procedure for total occlusion lesions and follow-up are summarised in Table 2. The mean interval between the initial and second BPA procedure for total occlusions was 6.0 ± 4.6 months. Twenty-one patients (21%) had not previously received BPA procedures, and the remaining 79 patients (79%) had previously experienced an average of 5.1 ± 4.5 BPA procedures. Therefore, haemodynamic status before the initial BPA procedure for total occlusions was mild in most patients (median mean PAP 26 mmHg). Eighty-four patients (84%) were not taking pulmonary hypertension medication, 15 (15%) were on monotherapy, and one (1%) received dual combination therapy before BPA for total occlusions. All parameters other than the cardiac index improved after BPA procedures for total occlusion lesions.

Lesion characteristics and complications of total occlusions

The procedural characteristics and incidences of complications are shown in Table 3. In addition to the 178 total occlusions, 274 additional lesions of other lesion types (median 2 [1–5] per procedure) were also treated in this study. Total occlusions were mainly located in the right lung (70%), and lower lobes (48%). The overall procedural success of BPA for total
occlusions, defined as the positioning of a guidewire in the true lumen and confirmed by IVUS, was 157 of the 178 lesions (88%) in the initial BPA procedure. In 14 of the 21 unsuccessful attempts, the IVUS catheter could not be passed through the occlusion due to the hardness of the lesion. In the remaining seven failed attempts, the IVUS catheter passed through the lesion but could not be confirmed to be in the true lumen, even after attempting to recross the guidewire with another stiffer wire using the parallel-wire technique under IVUS-guided method. No lesions with guidewires outside the vessel were detected on IVUS. The proportion of lesions with a flow grade of 2 or 3 in the initial BPA procedure was 53%. The patency rate, defined as the proportion of lesions with a flow grade of 2 or 3 at follow-up, was 63%. Complications were associated with 26 (15%) of the 178 initial BPA procedures. The clinical symptoms observed in these 16 patients (9%) included cough (7%), significant hypoxia (6%), and bloody sputum (4%). BRVI and LI were observed in 26 (15%) and 16 (9%) patients, respectively. No severe complications requiring mechanical ventilation or extra-corporeal membrane oxygenation support were noted.

Comparisons of BPA procedures for total occlusions between the segmental and sub-segmental groups

Comparisons of BPA procedures for total occlusions between the segmental and sub-segmental pulmonary arteries are summarised in Table 4. The success rate during the initial BPA procedure was similar between the groups. The segmental group had more hard lesions than the sub-segmental group did. The maximum balloon size for dilating the total occlusions was significantly larger in the segmental group than in the sub-segmental group. The frequency of LI was higher in the segmental group than in the sub-segmental group. The proportion of lesions with a flow grade of 2 or 3 immediately after the initial BPA procedure did not differ significantly between the two groups (47% vs. 61%, respectively; P = 0.13).
However, it was significantly higher in the sub-segmental group than in the segmental group (46% vs. 85%, respectively; $P < 0.01$) at follow-up, despite no additional treatment.

Figure 2 depicts the flow grade changes from immediately after the first BPA procedure to immediately before the second BPA procedure for total occlusions. In the sub-segmental group, flow grade improvement was observed in 36 lesions, with no change in 37 lesions and worsening in six lesions. In contrast, in the segmental group, flow grade improvement was observed in 10 lesions, with no change in 67 lesions and worsening in 22 lesions.

Maintenance or spontaneous improvement in flow grade to grade 2 or 3 at follow-up was predominantly observed in the sub-segmental group compared with the segmental group after the first BPA procedure for total occlusions.

**Determinants of a flow grade of 2 or 3 at follow-up**

Table 5 presents the results of the univariate and multivariate analyses of the determinants of lesions achieving a flow grade of 2 or 3 immediately before the second BPA procedure. The flow grade immediately after the initial BPA procedure (OR, 46.9 [95% CI: 12.54–176.78]; $P < 0.01$) and sub-segmental lesions (OR, 13.8 [95% CI: 3.24–58.94]; $P < 0.01$) were independently associated with a flow grade of 2 or 3 at follow-up.

**DISCUSSION**

This study investigated the current success, patency, and complication rates of BPA for total occlusions at a specialised BPA centre. Additionally, we compared the efficacy and safety of BPA for total occlusions in the segmental and sub-segmental pulmonary arteries. The major findings of this study are as follows: (1) The overall success rate of the initial BPA procedure for total occlusions was 88%, which was higher than that (52.2%) reported in 2012, (2)
Haemodynamic parameters, exercise capacity, and oxygenation improved after treatment of total occlusions without severe complications; (3) Total occlusions were mainly located in the right lung (70%) and lower lobes (48%); (4) Although flow grade immediately after the initial BPA procedure was similar between the groups, the proportion of lesions with a flow grade of 2 or 3 at follow-up was higher in the sub-segmental group than in the segmental group; and (5) A flow grade of 2 or 3 in the initial BPA procedure and sub-segmental lesions were associated with higher patency at follow-up. This study is the first to demonstrate the initial success and patency rates of BPA for total occlusions in patients with CTEPH based on flow grade.

The overall success rate of the initial BPA procedure for total occlusions improved from 52.2% in 2012\(^4\) to 88% in the present study. Recent reports from two European countries\(^5,17\) revealed that the success rates of BPA for total occlusions were 50% and 79.5%, respectively. Direct comparisons are difficult because the definition of a successful BPA procedure varies among reports. However, the success rate of BPA for total occlusions was much higher than previously reported. This is attributed to improvements in interventional devices, such as guiding catheters, guidewires, micro-catheters, and balloon catheters. Moreover, the learning curve of BPA operators may have influenced the improvement in the success rate of BPA. In contrast, the BPA complication (BRVI) rate was 15%, consistent with previous reports\(^5,17\) (11.7% and 18%, respectively). The slight increase in the complication rate compared with our previous report of 6%\(^4\) may be due to more aggressive treatment of total occlusions. However, no severe complications requiring mechanical ventilation or extra-corporeal membrane oxygenation support were noted.

The reason why total occlusions are mainly located in the right lung and lower lobes, remains speculative. This is consistent with our previous report\(^4\) indicating that 67% were located in
the right lung and 33% in the left lung. Because 75% of patients with CTEPH had a history of acute pulmonary embolism, acute clots may have triggered the formation of chronic thromboembolic material. Oser et al. reported that acute clots were mainly located in the lower lobes of the right lung. Chronic thromboembolic material is more likely to form in the right lower lobes, which may be related to the distribution of total occlusions.

The proportion of lesions achieving a flow grade of 2 or 3 immediately after the initial BPA procedure did not significantly differ between the segmental and sub-segmental groups. However, despite no additional treatment, the proportion of lesions with a flow grade of 2 or 3 at follow-up was significantly higher in the sub-segmental group than in the segmental group. Spontaneous improvement in flow grade may be more expected in sub-segmental lesions than in segmental lesions. In multivariate analysis, sub-segmental lesions were a determinant of high patency, with a flow grade > 2 at follow-up. It is unclear why spontaneous improvement in flow grade after the initial BPA procedure was more prominent in the sub-segmental group than in the segmental group. This may be due to anatomical differences between segmental and sub-segmental lesions, such as differences in the size of the vascular bed, lesion stiffness, and the absolute amount of thromboembolic material. If so, lesion recoil may occur more frequently in segmental lesions rich in fibrotic thromboembolic material than in sub-segmental lesions. Furthermore, it is possible that we may have unconsciously selected under-sized balloon catheters, because of the risk of procedural complications in BPA for segmental lesions.

The flow grade spontaneously improved at follow-up in some lesions, whereas it deteriorated in others. Among the 178 lesions in this study, 21 segmental and six sub-segmental lesions had a worse flow grade after BPA. Twelve of the 21 segmental lesions and all six of the sub-segmental lesions were re-occluded at follow-up. Considering that the lesions had a flow
grade of 1 immediately after BPA, the deterioration in flow grade may be dependent on the
flow grade immediately after BPA. This phenomenon has been observed with other
interventions. In treating chronic total occlusions of the coronary artery,\textsuperscript{21} a low TIMI flow
grade immediately after re-canalisation was associated with a lower patency rate immediately
before the second treatment. Reduced blood flow immediately after balloon angioplasty is
associated with a subsequently lower rate of patency of the femoral artery.\textsuperscript{22} The low flow
grade immediately after BPA may be related to the deterioration in flow grade at follow-up.
The reasons for the worse flow grade in segmental lesions may be as follows: Residual
stenosis or obstruction distal to the occluded site (grade 2 to grade 1 [n = 2 lesions]; grade 2
to grade 0 [n = 3 lesions]); collateral circulation from systemic arteries (grade 3 to grade 1 [n
= 1 lesion]; grade 1 to grade 0 [n = 1 lesion]); and dissection of the balloon site (grade 3 to
grade 2 [n = 3 lesions]). One reason for the worse flow grade in segmental lesions at follow-
up is residual stenosis or obstruction distal to the occluded site. Evaluating stenosis or
obstruction distal to the occluded site, including the microvasculature, is challenging
immediately after re-opening total occlusions because pulmonary arteries distal to the
occluded site usually remain small immediately after BPA. Therefore, stenosis or obstruction
distal to the occluded sites should be re-evaluated after distal blood flow has returned, and if
necessary, additional treatments should be provided. Residual stenosis or obstruction distal to
the occluded site may explain the worse flow grade at follow-up. This study revealed that the
late improvement in flow grade in the sub-segmental group was superior to that in the
segmental group. This may be explained by the higher frequency of residual stenosis or
obstruction distal to the occluded sites in the segmental group in comparison to the sub-
segmental group (due to differences in the number of branches and the size of the vascular
bed). Another reason is collateral circulation from systemic arteries, which is commonly
observed in patients with CTEPH and may be exacerbated by competition with retrograde
blood flow from collateral vessels. The last reason is dissection of the balloon site. Dissection at the proximal site could affect blood flow distal to the occluded site and worsen flow grade at follow-up. This study suggested that the late improvement in flow grade in the sub-segmental group was superior to that in the segmental group, and that late deterioration in flow grade was more prominent in the segmental group than in the sub-segmental group.

This study has some limitations. First, it was retrospectively conducted at a single centre with a limited number of patients and lesions. Second, in addition to treating total occlusions, other types of lesions, such as ring-like stenosis, web lesions, and sub-total occlusions, were simultaneously treated in each BPA procedure. Therefore, the therapeutic effects on other types of lesions should be considered. Third, the haemodynamic improvement after BPA was limited. This is because total occlusions are usually treated during the second or subsequent procedures due to the risk of complications and treatment efficacy. Consequently, around 80% of patients had undergone multiple BPA procedures before their treatment for total occlusions. Notably, significant improvements in oxygenation and the 6-minute walk test were observed after BPA for total occlusions in this study, even in patients with mild haemodynamic changes. In a recent study, 90% of patients with CTEPH discontinued home oxygen therapy and pulmonary hypertension medications after adequate BPA, which was not associated with subsequent haemodynamic deterioration or a decline in functional capacity. These findings may support the benefit of complete re-vascularisation, including treating total occlusions for further improvements in exercise intolerance and oxygenation in patients with CTEPH. Prospective randomised controlled trials evaluating not only baseline haemodynamic parameters but also oxygenation and exercise parameters, using cardiopulmonary exercise tests, are needed to confirm the clinical benefit of treating total occlusions. Fourth, the difference in clinical benefit between the segmental and sub-segmental groups has yet to be elucidated. Finally, we investigated haemodynamic changes
and changes in flow grade immediately after the initial BPA procedure for total occlusions to immediately before the second BPA procedure. The follow-up period was relatively long and variable, potentially affecting haemodynamic changes and changes in flow grade. This may be because the Japanese Medical Insurance System limits the number of BPA procedures per hospitalization. Consequently, patients with mild haemodynamics and those referred from distant locations were reluctant to be hospitalized frequently to receive BPA for a short period of time. However, there was no significant difference in the follow-up period between the segmental and sub-segmental groups.

CONCLUSIONS

Total occlusions can be safely and effectively treated with BPA at specialised centres. Given the higher patency rate at follow-up and lower risk of complications, BPA for total occlusions may be preferable for sub-segmental rather than segmental lesions. Further investigation is warranted to better understand the benefits and risks of treating total occlusions between segmental and sub-segmental lesions.
Acknowledgments

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Ethics statement

The research reported in this paper adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Patient consent statement

The authors confirm that patient consent forms have been obtained for this article.

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Disclosures

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References


### Tables

#### Table 1. Flow-grade score

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0: No reperfusion</td>
<td>Absence of any antegrade flow beyond the occlusion</td>
</tr>
<tr>
<td>Grade 1: Minimal reperfusion</td>
<td>Faint antegrade flow beyond the occlusion, with incomplete filling of the distal bed</td>
</tr>
<tr>
<td>Grade 2: Partial reperfusion</td>
<td>Delayed or sluggish antegrade flow, with complete filling of the distal territory</td>
</tr>
<tr>
<td>Grade 3: Complete reperfusion</td>
<td>Normal flow, which fills the distal bed completely</td>
</tr>
</tbody>
</table>
Table 2. Patient characteristics and haemodynamic parameters

<table>
<thead>
<tr>
<th>Variables</th>
<th>Before the first BPA procedure for total occlusions</th>
<th>Before the second (follow-up) BPA procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients, n</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>68 ± 10</td>
<td></td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>20 (20)</td>
<td></td>
</tr>
<tr>
<td>Systolic PAP (mmHg)</td>
<td>43 [36–53]</td>
<td>39 [33–48]*</td>
</tr>
<tr>
<td>Diastolic PAP (mmHg)</td>
<td>16 [12–19]</td>
<td>14 [10–18]*</td>
</tr>
<tr>
<td>Mean PAP (mmHg)</td>
<td>26 [22–32]</td>
<td>25 [20–30]*</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>2.5 [2.2–3.0]</td>
<td>2.5 [2.3–2.8]</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (WU)</td>
<td>4.5 [3.5–5.7]</td>
<td>3.9 [3.1–5.2]*</td>
</tr>
<tr>
<td>Measure</td>
<td>Before BPA</td>
<td>After BPA</td>
</tr>
<tr>
<td>------------------------------------------------------</td>
<td>------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Percutaneous oxygen saturation (%)</td>
<td>92 [90–95]</td>
<td>95 [92–97]*</td>
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<tr>
<td>Partial pressure of arterial oxygen (mmHg)</td>
<td>67 [61–74]</td>
<td>72 [65–79]*</td>
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<tr>
<td>6-minute walk test (m)</td>
<td>342 ± 104</td>
<td>365 ± 100*</td>
</tr>
<tr>
<td>Brain natriuretic peptide (pg/mL)</td>
<td>115 ± 29</td>
<td>61 ± 9*</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or median (25th–75th percentile). *P < 0.01 (vs. before BPA)

BPA, balloon pulmonary angioplasty; PAP, pulmonary artery pressure
**Table 3. Lesion characteristics**

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of total treated lesions, n</td>
<td>452</td>
</tr>
<tr>
<td>Number of procedures, n</td>
<td>178</td>
</tr>
<tr>
<td>Right lobe/left lobe, n (%)</td>
<td>125 (70)/ 53 (30)</td>
</tr>
<tr>
<td>Upper lobe/middle lobe or lingular segment/lower lobe, n (%)</td>
<td>52 (29)/40 (23)/86 (48)</td>
</tr>
<tr>
<td>Total procedure time (minutes)</td>
<td>100 ± 22</td>
</tr>
<tr>
<td>Total procedure time for total occlusions (minutes)</td>
<td>42 ± 32</td>
</tr>
<tr>
<td>Total radiation exposure time (minutes)</td>
<td>48 ± 11</td>
</tr>
<tr>
<td>Total volume of contrast medium (mL)</td>
<td>129 ± 39</td>
</tr>
<tr>
<td>Complications (per procedure), n (%)</td>
<td>26 (15)</td>
</tr>
<tr>
<td>Clinical symptoms (cough, significant hypoxia, and bloody sputum), n (%)</td>
<td>16 (9)</td>
</tr>
</tbody>
</table>
| Condition | Count (%)
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LI, n (%)</td>
<td>26 (15)</td>
</tr>
<tr>
<td>BRVI, n (%)</td>
<td>16 (9)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or number (%)

BPA, balloon pulmonary angioplasty; BRVI, BPA-related vascular injury; LI, lung injury
<table>
<thead>
<tr>
<th></th>
<th>Segmental group (n = 99)</th>
<th>Sub-segmental group (n = 79)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment success, n (%)</td>
<td>83 (84)</td>
<td>74 (94)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hard lesion, n (%)</td>
<td>67 (68)</td>
<td>12 (15)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Maximum balloon size (mm)</td>
<td>4 (3–5)</td>
<td>2.5 (2–3)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Complications, n (%)</td>
<td>20 (20)</td>
<td>6 (8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Clinical symptoms (cough, significant hypoxia, and bloody sputum), n (%)</td>
<td>9 (5)</td>
<td>7 (4)</td>
<td>1.00</td>
</tr>
<tr>
<td>LI, n (%)</td>
<td>20 (20)</td>
<td>6 (8)</td>
<td>0.02</td>
</tr>
<tr>
<td>BRVI, n (%)</td>
<td>11 (6)</td>
<td>5 (3)</td>
<td>0.30</td>
</tr>
<tr>
<td>Flow grade immediately after the first BPA procedure, n (%) (0–1/2–3)</td>
<td>52 (53)/47 (47)</td>
<td>31 (39)/48 (61)</td>
<td>0.13</td>
</tr>
</tbody>
</table>
Flow grade immediately before the second BPA procedure, n (%) (0–1/2–3) 53 (54)/46 (46) 13 (15)/66 (85) < 0.01

Data are presented as median (25th–75th percentile) or number (%)

BPA, balloon pulmonary angioplasty; BRVI, BPA-related vascular injury; LI, lung injury

Hard lesion = BPA procedures requiring a guidewire with a tip load ≥ 3 g to penetrate the occlusion
Table 5. ORs for lesions achieving flow-grade 2 or 3 immediately before the second BPA procedure

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate</th>
<th></th>
<th>Multivariate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P-value</td>
<td>OR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Age</td>
<td>0.68 (0.33–1.43)</td>
<td>0.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>0.97 (0.95–1.00)</td>
<td>0.92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean PAP</td>
<td>1.02 (0.98–1.06)</td>
<td>0.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac index</td>
<td>0.99 (0.59–1.70)</td>
<td>0.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary vascular resistance</td>
<td>1.00 (0.99–1.00)</td>
<td>0.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hard lesion</td>
<td>0.21 (0.11–0.41)</td>
<td>&lt; 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum balloon size</td>
<td>0.90 (0.71–1.14)</td>
<td>0.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flow grade immediately after the first BPA procedure (2–3)</td>
<td>32.8 (13.24–81.31)</td>
<td>&lt; 0.01</td>
<td>46.9 (12.54–176.78)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>
Sub-segmental lesions

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6.1 (2.98–12.42)</td>
<td>&lt; 0.01</td>
<td>13.8 (3.24–58.94)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Data are presented as estimated OR (95% CI)

BPA, balloon pulmonary angioplasty; CI, confidence interval; OR, odds ratio; PAP, pulmonary artery pressure

Hard lesion = procedures requiring a guidewire with a tip load ≥ 3 g to penetrate the occlusion
Figure legends

Figure 1. Pulmonary angiogram before and after BPA

A: Segmental lesion.

a. Right anterior segmental branches (A8) completely occluded (red arrowhead) before BPA.

b. Totally occluded lesion opened after BPA (yellow arrowhead).

B: Sub-segmental lesion.

a. Right anterior sub-segmental branch (A8) completely occluded (red arrowhead) before BPA.

b. Sub-segmental lesion opened after BPA (yellow arrowhead).

BPA, balloon pulmonary angioplasty.

Figure 2. Sankey diagram of changes in flow grade after BPA

Maintenance or improvement in flow grade (to 2 or 3) predominantly observed in the sub-segmental group compared with the segmental group.

BPA, balloon pulmonary angioplasty.