# Low incidence of restenosis after successful balloon pulmonary angioplasty in patients with chronic thromboembolic pulmonary hypertension

First Author: surname: Tabuchi, initial: IT

Short title: Restenosis after BPA for CTEPH

All Authors: Isao Tabuchi MD[1,2], Aiko Ogawa MD, PhD[3], Masataka Shigetoshi MD[1], Hiroto Shimokawahara MD, PhD[1], Hiroshi Ito MD, PhD[2], Hiromi Matsubara MD, PhD[1,3]

[1]Department of Cardiology, National Hospital Organization Okayama Medical Center, Okayama, Japan

[2]Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

[3] Department of Clinical Science, National Hospital Organization Okayama Medical Center, Okayama, Japan

**Correspondence to:**

Hiromi Matsubara MD, PhD

Departments of Cardiology and Clinical Science, National Hospital Organization Okayama Medical Center,

1711-1 Tamasu, Kita-ku, Okayama 701-1192, Japan

Tel.: +81-86-294-9911

Fax: +81-86-294-9255

E-mail: matsubara.hiromi@gmail.com

Total word count: 5462

**Abstract**

**Background:** Balloon pulmonary angioplasty (BPA) is now a treatment option for patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH). However, the incidence of restenosis and long-term changes in vessel diameters in pulmonary arteries after BPA are unknown. The present study investigated the incidence of restenosis by measuring changes in vessel diameter after BPA.

**Methods:** We reviewed 58 patients (168 lesions) with CTEPH who underwent single dilation for the target lesion (type A/B/C lesions) during BPA procedure followed by selective pulmonary angiography more than 6 months after final BPA procedure. The outcomes of BPA were assessed in terms of pulmonary artery diameters.

**Results:** In a median follow-up of 1.9 (1.2 - 2.7) years, restenosis occurred in only one case with a type C lesion after BPA (0.6%). In type A/B lesions, the minimal lumen diameter was significantly enlarged at follow-up after BPA (3.48 [2.59 - 4.34] to 4.22 [3.31 - 4.90] mm). In type C lesions, the minimal lumen diameter was unchanged at follow-up after BPA (3.15 [1.96 - 3.64] to 3.28 [2.38 - 4.61] mm).

**Conclusions:** The present results revealed that restenosis after BPA rarely occurs in type A/B/C lesions. Minimal lumen diameters for type A/B lesions continually increased and those for type C lesions did not decrease. Stent implantation in type A/B/C lesions would be unnecessary after BPA.

## Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a progressive disease associated with a poor prognosis. It is caused by organized thrombi in pulmonary arteries and vascular remodeling. If left untreated, CTEPH leads to increased pulmonary vascular resistance, hypoxia, and right ventricular failure [1]. Pulmonary endarterectomy (PEA) is the standard treatment for CTEPH according to current guidelines [2]. However, PEA is not suitable for all patients due to technical limitations and the influence of comorbidities [3]. Balloon pulmonary angioplasty (BPA) is an alternative therapy for patients with CTEPH that can significantly improve pulmonary hemodynamics, exercise capacity, and survival [4, 5, 6]. When BPA is successfully performed on a pulmonary artery with organized thrombi, the peripheral pulmonary artery can be visualized on a pulmonary angiogram immediately after BPA [4, 7]. However, the occurrence of restenosis and long-term changes in vessel diameters after BPA are unknown. Moreover, although stent implantation effectively reduces restenosis following coronary balloon angioplasty [8], its necessity for patients with CTEPH is unclear. Therefore, the present study investigated the incidence of restenosis after BPA by measuring changes in vessel diameters at follow-up.

## Methods

### Patient and Lesion Selection

Between July 2013 and March 2015, 210 consecutive patients with CTEPH underwent selective pulmonary angiography more than 6 months after final BPA procedure at the National Hospital Organization

Okayama Medical Center (Okayama, Japan) (Figure 1). CTEPH was diagnosed based on standard criteria [4, 9]. All patients were diagnosed as inoperable by expert surgeons. Patient exclusion criteria were as follows: BPA performed in more than two planned staged dilations in all lesions; poor pulmonary angiography images that prevented an angiographic analysis; and inability to measure vessel diameters due to poor separation of the target artery. Fifty-eight patients (189 lesions) were selected for evaluation. Five angiographic thromboembolic lesion types have been reported to date (type A, ring-like stenosis lesion; type B, web lesion; type C, subtotal lesion; type D, total occlusion lesion, and type E, tortuous lesion) [9]. We were unable to perform BPA with single dilation strategy in type D and E lesions and, thus, they were excluded (type D; 21 lesions and type E; 0 lesion). The remaining 168 lesions (58 patients) in which BPA was performed with single dilation strategy was examined. The present study was approved by the Institutional Review Board of the National Hospital Organization Okayama Medical Center (H29-RINKEN-016). The need for written informed consent was waived because of the retrospective nature of the present study.

**BPA Procedure and Selective Pulmonary Angiography**

We placed a 9F indwelling sheath (ArrowFlex, Teleflex, Durham, North Carolina) into a vein and brought a 6F long sheath (Bright Tip Sheath Introducer, Cordis/Johnson & Johnson, New Brunswick, New Jersey) to the main pulmonary artery via the 9F sheath, using a 0.035-inch wire (Radifocus Guide Wire M, Terumo, Tokyo, Japan). These BPA procedures and perioperative management were based on previously published reports [4, 7, 9, 10]. We routinely used the Eagle Eye Platinum (Volcano, San Diego, California) for

77 the intravascular ultrasound (IVUS) examination before and immediately after balloon dilation. After checking
78 the initial diameter of the vessel, we dilated the lesions only once by a smaller balloon (2 to 4 mm, IKAZUCHI
79 PAD, Kaneka, Osaka, Japan; 5 to 7 mm, Bandicoot RX, St. Jude Medical, St. Paul, Minnesota; Aviator Plus,
80 Cordis/Johnson & Johnson, New Brunswick, New Jersey; and 8 mm, Sterling Monorail, Boston Scientific,
81 Natick, Massachusetts) relative to the actual vessel diameter to avoid pulmonary vascular injury. In the
82 procedure, the maximum balloon size was limited to 100% of the actual vessel diameter (as measured by IVUS)
83 in type A lesions, 80% of that in type B lesions, and 60% of that in type C lesions. In addition, the balloon size
84 was further reduced by 20% when mean PAP before treatment exceeded 40 mm Hg [7]. The balloon was
85 inflated by hand until the indentation disappeared or until the balloon was fully expanded.
86 All patients underwent right heart catheterization before BPA and after final BPA. Right heart
87 catheterization and selective pulmonary angiography follow-ups were routinely scheduled at 6 months after final
88 BPA procedure and yearly thereafter. BPA and selective pulmonary angiography have already been described in
89 detail [4]. Briefly, we selected a branch of the pulmonary artery using a 6F guiding catheter (Mach 1 peripheral
90 MP and AL1; Boston Scientific, Natick, MA), and selective pulmonary angiography was performed by a
91 manual injection of non-ionized contrast medium during BPA. At follow-up, we performed selective pulmonary
92 angiography using a diagnostic catheter (5F MP; TERUMO; Tokyo, Japan and 4F AL1; FUKUDA DENSHI;
93 Tokyo, Japan) with a manual injection of non-ionized contrast medium. BPA and selective pulmonary
94 angiography were both conducted using 8-inch images.
95

**Clinical Outcomes**

The effectiveness of BPA was assessed based on improvements in the World Health Organization (WHO) functional class, hemodynamic parameters (systolic pulmonary arterial pressure [PAP], diastolic PAP, mean PAP, cardiac index, right atrial pressure, and pulmonary vascular resistance), plasma levels of brain natriuretic peptide, and 6-minute walk distance. Data were compared between measurements taken before the first procedure of BPA and those taken at the first follow-up 6 months after final BPA.

**Angiographic Analysis**

Representative images of pulmonary angiography before BPA, immediately after BPA, and at follow-up are shown in Figure 2. BPA and pulmonary angiographic cine images were acquired at 15 frames per second. A quantitative vascular analysis (QVA) was performed using CAAS Workstation 7.2.1 (Pie Medical Imaging, Maastricht, the Netherlands), referenced to the diameters of the contrast-filled 6F guiding and 5F diagnostic catheters. Automated distance calibration was used to determine pixel size. After calibrating pixel size, analyzes of the sites with MLD, PRD and DRD were performed during the deep inspiration as far as possible. Edge detection correction was performed if required. All angiograms were analyzed in a random sequence by two experienced observers who were blinded to the clinical characteristics of patients. Intraobserver and interobserver agreements were described by intraclass correlation coefficients (ICCs). For the intraobserver study, we compared the results from two examinations performed by the same observer. For the interobserver study, the results of two different observers were compared.

The minimal lumen diameter (MLD), proximal reference diameter (PRD), and distal reference diameter (DRD) were measured before the first procedure of BPA at the target lesion, immediately after the procedure of BPA, and at follow-up. The narrowest thromboembolic lesion diameter was defined as MLD. The largest lumen diameter within 10 mm proximal from MLD was defined as PRD. If there was a large side branch within 10 mm of MLD, the lumen diameter just distal to the large side branch was defined as PRD. The lumen diameter 10 mm distal from MLD was defined as DRD. Reference segment for the branch-ostial lesion was defined as the just proximal point of the branch bifurcation. When the automatically interpolated reference line was inappropriate, the reference line was manually corrected and used as the proximal reference diameter. The reference diameter (RD) was calculated as (PRD+DRD)/2. Acute gain was defined as the difference between MLD before and immediately after BPA. Late loss was defined as the difference between MLD immediately after BPA and that at follow-up. The presence of late loss was defined as late loss> 0 mm. Percent diameter stenosis was calculated as [1−(MLD/RD)] × 100. Binary restenosis was defined as >50% diameter stenosis at follow-up.

**Statistical Analysis**

Descriptive data are expressed as medians (interquartile ranges) for continuous variables and percentages for categorical variables. The WHO functional class is expressed as the median and number of patients in each class. The normal distribution of each data subset was examined using graphical methods and the Shapiro-Wilk test. Comparisons of each parameter measured before the first procedure of BPA and at the

first follow-up 6 months after final BPA were performed using a paired *t*-test or the Wilcoxon signed-rank test for each continuous variable. Categorical variables were compared using the $\chi^2$ test. The difference in QVA between measurements before and immediately after BPA at the target lesion and follow-up data was analyzed using the Friedman test followed by the Bonferroni correction. Intraobserver and interobserver agreement was evaluated using ICCs. All analyses were conducted using IBM SPSS 20 (IBM, Armonk, NY). The significance of differences was defined as $P < 0.05$.

## Results

### Patient Characteristics

The present study included 58 patients (50 females [86%] and 8 males [14%]) with inoperable CTEPH. Median age was 65 (57 - 70) years at the time of the first admission. Clinical characteristics are shown in Table 1. All patients were treated with anticoagulant therapy throughout the study period. Among PAH-targeted drugs, no patient received soluble guanylate cyclase stimulators before BPA. Comorbidities were as follows: dyslipidemia (23 patients), hypertension (14 patients), thyroid function disorder (3 patients), diabetes mellitus (3 patients), and coagulopathy (1 patients).

### Outcomes of BPA

Hemodynamics and exercise capacity significantly improved in all patients after BPA (Table 1). The number of patients classified as WHO functional class I or II significantly increased from 24% (14 patients)

153 before BPA to 98% (57 patients) after final BPA. Clinical and hemodynamic variables markedly improved after
154 BPA. Few patients required supplemental oxygen therapy after BPA. The number of patients on PAH-targeted
155 drugs was significantly lower at follow-up than before BPA. No patients were newly administered PAH-targeted
156 drugs after BPA.
157
158 **Angiographic Outcomes**
159 Fifty-eight patients underwent right heart catheterization and selective pulmonary angiography 1.9
160 (1.2 - 2.7) years after BPA procedure for the target lesion. A total of 168 lesions were selected for analysis. The
161 distribution of targeted vessels and lesion types is shown in Table 2. BPA-targeted vessels were predominantly
162 located in the right lobe (86.3%). Web lesions (type B) were predominant over other lesion types.
163 Approximately half of the patients (48%) had type B lesions only. Other patients had multiple lesion types (type
164 A and B lesions; 22%, type B and C lesions; 21%, type A, B and C lesions; 9%).
165 In the QVA analysis of type A/B lesions, PRD, MLD, and DRD were significantly larger after than
166 before BPA (Figure 3). These parameters were also larger at follow-up than immediately after BPA.
167 Angiographic restenosis did not occur in type A/B lesions (0/144 lesions) (Table 3). In the QVA analysis of type
168 C lesions, PRD, MLD, and DRD were significantly larger after than before BPA (Figure 4). No significant
169 differences were observed in these parameters between the follow-up and immediately after BPA. The median
170 balloon size was 4.0 mm (range: 1.5-8.0 mm) and balloon-to-artery ratio was 0.85 (range: 0.32-1.79). Seven
171 lesions (7 patients) were included in the intraobserver and interobserver studies. ICCs of the measurements are

presented in Table S1. ICCs were more than 0.81 in all parameters.

Angiographic restenosis only occurred in one type C lesion (1/24 lesions) (Figure 5A, Table 3). Overall, the restenosis rate was as low as 0.6% (1/168 lesions). Late loss was observed in 18 lesions (type B: 13 lesions, type C: 5 lesions). A representative case of late loss without restenosis is shown in Figure 5B. The pulmonary artery focally expanded immediately after BPA, and PRD and MLD returned to normal after reductions in PAP at follow-up.

**Discussion**

The catheter intervention of BPA dilates stenotic lesions in patients with CTEPH by using a balloon catheter. Recent studies reported hemodynamic improvements following BPA [4, 5, 6, 11, 12, 13, 14]. The continued development of BPA is underway with the goal of providing a therapeutic alternative for selected patients with inoperable CTEPH. Because BPA is an emerging treatment, many aspects have yet to be elucidated, such as the restenosis rate. Although the restenosis rate is considered to be low, no studies on BPA involving more than 50 patients with inoperable CTEPH have clearly documented the incidence of restenosis and necessity for stent implantation after BPA [4, 5, 6, 9, 11, 12, 13, 14, 15, 16].

In the present study, we examined the incidence of restenosis by measuring changes in vessel diameters before and immediately after BPA as well as at follow-up in patients with CTEPH. Currently, we perform BPA with staged dilation strategy. Because the 'true restenosis' rate cannot be evaluated in cases of staged dilation strategy, we needed to select lesions with a single dilation strategy we employed prior to 2015.

Type D and type E lesions were excluded because they are always treated by repetitive dilation, and thus, only type A/B/C lesions were evaluated.

Among 168 lesions, only one type C lesion (0.6%) showed restenosis. In this case, the lesion was totally occluded at follow-up. Because there was a period of INR<1.5 in this case, we speculate that the cause was the thrombotic occlusion due to poor control of anticoagulation. The large burden of a thrombus in a type C lesion [10] may also be related to susceptibility to reocclusion. There was no restenosis in type A or B lesions. The incidence of restenosis is lower after BPA than after coronary balloon angioplasty (32 - 40%) [17, 18], which may be attributed to histological differences in pulmonary and coronary arteries.

The results of QVA showed that vessel diameters were enlarged in type A/B/C lesions immediately after BPA. A similar technique to BPA, percutaneous coronary intervention, is used to dilate coronary arteries, and is widely applied to treat ischemic heart disease. Lumen enlargement in coronary balloon angioplasty is attributed to the combined effects of increasing the total cross-sectional area of the vessel (wall stretching) and reducing the area occupied by the plaque (plaque compression or redistribution) based on quantitative angiography and intravascular ultrasound measurements before and after balloon angioplasty [19, 20]. Although it was not evaluated in the present study, we speculate that the mechanism underlying lumen enlargement after BPA may differ to that following coronary balloon angioplasty. Enlargement mainly occurs due to overall vessel expansion induced by stretching of the arterial wall, as we previously demonstrated [10, 21]. Other mechanisms causing diameter enlargement may be the disruption of meshworks [21, 22] and the compression of thrombi [21].

We reported short-term outcomes in a case in which blood flow and lumen diameters were increased at follow-up after BPA [7]. By measuring a large number of vessel diameters in target lesions in the present study, we confirmed that MLD, PRD, and DRD in type A/B lesions were significantly larger at follow-up than immediately after BPA. In type C lesions, vessel diameters did not stenose or significantly increase.

In the present study, late loss after BPA markedly differed from angiographic late loss after coronary balloon angioplasty. The pulmonary artery was expanded immediately after BPA; however, PRD and MLD decreased at follow-up, suggesting that the excessively expanded target vessel diameter shrunk to the normal diameter of the pulmonary artery. The mechanisms underlying late loss after coronary balloon angioplasty are considered to involve smooth muscle cell migration, neointimal proliferation, elastic recoil, and negative arterial remodeling [23, 24]. However, because the dilation process differed between coronary angioplasty and BPA, the mechanisms underlying late loss may also have been different. We speculated that the following mechanism was involved in the occurrence of late loss in the present study. Similar to elastic recoil after coronary balloon angioplasty, MLD was expanded too far due to wall stretch immediately after BPA and then decreased because of elastic recoil at follow-up. The precise mechanism responsible for late loss after BPA currently remain unclear, and, thus, further studies involving intravascular ultrasound evaluations or histological analyses are warranted.

In the past decade, BPA has emerged as one of the treatment options for CTEPH. However, there are many unknown facts regarding BPA including restenosis rate. In the present study, we evaluated the restenosis rate in a long-term follow-up of approximately two years in a large number of lesions and found that restenosis

rarely occurred after BPA. Although coronary stenting plays a major role in the prevention of restenosis after coronary balloon angioplasty, pulmonary artery stenting does not appear to be necessary for type A/B lesions in CTEPH. In addition, the present results indicated that vessel diameters after BPA continually expanded, suggesting that pulmonary stenting would merely increase the risk of stent migration in patients with CTEPH.

**Limitations**

There are some limitations that need to be addressed. This was a retrospective, single-center study with a limited number of patients. Furthermore, 'true restenosis' cannot be evaluated in patients treated with a staged dilation strategy and, thus, we examined lesions treated with the single dilation strategy only. We were unable to evaluate type D and E lesions, which require staged dilation. The restenosis rate and changes in vessel diameters after BPA remain unclear for these lesion types. In addition, due to the many complications reportedly associated with BPA with the single dilation strategy for the target lesion, we recently changed to the staged dilation strategy. Therefore, the number of patients/lesions was limited. Additionally, the accuracy of QVA may have been reduced given that pulmonary angiography was done using 5F angiographic catheters.

**Conclusions**

The present study revealed that the long-term restenosis rate after BPA was very low (0.6%) and hemodynamic improvements were achieved in all cases. PRD, MLD, and DRD did not decrease at follow-up, and remained enlarged in type A/B lesions. Therefore, stent implantation in stenotic lesions is not required for

248 patients with CTEPH.

249

250 **Authorship clarification**

251 IT and HM conceived the work. IT and MS acquired the data. IT and AO performed the data analysis,

252 drafted the work. IT, AO, HS and HM interpreted the data. IT, AO, HS, HI and HM revised the manuscript. All

253 authors approved the final manuscript.

254

255 **Disclosures**

256 Dr. Ogawa received lecture fees from Nippon Shinyaku, Co., Ltd.; Pfizer Japan, Inc.; and Actelion

257 Japan, Ltd. Dr. Shimokawahara received lecture fees from Daiichi Sankyo Co., Ltd.; Bayer Yakuhin, Ltd.;

258 Nippon Shinyaku, Co., Ltd.; and Actelion Pharmaceuticals Japan, Ltd. Dr. Matsubara received lecture fees from

259 Nippon Shinyaku, Co., Ltd.; Bayer AG; Pfizer Japan, Inc.; Actelion Pharmaceuticals Ltd.; GlaxoSmithKline

260 plc.; United Therapeutics Corp.; AOP Orphan Pharmaceuticals AG.; Grupo Ferrer Internacional SA.; and

261 Kaneka Medix Co. Dr. Ogawa and Dr. Matsubara are involved in collaborative research with Nippon Shinyaku,

262 Co., Ltd. Other authors report no conflicts.

263 This research had no funding.

264

265 **Acknowledgements**

266 The authors are grateful to Akiko Ohina and Mihoko Yoshimori for their assistance in data collection.

267

## References


1. Lang IM, Madani M. Update on chronic thromboembolic pulmonary hypertension. Circulation. 2014;130:508-18.

2. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J. 2015;46:903-75.

3. Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation. 2011;124:1973-1981.

4. Mizoguchi H, Ogawa A, Munemasa M, Mikouchi H, Ito H, Matsubara H. Refined balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension. Circ Cardiovasc Interv. 2012;5:748-55.

5. Kataoka M, Inami T, Hayashida K, Shimura N, Ishiguro H, Abe T, et al. Percutaneous transluminal pulmonary angioplasty for the treatment of chronic thromboembolic pulmonary hypertension. Circ Cardiovasc Interv. 2012;5:756-62.

6. Ogawa A, Satoh T, Fukuda T, Sugimura K, Fukumoto Y, Emoto N, et al. Balloon Pulmonary Angioplasty for Chronic Thromboembolic Pulmonary Hypertension: Results of a Multicenter Registry. Circ Cardiovasc Qual Outcomes. 2017;10:e004029.

7. Shimokawahara H, Nagayoshi S, Ogawa A, Matsubara H. Continual Improvement in Pressure Gradient at the Lesion After Balloon Pulmonary Angioplasty for Chronic Thromboembolic Pulmonary Hypertension. Can J Cardiol. 2021;37:1232-1239.

8. Di Mario C, Moses JW, Anderson TJ, Bonan R, Muramatsu T, Jain AC, et al. Randomized comparison of elective stent implantation and coronary balloon angioplasty guided by online quantitative angiography and intracoronary Doppler. DESTINI Study Group (Doppler Endpoint STenting INternational Investigation). Circulation. 2000;102:2938-44.

9. Kawakami T, Ogawa A, Miyaji K, Mizoguchi H, Shimokawahara H, Naito T, et al. Novel Angiographic Classification of Each Vascular Lesion in Chronic Thromboembolic Pulmonary Hypertension Based on Selective Angiogram and Results of Balloon Pulmonary Angioplasty. Circ Cardiovasc Interv. 2016;9:e003318.

10. Shimokawahara H, Ogawa A, Mizoguchi H, Yagi H, Ikemiyagi H, Matsubara H. Vessel Stretching Is a Cause of Lumen Enlargement Immediately After Balloon Pulmonary Angioplasty: Intravascular Ultrasound Analysis in Patients With Chronic Thromboembolic Pulmonary Hypertension. Circ Cardiovasc Interv. 2018;11:e006010.

11. Olsson KM, Wiedenroth CB, Kamp JC, Breithecker A, Fuge J, Krombach GA, et al. Balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension: the initial German experience. Eur Respir J. 2017;49:1602409.

12. Kurzyna M, Darocha S, Pietura R, Pietrasik A, Norwa J, Manczak R, et al. Changing the strategy of balloon pulmonary angioplasty resulted in a reduced complication rate in patients with chronic thromboembolic pulmonary hypertension. A single-centre European experience. Kardiol Pol. 2017;75:645-654.

13. Kimura M, Kohno T, Kawakami T, Kataoka M, Tsugu T, Akita K, et al. Midterm Effect of Balloon Pulmonary Angioplasty on Hemodynamics and Subclinical Myocardial Damage in Chronic Thromboembolic Pulmonary Hypertension. Can J Cardiol. 2017;33:463-470.

14. Aoki T, Sugimura K, Tatebe S, Miura M, Yamamoto S, Yaoita N, et al. 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. Eur Heart J. 2017;38:3152-3159.

15. Inami T, Kataoka M, Shimura N, Ishiguro H, Yanagisawa R, Fukuda K, et al. Pressure-wire-guided percutaneous transluminal pulmonary angioplasty: a breakthrough in catheter-interventional therapy for chronic thromboembolic pulmonary hypertension. JACC Cardiovasc Interv. 2014;7:1297-306.

16. Ogo T, Fukuda T, Tsuji A, Fukui S, Ueda J, Sanda Y, et al. Efficacy and safety of balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension guided by cone-beam computed tomography

and electrocardiogram-gated area detector computed tomography. Eur J Radiol. 2017;89:270-276.

17. Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med. 1994;331:489-95.

18. Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. N Engl J Med. 1994;331:496-501.

19. Baptista J, Umans VA, di Mario C, Escaned J, de Feyter P, Serruys PW. Mechanisms of luminal enlargement and quantification of vessel wall trauma following balloon coronary angioplasty and directional atherectomy. Eur Heart J. 1995;16:1603-12.

20. Baptista J, di Mario C, Ozaki Y, Escaned J, Gil R, de Feyter P, et al. Impact of plaque morphology and composition on the mechanisms of lumen enlargement using intracoronary ultrasound and quantitative angiography after balloon angioplasty. Am J Cardiol. 1996;77:115-21.

21. Kitani M, Ogawa A, Sarashina T, Yamadori I, Matsubara H. Histological Changes of Pulmonary Arteries Treated by Balloon Pulmonary Angioplasty in a Patient with Chronic Thromboembolic Pulmonary Hypertension. Circ Cardiovasc Interv. 2014;7:857-859.

22. Raber L, Ueki Y, Lang IM. Balloon pulmonary angioplasty for the treatment of chronic

thromboembolic pulmonary hypertension. EuroIntervention. 2019;15:e814-e815.

23. Rensing BJ, Hermans WR, Strauss BH, Serruys PW. Regional differences in elastic recoil after percutaneous transluminal coronary angioplasty: A quantitative angiographic study. J Am Coll Cardiol. 1991;17:34-38.

24. Mintz GS, Popma JJ, Pichard AD, Kent KM, Satler LF, Wong C, et al. Arterial remodeling after coronary angioplasty: a serial intravascular ultrasound study. Circulation. 1996;94:35-43.

**Fig 1.** Flow diagram of patients/lesions for study inclusion

Lesion types of D and E are reported by Kawakami et al [9].

Pts, patients; BPA, balloon pulmonary angioplasty; mPAP, mean pulmonary arterial pressure.

**Fig 2.** Representative pulmonary angiographic images of successful BPA.

**a.** A web lesion (arrowhead) in a pulmonary artery in the right lower lobe before BPA. Delayed antegrade flow with complete filling of the distal pulmonary artery bed was observed.

**b.** Immediately after dilation of the target lesion (arrowhead) with a 2.5-mm balloon at 16 atm, the lesion was successfully dilated and pulmonary arterial flow increased angiographically.

**c.** At one-year follow-up after BPA, the pulmonary artery diameter at the target lesion (arrowhead) and peripheral arteries were further dilated.

**Fig 3.** Quantitative vascular analysis of type A/B lesions.

**a.** Representative pulmonary angiogram of a right apical segmental artery (A1).

**i.** Pulmonary angiogram before BPA. Since a large side branch was observed within 10 mm proximal of the minimal lumen diameter (MLD; arrowhead), the lumen diameter just distal to the large side branch was defined as the proximal reference diameter (PRD; dotted line). The lumen diameter within 10 mm distal from MLD was defined as the distal reference diameter (DRD; solid line). PRD, MLD, and DRD were 4.3, 1.2, and 5.3 mm, respectively.

**ii.** Pulmonary angiogram immediately after BPA. PRD, MLD, and DRD increased to 5.0, 5.1, and 6.7 mm, respectively.

**iii.** Pulmonary angiogram at 3.5 years follow-up after BPA. PRD, MLD, and DRD further increased to 7.0, 5.9, and 6.5 mm, respectively.

**b.** Changes in PRD. PRD increased immediately after BPA and was larger at follow-up than immediately after BPA.

**c.** Changes in MLD. MLD was larger at follow-up than immediately after BPA, not only increased immediately after BPA.

**d.** Changes in DRD. DRD was also larger at follow-up than immediately after BPA, not only increased immediately after BPA.

Error bars indicate standard deviations. *P < 0.05, **P < 0.01.

**Fig 4.** Quantitative vascular analysis of type C lesions.

**a.** Representative pulmonary angiogram of a left lower segmental artery (A9).

**i.** Pulmonary angiogram before BPA. The lumen diameter within 10 mm proximal from MLD (arrowhead) was defined as PRD (dotted line). PRD was 4.4 mm. MLD and DRD could not be measured and were assumed to be 0.0 mm.

**ii.** Pulmonary angiogram immediately after BPA. The lumen diameter within 10 mm distal from MLD was defined as DRD (solid line). PRD, MLD, and DRD were 4.3, 3.5, and 3.7 mm, respectively. PRD

was unchanged.

**iii.** Pulmonary angiogram at 1 year follow-up after BPA. PRD, MLD, and DRD were 3.5, 3.1, and 2.7 mm, respectively. The increases in MLD and DRD were maintained.

**b.** Changes in PRD. PRD was significantly larger after BPA. PRD was not larger at follow-up than immediately after BPA.

**c.** Changes in MLD. MLD was significantly larger after than before BPA. The increased diameter was maintained at follow-up.

**d.** Changes in DRD. DRD was significantly larger after than before BPA. Increases in DRD were maintained at follow-up.

Error bars indicate standard deviations. *P < 0.05, **P < 0.01.

**Fig 5.** Angiographic images of restenosis and late loss without restenosis.

**a.** Representative angiographic images of restenosis.

**i.** Pulmonary angiogram showing a subtotal lesion (arrowhead) in the right lower lobe artery (A10) before BPA. The proximal site of the lesion was dilated due to high pulmonary arterial pressure (mean pulmonary arterial pressure = 35 mmHg). The distal site of the lesion was shrunken and meandering (PRD = 7.6 mm).

**ii.** After dilation with a 5.0-mm balloon at 14 atm (arrowhead), the lesion was successfully dilated and PRD, MLD, and DRD increased (PRD = 6.5 mm, MLD = 4.3 mm, DRD = 4.9 mm).

**iii.** The dilated lesion was completely reoccluded (arrowhead) after 2.9 years.

**b.** Representative angiographic images of late loss without restenosis.

**i.** Pulmonary angiogram showing a web lesion (type B, arrowhead) in the right lower lobe artery (A8) before BPA. The proximal site of the lesion was dilated due to high pressure (mean pulmonary arterial pressure = 51 mmHg). The distal site of the lesion was shrunken and meandering (PRD = 4.2 mm, MLD = 2.3 mm, DRD = 2.2 mm).

**ii.** After dilation with a 6.0-mm balloon at 14 atm (arrowhead), the lesion was successfully dilated and PRD, MLD, and DRD were increased (PRD = 5.5 mm, MLD = 5.4 mm, DRD = 3.8 mm).

**iii.** At 3.7 years follow-up, PRD and MLD were smaller (PRD = 4.8 mm, MLD = 4.5 mm, DRD = 3.9 mm; late loss = 0.9 mm) than after BPA. The excessively expanded PRD and MLD shrunk to normal diameters and meandering of the distal site of the target lesion disappeared.

414 **Table 1.** Clinical and hemodynamic parameters before and 6 months after final balloon pulmonary angioplasty

415 (n = 58)

| | Before BPA | 6 months After BPA | P Value |
|---|---|---|---|
| WHO FC (median) | III | II | <0.01 |
| I, n (%) | 0 (0) | 25 (43) | |
| II, n (%) | 14 (24) | 32 (55) | |
| III, n (%) | 37 (64) | 1 (2) | |
| IV, n (%) | 7 (12) | 0 (0) | |
| 6MWD, m | 290 (180 - 365) | 410 (385 - 440) | <0.01 |
| BNP, pg/ml | 74.0 (38.8 - 366.1) | 31.9 (11.1 - 53.4) | <0.01 |
| sPAP, mmHg | 75 (58 - 83) | 34 (32 - 38) | <0.01 |
| dPAP, mmHg | 19 (13 - 26) | 9 (5 - 13) | <0.01 |
| mPAP, mmHg | 43 (35 - 47) | 21 (19 - 23) | <0.01 |
| RAP, mmHg | 6 (4 - 9) | 4 (2 - 7) | <0.01 |
| CI, L/min/$m^2$ | 2.5 (2.0 - 2.9) | 2.7 (2.3 - 3.0) | <0.05 |
| PVR, WU | 8.4 (6.5 - 11.8) | 3.3 (2.8 - 4.2) | <0.01 |
| Supplemental oxygen therapy, n (%) | 37 (64) | 6 (10) | <0.01 |
| PAH-targeted drug, n (%) | 31 (53) | 5 (9) | <0.01 |
| ERA, n (%) | 23 (40) | 3 (5) | <0.01 |

| | | | |
|---|---|---|---|
| PDE-5I, n (%) | 21 (36) | 4 (7) | <0.01 |
| parenteral $PGI_2$, n (%) | 1 (2) | 0 (0) | 0.315 |

Categorical data are shown as numbers (%) and continuous data as medians (interquartile ranges). The World Health Organization functional class (WHO FC) is presented as a median and the number of patients in each class. BPA, balloon pulmonary angioplasty; 6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; sPAP, systolic pulmonary arterial pressure; dPAP, diastolic pulmonary arterial pressure; mPAP, mean pulmonary arterial pressure; RAP, right atrial pressure; CI, cardiac index; PVR, pulmonary vascular resistance; WU, Wood units; PAH, pulmonary arterial hypertension; ERA, endothelin receptor antagonist; PDE-5I, phosphodiesterase 5 inhibitor; $PGI_2$, prostaglandin $I_2$.

**Table 2.** Lesion characteristics of target vessels (n = 168)

| Distribution (upper/middle or lingular/lower) | n |
|---|---|
| Right lung | 16/16/113 |
| Left lung | 0/3/20 |
| **Lesion type** | **n (%)** |
| Ring-like stenosis (Type A) | 16 (9.5) |
| Web (Type B) | 128 (76.2) |
| Subtotal (Type C) | 24 (14.3) |

Data are shown as numbers or numbers (%). Lesion types of A, B, and C are reported by Kawakami et al.[9]

425 **Table 3.** Angiographic measurements

| | Before BPA | Immediately after BPA | Follow-up |
|---|---|---|---|
| Type A/B lesions (n = 144) | | | |
| Reference diameter, mm | 3.65 (2.88 - 4.64) | 4.27 (3.36 - 5.06) | 4.39 (3.66 - 5.56) |
| Acute gain, mm | N/A | 0.81 (0.31 - 1.42) | N/A |
| Late loss, mm | N/A | N/A | −0.59 (−1.09 - −0.12) |
| Binary stenosis, % | N/A | N/A | 6.9 (−3.3 - 18.8) |
| Restenosis rate, % (n) | N/A | N/A | 0 (0) |
| Type C lesions (n = 24) | | | |
| Reference diameter, mm | N/A | 3.48 (2.90 - 4.31) | 3.88 (3.10 - 4.55) |
| Acute gain, mm | N/A | 3.15 (1.96 - 3.64) | N/A |
| Late loss, mm | N/A | N/A | −0.85 (−1.42 - 0.02) |
| Binary stenosis, % | N/A | N/A | 3.9 (−5.5 - 11.0) |
| Restenosis rate, % (n) | N/A | N/A | 4.2 (1) |

426 Data are shown as medians (interquartile ranges).

427 N/A, not applicable.