jaa Just accepted article

EuroIntervention

Title: **Extensive revascularization by balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension beyond hemodynamic normalization.**

Authors: Yuto Shinkura, MD; Kazuhiko Nakayama, MD, PhD; Kenichi Yanaka, MD; Hiroto Kinutani, MD, PhD; Naoki Tamada, MD; Yasunori Tsuboi, PT, Msc; Seimi Satomi-Kobayashi, MD, PhD; Hiromasa Otake, MD, PhD; Toshiro Shinke, MD, PhD; Noriaki Emoto, MD, PhD; Kenichi Hirata, MD, PhD

DOI: 10.4244/EIJ-D-17-00157

Citation: Shinkura Y, Nakayama K, Yanaka K, H Kinutani H, Tamada N, Tsuboi Y, Satomi-Kobayashi S, Otake H, Shinke T, Emoto N, Hirata K. Extensive revascularization by balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension beyond hemodynamic normalization. *EuroIntervention* 2017; Jaa-198 2017, doi: 10.4244/EIJ-D-17-00157

Manuscript submission date: 26 February 2017

Revisions received: 09 June 2017, 10 July 2017

Accepted date: 10 August 2017

Online publication date: 15 August 2017

Extensive revascularization by balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension beyond hemodynamic normalization

Yuto Shinkura[1], MD; Kazuhiko Nakayama[1], MD, PhD; Kenichi Yanaka[1], MD; Hiroto Kinutani[1], MD, PhD; Naoki Tamada[1], MD; Yasunori Tsuboi[1], PT, Msc; Seimi Satomi-Kobayashi[1], MD, PhD; Hiromasa Otake[1], MD, PhD; Toshiro Shinke[1], MD, PhD; Noriaki Emoto[1,2], MD, PhD; Ken-ichi Hirata[1], MD, PhD

[1]Division of Cardiovascular Medicine, Department of internal medicine, Kobe University Graduate School of Medicine, Japan

[2]Department of Clinical Pharmacy, Kobe Pharmaceutical University, Japan

Short running title: Extensive revascularization for CTEPH

Corresponding author: Kazuhiko Nakayama
Division of Cardiovascular Medicine, Department of internal medicine, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki, Chuo, Kobe, Hyogo 650-0017, Japan
Tel: +81-78-382-5846 Fax: +81-78-382-5859 E-mail:nakayama@med.kobe-u.ac.jp

Conflict of interest statement: The authors have no conflicts of interest to declare.
Total word count: 4112words
Word count of abstract: 200 words
Total number of figures: 5 figures
Total number of table: 4 tables

Abstract

Aims: Balloon pulmonary angioplasty (BPA) improves hemodynamics and exercise capacity in patients with chronic thromboembolic pulmonary hypertension (CTEPH). However, even after BPA many patients still suffered from exertional dyspnea. Our purpose is to clarify the clinical validity of extensive revascularization by BPA (ERBPA) beyond hemodynamic normalization.

Methods and results: 35 CTEPH patients with normalized or borderline mean pulmonary arterial pressure (mPAP) after BPA were retrospectively analyzed. We evaluated the clinical efficacy of ERBPA strategy in 15 patients (ERBPA group) by comparing with the natural course of 20 patients who could be followed without additional BPA (conventional BPA group). ERBPA reduced the number of pulmonary arterial segments with residual stenoses from 11.7±0.4 to 5.3±0.5 segments. Symptoms, six-minute walking distance, and VE/VCO_2 slope were significantly improved in the ERBPA group but not the conventional BPA group, which indicated that this improvement was due to ERBPA and not merely a natural progression after hemodynamic normalization. Complications accompanied with ERBPA were fewer than that of the initial BPA therapy.

Conclusion: ERBPA targeting residual stenoses can safely ameliorate symptoms and exercise capacity by additional improvement of hemodynamics. The results encourage us to optimize the current BPA goal to be more aggressive.

Keywords:

Balloon pulmonary angioplasty, extensive revascularization, hemodynamic normalization, chronic thromboembolism, exercise capacity, treatment goal, oxygenation

Condensed abstract

Balloon pulmonary angioplasty (BPA) can dramatically improve the prognosis and exercise capacity of patients with chronic thromboembolic pulmonary hypertension (CTEPH). However, the goals of BPA have not been established. The patients who achieved mean pulmonary arterial pressure normalization did not always recover to reach sufficient reperfusion of pulmonary vascular bed and still suffered from exertional dyspnea. The present study demonstrated that the strategy of extensive revascularization by BPA (ERBPA) beyond hemodynamic normalization could achieve further improvement of exercise capacity. A new therapeutic goal of BPA should be set to dilate residual lesions as much as possible for patients with CTEPH.

Abbreviations:

BPA: Balloon pulmonary angioplasty

CTEPH: Chronic thromboembolic pulmonary hypertension

ERBPA: extensive revascularization of BPA

PEA: Pulmonary endarterectomy

RHC: right heart catheterization

RPI: Reperfusion pulmonary injury

Introduction

Pulmonary endarterectomy (PEA) is a gold standard therapy for CTEPH, and balloon pulmonary angioplasty (BPA) is an alternative treatment option for patients with distal-type CTEPH[1]. The first report about BPA by Feinstein[2] showed significant reduction of mPAP from 42±12 to 33±10 mmHg in 2001. In 2012, a refined BPA was introduced

achieving a decreased mPAP (24mmHg)[3]. Recent studies tend to show further aggressive reduction of mPAP (21~23mmHg)[1,4,5.]

The indication of BPA is now recommended in the following two situations, 1) non-operable CTEPH[2], 2) residual PH after PEA[6]. However, it is not yet clear how we should set the endpoint of BPA. Lewczuk et al reported that patients with mPAP over 30mmHg had a poorer prognosis than patients with mPAP under 30mmHg[7]. Moreover, we have experienced many patients who still suffered from persistent exertional dyspnea accompanied by residual stenoses despite normalization of mPAP. Persistent stenosis after PEA was reported to be a cause of persistent symptoms[8].

The aim of this study was to clarify the efficacy and safety of extensive revascularization by BPA (ERBPA) by evaluating hemodynamics, exercise capacity, symptoms, and complications. If this approach is proven to be effective, the new therapeutic endpoint will be established for patients with not only CTEPH but also chronic thromboembolism without pulmonary hypertension (PH).

Methods

The Ethical Committees in Kobe University Hospital accepted the study protocol.

Extraction of study population

A total of 122 patients were diagnosed with CTEPH from July 1999 to July 2016 in Kobe University Hospital (Figure 1). 19 patients received medical management only. PEA was performed for 44 patients and BPA was performed for 59 patients. 12 patients were unable to reach a mPAP value of less than 25mmHg because of several reasons: 1) refusal of further BPA due to severe complications at a previous session, 2) end-stage renal disease, 3) advanced age, 4) multiple unsuitable lesions for BPA, 5) existence of

malignant cancer. Since the initiation of BPA in March 2011, we formerly set the endpoint as normalization of mPAP defined as less than 25mmHg (conventional BPA group). We modified the endpoint from hemodynamic normalization to revascularization of all remaining stenoses as much as possible regardless of mPAP since November 2014 (ERBPA group). 4 patients in CRPBA and 8 patients in conventional BPA group were excluded due to absence of follow-up right heart catheterization (RHC). Finally, 20 patients were analysed as the conventional BPA group, and 15 patients as ERBPA group.

BPA procedure

The BPA procedure was described in our previous reports[1,9]. We utilized mainly the femoral vein approach and inserted a 6Fr guiding sheath into the main pulmonary artery. Through the guiding sheath we engaged a 6Fr guiding catheter (Profit®; Goodman, Aichi, Japan) into the targeting sectional branch and passed a 0.014 inch guide wire (Athlete Bpahm®; Japan Lifeline, Tokyo, Japan). After we assessed the diameter and lesion type by using intravascular ultrasound (IVUS), we dilated vessel lesions with a 2.0-7.0 mm monorail balloon. In each hospitalization we performed two sessions of BPA and RHC one week after the latest session to evaluate the efficacy.

Clinical parameters

Hemodynamics, exercise capacity, lung function, and WHO functional class were evaluated at three points: 1) pre-initial BPA, 2) baseline (when mPAP was normalized), 3) follow up (more than three months after the final procedure). During each pulmonary angiography procedure, vessel lesions were classified according to the Japan Circulation Society criteria: web, band, abrupt narrowing, complete vascular obstruction, and pouch. We counted the number of pulmonary arterial segments involving at least one lesion

including sub-segmental branches. Six-minute walking test and cardiopulmonary exercise test were performed to assess exercise capacity. Clinical events from baseline were monitored until December 2016.

Occurrence of reperfusion pulmonary injury

We routinely performed chest X-ray and CT within 24 hours after each BPA session and reperfusion pulmonary injury (RPI) was assessed by at least two cardiologists and one radiologist. Occurrence rates of hemosputum, non-invasive pressure ventilator (NPPV), and intubation were evaluated.

Statistical analysis

Continuous variables were represented as mean±standard error. Differences between the groups were analysed by unpaired t-test. Differences between 'Baseline' and 'Follow up' were statistically compared by using paired t-test. The chi-square tests were utilized for comparison between categorical variables. Wilcoxon signed-ran test and Mann-Whitney test were used in cases of paired and unpaired comparisons for WHO-Fc. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed by using SPSS statistics 17.0 (SPSS Japan Inc., Tokyo, Japan)

Results

Characteristics at pre-initial BPA

Characteristics at pre-initial BPA are summarized in Table 1. Although the ERBPA group was female-dominant and younger on average than the conventional BPA group, there were no significant differences in hemodynamics, exercise capacity, symptoms, lung function, and oxygenation between the groups. All patients received more than six

months of anticoagulant therapy. Soluble guanylate cyclase stimulator (sGCs) was first approved for CTEPH in January 2014 in Japan. As such, endothelin receptor antagonist (ERA) and phosphodiesterase type 5 inhibitor (PDE5i) as off-label drugs were more frequently prescribed in the conventional BPA group, whereas sGCs were more frequently prescribed in the ERBPA group. However, the percentage of patients with PH targeted drugs was similar between both groups.

Alteration of clinical parameters and prognosis from baseline to follow up

No cardiovascular related events or death occurred from baseline except for a patient in conventional BPA group who passed away due to acute myeloid leukemia.

The time course of each parameter are shown in Figure2, Table 2, and 3. The duration from pre-initial BPA to follow up (conventional BPA vs ERBPA: 70.7 ± 4.9 vs 65.2 ± 8.0 weeks; p=0.55 in Table 2) and baseline to follow up (conventional BPA vs ERBPA: 51.7 ± 4.9 vs 52.1 ± 6.5 weeks; p=0.96) was not different between the groups. From baseline to follow up, an ERA in conventional BPA group and a PDE5i in ERBPA group were discontinued. Home oxygen therapy was initiated in two patients in the conventional BPA group and in four patients in the ERBPA group. In spite of minor alterations of the treatment, no statistical significance with regard to non-invasive therapy (PH targeted drug, warfarin, home oxygen therapy) was observed between the groups. The number of involved pulmonary arterial segments was significantly reduced only in the ERBPA group (11.8±0.4 vs 5.3±0.6 segments; p<0.01; Table 2), which provided significant improvement in hemodynamics (mPAP; 20.4±0.7 to 17.9±0.9 mmHg; p<0.01, PVR; 348±39 to 234±18 dyne*sec/cm^5; p<0.01; Figure 2), exercise capacity (Peak VO_2; 14.2 ±1.1 to 17.3±1.2 ml/min/kg; p=0.05, and VE/VCO_2 slope; 41.5±3.4 to 30.4±1.0; p=0.04; Table 3 and Figure 4). We were unable to observe improvement in resting cardiac

index and lung function including %DLco and oxygenation parameters (SaO_2; 94.1±0.8 to 94.8±0.9%; p=0.62; Table 3). At the time of follow up, all patients in the ERBPA group improved their WHO-Fc with no patients remaining in a class of more than WHO-Fc III (Figure 3). In contrast, five patients did not improve at follow up and three patients remained in WHO-Fc III in the conventional BPA group.

Features of target lesions and complications by ERBPA

Table 4 shows a comparison of treated branches and complications between the initial BPA series (until normalization of mPAP) and ERBPA (after normalization of mPAP). The most frequently observed lesions were web type, and the distribution of lesion types was similar in both groups. We avoided treating pouch lesions because of the risk of wire injury. There was a significantly reduced incidence of RPI in ERBPA compared with initial BPA therapy. As a result, the incidence of hemosputum and necessity of NPPV were significantly lower in ERBPA, and there were also no instances of intubation and death in ERBPA.

A representative case of ERBPA

A representative case of a 57 year-old female who underwent ERBPA for residual pulmonary arterial stenoses in the right upper lobes (Figure 5). After we treated vessel lesions in bilateral lower lobes by initial BPA sessions twice, mPAP was normalized and perfusion deficits at the site reflected in the iodine map detected by dual energy computed tomography (CT) were found to have improved. After performing additional dilatation of the residual stenoses in the right upper lobe as ERBPA, the patient further improved in hemodynamics (mPAP 22.0 to 16.2mmHg), exercise capacity (6MWD 350 to 430m, PeakVO_2 12.9 to 16.2 ml/min/kg), and symptoms (WHO-Fc II to I).

Discussion

This is the first study clarifying the efficacy of ERBPA coupled with additional dilatation of the remaining stenoses after hemodynamic normalization. ERBPA safely improved hemodynamics, resulting in expanded exercise capacity in contrast to no improvement in the conventional BPA group.

An added exercise improvement was brought by ERBPA above natural progression.

Previous reports have shown a natural progression of exercise capacity until two years after PEA[10,11]. We also observed significant improvement in peak VO_2 and a slight improvement in VE/VCO_2 slope in the conventional BPA group during the follow up period (Figure 4). However, if we compare the ERBPA and conventional BPA groups at follow up, ERBPA group demonstrated a better VE/VCO_2 slope, which is known as a more specific marker for CTEPH[12], than the conventional BPA group. During follow up, significant improvement of hemodynamic parameters were observed only in the ERBPA group but not in the conventional BPA group. These data suggested that an added exercise improvement was indeed due to ERBPA and not merely a natural progression seen in the conventional BPA group after hemodynamic normalization (Figure 4).

Mechanism of improved exercise capacity by ERBPA

We could still detect residual stenoses in many pulmonary arterial segments even after mPAP was normalized. The average number of involved segments after hemodynamic normalization was around 11-12 (Table 2), which is equal to two-thirds of a total of 18 segments in the lung. This highlighted the fact that setting a value of the mPAP to be less than 25mmHg alone is too passive a goal to enable full recovery of pulmonary blood flow. Residual stenoses will induce ventilation-perfusion mismatch, thereby promoting dead

space ventilation. Even though there are no symptoms at rest, residual stenoses is apparent as dyspnea when the ventilator requirement is increased upon exercise.

Furthermore, Bonderman et al reported that residual stenoses could be a cause of excessive elevation of right ventricular afterload at exercise[13]. They elegantly pointed out an abnormal pulmonary hemodynamic response to exercise in patients with persistent exertional dyspnea even after successful PEA. PVR in the patients is increased although healthy subjects show decreased PVR during exercise. In other words, CI at exercise is a more sensitive index to predict exercise capacity compared to resting CI. Although we observed the discrepancy of longitudinal changes between non-significant alteration of resting CI and progressive 6MWD increase after BPA (Figure 4), this discrepancy is acceptable because peak VO_2, which reflects exercising CI, provided a convincing correlation with 6MWD.

As such, the promotion of dead space ventilation and abnormal elevation of right ventricular afterload would be the pathophysiological mechanism derived by residual stenoses, which could be a cause of persistent exertional dyspnea. The approach by ERBPA to enable full recovery of pulmonary perfusion regardless of mPAP could be a novel strategy to relieve the persistent symptoms.

Safety and efficacy of ERBPA

We clearly demonstrated that the occurrence of RPI were significantly reduced in ERBPA than the initial BPA therapy (Table 4). Previously, the suggested associated factors for RPI were lesion type[5], a learning curve[3], and hemodynamics[2,9].

The lesions such as subtotal and total occlusion were reported to have a higher risk of wire injury than other lesions[5] due to difficulty of wire passage and vulnerability of peripheral vessels. Our target had no significant differences in lesion types between

ERBPA and initial BPA series, suggesting that the reduced frequency of RPI incidence was free from lesion types of targets.

Hemodynamic factors are another risk for RPI which frequently occurred in patients with over 35mmHg of mPAP[2]. In addition, we have reported that the cut off value for RPI is 19.5mmHg of mPAP at a lesion distal to the stenoses[9]. We assumed that the pressure in ERBPA should be lower than in the initial BPA series. Although we could not rule out the effect of a learning curve, this may explain why the severity of RPI in addition to the frequency were significantly lower in the ERBPA group (Table 4).

The effect on oxygenation of ERBPA

Although the initial BPA series improved oxygenation, ERBPA alone could not induce further improvement in oxygenation both at rest and during exercise (Table 3). There are two possible reasons for this observation.

At first, Aoki et al reported that BPA improved oxygenation by reducing intrapulmonary shunt[4]. A reduced degree of intrapulmonary shunt by BPA became more apparent, when the patients have more severe hemodynamics. Certainly, a depressor effect of mPAP by ERBPA was slight compared to the initial BPA series. As a result, improvement of intrapulmonary shunt may be insufficient to contribute significantly to an improvement in oxygenation. The second possible reason is that exercise-induced decrease in oxygenation was paralleled by a decrease in mixed venous oxygen tension as a consequence of an insufficient cardiac output response[13]. Residual lesions even after ERBPA were still present in approximately five segments (Table 2), which may cause an insufficient increase in cardiac output and reduction in SvO_2. The synergistic effect of the above factors hindered improvement of oxygenation at rest and during exercise. There is

a possibility that further treatment of residual lesions might enable full recovery of oxygenation, but further investigations are warranted.

Limitations

There are some limitations of this study. Firstly, this is a retrospective and observational study in a single centre that necessitates some caution in interpretation of data. As shown in Table 1, there was also some differences in patient characteristics including age and gender, as well as some discrepancy with regard to the duration of follow-up between the groups, introducing problems associated with a learning curve and possible cofounding between the groups. The registered case number was not large enough. Furthermore, components of oral medication varied between the two groups. In particular, riociguat was prescribed more frequently in the ERBPA group. We could not rule out the possibility that these factors influenced the results. Therefore, it is ideal that the findings from this study be confirmed in a multicentre prospective study.

Secondly, residual stenoses and obstructions remained in patients even after ERBPA. We could not always pass the guide wire through the hard ostial pouch lesions. In general, there is some technical difficulties with regard to the anatomical approach to the left upper lobe and distal lesions beyond sub-segmental branches. Even though the final pulmonary blood perfusion was not complete, we would like to emphasize the importance of correcting lesions to the best of our ability, so as to enable substantial improvement of every patient's symptoms and exercise capacity.

Third, we did not have a strategy to prioritize target selection for CRPBA. It is difficult to assess accurately the volume of pulmonary vascular bed distal to the lesion. We treated the accessible lesions as much as possible. However, if we could precisely predict the

treatable vascular bed volume depending on each target, the strategy of ERBPA will be more sophisticated.

Conclusions

We clarified that ERBPA strategy significantly enhanced exercise capacity compared with the conventional BPA approach by improving hemodynamics with fewer complications. It would be ideal if the new goal for patients with CTEPH is set to relieving residual stenoses regardless of mPAP.

Acknowledgements

None

Impact on daily practice

The present study demonstrated the therapeutic possibility of extensive revascularization by BPA aiming for full recovery of pulmonary blood flow. The residual stenoses in pulmonary arteries could be a cause of exertional dyspnea even after conventional invasive therapy. It is thus desirable to set therapeutic goals to dilate the remaining lesions in pulmonary arteries as much as possible for both CTEPH.

Funding

There is no grant support for this manuscript

Conflict of interest statement

Kazuhiko Nakayama have received research grants from Actelion Pharmaceuticals Japan Ltd. and Bayer Holding Ltd. Ken-ichi Hirata received research grants from Actelion

Pharmaceuticals Japan Ltd., and Bayer Holding Ltd. The other authors have no conflicts of interest to declare.

References

1. Taniguchi Y, Miyagawa K, Nakayama K, Kinutani H, Shinke T, Okada K, Okita Y, Hirata K, Emoto N. Balloon pulmonary angioplasty: an additional treatment option to improve the prognosis of patients with chronic thromboembolic pulmonary hypertension. *EuroIntervention* 2014;**10**:518–525.
2. Feinstein J a, Goldhaber SZ, Lock JE, Ferndandes SM, Landzberg MJ. Balloon pulmonary angioplasty for treatment of chronic thromboembolic pulmonary hypertension. *Circulation* 2001;**103**:10–13.
3. 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**:748–755.
4. Aoki T, Sugimura K, Nochioka K, Miura M, Tatebe S, Yamamoto S, Yaoita N, Suzuki H, Sato H, Kozu K, Miyata S, Satoh K SH. Effects of Balloon Pulmonary Angioplasty on Oxygenation in Patients With Chronic Thromboembolic Pulmonary Hypertension - Importance of Intrapulmonary Shunt. *Circ J* 2016;**80(10)**:2227–2234.
5. Kawakami T, Ogawa A, Miyaji K, Mizoguchi H, Shimokawahara H, Naito T, Oka T, Yunoki K, Munemasa M MH. Novel Angiographic Classification of Each Vascular Lesionin Chronic Thromboembolic Pulmonary Hypertension Based on Selective Angiogram and Results of Balloon Pulmonary Angioplasty. *Circ Cardiovasc Interv* 2016;**9**:e003318.
6. Shimura N, Kataoka M, Inami T, Yanagisawa R, Ishiguro H, Kawakami T, Higuchi Y, Ando M, Fukuda K, Yoshino H, Satoh T. Additional percutaneous transluminal pulmonary angioplasty for residual or recurrent pulmonary hypertension after pulmonary endarterectomy. *Int J Cardiol* 2015;**183**:138–142.

7. Lewczuk J, Piszko P, Jagas J, Porada A, Wójciak S, Sobkowicz B, Wrabec K. Prognostic factors in medically treated patients with chronic pulmonary embolism. *Chest* 2001;**119**:818–823.
8. Claessen G, Gerche A La, Dymarkowski S, Claus P, Delcroix M, Heidbuchel H. Pulmonary Vascular and Right Ventricular Reserve in Patients With Normalized Resting Hemodynamics After Pulmonary Endarterectomy. *J Am Hear Assoc* 2015;**4**:e001602.
9. Kinutani H, Shinke T, Nakayama K, Taniguchi Y, Otake H, Takaya T, Osue T, Konishi A, Emoto N, Hirata K ichi. High perfusion pressure as a predictor of reperfusion pulmonary injury after balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. *IJC Hear Vasc* 2016;**11**:1–6.
10. Leung Wai Sang S, Morin JF, Hirsch A. Operative and Functional Outcome after Pulmonary Endarterectomy for Advanced Thromboembolic Pulmonary Hypertension. *J Card Surg* 2016;**31**:3–8.
11. Matsuda H, Ogino H, Minatoya K, Sasaki H, Nakanishi N, Kyotani S, Kobayashi J, Yagihara T, Kitamura S. Long-term recovery of exercise ability after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension. *Ann Thorac Surg* 2006;**82**:1338–1343.
12. Zhai Z, Murphy K, Tighe H, Wang C, Wilkins MR, Gibbs JSR, Howard LS. Differences in ventilatory inefficiency between pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. *Chest* 2011;**140**:1284–1291.
13. Bonderman D, Martischnig AM, Vonbank K, Nikfardjam M, Meyer B, Heinz G, Klepetko W, Naeije R, Lang IM. Right ventricular load at exercise is a cause of persistent exercise limitation in patients with normal resting pulmonary vascular resistance after pulmonary endarterectomy. *Chest* 2011;**139**:122–127.

Figure 1: Flow chart of the study

ERBPA (extensive re-vascularization by BPA) group is compared with conventional BPA group retrospectively.

Figure 2: Time course of hemodynamic changes during study period

Between baseline and follow up, mPAP and PVR are significantly improved in only ERBPA group, but not in conventional BPA group. The values were expressed as median (○ or ●) and interquartile range (bar).

Figure 3: Changes in WHO functional class

The number of patients is expressed at each time point.

Figure 4: Comparison between ERBPA and conventional BPA groups in hemodynamics and exercise capacity

Despite of no significant differences between the groups at pre-initial BPA and baseline, ERBPA significantly improves mPAP, PVR, 6MWD, peakVO2, and VE/VCO2 slope in contrast of conventional BPA group from baseline to follow up. *:$p<0.05$ vs baseline in the same group, **: $p<0.01$ vs baseline in the same group

Figure 5: Pulmonary angiography and iodine map in dual energy CT in a representative case

At pre-initial BPA, perfusion deficits were observed at bilateral inferior and upper lobes (D). Normalization of mPAP was achieved after two sessions of BPA to lower lobes (white arrow: A, B) resulting improvement of perfusion (white arrow; D, E). ERBPA by the 3rd

and 4th sessions of BPA were performed targeting the residual stenosis (black arrow head; B, C) at right upper lobes, and improved the perfusion (black arrow head; E, F).

Table 1: Patient's characteristics at pre-initial BPA

Data presented as mean ± SEM or (percent). P-values are calculated by unpaired t-test (*; chi-square test, **; Mann-Whitney test). 6MWT; six-minute walking test, $DL_{CO;}$ diffusing capacity of the lung carbon monoxide, N.A.; not available, SpO_2; Oxygen saturation of peripheral, VO_2; oxygen consumption, VE/VCO_2; minutes ventilation-carbon dioxide production relationship, WHO; World Health Organization

Table 2: Comparison of each clinical condition between baseline and follow up

Data presented as mean ± SEM or (percent). Data of serial session order in Kobe University hospital presented as median (range). P-values are calculated by paired t-test or unpaired t-test (*; chi-square test, **; Mann-Whitney test). ERA; endothelin receptor antagonist, HOT; Home oxygen therapy, N.A.; not available, PDE5i; Phosphodiesterase 5-inhibitor, sGCs; soluble guanylate cyclase stimulator,

Table 3: Comparison of each parameter between baseline and follow up

Data presented as mean ± SEM or (percent). P-values are calculated by unpaired t-test or paired t-test (**; Mann-Whitney test). RAP; right atrium pressure, for other abbreviations, please refer to Table 1.

Table 4: Target lesions and complications

P-values are calculated by chi-square tests (*: unpaired t-test).

CVO: complete vascular obstruction, RPI: reperfusion pulmonary injury, NPPV: non-invasive positive pressure ventilation, N.A.: not available

Table 1: Patient's characteristics at pre-initial BPA

Variable	Conventional BPA Group (n=20)	ERBPA Group (n=15)	p value
Female (%)	12 (60%)	14 (93%)	**0.048***
Age	70.1 ± 2.0	62.8 ± 3.2	0.053
Treatment			
Endothelin receptor antagonist (%)	14 (70)	3 (20)	<0.01*
Phosphodiesterase 5-inhibitor (%)	6 (30)	0 (0)	0.03*
Soluble guanylate cyclase stimulator (%)	0 (0)	7 (47)	<0.01*
Any PH targeted drug (%)	16 (80)	10 (67)	0.45*
Warfarin (%)	20 (100)	15 (100)	N.A.
Home oxygen therapy (%)	6 (30)	6 (40)	0.72*
Hemodynamic data			

Mean pulmonary artery pressure (mmHg)	36.9±1.8	34.7 ± 2.1	0.33
Pulmonary capillary wedge pressure (mmHg)	8.3± 0.9	6.9 ± 0.7	0.22
Right atrium pressure (mmHg)	4.8 ± 0.8	4.6 ±0.6	0.85
Cardiac index (L/min/m^2)	2.6 ±0.1	2.4 ± 0.2	0.45
Pulmonary vascular resistance (dyne*sec/cm^5)	628 ± 68	665 ± 84	0.74
Symptom and Exercise capacity			
WHO functional class (I/II/III/IV)	3 (0 / 7 / 10 / 3)	3 (0 / 1 / 12 / 1)	0.29**
Six-minute walking distance (m)	324 ± 21	325 ±23	0.97
Peak VO_2 (ml/min/kg)	12.2 ± 1.1	12.0± 0.8	0.88
VE/VCO_2 slope	41.7 ±3.4	46.4 ±3.7	0.37
Oxygenation and Lung function			

%vital capacity (%)	91.0 ± 3.1	95.5±3.5	0.35
Forced expiratory volume 1% (%)	67.6 ± 2.6	72.4 ± 2.1	0.18
%DLco (%)	65.7± 9.7	60.4± 3.9	0.55
SpO_2 (%)	91.3 ± 0.9	92.2± 0.7	0.48
Minimum SpO_2 at 6MWT (%)	86.5± 1.1	87.9 ± 0.9	0.33

Table 2: Comparison of each clinical condition between baseline (normalization of mPAP) and follow up

Variables	Conventional BPA group (n=20)			ERBPA group (n=15)			Unpaired t-test, p-value	
	Baseline	Follow up	Paired t-test p-value	Baseline	Follow up	Paired t-test p-value	Baseline	Follow up
Study schedule								
Duration from pre-initial BPA (weeks)	20.3± 4.1	70.7 ± 4.9	<0.01	15.9 ± 3.7	65.2 ±8.0	<0.01	0.46	0.55
Duration from the BPA just before hemodynamic normalization (weeks)	1.4±0.2	51.7±4.9	<0.01	2.8±1.2	52.1±6.5	<0.01	0.19	0.96
Duration from last BPA (weeks)	1.4±0.2	51.7±4.9	<0.01	-22.1±4.1	27.2±4.9	<0.01	<0.01	<0.01
BPA procedure								

Average session number per a patient until each time point	2.9±0.3	0	N.A.	2.5±0.2	1.8±0.2	<0.01	0.53	N.A.
Serial session order in Kobe University hospital : Median (range)	42 (1-117)	N.A.	N.A.	128 (37-199)	150 (68-224)	0.07	<0.01	N.A.
Pulmonary arterial segments with residual stenosis	12.4 ± 0.5	12.2 ± 0.5	0.06	11.7 ± 0.4	5.3 ± 0.5	<0.01	0.29	<0.01
Non-invasive therapy								
ERA (%)	14 (70)	13 (65)	0.59	3 (20)	3 (20)	0.67	<0.01*	0.02*
PDE5i (%)	7 (35)	7 (35)	0.55	1 (7)	0 (0)	0.50	0.10*	0.03*
sGCs (%)	0 (0)	0 (0)	N.A.	7 (47)	7 (47)	0.64	<0.01*	<0.01*
Any PH targeted drug (%)	17 (85)	16 (80)	0.47	11 (73)	10 (67)	0.50	0.67*	0.45*
Warfarin (%)	20 (100)	20 (100)	N.A.	15 (100)	15 (100)	N.A.	N.A.	N.A.
HOT (%)	7 (35)	9 (45)	0.33	7 (47)	11 (73)	0.13	0.73*	0.17*

Table 3: Comparison of each parameter between baseline (normalization of mPAP) and follow up

Variables	Conventional BPA group (n=20)			ERBPA group (n=15)			Unpaired t-test, p-value	
	Baseline	Follow up	Paired t-test p-value	Baseline	Follow up	Paired t-test p-value	Baseline	Follow up
Hemodynamics								
mPAP (mmHg)	20.8 ±0.7	22.9 ±1.3	0.07	20.4 ± 0.8	17.9 ±0.8	<0.01	0.72	<0.01
PCWP(mmHg)	7.1 ± 0.9	7.9± 1.1	0.51	5.4 ± 0.7	6.7 ± 0.7	0.08	0.16	0.43
RAP (mmHg)	2.4 ± 0.7	3.7 ± 0.8	0.15	3.0 ±0.7	3.3 ± 0.7	0.31	0.55	0.74
CI (L/m^2)	2.7 ± 0.1	2.8 ± 0.1	0.54	2.4 ± 0.1	2.6 ± 0.2	0.27	0.09	0.44
PVR ($dyne*sec/cm^5$)	276 ±21	305 ± 44	0.44	342 ± 30	241 ± 18	<0.01	0.07	0.24
Symptom and Exercise Capacity								
WHO-FC (I/II/III/IV)	0 / 16 / 4 / 0	2 / 15 / 3 / 0	0.19**	0 / 11 / 3 / 1	5 / 10 / 0 /0	<0.01**	0.45**	0.03**

6MWD (m)	402 ± 27	363 ±20	0.24	368 ±29	409±29	<0.01	0.40	0.18
Peak VO_2 (ml/min/kg)	13.1 ± 0.6	14.9± 0.8	0.04	14.8 ±1.0	17.2 ± 1.2	0.03	0.16	0.15
VE/VCO_2 slope	38.4 ± 3.9	37.1 ± 2.8	0.49	39.6 ±2.6	30.4 ± 1.0	0.03	0.79	0.05
Oxygenation								
SpO_2 (%)	92.8 ±0.8	92.1± 0.7	0.27	94.6 ±0.7	94.8 ± 0.8	0.46	0.12	0.02
Minimum SpO_2 at 6MWT (%)	86.2 ± 1.1	87.8 ± 1.1	0.21	87.8 ±1.1	88.0± 1.3	0.81	0.31	0.90
$\%DL_{CO}$ (%)	65.5 ± 5.3	65.2 ±4.4	0.60	61.7 ± 2.6	58.3 ± 2.6	0.39	0.47	0.19

Table 4: Target lesions and complications

Lesion based analysis	Initial BPA series	ERBPA	p-value
Number of lesions	393	153	-
Web (%)	234 (60)	92 (60)	0.90
Band (%)	87 (22)	44 (29)	0.10
Abrupt narrowing (%)	60 (15)	14 (9)	0.06
CVO (%)	11 (3)	4 (3)	0.91
Pouch (%)	0 (0)	0 (0)	N.A.
Session based analysis	**Initial BPA series**	**ERBPA**	**p-value**
Number of sessions	99	27	-
Serial session order Median (range)	61 (1-199)	150 (68-224)	<0.01*
RPI by chest CT (%)	54 (52)	6 (26)	<0.01
RPI by chest X-ray (%)	26 (25)	0 (0)	<0.01
Hemosputum (%)	27 (26)	1 (3)	<0.01
NPPV (%)	23 (22)	1 (4)	0.02
Intubation (%)	4 (4)	0 (0)	0.29
Death (%)	0 (0)	0 (0)	N.A.

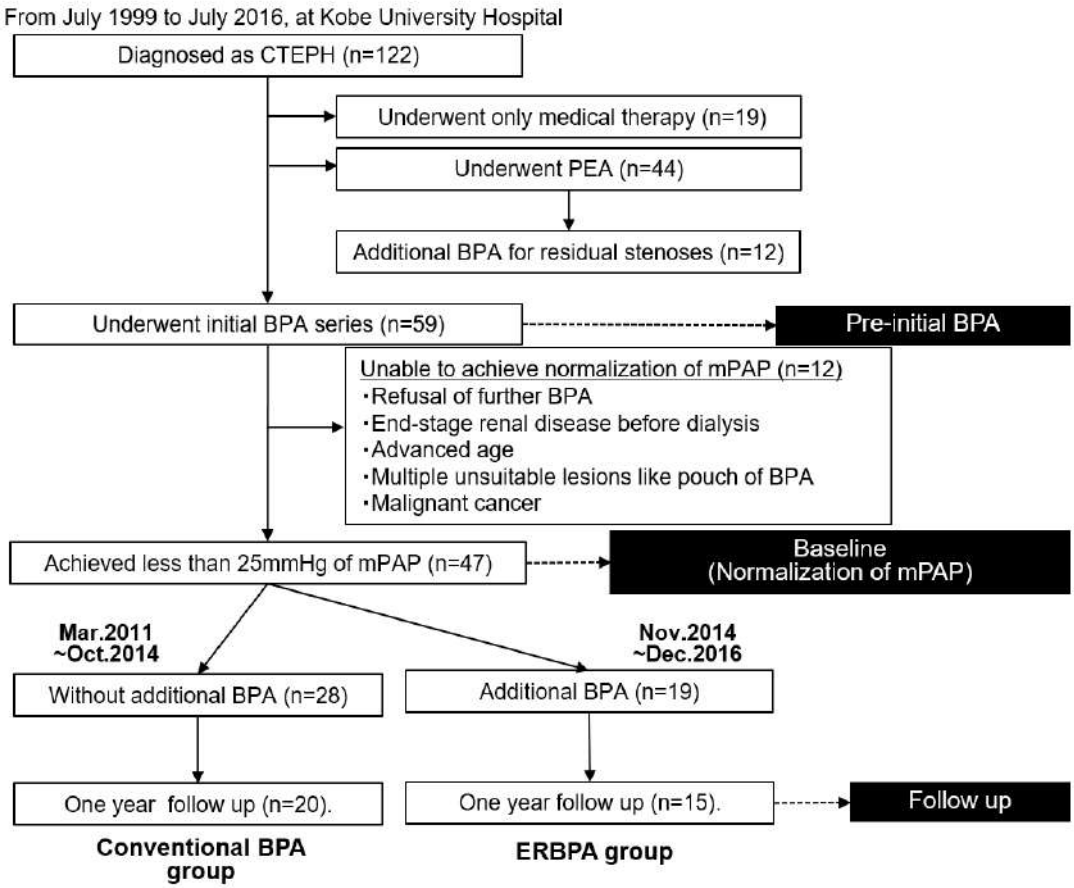

Figure 1: Flow chart of the study

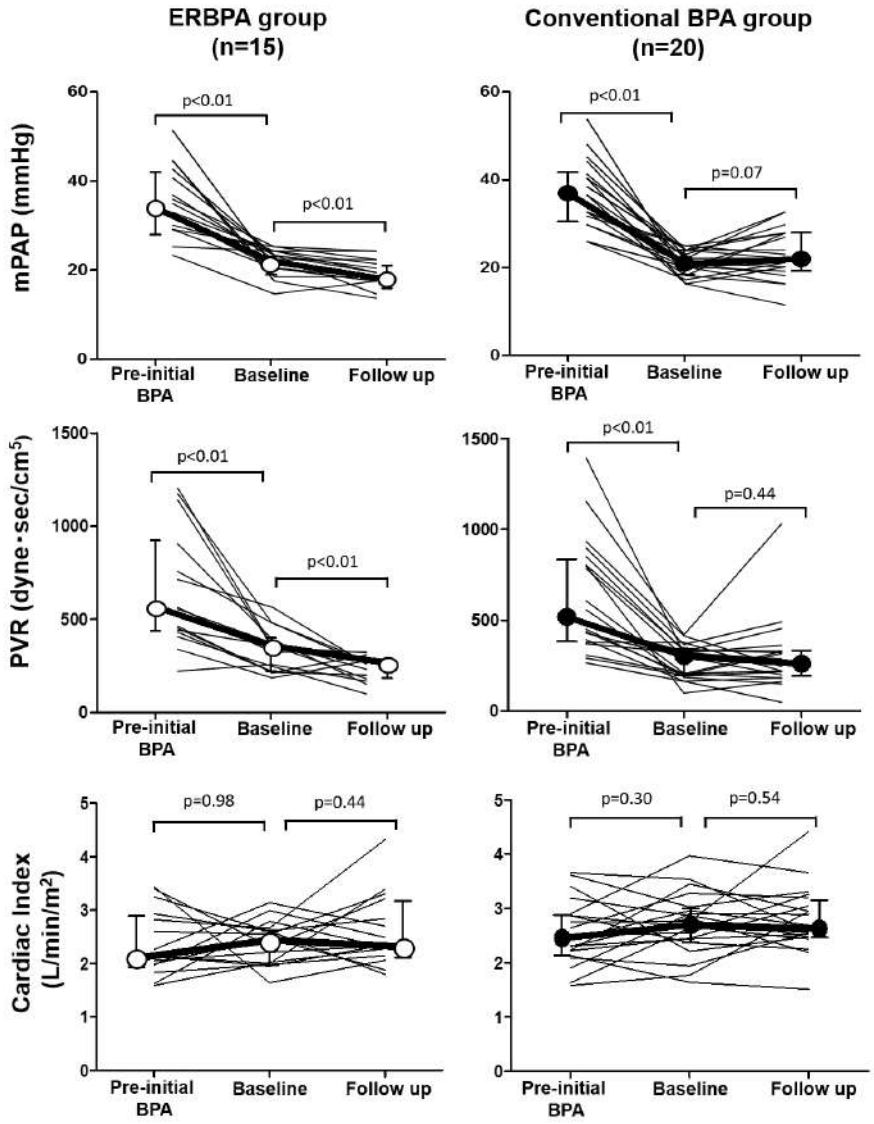

Figure 2: Time course of hemodynamic changes during study period

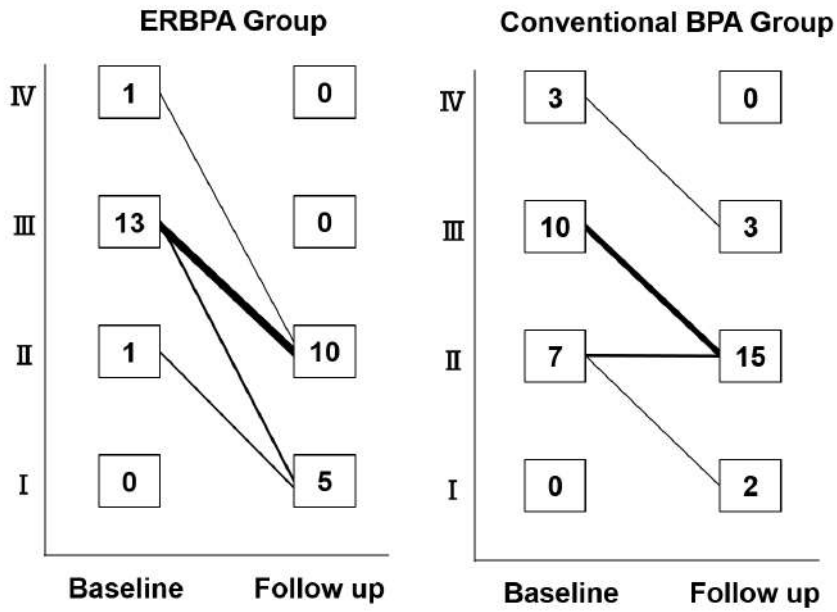

Figure 3: Changes in WHO functional class

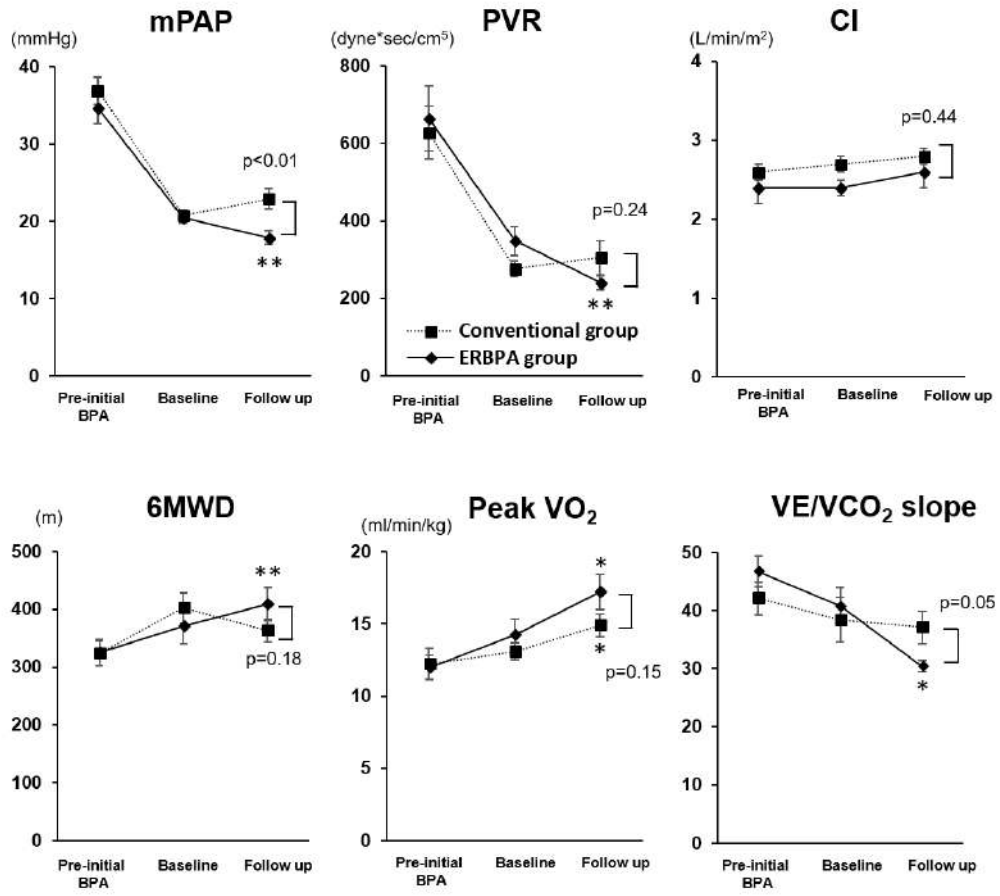

Figure 4: Comparison between ERBPA and conventional BPA groups in hemodynamics and exercise capacity

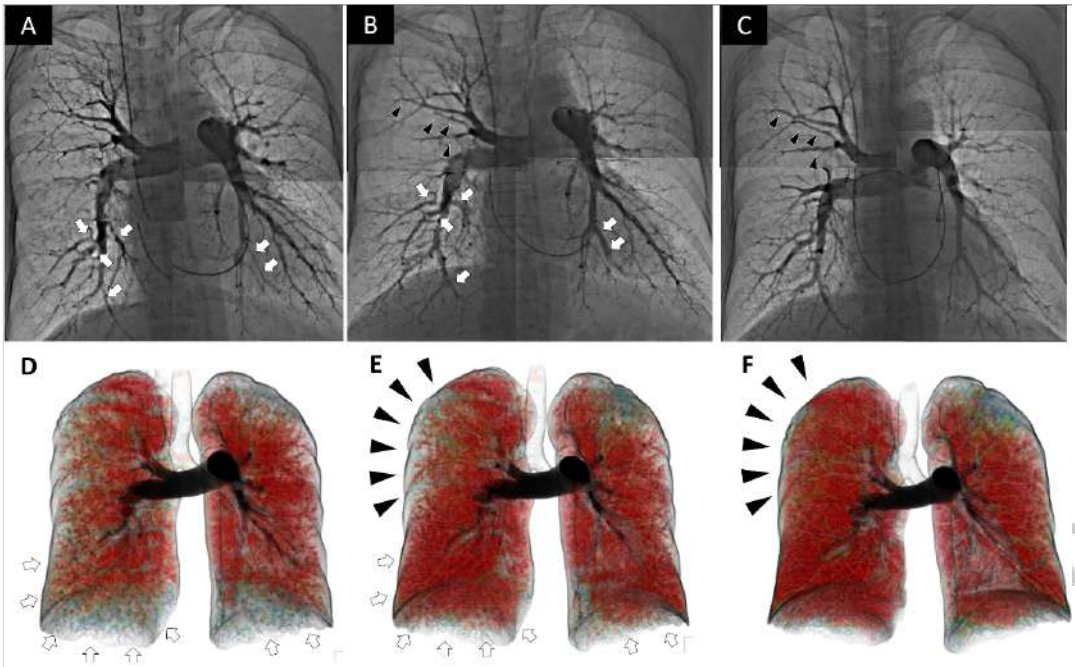

Figure 5: Pulmonary angiography and iodine map in dual energy CT in a representative case