Appropriate Balloon Pulmonary Angioplasty for Chronic Thromboembolic Pulmonary Hypertension Improves Right Ventricular Ejection Fraction via Lung Perfusion Scan

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Summary

Balloon pulmonary angioplasty (BPA) is a robust treatment and has been performed among patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH). A lung perfusion scan (LPS) is required for inspection in deciding the curative effect judgment and treatment lesion of BPA. Nevertheless, the impact of BPA in the improvement of right heart system function is not well known. We investigated whether BPA improves right heart function alongside other parameters.

We studied 20 patients with CTEPH (mean age 63.6 ± 15.9 years, male 30.0%) who underwent BPA. All study sets including right heart catheter, pulmonary angiography, 6-minute walk test (6MWT), blood gas analysis, and LPS were performed before BPA treatment. All parameters using right heart catheter and oxygenation level were measured at room air temperature. Regarding LPS, right ventricular ejection fraction (RVEF) was calculated using the first-pass method. These parameters before BPA were compared with those after BPA.

In total, 120 BPAs were performed (mean number of procedures/patient; 6.0 ± 2.4 sessions). Per BPA session, 6.0 ± 2.4 areas and 10.0 ± 4.3 lesions were treated with a volume of 181.3 ± 53.5 mL of contrast media. No complication required an invasive procedure. World Health Organization functional class, 6MWT, pulmonary artery pressure, pulmonary vascular resistance, and oxygenation level were significantly improved after BPA. RVEF via LPS was also significantly improved after BPA (45.0 ± 6.2% to 50.6 ± 2.9%, \(P < 0.001\)).

In the present study, we found that RVEF via LPS was improved through appropriate BPA alongside the other parameters. It would be useful to be able to evaluate right heart function.

Key words: First-pass method, Pulmonary artery pressure, Right heart catheter, Right heart function

Pulmonary hypertension (PH) is a major cause of right ventricular (RV) overload, which ultimately leads to RV failure and death. Chronic thromboembolic pulmonary hypertension (CTEPH) is classified into group 4 as a cause of PH according to the latest guideline for PH. CTEPH is caused by organized thrombi, causing pulmonary artery stenosis/occlusion and leading to abnormal pulmonary blood flow distribution. It is reported that the survival rate among patients with CTEPH is high, with > 50% of them experiencing death within 5 years when a mean pulmonary artery pressure (PAP) > 30 mmHg persists without any therapeutic intervention. Since CTEPH has been underdiagnosed and the rate of inoperable CTEPH could be as high as 60.9%, balloon pulmonary angioplasty (BPA) is the only therapeutic method that might radically cure patients with inoperable CTEPH.

Recently, the use of RV function for the prognostic evaluation of patients with CTEPH before BPA treatments has begun alongside PAP, 6-minute walk distance (6MWD), and the World Health Organization (WHO) functional class (WHO-fc). A lung perfusion scan (LPS) is often performed to make a diagnosis and decide on the curative effect judgment or treatment lesion of appropriate angioplasty for every patient with CTEPH treated with BPA. Nonetheless, the utility of RV ejection fraction (RVEF) using LPS has not been sufficiently reported. In this study, we investigated whether BPA improved RVEF using lung perfusion scan (LPS) among patients with inoperable CTEPH.

Methods

Patient population: We retrospectively enrolled 20 patients with inoperable CTEPH and performed 120 BPA procedures for those patients between January 2017 and May 2020 at the Toho University Omori Medical Center (Tokyo, Japan) (Table I). This study included 6 male and 14 female patients aged 40-82 years (mean 63.6 ± 15.9 years). All patients were diagnosed with CTEPH accord-
Table 1. Patients’ Clinical Characteristics at Baseline

| Variable                        | Mean ± SD       |
|---------------------------------|-----------------|
| Total number of CTEPH patients  | 20              |
| Age, years                      | 63.6 ± 15.9     |
| Male sex, n (%)                 | 6 (30.0)        |
| BSA, m²                         | 1.6 ± 0.2       |
| WHO-fc classification           | II: 1, III: 12, IV: 7 |
| 6MWD, m                         | 254.5 ± 205.3   |
| Heart rate, bpm                 | 79.7 ± 11.6     |
| Systolic blood pressure, mmHg   | 120.9 ± 30.0    |
| Diastolic blood pressure, mmHg  | 72.8 ± 16.3     |
| D dimer, μg/mL                  | 1.1 ± 1.0       |
| Serum creatinine level, mg/dL   | 0.8 ± 0.2       |
| BNP, pg/mL                      | 180.7 ± 246.9   |

Mean number of BPA sessions 6.0 ± 2.4

CTEPH indicates chronic thromboembolic pulmonary hypertension; BSA, body surface area; WHO fc, world health organization functional class; 6MWD, 6-minute walk distance; BNP, brain natriuretic peptide; HOT, home oxygen therapy; ERA, endothelin receptor antagonist; PGI2, prostacycline; PDE5, phosphodiesterase type 5; sGC, soluble guanylate cyclase; DOAC, direct oral anticoagulant; and BPA, balloon pulmonary angiography.ing to the NICE classification. Medical history, physical examination, LPS, and right heart catheter (RHC) were assessed, and pulmonary artery angiography (PAG) was performed. All patients were declared inoperable because of the location of thrombi, surgical accessibility, age, and comorbidities.

The Ethics Committee of Toho University Omori Medical Center approved this retrospective study. The opt-out can be found on the website of the Department of Cardiology, Toho University Omori Medical Center (M 20125).

Treatment strategies: We evaluated vital signs, WHO-fc, 6MWD, laboratory data, blood gas analysis (BGA), RHC parameters, and details of BPA and LPS that were performed within 5 days before and after BPA treatment. Additionally, we investigated the correlation between RVEF and other parameters before BPA.

Right heart catheter and blood gas analysis: We performed RHC placement at the time of diagnosis of CTEPH with PAG and before each BPA procedure. All parameters were measured more than 10 minutes after BPA at room air temperature. Right atrial pressure, RV pressure, PAP, and pulmonary capillary wedge pressure were measured during expiration. Cardiac output (CO) and cardiac index (CI) were measured by the thermodilution method. Svo₂ and hemoglobin were measured in pulmonary artery blood samples. Spo₂ and BGA were measured at the same time at room air temperature.

Pulmonary angiography: We performed global PAG using 25-cm (10-inch) images and BPA using the biplane angiographic system (Artis zee biplane; Siemens Medical Solutions, Forchheim, Germany). In the case of a diagnosis that required catheterization, we inserted a 6-Fr short sheath in the internal jugular vein; thereafter, we performed RHC and global PAG using either a 4-Fr or 5-Fr pigtail catheter (Figure 1A, B). At the time of pulmonary artery contrasting for the superior lobe (A1, A2, and A3), 8-10 mL of nonionized contrast medium was used in lightly wedging superior lobe branch through either the 4-Fr or 5-Fr pigtail catheter. Similarly, during pulmonary artery contrasting for the inferior lobe (A4, A5, A6, A7, A8, A9, and A10), we used 14-20 mL of nonionized contrast medium by auto-injection. However, we reduced the consumption of contrast media from a build and PAP. CTEPH was defined as multiple stenoses (ring-like stenosis, web, subtotal, total occlusion, and tortuous) through PAG.11,12

Lung perfusion scan: LPS is a required method of inspection in deciding the curative effect judgment and treatment lesion of appropriate BPA.16-18 We administered 370MBq ⁹⁹mTc-MAA followed by a 20-mL saline flush for measuring RVEF using the first-pass method before LPS. Planar dynamic acquisition was started before the tracer injection, and 2000 frames were acquired in 40 seconds (frame time of 0.02 seconds) at the 30° right anterior oblique position. All images were acquired using a dual-head gamma camera (Infinia GP3; GE Healthcare, Little Chalfont, UK) equipped with low-energy high-resolution collimators (Figure 2). RVEF was calculated by the performance of computer contouring of the right ventricle after end-diastole (ED) and end-systole (ES) counts were obtained. The ⁹⁹mTc-MAA count densities in the RV at the timing of ED and ES were calculated from 2000 images. RVEF was calculated using the following formula: (ED counts − ES counts) / ES counts.19 We compared the correlation between the primary endpoints that are the main evaluation items as prognostic factors and RVEF Absolute hemodynamic changes were calculated using the formula (each post-BPA parameter – each pre-BPA parameter) and were shown as changes in each parameter.

Balloon pulmonary angioplasty: In the case of BPA, we inserted a 9-Fr short sheath (Terumo, Tokyo, Japan) in the femoral vein; thereafter, a 6-Fr long sheath (Bright Tip Sheath Introducer; Cordis, New Brunswick, NJ) was introduced into the pulmonary main trunk with a 6-Fr guiding catheter (Mach 1 peripheral MP or AL1 or JR; Boston Scientific, Natick, MA) using a 0.035-inch wire (Radifocus Guide Wire M; Terumo, Tokyo, Japan). At this time, we used 4-6 mL of a nonionized contrast medium by manual injection and conducted BPA using 20-cm (8-inch) images (Figure 1C-H). We selected a branch of the pulmonary artery using a 6-Fr guiding catheter and performed angiography. We crossed a 0.014-inch wire (B-pahm 0.6, Japan Lifeline, Tokyo, Japan) to the target lesion and dilated the vessel using a balloon catheter of an appropriate size with the help of imaging that determined the size and type of vessels in only PAG images.11,12 Usually, we use a 2.0-mm balloon for initial dilatation, after which we dilate the vessel using balloon catheters of appropriate sizes (1.0-2.5 mm, Sapphire II PRO PTA, Orbus Neich, Tokyo, Japan; 3.0-3.5 mm, crosspander, Japan Life Line, Tokyo, Japan, NSE PTA, GOODMAN, Nagoya, Japan; 4.0-5.0 mm, Bandicoot RX, St. Jude Medical, St.

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Figure 1. Pulmonary angiography before and after balloon pulmonary angioplasty (BPA) and angiographic images of the segmental pulmonary artery during BPA. A: Angiographic image of representative right lower pulmonary artery before BPA. B: Angiographic image of the representative right lower pulmonary artery after 6 sessions of BPA. C: Angiographic image of left A5 segmental pulmonary artery taken at left anterior oblique (LAO) 60°. All the vessels of left A5a,b,c have subtotal lesions. D: All vessels (left A5a,b,c) were dilated initially with a 2.0-mm balloon. E: Immediately after the dilatation using a 2.0-mm balloon, segmental pulmonary arteries are recognized as defective; the first approach ends here to avoid rupture and dissection. F: Two months after the first approach, an angiographic image of the left A5 segmental pulmonary artery naturally expanded. G: After natural expansion, forming blood vessels with a larger (4.0 mm this time) balloon. H: Performing gradual balloon expansion can reduce complications and perform a reliable pulmonary angioplasty.

Paul, MN and Aviator Plus, Cordis, New Brunswick, NJ; 6.0-8.0 mm, Makaira, Fukuda Denshi, Tokyo, Japan) to avoid rupture and dissection of the pulmonary artery. The balloon is inflated manually until either the indentation disappears or the balloon has fully expanded (4-16 atm). We avoid using vasodilator therapy and home oxygen therapy (HOT) as much as possible. During coughing, desaturation, and tachycardia, we stop the BPA procedure and wedge a guide catheter until the pressure wave pattern disappears. If we do not notice any improvement, we either expand the balloon lightly or use protamine competed with heparin to stop bleeding. In the worst-case scenario, we use a gelatin sponge as a styptic or NPPV. It is important that we never contrast it from the risk of recurrence of bleeding after hemostasis.

The endpoint of BPA at our institution is based on less than the mean PAP of 25 mmHg or upper limit of 10 BPA sessions. Oral vasodilators are introduced when PAP
Figure 2. Explanation of the first-pass method. A, B: First, observe the flow of 99mTc-MAA from the vein to the pulmonary artery and determine the start and end frames of the right ventricular phase while checking the images. C, D: After setting the region of interest (ROI) in the right ventricle, it is not synchronized with the electrocardiogram, so the R wave is manually decided. E: Then, count 99mTc-MAA in the ROI during the diastole and systole of the right ventricle. RVEF was calculated by end-diastole counts and end-systole counts of 99mTc-MAA.

Statistical analysis: All statistical analyses were performed using R (The R Foundation for Statistical Computing, Vienna, Austria), which is a modified version of R commander designed to add statistical functions frequently used in biostatistics. Quantitative results are expressed as mean ± standard deviation. Changes in clinical parameters, RHC parameters, and LPS parameters were compared using the paired t-test. Pearson’s correlation coefficient (r) was used to assess correlations of right heart functions with LPS. P values of < 0.05 were considered significant.

Results

Baseline patient characteristics: Table I shows baseline patient characteristics. Nineteen of the 20 patients (95.0%) had WHO-fc III/IV. Eleven (55.0%) used oral therapy for PH as vasodilator therapy before BPA, and 16 (80.0%) used HOT. Endothelin receptor antagonists, oral prostanoid analogs, phosphodiesterase-5 inhibitors, and soluble guanylate cyclase stimulators were used for 4 (20.0%), 6 (30.0%), 2 (10.0%), and 5 (25.0%) patients, respectively. As for anticoagulant therapy, 5 patients (25.0%) were treated with warfarin, and 15 patients (75.0%) were treated with apixaban (Table I).

Outcome and complications of balloon pulmonary angioplasty: A total of 120 BPAs were performed for 20 patients (mean procedures per patient, 6.0 ± 2.4 sessions). The mean duration between before and after BPAs was 366 ± 267 days. On average, during each BPA session, we treated for 6.0 ± 2.4 areas and 10.0 ± 4.3 lesions using 1.7 ± 0.5 wires, 2.8 ± 0.8 balloons, 181.3 ± 56.6 mL of contrast media, and 63.7 ± 12.6 minutes of radiation time. As for the complications, the development of hemosputum and the use of gelatin sponge as a styptic occurred in 10 (8.3%) and 7 (5.8%) of 120 BPAs. There were no complications requiring an invasive procedure.

Table II lists the hemodynamic effects of BPA. BPA for inoperable CTEPH patients indicates that WHO-fc, six-minute walk distance (6MWD), brain natriuretic peptide, PAP, pulmonary vascular resistance (PVR), and oxygenation levels were all significantly improved. PAP was significantly decreased after BPA (mean PAP fell from 41.6 ± 8.2 to 23.9 ± 5.7 mmHg, P < 0.001). Similarly, PVR and WHO-fc were significantly decreased. Both 6 MWD and oxygenation levels were significantly improved. The number of patients who received vasodilator therapy decreased from 11 (55.0%) to 6 (30%), and the number of patients using HOT dropped from 16 (80%) to 2 (10%). CO and CI did not change before and after BPA.
Table II. Hemodynamic Effects of Balloon Pulmonary Angiography in Inoperable Chronic Thromboembolic Pulmonary Hypertension (n = 20)

| WHO-functional class | Pre-BPA | Post-BPA | P value |
|----------------------|---------|----------|---------|
| 3.3 ± 0.6            | 1.4 ± 0.5 | <0.001   |
| 6MWD, m              | 254.1 ± 205.3 | 426.8 ± 137.1 | <0.001 |
| BNP, pg/mL           | 180.7 ± 246.9 | 59.4 ± 68.4 | 0.01    |

Treatment

| HOT, n (%)           | 16 (80.0) | 2 (15.0) | <0.001 |
|----------------------|-----------|----------|---------|
| Number of PAH targeted drugs: 1, n (%) | 8 (40.0) | 3 (15.0) |         |
| Number of PAH targeted drugs: 2, n (%) | 0 (0.0)  | 3 (15.0) |         |
| Number of PAH targeted drugs: 3, n (%) | 3 (15.0) | 0 (0.0)  |         |
| ERA, n (%)           | 4 (20.0)  | 1 (5.0)  |         |
| Oral PGI2, n (%)     | 6 (30.0)  | 2 (10.0) |         |
| PDE5 inhibitor, n (%)| 2 (10.0)  | 1 (5.0)  |         |
| sGC, n (%)           | 5 (25.0)  | 4 (20.0) |         |
| CCB, n (%)           | 4 (20.0)  | 3 (15.0) |         |
| Diuretics, n (%)     | 10 (75.0) | 11 (55.0)|         |
| Warfarin, n (%)      | 5 (25.0)  | 6 (30.0) |         |
| DOAC (only apixaban), n (%) | 15 (75.0) | 14 (70.0)|         |

RHC data (room air)

| Heart rate, bpm      | 77.1 ± 12.5 | 68.8 ± 15.9 | <0.001 |
| PCWP, mmHg           | 8.6 ± 3.1   | 9.5 ± 4.7   | 0.412  |
| Systolic PAP, mmHg    | 68.5 ± 13.5 | 37.6 ± 9.6  | <0.001 |
| Diastolic PAP, mmHg   | 25.9 ± 7.0  | 15.7 ± 4.9  | <0.001 |
| Mean PAP, mmHg       | 41.6 ± 8.2  | 23.9 ± 5.7  | <0.001 |
| RAP, mmHg            | 7.4 ± 4.1   | 6.2 ± 2.8   | 0.161  |
| CO, L/minute         | 5.4 ± 1.4   | 4.9 ± 1.2   | 0.133  |
| CI, L/minute/m²      | 3.5 ± 0.8   | 3.1 ± 0.6   | 0.100  |
| PVR, dynes×sec×cm⁻⁵  | 536.9 ± 211.1 | 255.9 ± 91.3 | <0.001 |
| Hemoglobin, mg/dL    | 13.1 ± 1.9  | 13.1 ± 2.0  | 0.118  |
| SvO₂, %              | 58.8 ± 11.1 | 66.7 ± 4.6  | <0.001 |
| Oxygenation level (room air) |
| SpO₂, %              | 89.1 ± 5.7  | 94.6 ± 2.3  | 0.001  |
| PaO₂, %              | 61.2 ± 11.4 | 81.0 ± 14.3 | <0.001 |
| SaO₂, %              | 89.4 ± 5.0  | 95.2 ± 1.9  | <0.001 |

Table III. Lung Perfusion Scan Data of Balloon Pulmonary Angiography for Inoperable Chronic Thromboembolic Pulmonary Hypertension (n = 20)

| LPS data                  | Pre-BPA       | Post-BPA      | P value |
|---------------------------|---------------|---------------|---------|
| RVEF, %                   | 45.0 ± 6.2    | 50.6 ± 2.9    | <0.001 |
| Average heart rate, bpm   | 78.1 ± 12.3   | 76.2 ± 13.7   | 0.109  |
| ED counts                 | 499.7 ± 258.4 | 233.6 ± 110.8 | <0.001 |
| ES counts                 | 278.2 ± 149.4 | 116.1 ± 58.3  | <0.001 |

LPS indicates lung perfusion scan; BPA, balloon pulmonary angiography; RVEF, right ventricular ejection fraction; ED, end-diastole; and ES, end-systole.

Table IV shows the rate of change in each hemodynamic and oxygenation parameter. Figure 3 shows the correlation between ΔRVEF and Δeach parameter. ΔRVEF was positively correlated with Δheart rate, ΔPCWP, ΔSvO₂, ΔSpO₂, ΔPaO₂, and ΔSaO₂.

Lung perfusion scan parameters: Table III shows parameters by LPS. RVEF was significantly improved after BPA. The improvement of RVEF did not differ by the duration of BPAs between ≥1 year and <1 year. (ΔRVEF: 6.6 ± 6.0 versus 4.9 ± 6.0, P = 0.54). ED and ES counts were significantly decreased by BPA. Table IV shows the rate of change in each hemodynamic and oxygenation parameter.
Figure 3. The correlation between main evaluation items and Δright ventricular ejection fraction (RVEF). A: Δsystolic pulmonary artery pressure (PAP) and ΔRVEF show a positive correlation. B: Δmean PAP and ΔRVEF show a positive correlation. C: Δdiastolic PAP and ΔRVEF do not show any correlation. D: Δ6-minute walk distance (6MWD) and ΔRVEF do not show any correlation. E: Δcardiac output (CO) and ΔRVEF do not show any correlation. F: Δcardiac index (CI) and ΔRVEF do not show any correlation. G: Δpulmonary vascular resistance (PVR) and ΔRVEF do not show any correlation. H: Δpartial pressure of arterial oxygen (PaO₂) and ΔRVEF do not show any correlation. I: Δoxygen saturation of arterial blood measured by blood gas analysis (SO₂) and ΔRVEF do not show any correlation. J: Δmixed venous oxygen saturation (SvO₂) and ΔRVEF do not show any correlation.
with Δsystolic PAP and Δmean PAP, whereas Δdiastolic PAP, ΔCO, ΔCI, ΔPVR, Δ6MWD, and Δoxygenation levels were not correlated with ΔRVEF.

Discussion

In this study, we demonstrated that BPA significantly improved RVEF via LPS among patients with inoperable CTEPH. Additionally, ΔRVEF was positively correlated with Δsystolic and mean PAP.

Several reports have indicated that a decrease in PAP via BPA among patients with inoperable CTEPH increased RV functions calculated using CMR or echocardiography. In contrast, LPS is frequently performed before and after BPA for therapeutic judgments. The correlations between the improvements in RVEF and other functional factors were reported in previous studies. Sato et al. investigated whether BPA improved biventricular functions calculated by CMR among 30 patients with inoperable CTEPH. In the study of patients with a mean PAP of 40.8 mmHg, RVEF was improved from 41.3% to 50.7%. Although we have not shown the comparative impact of RVEF between LPS and CMR or echocardiography in the present study, these results are in line with our findings, demonstrating a similar improvement of RVEF calculated using LPS among patients with inoperable CTEPH (RVEF; 45.0% to 50.6%).

We observed that a change in RVEF was corrected with a change in systolic PAP and mean PAP; nevertheless, their correlations were significant but only modest. One explanation for these findings might be that RVEF at baseline was relatively preserved in this study. Although the reason is unclear and the mean PAP we found in our study (mean PAP 41.6 mmHg) was as high as what was reported in previous studies, ranging between 39.4 and 42.6 mmHg, RVEF at baseline in these studies varied widely (34%-41%) among patients with inoperative CTEPH.

In this study, we demonstrated that the decrease in the rate of use of PAH-targeted drugs (11 to 6) and the use of HOT (16 to 2) was increased by performing multiple BPA sessions (mean number of sessions: 6.0 ± 2.4). Improvement of PAP is thought to depend on the number of BPA sessions and target vessels. Akagi et al. reported that reducing PAP is paramount in improving pulmonary artery hypertension and reducing the mortality rate. Our results indicated that multiple BPA sessions for numerous target vessels resulted in significantly reduced PAP and improved RVEF. Additionally, the mechanism of why CO has not increased despite increased RVEF after BPA is unclear. Conclusions are still controversial, as previous studies have shown mixed results, showing that BPA increased CO or it was equivocal. Because of the relatively small sample size of these studies as well as the present study, the relationship between BPA and CO in a large population of CTEPH would be warranted. The association between the improvement in RVEF via LPS and prognosis needs to be explored in the future.

Study limitations: This study has several limitations. Our study sample was relatively small. Additionally, we did not have data that directly investigated the correlation of LPS with other modalities such as CMR or echocardiography for tricuspid annular plane systolic excursion or RV fractional area change. It has been well known that spatial resolution is less effective than CMR or echocardiography in the assessment of cardiac volumetric. Finally, quantitative measurements of lung perfusion area after BPA were not assessed in the current study. Future studies examining the improvement of lung perfusion area and RVEF via LPS are warranted, and our group is currently pursuing such investigations.

Conclusions

Appropriate BPA for CTEPH improved RVEF calculated with the help of an LPS. The improvement in RVEF was correlated with an improvement in PAP. LPS can be useful in assessing RVEF after BPA.

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Disclosure

Conflicts of interest: All authors declare no potential conflict of interest.

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