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Effects of Balloon Pulmonary Angioplasty on Oxygenation in Patients With Chronic Thromboembolic Pulmonary Hypertension

– Importance of Intrapulmonary Shunt –

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Background: Although balloon pulmonary angioplasty (BPA) improves the hemodynamics and prognosis of patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH), the mechanisms of improvement in oxygenation remain to be elucidated.

Methods and Results: From August 2013 to May 2015, we performed a total of 113 BPA procedures in 24 patients with inoperable CTEPH (mean 4.7 procedures per patient). Median age was 70 [60, 74] years and 18 were female (75%). We examined hemodynamics, respiratory functions, and intrapulmonary shunt before and after the BPA procedure. Mean pulmonary arterial pressure (37 [28, 45] to 23[19, 27] mmHg, P<0.01), pulmonary vascular resistance (517 [389, 696] to 268 [239, 345] dyne/s/cm^5) and 6-min walk distance (390 [286, 484] to 490 [411, 617] m, P<0.01) were significantly improved after BPA therapy. Furthermore, arterial oxygen partial pressure (PaO_2, 54.8 [50.0, 60.8] to 65.2 [60.6, 73.2] %, P<0.01) and intrapulmonary shunt (23.4±6.0% to 19.3±5.0%, P<0.01) were also significantly ameliorated. In the multivariate analysis, decrease in intrapulmonary shunt after BPA was significantly correlated with improvement of both PaO_2 (r^2=0.26, P<0.01) and SaO_2 (r^2=0.49, P<0.01) after BPA.

Conclusions: These results indicated that BPA improved not only pulmonary hemodynamics but also oxygenation with a resultant decrease in intrapulmonary shunt.

Key Words: Balloon pulmonary angioplasty; Chronic thromboembolic pulmonary hypertension; Intrapulmonary shunt; Oxygenation

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by persistent pulmonary arterial obstruction from organized thrombus and fibrous tissue.[1–4] Although novel medications for PH have been developed in the past decade, CTEPH still remains a serious disease with poor prognosis.[5]

Among patients with PH, including those with CTEPH, hypoxemia is a potential therapeutic target to improve exercise capacity and prognosis.[6–8] Although the mechanisms of deterioration of oxygenation in CTEPH patients remain to be fully elucidated, it could be caused by the intrapulmonary shunt associated with elevation of pulmonary arterial pressure and ventilation-perfusion mismatch caused by pulmonary arterial occlusion.[9,10]

Although pulmonary thromboendarterectomy (PEA) is an established treatment for CTEPH,[11–13] a feasible and effective therapeutic strategy for inoperable CTEPH remains to be developed. In 2001, Feinstein et al reported for the first time the possible effectiveness of balloon pulmonary angioplasty (BPA) for inoperable CTEPH; however, they also reported the frequent adverse effects of the procedure.[14] In the past decade, we and others reported that BPA improves the hemodynamics, cardiac function and prognosis of distal-type CTEPH without severe complications.[15–20] However, the effects of BPA on oxygenation in patients with inoperable CTEPH remain to be elucidated.

In the present study, we thus examined before and after BPA the oxygenation, respiratory and hemodynamic parameters,

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including intrapulmonary shunt, that could affect oxygenation in patients with inoperable CTEPH.

Methods

The protocols of the present study were approved by the institutional review board of the Tohoku University Hospital (No. 2014-1-875). We obtained written consent for participation from all patients.

Patients

We enrolled 25 consecutive patients with CTEPH who underwent BPA from August 2013 to May 2015. They were diagnosed as having inoperable CTEPH based on standard criteria.[2,3] All patients had symptoms of World Health Organization (WHO) functional class II or more. After excluding 1 patient who had pre-existing lung disease, we examined the hemodynamics and respiratory function before and after BPA in the remaining 24 patients (24/25, 96%). They had been treated with appropriate combinations of oral vasodilators and anticoagulation therapy with warfarin. Other clinical data, including B-type natriuretic peptide (BNP) level, 6-min walk distance (6MWD) and duration from symptom onset to first BPA, were also obtained. Each parameter was examined before first BPA and 6 months after last BPA.

BPA

We performed a total of 113 BPA procedures in the 24 patients with CTEPH (mean, 4.7 procedures per patient). BPA was performed via the right femoral vein to treat the pulmonary arterial branches.[15,21] Targeted vessels were selected on the basis of comprehensive findings, including webs, bands, abrupt narrowing and complete obstructions, derived from angiography, 3D-reconstructd computed tomography and intravascular imaging modalities, including optical coherence computed tomography.[4,22,23] Under continuous intravenous infusion of heparin (400 U/h), we used a soft-tipped 0.035-inch wire (Large Focus®, Terumo, Tokyo, Japan) to selectively engaged a 6Fr guide catheter (Heartrail®, Terumo) to the targeted vessels in a 6Fr long sheath (Large Focus Introducer®, Terumo). We selected a balloon size based on the targeted vessel diameter measured by angiography and/or intravascular imaging modalities, including optical coherence tomography (St. Jude Medical, St. Paul, MN, USA) or optical frequency domain imaging (Terumo). After crossing a 0.014-inch guide wire (Chevalier®, Cordis, CA, USA) through the lesion, we carefully inflated the balloons (size range, 1.5–3.5 mm, IKAZUCHI®; size range, 4.0–6.0 mm, Bandicoot®, Kaneka, Osaka, Japan).[15,21] The BPA procedure was limited maximally to 3 lobes in 1 procedure and was repeated at an interval of 4–8 weeks in all patients. BPA was repeated until the mean pulmonary artery pressure (mPAP) became less than 30 mmHg.[15]

Hemodynamics Studies

Right heart catheterization was performed with a 6Fr Swan-Ganz catheter (Edwards Life Science, Irvine, CA, USA) while supine. Hemodynamic parameters, including mPAP, pulmonary arterial wedge pressure (PAWP), right atrial pressure (RAP), cardiac output (CO) and pulmonary vascular resistance (PVR), were measured before first BPA and more than 6 months after the last BPA. PAWP and RAP were measured at end-expiration, and mPAP was calculated using average systolic and diastolic PAPs of 10 consecutive beats. CO was determined by the indirect Fick method and corrected for body surface area (cardiac index, CI). At the time of diagnosis, intracardiac shunt was evaluated by dye dilution curves,[24] showing that none of the patients in the present study had intracardiac shunt.

Respiratory Function Tests

As well as hemodynamic evaluation, pulmonary function was also assessed for percent vital capacity (%VC), forced expiratory volume percent in 1 s (FEV1.0%), and diffusion capacity of carbon monoxide as percent of predicted (%DLco) using a spirometer (CHESTAC 8900, Nihon Kohden, Tokyo, Japan). To measure oxygen (O_2) saturation/partial pressure (PaO_2) in the artery and pulmonary artery, blood gas analyses were performed using arterial and pulmonary arterial blood samples obtained during right heart catheterization in room air. To calculate intrapulmonary shunt, O_2 was given with a reservoir mask at a flow rate of 10 L/min for 5 min.[25] It has been reported that intrapulmonary shunt varies by the fraction of inspired O_2 and that hypoxic conditions increase intrapulmonary shunt.[26] To minimize the influence of variation in SaO_2 on intrapulmonary shunt, we used intrapulmonary shunt during O_2 administration for the analyses. After administration of O_2, we performed blood gas analyses again to obtain intrapulmonary shunt, which was calculated with the following formula:[25]

$$\frac{Cc\cdot O_2 - CaO_2}{Cc\cdot O_2 - CvO_2} = \frac{Hb\times 1.36\,(1-SaO_2) + 0.0031\,(P_AO_2 - PaO_2)}{Hb\times 1.36\,(1-SvO_2) + 0.0031\,(P_AO_2 - PvO_2)} \times 100$$

$Cc\cdot O_2$, pulmonary capillary O_2 content; Hb, hemoglobin (g/dl); CaO_2, arterial O_2 content; CvO_2, mixed venous O_2 content; SaO_2, arterial O_2 saturation; SvO_2, mixed venous O_2 saturation; P_AO_2, alveolar O_2 partial pressure; PaO_2, arterial O_2 partial pressure; and PvO_2, mixed venous O_2 partial pressure.

To compare intrapulmonary shunt in room air with that after O_2 administration for 5 min, intrapulmonary shunt was calculated using blood gas samples in room air as well.

Statistical Analysis

Continuous variables are expressed as mean±SD or median [interquartile range (IQR)]. Changes in each parameter were compared using paired t-test or Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical data, as appropriate. The correlations between parameters were analyzed with linear regression models for univariate analyses and multiple regression models for multivariate analyses. Multicollinearity, defined as determination coefficient ≥0.64, was not observed between each parameter used in the multivariate models. A P value <0.05 was considered to be statistically significant. All analyses were performed using JMP 10.0 (SAS Institute, Cary, NC, USA).

Results

Patients Characteristics

We enrolled 24 consecutive patients and their baseline characteristics are shown in Table 1. Median age was 70 [60, 74] years and 18 were female (75%). They had symptoms of WHO functional class II or more (II/III/IV, 12/11/1 (50/46/4%), respectively). Median duration from symptom onset to first BPA was 13 [6, 31] months. Median values of mPAP, PVR and BNP level were 37 [28, 45] mmHg, 517 [389, 696] dyne/s/cm^5, and 108 [43, 198] pg/dl, respectively. Median SaO_2 was 88.6 [86.2, 91.5] % and mean intrapulmonary shunt was 23.4±6.0%. O_2 administration during right heart catheterization changed the distribution range of SaO_2 from wide (88.6, [86.1, 91.8] %) to narrow (99.5, [99.5, 99.8] %). Pulmonary function tests at baseline showed normal median values for

Table 1. Baseline Characteristics of Inoperable CTEPH Patients (n=24) and Effects of BPA

	Before BPA	After BPA	P value
Age (years)	70 [60, 74]		
Female (%)	18 (75%)		
Duration symptoms (months)	13 [6, 31]		
Exercise capacity			
WHO functional class (I/II/III/IV) (%)	0/12/11/1 (0/50/46/4)	5/19/0/0 (24/76/0/0)	0.04
6MWD (m)	390 [286, 484]	490 [411, 617]	<0.01
Hemodynamics			
mPAP (mmHg)	37 [28, 45]	23 [19, 27]	<0.01
PAWP (mmHg)	11±3	9±4	0.02
RAP (mmHg)	7±3	5±4	0.02
CI (L/min/m^2)	2.38 [2.01, 2.76]	2.39 [2.07, 2.67]	0.96
PVR (dyne·sec·cm^{-5})	517 [389, 696]	268 [239, 345]	<0.01
BNP (pg/dl)	112 [49, 199]	27.5 [14.6, 58.4]	<0.01
Respiratory parameters			
SaO_2 (%)	88.6 [86.1, 91.8]	92.9 [91.3, 94.5]	<0.01
PaO_2 (mmHg)	54.8 [50.0, 60.8]	65.2 [60.6, 73.2]	<0.01
SvO_2 (%)	63.9 [58.3, 66.8]	66 [63.3, 66.7]	<0.01
PvO_2 (mmHg)	34.4 [31.9, 35.5]	36.0 [34.5, 37.9]	<0.01
A-a DO_2 (Torr)	50.6±8.0	35.4±10.9	<0.01
Intrapulmonary shunt (%)	23.4±6.0	19.3±5.0	<0.01
Intrapulmonary shunt in room air (%)	32.1±11.0	23.6±9.5	<0.01
%VC (%)	99.0±17.0	101 [92, 110]	0.1
FEV1.0% (%)	77.2±9.2	73.1±8.9	0.12
%DLco (%)	93.6 [74.6, 126.0]	88 [67, 122]	0.11
Medications (%)			
PDE5i	17 (71)	7 (29)	<0.01
ERA	1 (4)	1 (4)	1
Oral PGI_2	5 (21)	3 (12)	0.70
Epoprostenol	2 (8)	0 (0)	0.49
sGC activator	3 (12)	4 (17)	1
Home oxygen therapy (%)	19 (79)	13 (54)	0.01

BNP, B-type natriuretic peptide; BPA, balloon pulmonary angioplasty; CI, cardiac index; CTEPH, chronic thromboembolic pulmonary hypertension; ERA, endothelin receptor antagonist; FEV1.0%, forced expiratory volume percent in 1 s; mPAP, mean pulmonary arterial pressure; PaO_2, arterial oxygen partial pressure; PAWP, pulmonary arterial wedge pressure; PDE5i, phosphodiesterase-5 inhibitor; PGI_2, prostacyclin; PvO_2, mixed venous oxygen partial pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SaO_2, arterial saturation oxygen; sGC, soluble guanylate cyclase; SvO_2, mixed venous oxygen saturation; 6MWD, 6-min walk distance; %DLco, diffusion capacity of carbon monoxide as percent of predicted; %VC, vital capacity as percent of predicted.

%VC, FEV1.0% and %DLco. Before the first BPA, 22 patients (92%) were treated with vasodilators, including phosphodiesterase-5 inhibitors in 17 (72%), an endothelin receptor antagonist in 1 (4%), an oral prostacyclin analog in 5 (21%), epoprostenol in 2 (8%) and soluble guanylate cyclase stimulator in 3 (12%); 7 patients (28%) received combination therapy at baseline and 19 patients (79%) required home O_2 therapy.

Effects of BPA on Exercise Capacity and Hemodynamics

Mean number of BPA procedures per patient was 4.7±1.5. All procedures were successfully performed without periprocedural deaths, severe lung bleeding or reperfusion lung edema requiring mechanical ventilation. BPA significantly improved 6MWD and WHO functional class (Table 1). Hemodynamic parameters, including mPAP, PAWP, RAP and PVR, were significantly improved after BPA (Table 1). Although the usage rates of phosphodiesterase-5 inhibitors, oral prostacyclin and epoprostenol were decreased after BPA, soluble guanylate cyclase activator (riociguat) was used more frequently after BPA (Table 1).

Effects of BPA on Oxygenation and Lung Function

Lung function tests, including %VC, FEV1.0% and %DLco, were comparable before and after BPA, whereas SaO_2, PaO_2 and A-a DO_2 significantly improved after BPA (Table 1). Furthermore, intrapulmonary shunt and the percentage of patients who required home O_2 therapy were significantly decreased after BPA (Table 1).

To elucidate the predictor(s) for the increase in PaO_2 and SaO_2 after BPA, correlations between baseline parameters and increases in PaO_2 and SaO_2 were examined. Univariate analysis for PaO_2 showed that there were no baseline parameters to predict an increase in PaO_2 (Table 2A). Univariate analysis for SaO_2 showed that higher age, higher mPAP, lower SaO_2, lower SvO_2 and higher intrapulmonary shunt at baseline were significantly correlated with the increase in SaO_2 after BPA (Table 3A). Multivariate analysis using those parameters indicated that lower SaO_2 at baseline was an independent predictor

Table 2. Correlations Between Change in PaO_2 and That in Each Parameter in 24 Inoperable CTEPH Patients

	Univariate analysis				
	r^2	Estimate	SE	t ratio	P value
A. Parameters at baseline					
Age (years)	0.16	0.31	0.15	2.03	0.05
Duration from onset of symptom (months)	<0.01	−0.01	0.05	−0.19	0.85
mPAP (mmHg)	<0.01	0.01	0.18	0.05	0.96
PAWP (mmHg)	<0.01	0.13	0.48	0.27	0.79
RAP (mmHg)	0.18	−1.01	0.46	−2.21	0.04
CI (L/min/m^2)	0.03	2.79	3.13	0.89	0.38
PVR (dyne·sec·cm^{-5})	<0.01	<0.01	<0.01	0.01	0.99
PaO_2 (%)	0.07	−0.21	0.17	−1.25	0.22
PvO_2 (%)	<0.01	0.14	0.59	0.24	0.8
Intrapulmonary shunt at baseline (%)	<0.01	0.06	0.26	0.23	0.82
B. Change (Δ) in parameters before and after BPA					
ΔmPAP (mmHg)	0.09	−0.33	0.23	−1.44	0.16
ΔPAWP (mmHg)	−0.05	−0.01	0.42	−0.02	0.99
ΔRAP (mmHg)	0.08	0.66	0.48	1.39	0.18
ΔCI (L/min/m^2)	0.06	−3.19	2.82	−1.13	0.27
ΔPVR (dyne·sec·cm^{-5})	0.01	0	0	−0.46	0.65
ΔPvO_2 (%)	0.04	0.6	0.62	0.97	0.34
ΔIntrapulmonary shunt (%)	0.26	−0.73	0.26	−2.8	0.01

Abbreviations as in Table 1.

Table 3. Correlations Between Change in SaO_2 and That in Each Parameter in 24 Inoperable CTEPH Patients

	Univariate analysis					Multivariate analysis			
	r^2	Estimate	SE	t ratio	P value	Estimate	SE	t ratio	P value
A. Parameters at baseline									
Age (years)	0.18	0.16	0.07	2.23	0.04	0.07	0.06	1.1	0.29
Duration from onset of symptom (months)	0.14	0.04	0.02	1.87	0.08				
mPAP (mmHg)	0.23	0.2	0.08	2.6	0.02	0.02	0.08	0.2	0.85
PAWP (mmHg)	0.1	0.39	0.23	1.55	0.14				
RAP (mmHg)	0.05	−0.26	0.24	−1.08	0.29				
CI (L/min/m^2)	<0.01	0.32	1.5	0.21	0.84				
PVR (dyne·sec·cm^{-5})	0.05	<0.01	<0.01	1.12	0.27				
SaO_2 (%)	0.6	−0.49	0.09	−5.74	<0.01	−0.72	0.24	−3.03	<0.01
SvO_2 (%)	0.16	−0.19	0.09	−2.08	0.04	0.14	0.11	1.28	0.22
Intrapulmonary shunt at baseline (%)	0.25	0.30	0.11	2.71	0.01	−0.20	0.15	−1.38	0.18
B. Change (Δ) in parameters before and after BPA									
ΔmPAP (mmHg)	0.24	−0.27	0.1	−2.67	0.01	0.09	0.1	0.84	0.79
ΔPAWP (mmHg)	0.1	−0.29	0.18	−1.58	0.13				
ΔRAP (mmHg)	0.12	0.4	0.23	1.76	0.09				
ΔCI (L/min/m^2)	<0.01	−0.25	1.41	−0.18	0.86				
ΔPVR (dyne·sec·cm^{-5})	0.05	0	0	−1.12	0.27				
ΔSvO_2 (%)	0.27	0.32	0.11	2.91	<0.01	0.31	0.1	3.01	<0.01
ΔIntrapulmonary shunt (%)	0.49	−0.49	0.11	−4.68	<0.01	−0.48	0.10	−4.72	<0.01

Abbreviations as in Table 1.

for an increase in SaO_2 after BPA (**Figure 1**, **Table 3A**).

To examine the mechanisms of improvement of oxygenation after BPA, the correlations between changes in each parameter and increases in PaO_2 and SaO_2 after BPA were examined. Univariate analysis for PaO_2 showed that only a decrease in intrapulmonary shunt was significantly correlated with an increase in PaO_2 (**Figure 2**, **Table 2B**). Univariate analysis for SaO_2 showed that a decrease in mPAP and intrapulmonary shunt and an increase in SvO_2 were significantly correlated with the increase in SaO_2 after BPA (**Table 3B**). Multivariate analysis showed that a decrease in intrapulmonary shunt and an increase in SvO_2 after BPA were significantly correlated with the increase in SaO_2 (**Figure 3**, **Table 3B**). We also used another model excluding SvO_2 because both SvO_2 and intrapulmonary shunt were included in the same formula to calculate intrapulmonary shunt. Even after excluding SvO_2,

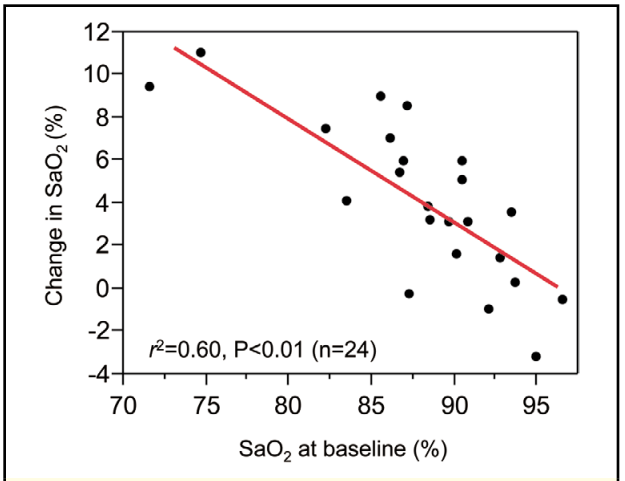

Figure 1. Significant correlation between arterial oxygen saturation (SaO_2) at baseline and changes in SaO_2 after balloon pulmonary angioplasty.

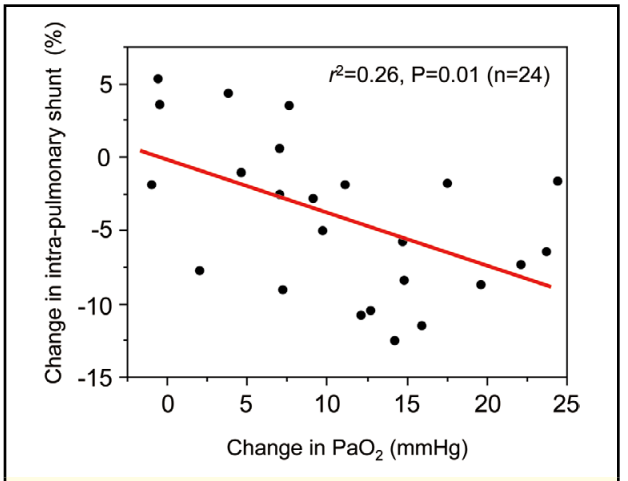

Figure 2. Significant correlations between changes in arterial oxygen partial pressure (PaO_2) and those in intrapulmonary shunt after balloon pulmonary angioplasty.

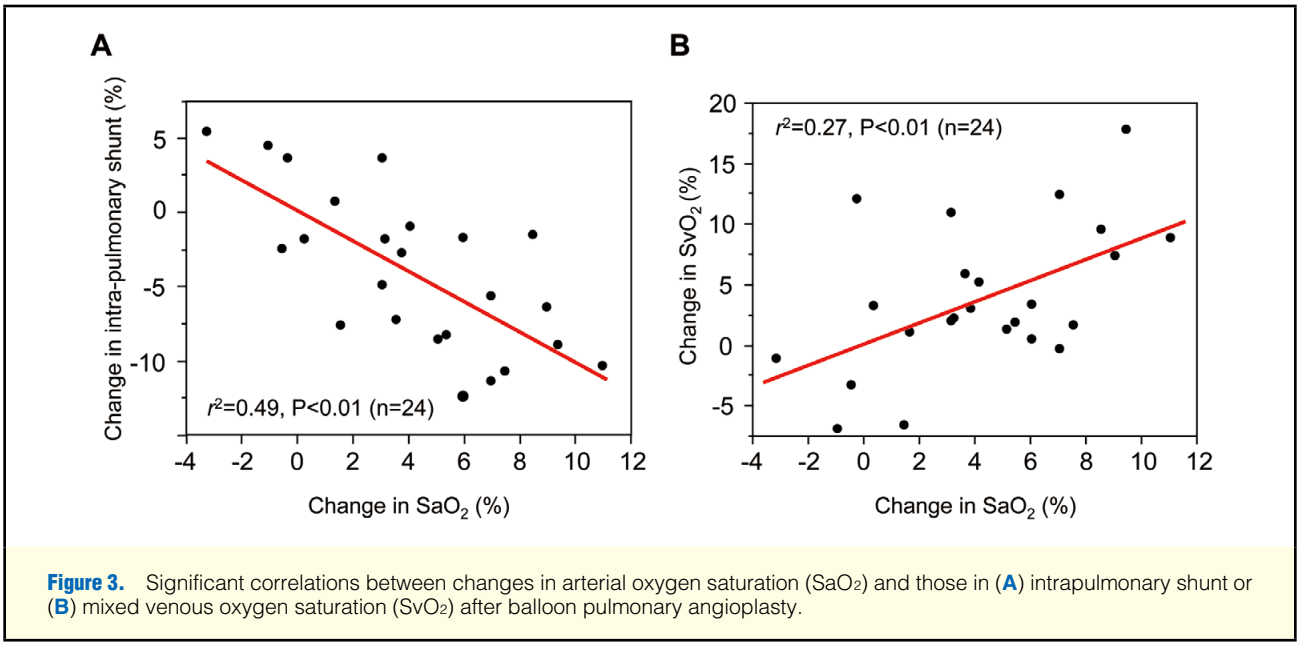

Figure 3. Significant correlations between changes in arterial oxygen saturation (SaO_2) and those in (**A**) intrapulmonary shunt or (**B**) mixed venous oxygen saturation (SvO_2) after balloon pulmonary angioplasty.

change in intrapulmonary shunt showed a significant correlation with improvement of SaO_2 (**Table S1**). The same analysis using intrapulmonary shunt in room air instead of O_2 administration was performed, showing results similar to those using intrapulmonary shunt after O_2 administration (**Tables S2**,**S3**).

When comparing SaO_2 after BPA among the subgroups stratified by median values of intrapulmonary shunt and SvO_2, SaO_2 levels after BPA were greater in the subgroups with lower intrapulmonary shunt than in those with higher intrapulmonary shunt (**Figure 4**).

The difference in intrapulmonary shunt calculated between room air and O_2 inhalation for 5 min was greater in patients with hypoxemia at baseline compared with those without it (**Figure S1**).

Relationship of Intrapulmonary Shunt With Pulmonary Pressure, PaO_2 and SaO_2

At baseline, there was a significant correlation between mPAP and intrapulmonary shunt (**Figure 5A**). Furthermore, changes in intrapulmonary shunt and those in mPAP after BPA were significantly correlated (**Figure 5B**). Also, intrapulmonary shunt at baseline was significantly correlated with PaO_2 and SaO_2 at baseline (**Figure S2A**,**B**).

Discussion

The novel findings of the present study are as follows: (1) BPA improved not only pulmonary hemodynamics but also oxygenation, (2) BPA also reduced intrapulmonary shunt and increased SvO_2, (3) low SaO_2 at baseline was a significant predictor for improvement of SaO_2 after BPA, and (4) decrease

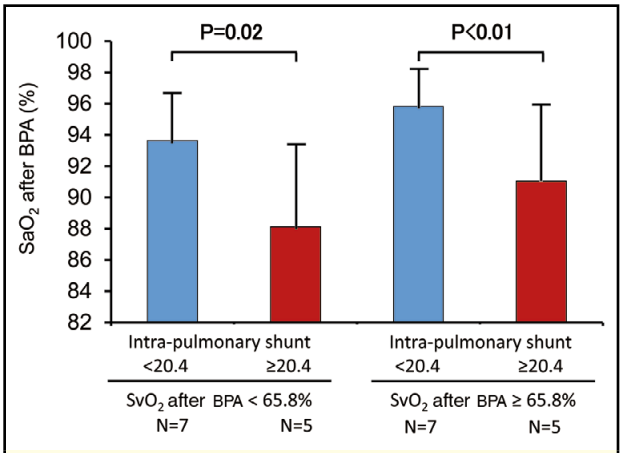

Figure 4. Comparison of SaO_2 after balloon pulmonary angioplasty (BPA) among 4 subgroups stratified by median values of mixed venous oxygen saturation (SvO_2: 65.8%) and intrapulmonary shunt (20.4%) after BPA.

in intrapulmonary shunt had a significant association with improvement of oxygenation independent of amelioration of pulmonary arterial pressure. To the best of our knowledge, this is the first study to demonstrate beneficial effects of BPA on respiratory function and the association between improvement in intrapulmonary shunt and oxygenation.

Intrapulmonary Shunt in CTEPH Patients

Although hypoxemia is a common cause of exercise intolerance in CTEPH patients, the mechanism(s) of the hypoxemia remains to be elucidated.[2] It was reported that hypoxemia in patients with pulmonary embolism was caused by ventilation-perfusion mismatch and that hypoxemia is amplified by low SvO_2 together with a decrease in CO.[9,10] Although, intracardiac shunt, such as right to left atrial shunt through a patent foramen ovale, is associated with hypoxemia,[24,25] the patients in the present study did not have intracardiac shunts. Indeed, intrapulmonary shunt could contribute to the hypoxemia in CTEPH.[10,25] It is considered that there are 2 types of intrapulmonary shunting: one is "true shunt", which means flow past unventilated or collapsed alveoli or preexisting arterial-venous anastomoses; and the another is blood flow past units with low ventilation-perfusion ratio, where blood is not completely oxygenated.[9,10,25] Because CTEPH is less associated with ventilation abnormalities, there should be no unventilated alveoli.[27] Indeed, in the present study, lung function tests and computed tomography of the lung showed no evidence of respiratory disease. Thus, intrapulmonary shunt, such as pre-existing arterial-venous anastomoses and low ventilation-perfusion units, is likely involved. Shunt flow via pre-existing arterial-venous anastomosis is increased by elevated PAP.[10] Intrapulmonary shunt is also increased along with a low ventilation-perfusion ratio as a consequence of pulmonary arterial occlusion.[10] Furthermore, recanalization of pre-existing pulmonary arterial-venous anastomoses by elevated PAP increases intrapulmonary shunt.[10] Previous studies have demonstrated that intrapulmonary arteriovenous pathways may be recruited with physiological exercise,[28] thus limiting the increase in PAP despite high CO.[29] Intrapulmonary shunt in PH may be regulated by pulmonary vascular pressure and flow.[30] Indeed, collateral vessels are noted around occluded pulmonary arteries in biopsy samples obtained from CTEPH patients.[31] In the present study, the mean value of intrapulmonary shunt (21.9±7.0%) was higher than the physiological level (5%) in healthy subjects.[25] In the present study, intrapulmonary shunt and mPAP were significantly correlated and changes in both parameters also showed a significant positive correlation, suggesting that elevated PAP reflects increased intrapulmonary shunt.

Beneficial Effects of BPA on Hypoxemia in CTEPH Patients

The present study demonstrated that a decrease in intrapulmonary shunt and mPAP and an increase in SvO_2 contributed to the improvement of SaO_2 after BPA. In particular, the changes in intrapulmonary shunt and SvO_2 were independent predic-

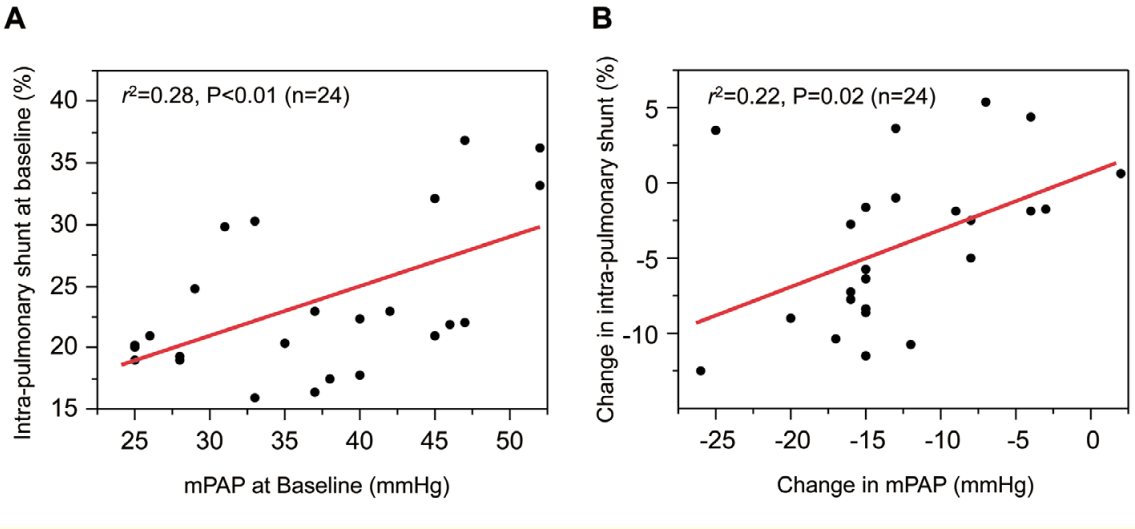

Figure 5. Correlations between mean pulmonary arterial pressure (mPAP) and intrapulmonary shunt at (**A**) baseline and (**B**) after balloon pulmonary angioplasty.

tors for improvement of SaO_2 after BPA, whereas the change in intrapulmonary shunt was the only parameter associated with the increase in PaO_2. It is possible that BPA decreases mPAP by recanalizing occluded pulmonary arteries and simultaneously improving the ventilation-perfusion mismatch, resulting in a reduction in intrapulmonary shunt. In the present study, low intrapulmonary shunt after BPA was associated with higher SaO_2 after BPA despite the SvO_2 level after BPA.

The present study also demonstrated that a reduction in intrapulmonary shunt after BPA was significantly associated with improvement of oxygenation independently of lowering of PAP. Similar to PEA, which improves the distribution of the ventilation-perfusion relationship,[32,33] BPA improves the relationship with subsequent improvement of oxygenation. In the present study, a change in intrapulmonary shunt was an independent predictor of improvement of PaO_2 and SaO_2. Thus, correction of the ventilation-perfusion ratio by BPA, as compared with a decrease in PAP, may play a more important role in ameliorating oxygenation in CTEPH patients. The present study demonstrated that low SaO_2 at baseline was a significant predictor for improvement of SaO_2 after BPA, but not of PaO_2 after the procedure. This discrepancy may result from the characteristics of the O_2 dissociation curve, in which improvement in SaO_2 in hypoxic conditions contributes to the improvement of oxygenation to a greater extent than in normoxia. In contrast, the decrease in intrapulmonary shunt was significantly associated with increases in both of PaO_2 and SaO_2, suggesting the possible mechanism by which the decrease in intrapulmonary shunt by BPA improves oxygenation in CTEPH patients. Although hypoxemia is defined as low PaO_2, SaO_2 is commonly used to evaluate oxygenation in clinical practice. Thus, attention should be paid to the discrepancy when assessing the effect of BPA on oxygenation.

Study Limitations

First, we were unable to directly evaluate the ventilation-perfusion ratio that might be associated with oxygenation in CTEPH patients. However, we assessed intrapulmonary shunt, which is one of the factors that influence ventilation-perfusion mismatch. Because PEA also improves ventilation-perfusion mismatch and reduces dead-space ventilation,[32–34] BPA could also improve the mismatch. Second, in the present study, the decision to discontinue home O_2 therapy was made by the attending physician. Third, the use of vasodilators might have affected the extent of intrapulmonary shunt. Fourth, intrapulmonary shunt was calculated using blood samples after O_2 inhalation for 5 min to minimize the influence of SaO_2 variation. As shown in **Figure S1**, O_2 administration reduced intrapulmonary shunt in patients with hypoxemia at baseline to a greater extent than in those without it; however, O_2 administration for 5 min might be relatively short to cause sufficient effects. Finally, the number of patients was relatively small. Thus, the present findings need to be confirmed in future studies with a large number of patients.

Conclusions

In the present study, we were able to demonstrate that BPA improved not only pulmonary hemodynamics but also oxygenation with a resultant decrease in intrapulmonary shunt.

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Disclosures

None.

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Supplementary Files

Supplementary File 1

Table S1. Correlation between change in SaO_2 and that in each parameter after excluding SvO_2

Table S2. Correlations between change in PaO_2 and that in each parameter

Table S3. Correlations between change in SaO_2 and that in each parameter

Figure S1. Difference in intrapulmonary shunt between conditions of room air and O_2 inhalation.

Figure S2. Correlation between intrapulmonary shunt and PaO_2/SaO_2.

Please find supplementary file(s);
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