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Differential effects of balloon pulmonary angioplasty on chronic thromboembolic pulmonary disease

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ABSTRACT

Background Decreased diffusing capacity of the lungs for carbon monoxide (DLco) is associated with microvascular damage in chronic thromboembolic pulmonary hypertension (CTEPH). Balloon pulmonary angioplasty (BPA) is an effective treatment for CTEPH, but the efficacy of BPA in patients with CTEPH with low DLco remains unclear because BPA does not directly address microvascular damage. This study investigates the influence of microvasculopathy on BPA in CTEPH according to DLco.

Methods We retrospectively analysed data from patients with inoperable CTEPH who underwent BPA at the University of Tokyo Hospital from July 2011 to August 2023. The patients were classified into two groups based on their preprocedural DLco (normal DLco (ND) and low DLco (LD) groups), with a DLco cut-off value of 80%. We compared the patient characteristics and effectiveness of BPA between the groups.

Results Among the 75 patients, 36 were in the LD group. The LD group had a shorter 6-minute walking distance (324±91 vs 427±114 m) than the ND group but the mean pulmonary artery pressure (mPAP) was similar (38.9±7.3 vs 41.1±9.2 mm Hg) before BPA. BPA improved the haemodynamic status and exercise tolerance in both groups. The LD group exhibited a higher mPAP (25.1±7.4 vs 21.5±5.6 mm Hg) and required more sessions of BPA (median 6 vs 4). Based on the analysis of covariance adjusted for baseline values, low DLco significantly correlated with mPAP (sβ=−0.304, 95% CI −7.015 to −1.132, p=0.007) and pulmonary vascular resistance (sβ=−0.324, 95% CI −141.0 to −29.81, p=0.003).

Conclusions BPA was associated with an improvement in the haemodynamic status and exercise tolerance in patients with CTEPH even with low DLco. However, low DLco may attenuate the effect of BPA on mPAP and pulmonary vascular resistance and require more treatment sessions.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In chronic thromboembolic pulmonary hypertension (CTEPH), microvascular damage may reduce blood flow to the microvasculature and decrease the diffusing capacity of the lungs for carbon monoxide (DLco).
⇒ Balloon pulmonary angioplasty (BPA) improves haemodynamics in patients with CTEPH by dilating distal pulmonary artery obstruction; however, BPA has no direct effect on the microvasculature, and the response to BPA varies among patients.

WHAT THIS STUDY ADDS

⇒ BPA was associated with an improvement in haemodynamics and exercise tolerance even in patients with CTEPH with low DLco; however, additional BPA sessions were required.
⇒ Low DLco could be attenuated with the effectiveness of BPA on mean pulmonary artery pressure and pulmonary vascular resistance.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In inoperable CTEPH, BPA improves haemodynamics and exercise tolerance regardless of DLco; however, low DLco may attenuate the haemodynamic improvement, requiring additional BPA sessions.

INTRODUCTION

In recent years, the treatment of chronic thromboembolic pulmonary hypertension (CTEPH) has seen remarkable progress, with advances in pulmonary endarterectomy (PEA)[1] and balloon pulmonary angioplasty (BPA),[2 3] as well as the introduction of new drugs.[4] As a result, patients with CTEPH, who previously had a poor prognosis,[5] now have a good long-term prognosis,[6] and the treatment goals of CTEPH have shifted to normalisation of oxygenation and quality of life improvement.[7 8] Normalisation of ventilatory–perfusion mismatch has been proposed as a way to achieve these new treatment goals; however, no good treatment strategy has been established.[9] One factor associated with treatment difficulty is the presence of pulmonary artery microvasculopathy.[10] At present, the only direct treatment for microvasculopathy is medical therapy using pulmonary artery vasodilators, but medical treatment is not as effective as PEA or BPA in improving haemodynamics.[11 12] Although PEA and BPA can facilitate the delivery of pulmonary vasodilators to the pulmonary artery microvasculature by increasing blood flow, direct intervention is not possible.[13] With BPA, the required number of sessions to achieve haemodynamic improvement differs between patients. This suggests that the therapeutic response may vary between patients.[11 12]

The diffusing capacity of the lungs for carbon monoxide (DLco), a respiratory function index,

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decreases for a variety of reasons, including microvascular thrombosis, which reduces the blood supply to the microvasculature.[14] In patients with CTEPH, decreased DLco may indicate the presence of pulmonary arterial microvasculopathy,[15] and low DLco has also been reported to be associated with poor outcomes in patients who undergo medical therapy without BPA.[16] We considered that patients with CTEPH with low DLco have more severe pulmonary artery micovasculopathy than patients with CTEPH with normal DLco. Few studies have reported on the effects of BPA for the treatment of CTEPH focusing on DLco. Therefore, we hypothesised that CTEPH with low DLco may be refractory to BPA treatment because BPA does not directly affect pulmonary artery microvasculopathy.

METHODS

Study population

We retrospectively analysed the data of 84 consecutive patients with CTEPH who underwent BPA and whose condition was inoperable or who had residual pulmonary hypertension (PH) after PEA at the University of Tokyo Hospital from July 2011 to August 2023. The patients were diagnosed with CTEPH based on coexisting PH assessed by right heart catheterisation (RHC). Coexisting PH was defined according to published guidelines.[17] The patients were classified into two groups based on their preprocedural DLco values: normal DLco (ND) group and low DLco (LD) group. The DLco cut-off value was defined as 80%, which is the lower limit of normal according to previous reports.[14 16 18] The study end date was 31 August 2023. The study conformed to the principles outlined in the Declaration of Helsinki.

Examinations

We performed RHC before the initial BPA procedure and during the follow-up phase after the last BPA procedure. Right atrial pressure (RAP), pulmonary artery pressure (PAP) and pulmonary capillary wedge pressure were measured using a Swan-Ganz catheter (Edwards Lifesciences, Irvine, California, USA). Cardiac output (CO) was determined with the thermodilution method, and pulmonary vascular resistance (PVR) was calculated. The WHO functional score, brain natriuretic peptide concentration, respiratory function and 6-minute walk test results were also assessed at the time of hospitalisation for RHC. DLco was measured using FUDAC-7C (FUKUDA DENSHI, Tokyo, Japan), and the predicted value was calculated based on Burrow's formula.[19] DLco values were adjusted for haemoglobin concentration.

BPA procedure and complications

The BPA procedure has been described previously.[20] We treated ring-like, web, subtotal and total lesions. We used a smaller balloon in the first session for each lung to avoid lung injury. We then used a larger balloon from the second session because of dilated vessels with increased blood flow through the first session.[21] The initial goal of BPA was to achieve a mean PAP (mPAP) of <30 mm Hg based on previous studies,[5] and additional BPA was performed in patients with residual PH symptoms, such as dyspnoea on exertion. Regarding BPA-related complications, haemosputum and haemoptysis were defined as events that occurred from the BPA session to the time of discharge. Contrast agent-related renal dysfunction was defined as an increase in the serum creatinine concentration by >0.5 mg/dL or 25% from the previous value within 72 hours after iodine contrast administration. Pneumothorax and lung injury were detected by CT imaging performed immediately after each BPA session. Non-invasive positive pressure ventilation was used for lung injury if the oxygen saturation could not be maintained above 95% with oxygen inhalation.

Statistical analysis

Continuous variables are expressed as the mean±SD or median (IQR) and were compared between the two groups using the unpaired Student's t-test or the Mann-Whitney U test, depending on the data distribution. Ordinal values are expressed as numbers and were compared between the two groups using the Mann-Whitney U test. Nominal values are presented as number (percentage) and were compared using the χ^2 test or Fisher's exact test. The paired t-test or Wilcoxon's signed-rank test was used to compare haemodynamic, laboratory and functional data, as appropriate, and the mean value of the change from baseline is expressed as the mean (SE). We used the analysis of covariance to examine the impact of DLco on haemodynamic and exercise tolerance at follow-up while correcting for baseline values. With the analysis of covariance, multiple testing of the number of parameters was corrected using the Bonferroni method, and $0.05 \div 7 = 0.0071$ was used as the significance level. Missing data were omitted from each analysis. Sensitivity analyses with best-case and worst-case imputation and multiple imputation (m=100) were performed using the linear model with patient background and initial haemodynamics as predictors. All analyses were performed using GraphPad Prism V.9.3.1 for Windows (GraphPad Software, San Diego, California, USA) and SPSS Statistics V.28.0 software (IBM, New York, New York, USA).

RESULTS

Patient characteristics

Among the 84 patients, 8 were excluded because of a lack of initial respiratory data before the BPA procedure and 1 was excluded because of a lack of haemodynamic data after BPA treatment. Overall, 75 patients with CTEPH who underwent BPA and follow-up RHC were categorised into the LD group (n=36) or the ND group (n=39) (figure 1). The mean age of the overall study population was 61±14 years, and 50 patients (66.7%) were female. The LD group had a significantly higher proportion of female than the ND group (83.3% vs 51.3%, p=0.003). The median follow-up duration was 983 (527–1606) days, with no significant difference between the two groups (1070 (556–1623) vs 833 (472–1581) days, p=0.371). Patients in the LD group had a lower arterial oxygen saturation (SaO_2)

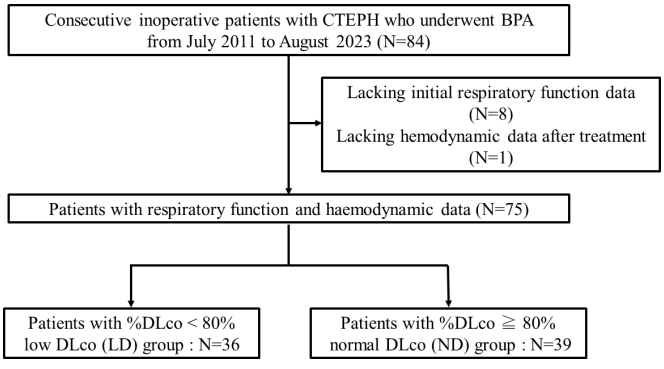

Figure 1 Flowchart of the study. %DLco, diffusing capacity of the lungs for carbon monoxide as a percentage of predicted; BPA, balloon pulmonary angioplasty; CTEPH, chronic thromboembolic pulmonary hypertension; DLco, carbon monoxide diffusing capacity.

Table 1 Comparison of baseline characteristics between the low DLco and normal DLco groups

	Low DLco (n=36)	Normal DLco (n=39)	P value
Age, year	61.1±15.2	60.9±12.6	0.961*
Women	30 (83.3)	20 (51.3)	0.003†
Body mass index, kg/m^2	24.0±5.0	22.6±4.4	0.192*
WHO functional class (I/II/III/IV)	0/5/29/2	0/9/30/0	0.186§
Smoking history	18 (50.0)	16 (41.0)	0.435†
Median follow-up days, days	1070 (566–1623)	833 (472–1581)	0.371§
Brain natriuretic peptide, pg/mL	73.4 (18.5–173.2)	121.0 (57.3–339.9)	0.075§
Heart rate, bpm	77±12	75±14	0.412*
Comorbidities¶	18 (50.0)	14 (35.9)	0.217†
Asthma	6 (16.7)	2 (5.1)	0.143‡
Interstitial pneumonia	1 (2.8)	0	0.480‡
Lung cancer	0	1 (2.6)	>0.999‡
Tuberculosis	1 (2.8)	1 (2.6)	>0.999‡
Pneumonitis	2 (5.6)	1 (2.6)	0.605‡
Chronic obstructive pulmonary disease	0	4 (10.3)	0.116‡
Atypical mycobacteria	1 (2.8)	1 (2.6)	>0.999‡
Sleep disordered breathing	1 (2.8)	1 (2.6)	>0.999‡
Depression	3 (8.3)	3 (7.7)	>0.999‡
Malignancy (except for lung cancer)	6 (16.7)	5 (12.8)	0.751‡
Atrial fibrillation	1 (2.8)	0	0.480‡
Coagulopathy	1 (2.8)	2 (5.1)	>0.999‡
Respiratory function			
FEV1.0%, %	73.9±9.3	74.0±10.9	0.996*
%VC, %	88.0±14.8	95.9±13.1	0.016*
%DLco, %	67.9±8.2	94.4±10.7	<0.001*
Medication			
Riociguat administration	12 (33.3)	17 (43.6)	0.362†
Diuretics	15 (41.7)	12 (30.8)	0.326†
Warfarin	20 (55.6)	23 (59.0)	0.765†
Direct anticoagulant drug	16 (44.4)	16 (41.0)	0.765†

Data are presented as the mean±SD, median (IQR) or n (%). The p value was calculated by the independent t-test (*), χ^2 test (†), Fisher's exact test (‡) or Mann-Whitney U test (§) between the two groups. ¶Some patients had multiple comorbidities.
%DLco, diffusing capacity of the lungs for carbon monoxide as percent of predicted; DLco, diffusing capacity of the lungs for carbon monoxide; FEV1.0%, forced expiratory volume percentage in 1 s; %VC, vital capacity percentage.

(89.1% (86.5–92.5%) vs 92.3% (91.0–94.7%), p=0.001), a lower vital capacity percentage (%VC) (88.0%±14.8% vs 95.9%±13.1%, p=0.016) and a lower percent of predicted DLco (%DLco) (67.9%±8.2% vs 94.4%±10.7%, p<0.001) than the ND group. The median %DLco was 80.4%. There were no statistically significant differences in heart rate; rate of comorbidities, such as respiratory disorders, depression, malignancy, atrial fibrillation and coagulopathy; rate of riociguat administration; and anticoagulant status between the two groups (all p>0.116). The patients' characteristics are shown in table 1.

Haemodynamic and exercise tolerance efficacy of BPA

The haemodynamic status and exercise tolerance parameters after BPA are shown in table 2 and figure 2. Baseline haemodynamics did not differ between the two groups; however, the 6-minute walk distance (6MWD) at baseline was shorter in the LD group (324±91 vs 427±114 m). Regarding haemodynamics, the mean RAP (mRAP), mPAP, CO, PVR, SaO_2 and mixed venous oxygen saturation improved compared with baseline in the ND group, whereas the mRAP and CO were not improved in the LD group. After BPA, there was still a difference in mPAP (25.1±7.4 vs 21.5±5.6 mm Hg, p=0.020) and PVR (282.1±159.4 vs 203.2±84.6 dyne·s/cm^{-5}, p=0.009). On the basis of the analysis of covariance adjusted for baseline values, DLco was significantly associated with an improvement in mPAP (sβ=−0.304, 95% CI −7.015 to −1.132, p=0.007) and PVR (sβ=−0.324, 95% CI −141.0 to −29.81, p=0.003). The mean reduction in mPAP was −19.7 mm Hg in the ND group and −13.9 mm Hg in the LD group, and the reduction in PVR was −423.0 dynes/cm^5 in the ND group and −306.9 dynes/cm^5 in the LD group. Both groups showed improvements in 6MWD after BPA. There were also differences between both groups at baseline. The sensitivity analysis for the missing values of 6MWD showed the robustness of the results (best-case imputation: coefficient 0.196, 95% CI −2.665 to 98.80, p=0.063; worst-case imputation: coefficient 0.052, 95% CI −26.42 to 48.59, p=0.557; multiple imputation: coefficient 0.050, 95% CI −27.19 to 48.05, p=0.587). Furthermore, we evaluated the association of DLco with postprocedural haemodynamic and functional parameters considering DLco as a continuous variable (online supplemental table 1, figure 1), and the results were consistent with the results of the binary analysis.

BPA procedure

The procedural results of BPA are shown in table 3. The total number of BPA procedures was 246 sessions in the LD group and 208 sessions in the ND group, and the patients in the LD group tended to need more BPA sessions than those in the ND group (6 (4–10) vs 4 (4–6), p=0.059). There was no significant difference between the two groups in the number of lung segments treated per procedure (6.2±2.8 vs 6.1±2.7, p=0.720), number of pulmonary vessels treated per procedure (11.3±6.0 vs 11.0±6.0, p=0.622), ratio of total occluded lesions to treated branches (1.7 vs 1.5, p=0.717), or volume of contrast medium used per session (118.9±41.8 vs 125.6±41.1 mL, p=0.096). The total number of treated segments per patient and the total number of treated pulmonary vessels per patient were significantly higher in the LD group than in the ND group (42.4±2.8 vs 32.6±2.7, p=0.026, and 77.3±6.0 vs 58.9±6.0, p=0.039, respectively). Haemosputum and haemoptysis occurred in 21 sessions (8.5%) in the LD group and in 23 sessions (11.1%) in the ND group. Non-invasive positive pressure ventilation was used in 11 sessions (4.5%) in the LD group and in 10 sessions (4.8%) in the ND group, with no statistically significant differences. No BPA-related deaths occurred in either group.

DISCUSSION

In this study, %DLco was ≤80% in 48% of patients with CTEPH. Our data showed that BPA improved the patients' haemodynamics, 6MWD and oxygenation despite CTEPH with low DLco. However, the improvements in mPAP and PVR were smaller in patients with low DLco than in those with normal DLco, and more BPA sessions were required to achieve haemodynamic improvement. Only patients in the ND group showed an improvement in CO after BPA.

In the comparison between the two groups, no difference was found in mPAP or PVR at baseline. However, differences were observed after treatment, although fewer BPA sessions were needed in the ND group. This finding indicates that the ND group was more likely to respond to BPA than the LD group. Considering the close relationship between DLco and microvasculopathy, the low treatment efficacy might have been caused by pulmonary artery microvasculopathy, and the patients in the ND group might have had fewer microvasculopathies. Various types

Table 2 Comparison of haemodynamic status and exercise tolerance before and after BPA in the low DLco and normal DLco groups

	Low DLco (n=36)			Normal DLco (n=39)			Normal vs low DLco (comparison of post-value*)		
	Baseline	Follow-up	Change	Baseline	Follow-up	Change	Standardised regression coefficient	95% CI	P value
Haemodynamics									
mean RAP, mm Hg	6.2±3.0	6.5±3.0	0.3 (0.6)	6.6±2.9	5.4±1.9	−1.2 (0.6)	−0.233	(−2.374 to −0.023)	0.046
mean PAP, mm Hg	38.9±7.3	25.1±7.4	−13.9 (1.5)	41.1±9.2	21.5±5.6	−19.7 (1.5)	−0.304	(−7.015 to −1.132)	0.007
Cardiac output, L/min	4.7±1.6	4.7±1.2	0.0 (0.2)	4.2±0.9	4.7±1.3	0.47 (0.2)	0.109	(−0.232 to 0.768)	0.288
PVR, dyn·s/cm^{-5}	589.1±290.1	282.1±159.4	−306.9 (42.4)	625.8±197.9	203.2±84.6	−423.0 (34.6)	−0.324	(−141.0 to 29.81)	0.003
SaO_2, %	89.1 (86.8–92.5)	94.9 (91.2–96.0)	4.2 (0.9)	92.6 (91.0–94.7)	96.4 (95.5–97.0)	3.7 (0.5)	0.261	(0.294 to 3.351)	0.020
SvO_2, %	61.9 (57.3–68.6)	70.3 (67.1–73.4)	6.9 (1.6)	67.3 (62.4–70.3)	74.0 (69.9–75.8)	7.8 (1.2)	0.247	(0.344 to 6.057)	0.029
6-minute walk distance, m	324±91 (n=32)	409±96 (n=34)	86 (14) (n=32)	427±114 (n=37)	489±95 (n=35)	66 (13) (n=34)	0.076	(−22.43 to 53.89)	0.413

Values are presented as the mean±SD, median (IQR) or mean (SE).
*Based on the analysis of covariance adjusted for baseline value.
BPA, balloon pulmonary angioplasty; DLco, diffusing capacity of the lungs for carbon monoxide; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SaO_2, arterial oxygen saturation; SvO_2, mixed venous oxygen saturation.

of vascular lesion may exist in patients with CTEPH,[10 22] and microvasculopathy is one such vascular lesion that is difficult to treat with BPA. Additionally, low DLco is a poor prognostic factor in patients with CTEPH who are treated by medical therapy without BPA,[16] probably as a result of microvascular damage to the pulmonary arteries. BPA has become the standard of care for inoperable CTEPH, which is rarely managed with drugs alone, and BPA improves mortality. The results of this study suggest that low DLco in patients with inoperable CTEPH may be both a prognostic indicator and a predictor of resistance to BPA treatment. The lack of significant differences in the number of treated segments and branches between the two groups in each session suggests that the results of our study were not due to the BPA technique. Additionally, riociguat, a pulmonary vasodilator, has the potential to directly affect pulmonary artery microvasculopathy.[23] There was no difference in the prescription rate between the two groups, suggesting that it did not influence the results of this study. One possible explanation for the lower effectiveness of BPA treatment in patients with low DLco is that the BPA target vessel is the distal portion of the pulmonary artery and BPA has no direct therapeutic action on microvasculopathy. In one study that evaluated microangiopathy by observing subpleural perfusion with dual-energy CT, there was no significant improvement in DLco, even after haemodynamic improvement, similar to our results.[24] These findings indicate that BPA does not have a sufficient effect on microvasculopathy immediately or during the follow-up period in patients with CTEPH, despite the fact that it improves blood flow.

The ND group showed improvements in mRAP and CO after BPA compared with baseline. This may have occurred because BPA improves pulmonary artery blood flow by compressing organised thrombi to the vessel wall, thereby increasing left ventricular preload and ameliorating circulatory dynamics. In the LD group, however, the changes in CO and mRAP after BPA might have been influenced by microvascular impairment, preventing an increase in left ventricular preload despite increased pulmonary artery blood flow. Although riociguat, which directly affects microvasculopathy in CTEPH, increases CO, it is generally assumed that BPA does not improve CO as much as mPAP or PVR.[11 12 25 26] Considering the results of this

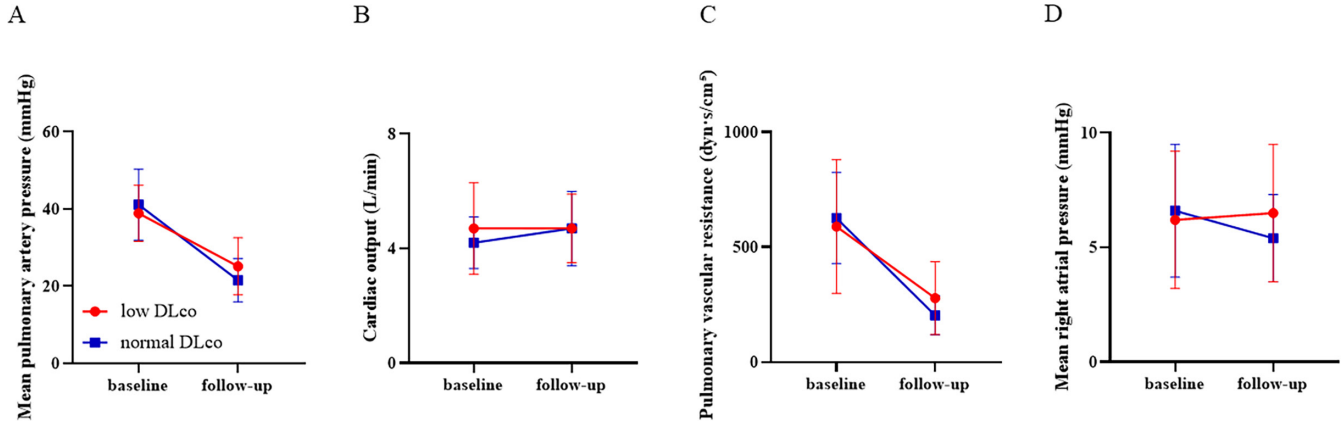

Figure 2 Haemodynamic statuses in the low DLco (LD) and normal DLco (ND) groups before and after balloon pulmonary angioplasty. The line graphs show the (A) mean pulmonary artery pressure, (B) cardiac output, (C) pulmonary vascular resistance and (D) mean right atrial pressure at baseline and during follow-up. The lines for haemodynamic status indicate the mean value with SE. The red line corresponds to the LD group, and the blue line corresponds to the ND group. DLco, carbon monoxide diffusing capacity.

Table 3 Procedural characteristics of BPA

	Low DLco (n=36)	Normal DLco (n=39)	P value
Procedural			
Total number of BPA procedures	246	208	
Median number of BPA procedures per patient	6 (4–10)	4 (4-6)	0.059*
Number of treated lung segments per procedure	6.2±2.8	6.1±2.7	0.720†
Total number of treated segments per patient	42.4±2.8	32.6±2.7*	0.026†
Number of pulmonary vessels per procedure	11.3±6.0	11.0±6.0	0.622†
Ratio of total occluded lesion to treated branches, %	1.7	1.5	0.717‡
Total number of treated pulmonary vessels per patient	77.3±6.0	58.9±6.0*	0.039†
Fluoroscopy time per procedure, min	56.8±18.1	64.2±20.4*	<0.001†
Contrast medium per procedure, mL	118.9±41.8	125.6±41.1	0.096†
Complication (number of procedure)			
Haemosputum or haemoptysis	21 (8.5)	23 (11.1)	0.819†
Contrast agent-related renal dysfunction	0	0	>0.999§
Pneumothorax	0	0	>0.999§
Use of NPPV	11 (4.5)	10 (4.8)	0.865†
Use of ECMO	0	0	>0.999§
Death related to BPA	0	0	>0.999§

Data are presented as the mean±SD, median (IQR) or n (%).
The p value was calculated by the independent t-test (*), χ^2 test (†), Fisher's exact test (‡) or Mann-Whitney U test (§) between the two groups.
BPA, balloon pulmonary angioplasty; DLco, diffusing capacity of the lungs for carbon monoxide; ECMO, extracorporeal membrane oxygenation; NPPV, non-invasive positive pressure ventilation.

study, the lack of an improvement in CO may be associated with the presence of microangiopathy. Meanwhile, PEA improves CO to a greater extent than BPA, despite treatment of only the proximal portion,[1 27] suggesting that microangiopathy, which is involved in DLco reduction, is not the only factor that affects the change in CO after treatment. However, further investigation is needed to explore the determinant factors. Furthermore, given that the results of the analysis of covariance adjusted for baseline CO (sβ = 0.109, 95% CI −0.232 to 0.768, p=0.288) and mRAP (sβ = −0.233, 95% CI −2.374 to −0.023, p=0.046) were not statistically significant, the relationship between DLco and improvements in CO and mRAP is limited.

The SaO_2, 6MWD and %VC were consistently worse in the LD group than in the ND group, both before and after treatment. DLco and %VC are related to oxygenation and exercise tolerance[28 29]; therefore, it is possible that the LD group, which had a lower %VC and %DLco, had lower oxygen saturation and a shorter 6MWD than the ND group. A study at a Japanese expert centre for BPA treatment showed that the changes in mPAP and PVR after 12 months from baseline were −16.3 mm Hg and −332.4 dynes, respectively.[11] Additionally, the average number of sessions per patient, the number of treated pulmonary vessels per treatment and the number of treated segments were not much different[11] compared with our results, indicating that our BPA procedure is acceptable. Finally, the BPA-associated complication rates were not significantly different between the two groups in the present study. This suggests that microvascular disease does not affect the complication rate of BPA.

The cut-off value for %DLco in this study was set at 80% of the lower limit of normal for %DLco based on previous reports[16 18] and the median value in the present study. The results of the regression analysis showed a consistent correlation between lower DLco values and higher follow-up mPAP and PVR values, both by dividing patients into two groups by the DLco cut-off value of 80% and by treating this metric as a continuous variable (online supplemental table 1). According to online supplemental figure 1, alternate cut-off values other than 80% could also be considered. However, we adopted the 80% cut-off because it enabled comparison with previous reports.[16 18]

This study had several limitations. First, this was a small-scale, single-centre, retrospective observational study, which may limit the applicability of the results to other populations. Second, patients were excluded from the study if they were too sick to undergo pulmonary function testing. Third, there may have been bias in the technical skills of the BPA procedure because of the study duration and the fact that almost all procedures were performed by a single operator. However, the median year in which the BPA procedures were performed was 2019 for the LD group and 2017 for the ND group, and the impact of skill on the results of this study was considered minimal. Fourth, considering the pathology of CTEPH, low DLco in CTEPH is mainly caused by the reduction in blood supply to the microvasculature. However, the value of DLco varies according to many factors, and our DLco result may not only represent pulmonary artery microvascular damage. Furthermore, microvasculopathy can be more precisely evaluated by subpleural hypoperfusion measured by digital subtraction angiography and upstream resistance measurement; however, these tests were not performed. The cut-off value for DLco was 80%, but verification of the validity of this value is insufficient, so further studies are needed.

CONCLUSIONS

BPA is associated with improved haemodynamics and exercise tolerance even in patients with CTEPH with low DLco. DLco may attenuate the effects of BPA on mPAP and PVR, and require additional sessions of BPA.

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contributed final approval of the manuscript submitted. SM is the guarantor of this manuscript.

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Patient consent for publication Not applicable.

Ethics approval This retrospective study was approved by the Institutional Review Board of the University of Tokyo (No. 2650) and we applied an opt-out procedure to obtain consent on this study.

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Supplemental Table 1. Linear regression analysis of haemodynamics and 6-minute walking distance on binary DLco (normal/low) and continuous DLco

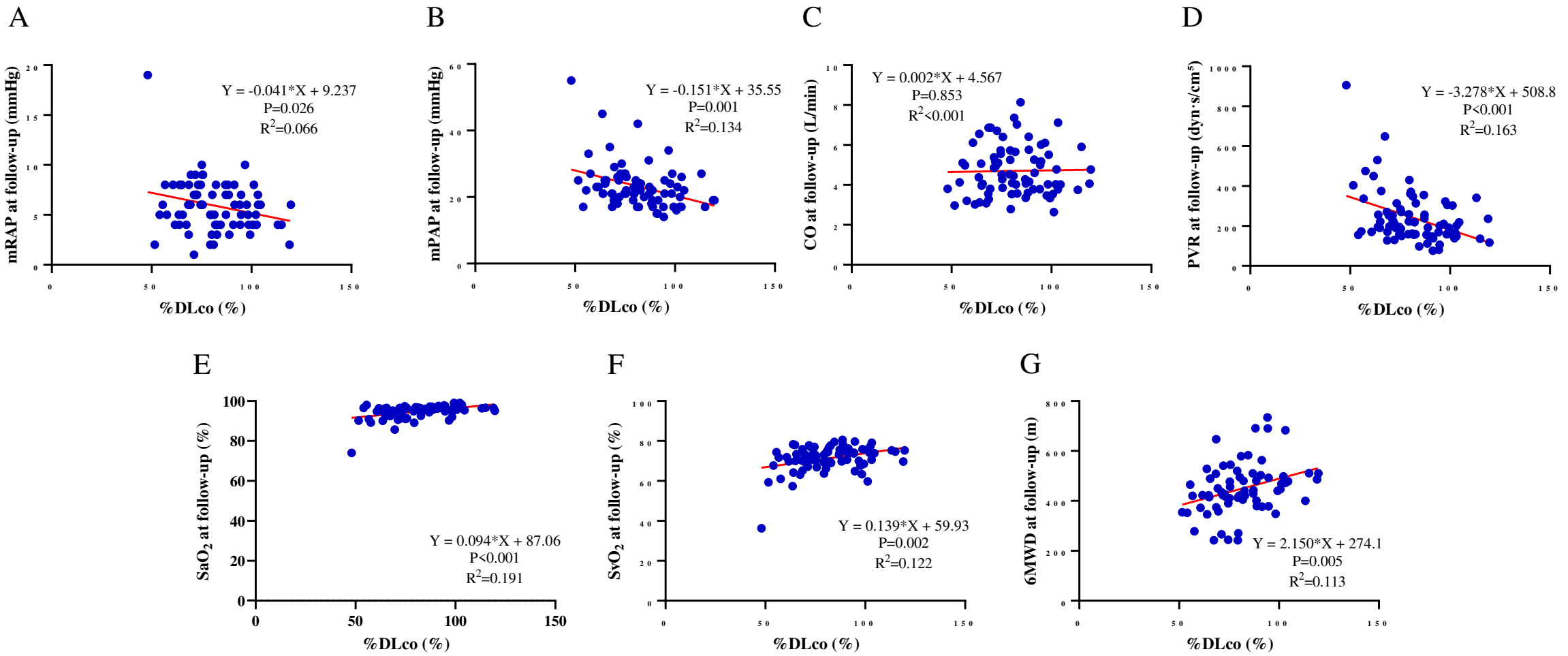
	DLco as a binary scale (Normal vs Low DLco)*1			**DLco as a continuous value*2**		
	Standardised regression coefficient	95% CI	P	Standardised regression coefficient	95% CI	P
Haemodynamics						
mean RAP, mmHg	-0.233	(-2.374, -0.023)	0.046	-0.254	(-0.076, -0.004)	0.029
mean PAP, mmHg	-0.304	(-7.015, -1.132)	0.007	-0.374	(-0.242, -0.067)	<0.001
Cardiac output, L/min	0.109	(-0.232, 0.768)	0.288	0.077	(-0.009, 0.021)	0.448
PVR, dyn・s/cm^{-5}	-0.324	(-141.0, -29.81)	0.003	-0.412	(-4.981, -1.708)	<0.001
SaO_2, %	0.261	(0.294, 3.351)	0.020	0.332	(0.027, 0.117)	0.002
SvO_2, %	0.247	(0.344, 6.057)	0.029	0.292	(0.029, 0.205)	0.010
6-min walk distance, m	0.076	(-22.43, 53.89)	0.413	0.053	(-0.824, 1.503)	0.562

The values on the left (binary DLco) are the same as in Table 2; however, the results are also presented here to allow the similarity with the values on the right (continuous DLco) to be visualised.

*1 Based on the analysis of covariance adjusted for baseline values.

*2 Based on the linear regression model with continuous DLco and the baseline value as explanatory variables.

BPA, balloon pulmonary angioplasty; DLco, diffusing capacity of the lungs for carbon monoxide; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SaO_2, arterial oxygen saturation; SvO_2, mixed venous oxygen saturation.



Supplemental Figure. 1 the scatterplots of the association between follow-up values in each parameter and baseline DLco values

The graphs show (A) mRAP, (B) mPAP, (C) CO, (D) PVR, (E) SaO_2, (F) SvO_2, and (G) 6MWD. The red line means approximate curve. %DLCO, diffusing capacity of the lungs for carbon monoxide as percent of predicted; 6MWD, 6-min walking distance; CO, cardiac output; DLco, diffusing capacity of the lung for carbon monoxide; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; PVR, pulmonary vascular resistance; SaO_2, arterial oxygen saturation; SvO_2, mixed venous oxygen saturation.