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ORIGINAL ARTICLE

Increasing mixed venous oxygen saturation is a predictor of improved renal function after balloon pulmonary angioplasty in patients with chronic thromboembolic pulmonary hypertension

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Abstract

Balloon pulmonary angioplasty (BPA) has emerged as an effective treatment for patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH). Renal function has been identified as a prognostic marker in patients with pulmonary hypertension in previous studies. We, therefore, aimed to investigate the clinical parameters associated with improvements in renal function in patients with CTEPH. A total of 45 consecutive patients with inoperable CTEPH undergoing BPA (mean age 62.2 ± 15.1 years) were included in the study. We evaluated the patients' clinical characteristics at baseline and at 1-year post-BPA, and investigated the association between renal function and hemodynamic parameters, including right heart function. Hemodynamics and renal function showed sustained improvements at 1 year after BPA in 64.4% of patients. Improved estimated glomerular filtration rate (eGFR) was significantly correlated with increased cardiac index ($r = 0.433$, $p = 0.003$) and mixed venous oxygen saturation (SvO_2; $r = 0.459$, $p = 0.002$), and with decreased mean pulmonary arterial pressure ($r = -0.420$, $p = 0.004$) and pulmonary vascular resistance ($r = -0.465$, $p = 0.001$). Multivariate analysis revealed that an increase in SvO_2 immediately after the final BPA was associated with improved eGFR after the 1st year (odds ratio 1.041; 95% confidence interval 1.004–1.078; $P = 0.027$). The cut-off value for predicting improved eGFR was an increase in SvO_2 after the final BPA of >125.4% over the baseline value (specificity 100%, sensitivity 24.1%). In conclusion, BPA improved symptoms, right heart function, hemodynamics, and renal function up to the chronic phase. Increasing SvO_2 by >125.4% above baseline in the acute phase is important for improving renal function at 1 year after BPA in CTEPH patients.

Keywords Balloon pulmonary angioplasty · Chronic thromboembolic pulmonary hypertension · Renal function · Mixed venous oxygen saturation · Cardiac index

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening disease characterized by obstruction of the pulmonary arteries by organized thrombi and fibrous stenosis, leading to progressive pulmonary hypertension and right ventricular failure [1, 2]. Pulmonary endarterectomy (PEA) is an established and standard treatment for CTEPH [3]; however, 30–40% of CTEPH patients are considered inoperable based on the surgeon's assessment [4]. Balloon pulmonary angioplasty (BPA) has recently emerged as an effective and safe treatment for patients with inoperable CTEPH [5,6]. We and others previously demonstrated that BPA improved World Health Organization functional class (WHO-FC), 6-min walk distance, right ventricular function, mean pulmonary arterial pressure (mPAP), and pulmonary vascular resistance (PVR) in patients with CTEPH in the acute phase [7, 8]. However, the long-term benefits of BPA in terms of organ function have not been fully elucidated. Given that renal function is associated with prognosis in patients with pulmonary hypertension [9, 10], the current

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study aimed to investigate the clinical features of CTEPH at 1 year after BPA, and to determine the best parameters for improving renal function based on catheter and echocardiographic data.

Materials and methods

Study population

We enrolled 59 consecutive patients with inoperable CTEPH who underwent BPA at Keio University Hospital between November 2012 and June 2016, and followed them up for 1 year (32 women (68%), mean age (± standard deviation): 61.7 ± 15.5 years). Of these, we excluded five patients who underwent PEA before BPA, five patients with no cardiac-output data, and four patients with no follow-up examination. Patients performed 6-min walk distance tests before and 1 year after BPA. Serological tests included brain natriuretic peptide, albumin, and creatinine levels measured before, immediately after, and 1 year after the final BPA procedure. Estimated glomerular filtration rate (eGFR) was calculated by the modification of diet in renal disease equation using serum creatinine level [11]. Body weight, medication, and home oxygen therapy were recorded on the day of catheterization. This study was approved by the ethics committee of Keio University, and written informed consent was received from all patients prior to inclusion in the study.

Balloon pulmonary angioplasty and right heart catheterization

BPA was performed as described previously [8,12]. All patients in this study were considered for PEA by the CTEPH team including surgeons, and inoperability was based on surgically inaccessible lesions or comorbidities such as advanced age and poor physical condition. Patients with residual pulmonary hypertension after PEA werealso considered inoperable. Inoperable patients with World Health Organization (WHO) functional class ≥ II were treated with one or more pulmonary hypertension-targeted drugs. The indications for BPA required all of the following [13]: (1) inoperable for PEA; (2) WHO functional class ≥ II after treatment with targeted medication; (3) patients who understood the risks and benefits of both BPA and PEA and who chose BPA; and (4) patients without serious complications. After BPA, targeted drugs were reduced when the symptoms disappeared. BPA was performed by inserting an 8- or 9-Fr indwelling sheath through the right jugular or right femoral vein. A 6-Fr long introducer sheath was then advanced via the indwelling sheath to the main pulmonary artery trunk using a 0.035-in. wire, and a 6-Fr multipurpose type, Judkins right, or Amplatz left-guiding catheter was inserted through the 6-Fr long sheath and advanced to the target vessels. Balloon size was determined based on the target-vessel diameter measured by angiography and/or intravascular ultrasound. The balloons (size range 1.0–8.0 mm) were inflated manually until the indentation disappeared or until the balloon was fully inflated (2–14 atm). After ballooning, improved peripheral blood flow was confirmed angiographically. We aimed to treat all stenotic lesions.

Right heart catheterization was performed using a 6- or 7-Fr Swan-Ganz catheter (Swan-Ganz CCO CEDV; Edwards Lifesciences, Irvine, CA, USA) before the first BPA (baseline), immediately after the final BPA (after final BPA), and 1 year after the final BPA (1 year after BPA) (mean follow-up 13.9 ± 1.5 months). Hemodynamic parameters including right atrial pressure (RAP), pulmonary arterial pressure (PAP), pulmonary arterial wedge pressure, and cardiac output were measured at the right heart catheterization. Cardiac output was determined by the thermodilution method and cardiac index (CI) was calculated by dividing cardiac output by body surface area.

Echocardiography

Echocardiography was performed in all patients using a Vivid-E9 ultrasound system (GE Healthcare, Horten, Norway) at baseline, after final BPA, and 1 year after BPA. Additional information regarding echocardiography has been published previously [8]. Tricuspid regurgitation was classified into four grades: 0, none or trivial; 1, mild; 2, moderate; and 3, severe [14]. Quantification of right and left atrial areas was assessed from apical four-chamber views at end-systole. The data were analyzed using commercial software (EchoPAC; GE Healthcare). Three patients with atrial fibrillation lacked data on the ratio between *E* velocity and *A* velocity, one lacked information on deceleration time, and four lacked right ventricular S′ data.

Statistical analysis

Quantitative values are reported as mean ± standard deviation. Significant differences were determined using the unpaired Student's *t* test or Mann–Whitney *U* test for continuous variables, and χ^2 or Fisher's exact probability test for categorical variables, as appropriate. One-way analysis of variance for repeated measures, followed by a Bonferroni or Tukey post hoc test, was used as appropriate. Correlations between variables were assessed by Pearson's or Spearman's correlation, as required. Multiple logistic regression with stepwise forward selection was used to identify the factors associated with eGFR increase 1 year after BPA, with hemodynamics and right heart function as known pulmonary arterial hypertension (PAH) risk markers [15]. The predictive power for an increase in eGFR 1 year after BPA

was estimated using the *C*-statistic derived from the area under the receiver operating characteristic curve with the parameters used in the multivariable analysis. Two-tailed probability values <0.05 were considered statistically significant, and all statistical analyzes were performed using SPSS Statistics 23.0 software (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics and beneficial effects of BPA

The patients' clinical characteristics at baseline, after final BPA, and 1 year after BPA are shown in Table 1. BPA was performed an average of 5.9 ± 2.0 times per patient. Among 269 procedures, hemoptysis occurred in 13 procedures (4.8%) in seven patients. Oxygen therapy was required in three procedures, but no procedures required intubation or extracorporeal membrane oxygenation. There were no periprocedural deaths, and no deaths or hospitalizations secondary to cardiovascular events during the follow-up period. Twenty-two patients underwent pulmonary angiography 1 year after BPA. Thromboembolic lesions were dilated and blood flow recovered markedly 1 year after BPA (Fig. 1a) [12]. Echocardiography also showed that both right heart dilatation and ventricular septal shift at baseline improved 1 year after BPA (Fig. 1b). Cardiac output did not change significantly, while mPAP, PVR, mean RAP (mRAP), and mixed venous oxygen saturation (SvO_2) all improved from baseline to 1 year after BPA. The data at baseline, after BPA, and 1 year after BPA, respectively, were as follows: cardiac output: 5.5 ± 1.8, 5.0 ± 1.2, 4.9 ± 1.1 L/min ($P = 0.052$); mPAP: 37.3 ± 10.5, 18.4 ± 3.6, 19.5 ± 3.8 mmHg ($P < 0.001$); PVR: 450.8 ± 279.6, 200.1 ± 93.2, 205.9 ± 93.0 dyn s/cm^5 ($P < 0.001$); mRAP: 6.80 ± 3.15, 1.96 ± 1.62, 2.91 ± 2.08 mmHg ($P < 0.001$); SvO_2: 64.4 ± 9.8, 68.7 ± 5.7, 68.8 ± 6.1% ($P = 0.034$) (Fig. 1 c-1 to c-5). All patients were classed as WHO-FC I or II after the final BPA and 1 year after BPA. The 6-min walk distance increased 1 year after BPA compared with baseline (305.6 ± 98.7–446.0 ± 110.1 m), and the number of patients requiring home oxygen therapy decreased after the final BPA. Targeted drugs were adjusted after BPA depending on the patients' symptoms, and the number of patients taking PAH drugs, including endothelin receptor antagonists and oral prostanoids, decreased. Although there was no change in the use of loop diuretics or thiazides, brain natriuretic peptide levels decreased significantly 1 year after BPA compared with baseline (253.8 ± 547.7–46.9 ± 57.7 pg/mL). Regarding echocardiographic parameters, indices of right ventricular function, including right ventricular fractional area change, right ventricular S′, and tricuspid annular plane systolic excursion, improved after BPA, whereas the parameters of left ventricular function, such as left ventricular ejection fraction, ratio between *E* velocity and *A* velocity, and deceleration time, did not change (Table 1).

Parameters correlated with improved renal function 1 year after BPA

Patients were assigned to the increased or decreased eGFR group according to their changes in eGFR from baseline to 1 year after BPA. The clinical characteristics and hemodynamic data for patients in the increased eGFR ($n = 29$) and decreased eGFR groups ($n = 16$) at baseline, after final BPA, and 1 year after BPA are shown in Table 2. The contrast dose during BPA was similar in the increased and decreased eGFR groups [all contrast dose (mL): 1285 ± 535 vs. 1073 ± 349 ($P = 0.218$); contrast dose per session (mL) 197.6 ± 46.9 vs. 212.4 ± 29.5 ($P = 0.325$), respectively].

Baseline measures of brain natriuretic peptide ($P < 0.001$), PVR ($P = 0.002$), and mPAP ($P = 0.010$) were higher in the increased eGFR compared with the decreased eGFR group, while baseline eGFR ($P = 0.008$) was lower and cardiac output ($P = 0.073$) was the same in the increased eGFR compared with the decreased eGFR group. Serum albumin level ($P = 0.022$) increased and brain natriuretic peptide ($P < 0.001$) decreased 1 year after BPA compared with baseline in the increased eGFR group, whereas these levels did not change in the decreased eGFR group. However, WHO-FC, 6-minute walk distance, the number of patients requiring home oxygen therapy, PVR, and mPAP all improved 1 year after BPA in both groups. These results suggested that BPA improved symptoms, exercise capacity, and pulmonary hypertension, even in patients in whom the eGFR decreased (Table 2). The number of patients treated with endothelial receptor antagonist and oral prostaglandin I_2 decreased from baseline to 1 year after BPA in both the increased and decreased eGFR groups, while the use of phosphodiesterase-5 inhibitors or soluble guanylate cyclase was unchanged in both groups (data not shown). CI and venous congestion are important factors related to renal function in heart failure patients [10,16–18]. To reveal the factors associated with improved eGFR, we investigated the correlation between the relative change in eGFR and risk markers for PAH [15] from baseline to 1 year after BPA. mPAP decreased from baseline to 1 year after BPA in all patients. The relative increase in eGFR was significantly correlated with relative changes in CI ($P = 0.003$), SvO_2 ($P = 0.002$), mPAP ($P = 0.04$), and PVR ($P = 0.001$) from baseline to 1 year after BPA, but not with decreased mRAP ($P = 0.095$) or right atrial area ($P = 0.476$) (Fig. 2).

Table 1 Clinical characteristics and medications ($n = 45$)

	Baseline	After the final BPA	1 year after BPA	ANOVA p value
Clinical characteristics				
Body weight (kg)	58.8 ± 14.1	58.4 ± 14.0	60.6 ± 14.0	< 0.001†,‡
Body mass index (kg/m^2)	22.9 ± 4.0	22.7 ± 3.9	23.6 ± 4.0	< 0.001†,‡
WHO-FC (n, %)				< 0.001
I or II	7 (16)	45 (100)	45 (100)	
III or IV	38 (84)	0 (0)	0 (0)	
Six-minute walk distance (m)	305.6 ± 98.7	–	446.0 ± 110.1	< 0.001†
Home oxygen therapy (n, %)	27 (60)	6 (13)	1 (2)	< 0.001
Brain natriuretic peptide (pg/mL)	253.8 ± 547.7	33.1 ± 33.3	46.9 ± 57.7	< 0.001*,†
Albumin (g/dL)	4.0 ± 0.4	4.1 ± 0.3	4.2 ± 0.3	0.004†,‡
Creatinine (mg/dL)	0.89 ± 0.27	0.83 ± 0.25	0.84 ± 0.24	0.021*,†
eGFR (mL/min/1.73 m^2)	61.0 ± 19.0	65.3 ± 19.4	63.5 ± 18.1	0.033*
Drug				
Loop diuretics (n, %)	27 (60)	30 (67)	27 (60)	0.834
Thiazides (n, %)	1 (2)	1 (2)	0(0)	0.602
Furosemide-equivalent doses (mg)	23.1 ± 26.5	22.7 ± 22.7	17.6 ± 18.7	0.133
Phosphodiesterase-5 inhibitor/soluble guanylate cyclase (n, %)	26 (58)	31 (69)	11 (24)	0.117
Endothelin receptor antagonist (n, %)	18 (40)	13 (29)	4 (9)	0.003
Oral prostaglandin I_2 (n, %)	18 (40)	2 (4)	1 (2)	< 0.001
Calcium channel blocker (n, %)	11 (24)	8 (18)	8 (16)	0.659
Echocardiographic measurements				
Left ventricular end-diastolic diameter (mm)	41.3 ± 6.4	44.2 ± 4.3	43.9 ± 5.3	0.019*,†
Left ventricular end-systolic diameter (mm)	25.2 ± 4.4	26.7 ± 4.0	26.4 ± 4.0	0.467
Left ventricular ejection fraction (%)	70.5 ± 7.7	69.9 ± 8.0	70.1 ± 6.9	0.887
E/A[a]	0.90 ± 0.48	0.91 ± 0.33	1.00 ± 0.47	0.478
Deceleration time (s)[b]	235.4 ± 63.3	224.0 ± 58.4	223.3 ± 52.3	0.755
Inferior vena cava (mm)	14.2 ± 4.3	12.1 ± 2.6	13.3 ± 2.7	0.007*
Tricuspid regurgitation peak gradient (mmHg)	42.1 ± 19.6	25.9 ± 11.9	24.5 ± 12.1	< 0.001*,†
TAPSE (mm)	16.2 ± 4.4	18.7 ± 4.0	18.6 ± 4.1	< 0.001*,†
Right ventricular S′ (cm/s)[c]	10.6 ± 2.4	11.3 ± 2.7	11.6 ± 2.1	0.005†
Right ventricular fractional area change (%)	23.3 ± 10.1	29.7 ± 8.0	35.0 ± 8.6	< 0.001*,†,‡
Tricuspid regurgitation grade (n)				0.196
None or trivial	17	24	21	
Mild	19	13	17	
Moderate	6	8	7	
Severe	3	0	0	
Right arterial area (cm^2)	17.4 ± 7.2	14.7 ± 4.5	13.8 ± 4.9	< 0.001*,†
Left arterial area (cm^2)	14.0 ± 4.2	16.1 ± 4.1	17.0 ± 15.7	0.311

Data are expressed as mean ± standard deviation. Six-minute walk distance was analyzed using Student's t test. One-way analysis of variance or Friedman's test was used to compare more than two groups. WHO-FC, home oxygen therapy, medications, and tricuspid regurgitation grade were analyzed using the χ^2 test

E/A ratio between *E* velocity and *A* velocity, *eGFR* estimated glomerular filtration rate, *TAPSE* tricuspid annular plane systolic excursion, *WHO-FC* World Health Organization functional class

*$p < 0.05$, baseline vs after the final BPA

†$p < 0.05$, baseline vs 1 year after BPA

‡$p < 0.05$, after the final BPA vs 1 year after BPA

[a]$n = 42$

[b]$n = 44$

[c]$n = 41$

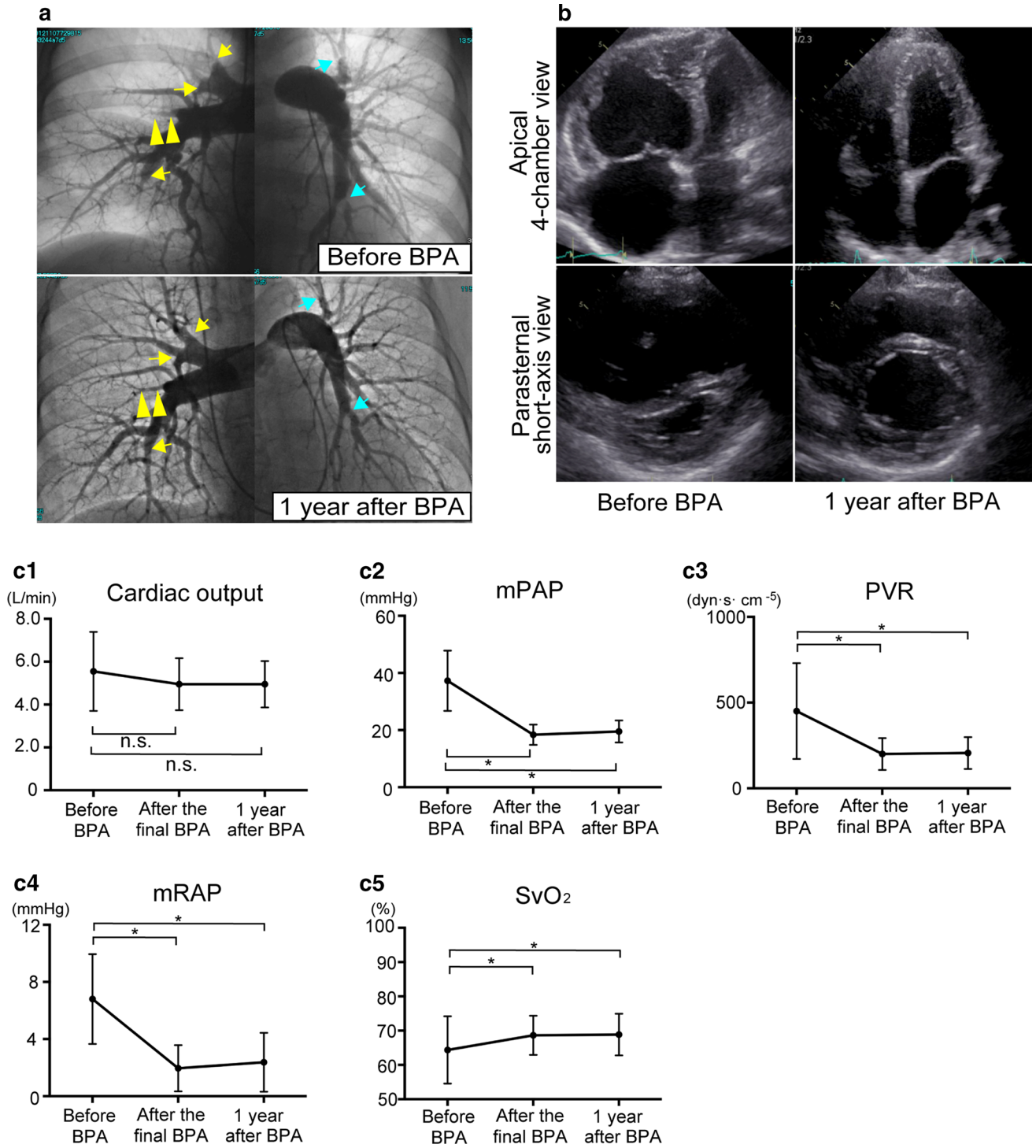

Fig. 1 Representative pulmonary angiographic and echocardiogram images, and hemodynamic changes in a patient with chronic thromboembolic pulmonary hypertension before and 1 year after balloon pulmonary angioplasty. **a** Representative pulmonary angiographic image showing subtotal (yellow arrows), web (yellow arrowheads), and ring-like stenosis lesions (blue arrows) in bilateral pulmonary arteries before balloon pulmonary angioplasty (BPA) (top). Arrows and arrowheads indicate the same arteries in lower image. The lesions dilated and improved blood flow was apparent 1 year after BPA. **b** Apical four-chamber view and parasternal short-axis view before BPA showing right heart dilatation and interventricular septal bowing (left). The size of the right atrium and ventricle decreased, and ventricular septal shift improved dramatically 1 year after BPA (right). **c** Changes in cardiac output, mean pulmonary arterial pressure (mPAP), pulmonary vascular resistance (PVR), mean right atrial pressure (mRAP), and mixed venous oxygen saturation (SvO_2) at baseline, after the final BPA, and 1 year after the last BPA ($n=45$). Differences between baseline, after the final BPA, and 1 year after BPA in both groups were analyzed by repeated measures one-way analysis of variance. $^*P<0.05$

Table 2 Data of the increased eGFR and decreased eGFR groups 1 year after BPA compared with baseline ($n=45$)

	Increased eGFR group (1 year after BPA vs baseline) ($n=29$)				Decreased eGFR group (1 year after BPA vs baseline) ($n=16$)				Two-way repeated measures ANOVA p value
	Baseline	After the final BPA	1 year after BPA	p value	Baseline	After the final BPA	1 year after BPA	p value	
WHO-FC				< 0.001				< 0.001	–
I or II (n)	3	29	29		4	16	16		
III or IV (n)	26	0	0		12	0	0		
Six-minute walk distance (m)	318.2 ± 92.0	–	456.5 ± 101.9	< 0.001	282.7 ± 109.1	–	428.7 ± 125.1	< 0.001	0.252
Home oxygen therapy (n, %)	15 (52)	2 (7)	1 (3)	< 0.001	12 (75)	4 (25)	0 (0)	< 0.001	–
Brain natriuretic peptide (pg/mL)	372.9 ± 654.6	33.0 ± 30.9	45.7 ± 40.4	< 0.001*,†	37.9 ± 53.8	33.2 ± 38.3	49.1 ± 81.9	0.646	0.048§
Body weight (kg)	58.9 ± 14.5	58.8 ± 14.5	60.9 ± 14.1	0.009†,‡	58.7 ± 13.7	57.8 ± 13.7	59.9 ± 14.3	< 0.019‡	0.960
Albumin (g/dL)	3.95 ± 0.39	4.06 ± 0.31	4.19 ± 0.25	0.022†	4.08 ± 0.33	4.08 ± 0.36	4.26 ± 0.39	0.081	0.254
eGFR (mL/min/1.73m^2)	56.1 ± 18.9	62.6 ± 19.1	64.1 ± 19.2	< 0.001*,†	69.9 ± 16.2	70.1 ± 19.7	62.4 ± 16.4	< 0.001†,‡	0.018§
Creatinine (mg/dL)	0.96 ± 0.29	0.86 ± 0.27	0.83 ± 0.25	< 0.001*,†	0.76 ± 0.18	0.77 ± 0.20	0.85 ± 0.23	< 0.001†,‡	0.020§
Cardiac output (L/min)	5.21 ± 1.77	4.63 ± 0.95	4.99 ± 1.08	0.422	6.16 ± 1.86	5.53 ± 1.45	4.86 ± 1.12	0.010†	0.101
Cardiac index (L/min/m^2)	3.15 ± 0.82	2.83 ± 0.34	3.02 ± 0.57	0.255	3.78 ± 1.10	3.41 ± 0.69	2.90 ± 0.40	0.028†	0.037§
SvO_2 (%)	61.9 ± 10.2	68.8 ± 5.4	69.1 ± 5.3	0.011*,†	68.8 ± 7.5	68.4 ± 6.5	68.4 ± 7.5	0.939	0.022§
Mean right atrial pressure (mmHg)	7.3 ± 3.2	1.8 ± 1.4	3.1 ± 1.8	< 0.001*,†	5.9 ± 2.9	2.2 ± 2.0	2.6 ± 2.6	< 0.001*,†	0.145
Pulmonary vascular resistance (dyn/s/cm^5)	537.1 ± 289.0	223.1 ± 96.4	212.2 ± 88.2	< 0.001*,†	294.3 ± 148.1	158.4 ± 72.3	194.5 ± 103.3	< 0.001*,†	0.004§
Mean pulmonary arterial pressure (mmHg)	40.2 ± 11.2	18.7 ± 3.8	19.9 ± 3.2	< 0.001*,†	31.9 ± 6.6	17.8 ± 3.0	18.8 ± 4.8	< 0.001*,†	0.010§

WHO-FC data and home oxygen therapy were analyzed using the χ^2 test. Differences between baseline, after the final BPA, and 1 year after BPA in both groups were analyzed by repeated measures one-way analysis of variance

eGFR estimated glomerular filtration rate, *WHO-FC* World Health Organization functional class

*$p<0.05$, baseline vs after the final BPA

†$p<0.05$, baseline vs 1 year after BPA

‡$p<0.05$, after the final BPA vs 1 year after BPA. Differences between both groups were analyzed by two-way repeated measures ANOVA

§$p<0.05$

Predictors of increased eGFR 1 year after final BPA

Relative changes in CI, mPAP, PVR, and SvO_2 were correlated with relative change in eGFR (Fig. 2). We, therefore, conducted a multivariate analysis using these four parameters (model 1), which identified a relative increase in SvO_2 from baseline to immediately after the final BPA as a significant predictor of increased eGFR 1 year after BPA [odds

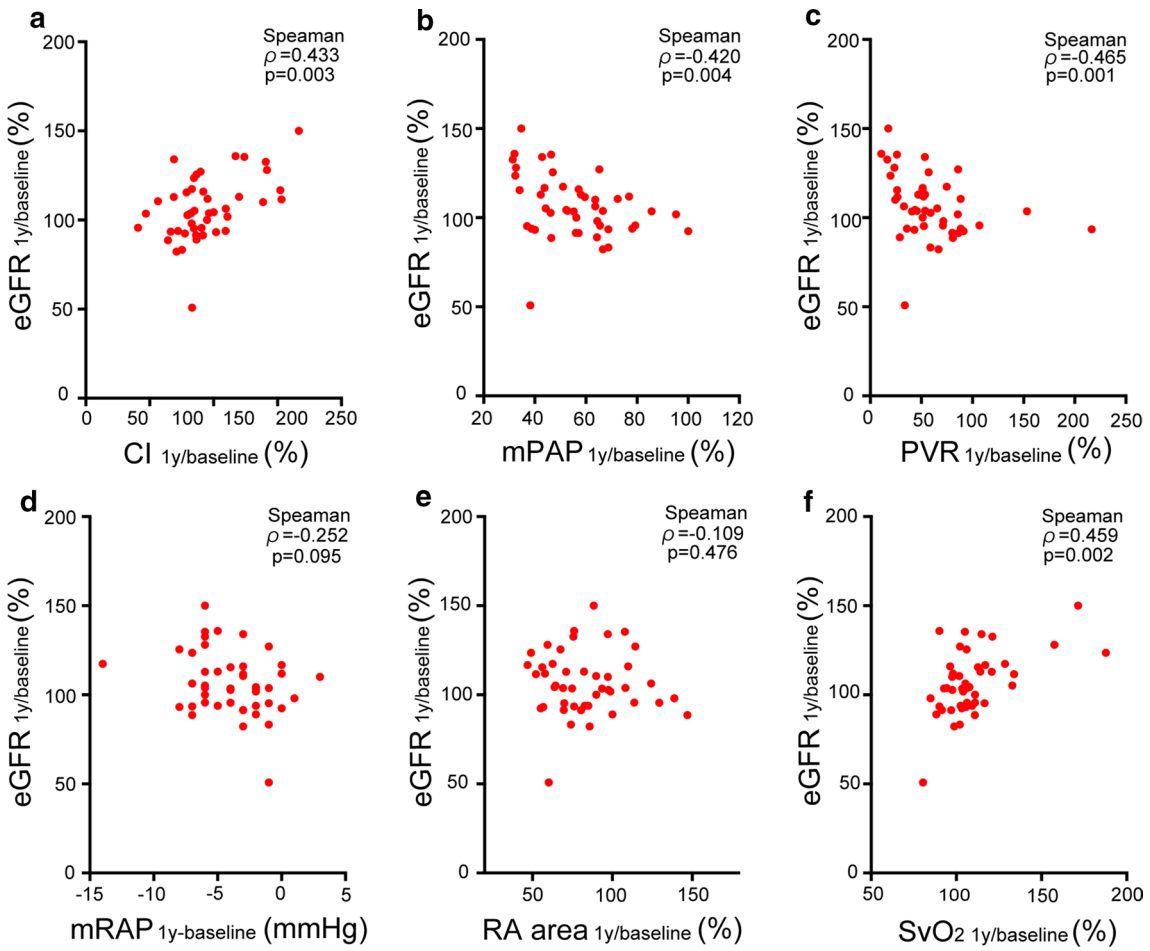

Fig. 2 Correlation between relative change in eGFR and hemodynamic parameters from baseline to 1 year after balloon pulmonary angioplasty. **a** Cardiac index $(CI)_{1y/baseline}$, **b** mean pulmonary arterial pressure $(mPAP)_{1y/baseline}$, **c** pulmonary vascular resistance $(PVR)_{1y/baseline}$, and **f** mixed venous oxygen saturation $(SvO_2)_{1\ y/baseline}$ were significantly correlated with $eGFR_{1y/baseline}$, while **d** mean right atrial pressure $(mRAP)_{1y\text{-}baseline}$ and **e** right atrium (RA) $area_{1y/baseline}$ were not correlated with $eGFR_{1y/baseline}$. $CI_{1y/baseline}$, $mPAP_{1y/baseline}$, $PVR_{1y/baseline}$, RA $area_{1y/baseline}$, and $SvO_{21y/baseline}$ indicate relative change in each measurement; $mRAP_{1y\text{-}baseline}$ indicates change from baseline to 1 year after balloon pulmonary angioplasty (BPA). The difference between baseline and 1 year after BPA in mRAP was analyzed because mRAP at baseline was 0 mmHg in some patients. *1y/baseline* relative change from baseline to 1 year after BPA, *1y-baseline* difference from baseline to 1 year after BPA

Table 3 Univariate and multivariate logistic regression analyzes for predicting increased eGFR from baseline to 1 year after BPA, model 1: relative change of hemodynamic parameters

Variable	Univariate		Multivariate	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Cardiac index (after the final BPA/baseline)	1.001 (0.972–1.032)	0.931		
Mean pulmonary arterial pressure (after the final BPA/baseline)	0.948 (0.898–1.000)	0.052		
Pulmonary vascular resistance (after the final BPA/baseline)	0.984 (0.955–1.014)	0.285		
SvO_2 (after the final BPA/baseline)	1.090 (1.008–1.178)	0.030	1.090 (1.008–1.178)	0.030

The outcome was nominal variable of increased eGFR from baseline to 1 year after BPA

eGFR estimated glomerular filtration rate, *SvO_2* mixed venous oxygen saturation

ratio (OR), 1.090; 95% confidence interval: 1.008–1.178; $P=0.030$] (Table 3). Additional multivariate analysis incorporating the pre-procedural values of these four parameters was also performed (model 2), which showed that high pre-procedural PVR predicted increased eGFR 1 year after BPA (OR, 1.006 per unit increment; 95% confidence interval 1.001–1.010; $P=0.010$) (Table 4).

According to receiver operating characteristic curve analysis, relative change in SvO_2 from baseline to after the final BPA significantly predicted increased eGFR 1 year after BPA compared with baseline, with the highest area under the curve (0.739; $P=0.008$) (Fig. 3). We calculated a cut-off value for eGFR increase 1 year after BPA with > 95% specificity, and showed that a relative increase in SvO_2 after the final BPA of >125.4% over baseline value predicted an eGFR increase 1 year after BPA, with a specificity of 100% and sensitivity of 24.1%.

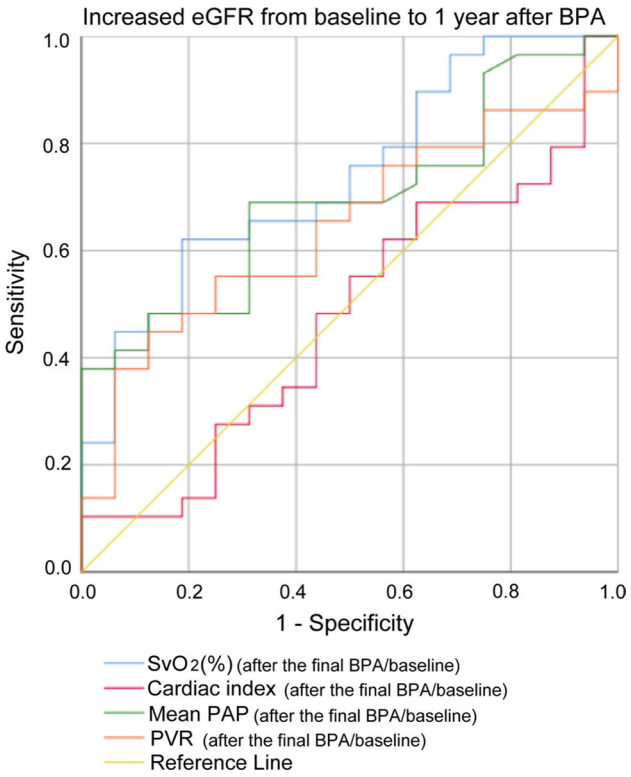

Fig. 3 Receiver operating characteristic curves of relative change in hemodynamic parameters from baseline to immediately after the final balloon pulmonary angioplasty (BPA) predicting increased eGFR 1 year after BPA. A relative increase in SvO_2 immediately after the final BPA significantly predicted increased eGFR 1 year after BPA with the largest area under curve (AUC). SvO_2 (after final BPA/baseline): AUC 0.739, 95% confidence interval 0.592–0.886, $P=0.008$; mPAP (after final BPA/baseline): AUC 0.694, 95% confidence interval 0.541–0.847, $P=0.033$; PVR (after final BPA/baseline): AUC 0.642, 95% confidence interval 0.480–0.804, $P=0.118$; CI (after final BPA/baseline): AUC 0.476, 95% confidence interval 0.299–0.653, $P=0.794$. *CI* cardiac index, *mPAP* mean pulmonary arterial pressure, *PVR* pulmonary vascular resistance, SvO_2 mixed venous oxygen saturation

Discussion

The current study revealed that hemodynamic parameters, renal function, and patients' symptoms improved after the final BPA in patients with CTEPH, and these improvements were maintained even 1 year after BPA. A relative increase in SvO_2 after the final BPA played an important role in the improved renal function 1 year after BPA.

Correlation between improved renal function and hemodynamic parameters in chronic phase of CTEPH

We examined eGFR before and after BPA, as a clinically relevant parameter indicating organ perfusion [16, 19], to evaluate the effect of hemodynamic improvements on organ function in patients with CTEPH. A previous study revealed that reduced renal function was an important predictor of death in patients with PAH [9], while increased CI and relief of renal congestion were important factors for improving renal function in patients with heart failure [10, 16–18, 20]. Echocardiographic or catheter parameters such as right atrial area, mRAP, CI, and SvO_2 are useful for prognostic risk assessment, according to the European Society of Cardiology guidelines for pulmonary hypertension patients [15]. Among these variables, relative changes in CI, SvO_2, mPAP, and PVR from baseline to 1 year after BPA were significantly correlated with relative changes in eGFR in the same

Table 4 Univariate and multivariate logistic regression analyzes for predicting increased eGFR from baseline to 1 year after BPA, model 2: preprocedural values of hemodynamic parameters

Variable	Univariate		Multivariate	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Cardiac index	0.470 (0.214–1.032)	0.060		
Mean pulmonary arterial pressure	1.104 (1.019–1.197)	0.016		
Pulmonary vascular resistance	1.006 (1.001–1.010)	0.010	1.006 (1.001–1.010)	0.010
SvO_2	0.904 (0.823–0.992)	0.034		

The outcome was nominal variable of increased eGFR from baseline to 1 year after BPA

eGFR estimated glomerular filtration rate, SvO_2 mixed venous oxygen saturation

period in the current study, while changes in indicators of renal congestion such as mRAP and right atrial area were not correlated. These results suggested that improving renal congestion was insufficient for improving renal function, and it is important to directly confirm improved organ perfusion after BPA.

Relative increase in SvO_2 was a marker of therapeutic effects of BPA

It is important to determine a therapeutic goal for BPA; however, there is currently no reliable parameter forevaluatingoutcomes in the chronic phase after BPA. One study found that mPAP ≥ 38 mmHg after PEA was associated with a poor prognosis in patients with CTEPH [21], while another study found no such correlation [22]. In addition, post-procedural PVR and CI were previously correlated with prognosis after PEA or BPA [4, 12, 21], and can thus also be used as hemodynamic indicators of treatment goals for BPA. According to our multivariable analysis, a relative increase in SvO_2, but not in mPAP, PVR, or CI, immediately after the last BPA session could predict long-term effects on renal function in patients with CTEPH. Among these hemodynamic parameters, CI is easily affected by other hemodynamic factors in the catheterization room, such as body fluid volume, blood pressure, and heart rate. In contrast, SvO_2, which reflects the oxygen supply to the whole body, might be an appropriate indicator of the long-term therapeutic effects of BPA in these patients. Indeed, patients with post-procedural SvO_2 higher than approximately 125% of baseline showed improved renal function in the chronic phase, with 100% specificity, after BPA. These results indicate that a relative increase in SvO_2, by dilatation of as many stenosed pulmonary arteries as possible, is crucial for improving organ function. However, the pre-procedural hemodynamic parameters differed between patients with increased and decreased eGFR, and pre-procedural values, as well as relative change in hemodynamic parameters, both affected eGFR increase after BPA. Further studies with more patients are needed to evaluate the effects of pre-procedural hemodynamic values on changes in eGFR.

Limitations

The current study had several limitations. We were unable to investigate prognosis or other cardiac events because no patients died or were admitted for heart failure after the final BPA. Instead, we chose increased eGFR as the study outcome, because renal function is known to be associated with prognosis in patients with PAH [9]. Furthermore, this was a retrospective single-center study and did not include a control group without BPA. Future long-term and multicenter studies are, therefore, needed to evaluate the clinical significance of increased eGFR on cardiac events, including death and hospitalization.

Targeted medical therapy with the soluble guanylate cyclase stimulator Riociguat is recommended for patients with inoperable CTEPH, according to current guidelines [13, 15]. Therefore, inoperable patients in our cohort were treated with PAH-targeted drugs followed by BPA. Although the policy regarding medication after BPA has not been clarified in the guidelines, PAH-targeted drugs were reduced in patients without symptoms after BPA in this study.

Pre-procedural eGFR was lower in patients with subsequently increased eGFR compared with those with decreased eGFR. We evaluated the effect of increased SvO_2 on the increase in eGFR after BPA independently of eGFR at baseline by comparing the relative increases in SvO_2 from baseline to after the final BPA between patients with increased and decreased eGFR separately in patients with lower ($n = 23$) and higher pre-procedural eGFR ($n = 22$). Although there was no significant difference, the average relative increase in SvO_2 was higher in patients with increased eGFR compared with those with decreased eGFR among both pre-procedural eGFR groups (lower pre-procedural eGFR: 102.9% ($n = 4$) vs 118.6% ($n = 19$), $P = 0.366$; higher eGFR group: 98.8% ($n = 12$) vs 107.0% ($n = 10$), $P = 0.050$). However, the statistical validity of these results was limited by the small number of patients in each group, and further studies with more patients are necessary.

Conclusions

The current study demonstrated that BPA improved symptoms, right ventricular function, and hemodynamics in patients with CTEPH up to 1 year after the final procedure. To maintain improvements in renal function in the chronic phase, it is necessary to ensure that BPA produces an adequate increase in SvO_2 during the acute phase in patients with CTEPH.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

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