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ORIGINAL RESEARCH

Predictors of Improvement in Exercise Tolerance After Balloon Pulmonary Angioplasty for Chronic Thromboembolic Pulmonary Hypertension

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BACKGROUND: Balloon pulmonary angioplasty (BPA) improves exercise tolerance and hemodynamic parameters in patients with chronic thromboembolic pulmonary hypertension. However, it is still unclear which patient characteristics contribute to the improvement in exercise tolerance after BPA in chronic thromboembolic pulmonary hypertension.

METHODS AND RESULTS: We retrospectively analyzed 126 patients with chronic thromboembolic pulmonary hypertension (aged 63±14 years; female, 65%) who underwent BPA without concomitant programmed exercise rehabilitation at Keio University between November 2012 and April 2018. Hemodynamic data and 6-minute walk distance (6MWD), as a measure of exercise tolerance, were evaluated before and 1 year after BPA. The clinical characteristics that contributed to improvement in exercise tolerance were elucidated. The 6MWD significantly increased from 372.0 m (256.5–431.3) to 462.0 m (378.8–537.0) 1 year after BPA (P<0.001). The improvement rate in the 6MWD after BPA exhibited a good correlation with age, height, mean pulmonary artery pressure, and 6MWD at baseline (Spearman rank correlation coefficients=−0.28, 0.24, −0.40, and 0.44, respectively). Additional multivariable linear regression analysis revealed that young age, tall height, high mean pulmonary artery pressure, short 6MWD at baseline, and high lung capacity at baseline were significant predictors of the improvement in 6MWD by BPA (standardized partial regression coefficient −0.39, 0.22, 0.19, −0.62, and 0.25, P<0.001, 0.007, 0.011, <0.001, and <0.001, respectively).

CONCLUSIONS: BPA without concomitant programmed exercise rehabilitation significantly improves exercise tolerance. This was particularly true in young patients with high stature, high mean pulmonary artery pressure, short 6MWD, and lung capacity at the time of diagnosis.

Key Words: balloon pulmonary angioplasty ■ chronic thromboembolic pulmonary hypertension ■ exercise tolerance

Patients with chronic thromboembolic pulmonary hypertension (CTEPH) and poorly controlled pulmonary artery pressure (PAP) have a poor prognosis mainly because they are complicated by right heart failure.[1] In addition, CTEPH deteriorates exercise tolerance and excessively reduces the quality of life.[1–3] Decreased exercise capacity is related to several factors, such as the severity of pulmonary hypertension (PH),[3] increased dead-space ventilation due to pulmonary artery obstruction,[4,5] weakened quadriceps strength, and decreased peripheral oxygen use.[6]

Current treatment options for CTEPH include drug therapy,[7–9] pulmonary endarterectomy (PEA),[10,11] and balloon pulmonary angioplasty (BPA).[11,12] BPA is

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CLINICAL PERSPECTIVE

What Is New?

- We identified the clinical characteristics that contribute to improved exercise tolerance after balloon pulmonary angioplasty without concomitant programmed exercise rehabilitation for chronic thromboembolic pulmonary hypertension.
- Young age, tall stature, short 6-minute walk distance, high mean pulmonary artery pressure, and high lung capacity at the time of diagnosis predicted improvement in exercise tolerance after balloon pulmonary angioplasty.

What Are the Clinical Implications?

- To predict the efficacy of balloon pulmonary angioplasty on exercise tolerance, it is necessary to assess physical activity, respiratory function, and severity of pulmonary hypertension before balloon pulmonary angioplasty.

Nonstandard Abbreviations and Acronyms

6MWD	6-minute walk distance
6MWT	6-minute walk test
%VC	lung capacity
BPA	balloon pulmonary angioplasty
CTEPH	chronic thromboembolic pulmonary hypertension
mPAP	mean pulmonary artery pressure
PEA	pulmonary endarterectomy
PH	pulmonary hypertension
RHC	right heart catheterization

conventionally considered when patients with CTEPH are deemed ineligible for PEA.[13] Recently, the efficacy of a sequential hybrid strategy of PEA and BPA was reported.[14] Furthermore, another study reported no significant difference in the long-term survival between operated and nonoperated CTEPH, and a combination approach of PEA and BPA might introduce notable improvements.[15] Although future clinical studies are warranted, growing evidence indicates that BPA has a possible indication not only for those who are not eligible for PEA but also for other patients with CTEPH in combination with PEA or medical therapy. Successful BPA for vascular stenosis or obstruction improved symptoms, pulmonary function, exercise tolerance, and hemodynamic status.[16–19] However, the clinical characteristics that contribute to an improvement in exercise tolerance after BPA are still unclear. Thus, it is worthwhile to elucidate the effect of BPA on exercise tolerance because a higher level of physical fitness may extend healthy life expectancy.

This study aimed to identify patient cohorts that would have a favorable improvement in exercise tolerance (as measured by the 6-minute walk test: 6MWT) by BPA without concomitant programmed exercise rehabilitation. A retrospective analysis was performed on patients with CTEPH who had undergone BPA at a time when exercise training had not been introduced for CTEPH in our institute.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patient Population and Ethics Approval

A total of 145 patients with CTEPH underwent BPA without exercise training between November 2012 and April 2018, and 13 patients were lost to follow-up. Of the remaining 132 patients, 5 were excluded because their 6MWT data were not accessible. In addition, 1 patient who exhibited a mean pulmonary artery pressure (mPAP) of 18 mm Hg was excluded because the criterion of mPAP ≥20 mm Hg was defined as PH.[20] Finally, 126 patients were analyzed (Figure 1).

Written informed consent was obtained from all patients, and the study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and approved by the Ethics Review Subcommittee of the Keio University Research Ethics Committee (Permission no. 20120224).

Study Design

Right heart catheterization (RHC) and the 6MWT were performed in all patients at diagnosis. All patients underwent BPA for CTEPH. Every patient was followed up 1 year after the final BPA session with reexamination of both RHC and 6MWT score. We retrospectively analyzed the data.

Demographic Data and Examinations

Clinical data regarding patients' age, sex, body mass index, home oxygen therapy status, medical history, and medications were collected. The World Health Organization functional classification was used to assess CTEPH symptoms. In addition, pulmonary function tests, such as lung capacity (%VC), forced expiratory volume in 1 sec, and carbon monoxide diffusing capacity, and blood sampling data, such as estimated glomerular filtration rate and BNP (brain natriuretic peptide) levels, were recorded at diagnosis and 1 year after the final BPA session.

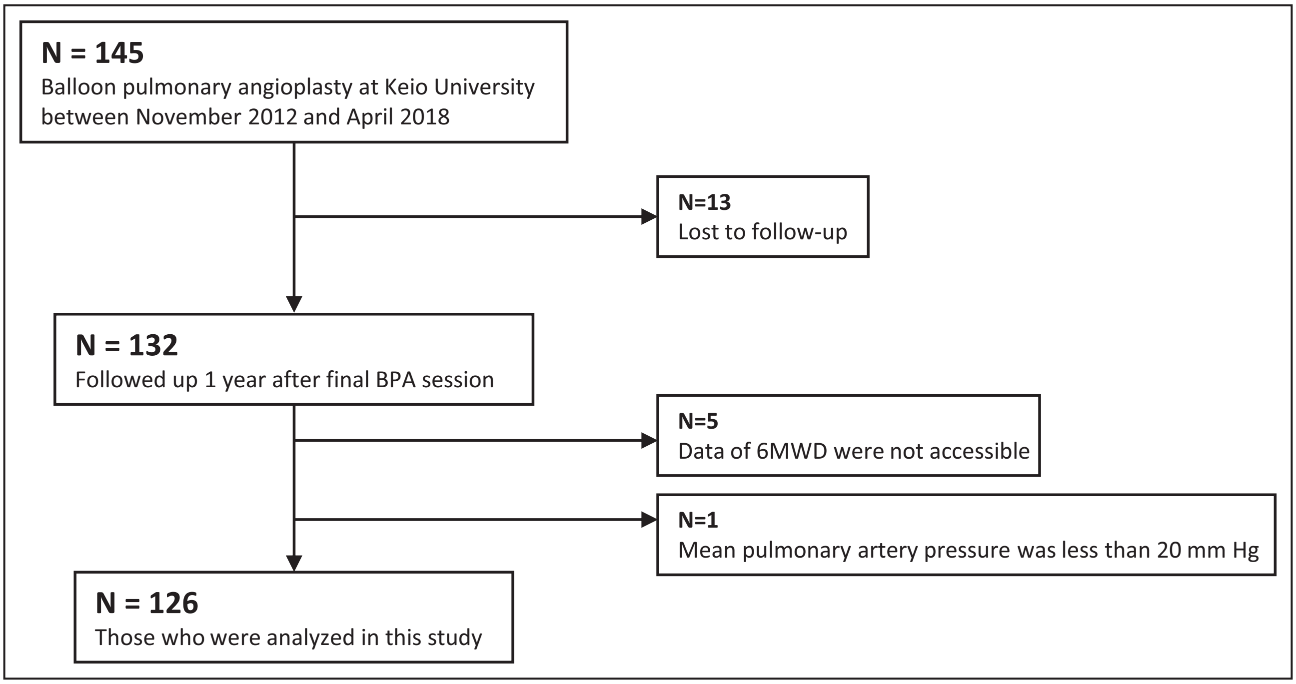

Figure 1. Flow chart of patient selection.
6MWD indicates 6-minute walk distance; and BPA, balloon pulmonary angioplasty.

RHC and BPA

RHC was performed in all patients to assess the right atrial pressure, PAP, pulmonary capillary wedge pressure, cardiac index, pulmonary vascular resistance, and mixed venous oxygen saturation. All RHC procedures were performed under the same conditions, breathing room air, with or without oxygen therapy. BPA was divided into several sessions to prevent complications associated with pulmonary reperfusion injury. The therapeutic goal of BPA is to treat lesions as extensively as possible, in addition to normalizing PAP.

Six-Minute Walking Test

6MWT was conducted in a 30-m corridor with percutaneous oxygen saturation monitoring. At the end of the test, the 6-minute walk distance (6MWD) was recorded.

Statistical Analysis

We evaluated the baseline characteristics, including patient demographics and variables of RHC and 6MWT data at diagnosis and 1 year after the final BPA. Normally distributed continuous variables were presented as mean±SD, whereas nonnormally distributed data were reported as median and interquartile range. Categorical variables were expressed as frequencies and proportions. Comparisons of variables at baseline and 1 year after final BPA were conducted by paired *t*-test or Wilcoxon signed-rank test. We also used the McNemar test to assess the difference in the frequency of home oxygen therapy use before and after BPA. Spearman rank correlation analysis and simple and multivariable linear regression analyses were performed to determine the factors associated with improvement in the 6MWD after BPA. Improvement in 6MWD after BPA was defined as Δ6MWD, that is, post-6MWD minus pre-6MWD. Multivariable linear regression analysis was performed using a stepwise selection method. Age, height, pre-6MWD, mPAP, left ventricular ejection fraction, tricuspid annular plane systolic excursion (TAPSE), cardiac index, %VC, forced expiratory volume in 1 sec, and carbon monoxide diffusing capacity were chosen as independent variables because they were thought to clinically contribute to improvements in exercise tolerance. Coefficients are shown with 95% CIs. All *P* values were 2 sided, with a significance threshold of $P<0.05$. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY).

RESULTS

Patients' Characteristics

The baseline characteristics of the patients are summarized in Table 1. There was no significant difference in patients' characteristics between the 126 enrolled patients and the 13 lost to follow-up (Table S1). The

Table 1. Baseline Characteristics

		N=126
Age, y		63.1±13.6
Sex (female/male)		82/44
Height, cm		159.6±10.1
Body weight, kg		59.1±14.2
Body mass index, kg/m^2		23.0±4.1
World Health Organization functional class (I/II/III/IV)		0/31/88/7
Brain natriuretic peptide, pg/mL		50.3 (24.7–252.1)
Estimated glomerular filtration rate, mL/min per 1.73 m^2		56.0 (47.0–70.0)
Past history of pulmonary endarterectomy, %		8 (6.3%)
Home oxygen therapy, %		73 (57.9%)
Echocardiographic features		
Left ventricular ejection fraction, %		70 (65.2–76.0)
Early mitral inflow velocity/mitral annular early diastolic velocity		7.4 (6.2–9.4)
Tricuspid annular plane systolic excursion, mm		18.5 (16.0–21.0)
Tricuspid valve annulus-s’, cm/sec		11.1 (9.7–12.6)
Medications		
Vasodilators, %		83 (65.9%)
Vasodilators	Soluble guanylate cyclase stimulator (%)	22 (17.5%)
	Phosphodiesterase type 5 inhibitor (%)	51 (40.5%)
	Prostaglandin I2 analog (%)	36 (28.6%)
	Endothelin receptor antagonist (%)	41 (32.5%)
Diuretics, %		81 (64.3%)

mean age was 63.1±13.6 years, and 82 (65%) of the 126 patients were female. All patients had class II or higher symptoms, according to the World Health Organization functional classification, at the time of diagnosis. Eight (6.3%) patients had undergone PEA in the past and still presented with PH. Moreover, 73 (57.9%) patients received home-based oxygen therapy. Echocardiography revealed that the median left ventricular ejection fraction was 70% (65.2%–76.0%), which was well preserved. Right ventricular function was assessed by TAPSE and tricuspid valve annulus-s’. The median TAPSE and tricuspid valve annulus-s’ values in this CTEPH cohort were 18.5 mm (16.0–21.0) and 11.1 cm/sec (9.7–12.6), respectively, which were slightly lower than those in the normal group. Vasodilators, such as soluble guanylate cyclase stimulator, phosphodiesterase type 5 inhibitor, prostaglandin I2 analog, endothelin receptor antagonist, and diuretics were used for some patients at baseline (17.5%, 40.5%, 28.6%, 32.5%, and 64.3%, respectively). New drugs or increased dosages of drugs were introduced in 13 patients within a month before BPA (Table S2).

Efficacy of BPA

In our cohort, mPAP significantly decreased from 35.0 mm Hg (29.0–45.0) to 20.0 mm Hg (17.0–23.0) after BPA (P<0.001), as well as the pulmonary vascular resistance from 523.0 to 238.0 dyne·sec·cm^{-5} (P<0.001). BPA also improved the mixed venous oxygen saturation and cardiac output. These aggressive BPAs significantly improved 6MWD from 372.0 (256.5–431.3) to 462.0 m (378.8–537.0) (P<0.001, Table 2, Figure 2A) without combined exercise training. The World Health Organization functional classification was ameliorated, and the use of home oxygen therapy also decreased (P<0.001, Figure 2B and 2C). The %VC and carbon monoxide diffusing capacity were improved from 94.7% (82.6%–102.8%) to 99.9% (88.5%–111.0%) and from 47.8% (38.4%–55.8%) to 51.5% (43.6%–64.0%), respectively (P<0.001), whereas the forced expiratory volume in 1 sec was not affected. Regarding medications, vasodilators and diuretics were used similarly both at baseline and follow-up (Table S3). Among vasodilators, soluble guanylate cyclase stimulator was used more frequently at follow-up than baseline, whereas usage of other types of vasodilators was decreased after BPA.

Predictors of Improved Exercise Tolerance

Improvement in exercise tolerance correlated well with that in hemodynamic status represented by mPAP (Figure 3, Spearman rank correlation coefficient=−0.445). However, the scatterplot showed that some patients exhibited good 6MWD improvement despite the poor improvement of hemodynamics and vice versa. Therefore, we next investigated the relationship between Δ6MWD and patients’ characteristics obtained before the BPA to predict whether patients would exhibit good or poor improvement in exercise tolerance in advance of BPA. Age and pre-6MWD were negatively correlated with Δ6MWD, and their Spearman rank correlation coefficients were −0.28 and −0.40, respectively (Figure 4). On the contrary, height and mPAP correlated positively, with coefficients of 0.24 and 0.44, respectively. We also performed a simple regression analysis to investigate which patient characteristics predicted improvement in 6MWD, with the intention of using them as independent variables in the following multivariable regression analysis (Table S4). Independent variables that showed significant relationships with Δ6MWD were age, height, BNP, pre-6MWD, mean right atrial pressure, mPAP, mixed venous oxygen saturation, pulmonary vascular resistance, and TAPSE. Thirteen patients who experienced a change of either medication within a month before BPA did not achieve significantly better improvement in 6MWD than those whose

Table 2. Comparison of Each Parameter Between Pre- and Post-Balloon Pulmonary Angioplasty

	Pre-BPA	Post-BPA	Amount of change	*P* value
6-minute walk distance, m	372.0 (256.5 to 431.3)	462.0 (378.8 to 537.0)	84.5 (23.3 to 173.8)	<0.001*
World Health Organization functional class (I/II/III/IV)	0/31/88/7	62/64/0/0		<0.001*
Home oxygen therapy, %	73 (57.9%)	9 (7.1%)		<0.001*
Forced expiratory volume in 1 sec	70.8±9.0	70.7±8.1	−1.6±5.0	0.723
Lung capacity	93.2±14.8	99.0±15.3	5.8±6.8	<0.001*
Carbon monoxide diffusing capacity	48.1±13.0	53.0±14.7	5.0±9.6	<0.001*
Brain natriuretic peptide, pg/mL	50.3 (24.7 to 252.1)	27.1 (13.0 to 52.0)	−16.0 (−178.3 to 3.8)	<0.001*
Mean right atrial pressure, mm Hg	6.0 (4.0 to 9.0)	2.5 (1.0 to.0)	−3.0 (−5.5 to −0.50)	<0.001*
Mean pulmonary artery pressure, mm Hg	35.0 (29.0 to 45.0)	20.0 (17.0 to 23.0)	−17.0 (−23.0 to −9.0)	<0.001*
Mean pulmonary capillary wedge pressure, mm Hg	8.0 (6.0 to 11.0)	7.0 (5.0 to 10.0)	0.0 (−3.0 to 2.0)	0.194
Mixed venous oxygen saturation, %	64.2 (57.3 to 69.7)	70.2 (66.5 to 74.1)	6.2 (1.1 to 11.2)	<0.001*
Percutaneous oxygen saturation, %	90.4 (87.5 to 93.3)	94.9 (93.1 to 96.4)	4.0 (−0.20 to 7.4)	<0.001*
Cardiac output, L/min	3.6 (2.9 to 4.6)	4.1 (3.3 to 4.8)	0.26 (−0.30 to 1.2)	<0.001*
Cardiac index, L/min·m^2	2.2 (1.9 to 2.8)	2.4 (2.1 to 2.9)	0.16 (−0.19 to 0.73)	0.001*
Pulmonary vascular resistance, dyne·sec·cm^{-5}	523.0 (388.4 to 953.1)	238.0 (175.8 to 303.3)	−309.7 (−707.8 to −114.8)	<0.001*

BPA indicates balloon pulmonary angioplasty.
*If <0.05.

medications were not changed (*P*=0.232). Further assessment was performed using multivariable stepwise regression analysis, which revealed that age, height, pre-6MWD, mPAP, and %VC were significant predictors of improvement in 6MWD in patients with CTEPH who underwent BPA (standardized partial regression coefficient. −0.39, 0.22, −0.62, 0.19, and 0.25, respectively, Table 3). This analysis suggests that patients' physical status, hemodynamic parameters, and respiratory function at the time of diagnosis are key to predicting improvement in exercise tolerance in patients with CTEPH who are candidates for BPA.

DISCUSSION

In this retrospective study, among 126 patients with CTEPH who underwent BPA without exercise training, we found that age, height, 6MWD, mPAP, and %VC at the time of diagnosis predicted improvement in exercise tolerance from before to after BPA. Although previous studies have reported that BPA for CTEPH significantly improved the 6MWD,[18,19,21,22] it remains unclear, especially in those who could not benefit from BPA. We identified the characteristics of patients that predicted the improvement rate of 6MWD, which in turn revealed the patient cohorts that should be recommended for additional exercise training to improve exercise tolerance.

BPA Significantly Improved Hemodynamic Status and 6MWD

To investigate the effect of BPA on exercise tolerance, we retrospectively analyzed patients with CTEPH who underwent BPA at a time when concomitant programmed exercise rehabilitation had not been introduced in our hospital. BPA ameliorated mPAP from 35 mm Hg to 20 mm Hg and 6MWD from 372 m to 462 m, which exceeded the low-risk category criteria of 6MWD (440 m) in the European Society of Cardiology and European Respiratory Society guideline.[23] A study reported that extensive revascularization by BPA significantly improved hemodynamic parameters, symptoms, and exercise tolerance for those who had already achieved <25 mm Hg of mPAP by initial BPA but had residual stenoses.[24] Another study demonstrated the efficacy of extensive BPA in improving exercise tolerance and quality of life.[25] Similarly, our data suggested that aggressive treatment by BPA targeted lesions extensively as possible, resulting in the median mPAP of 20 mm Hg after BPA and improved exercise tolerance despite the

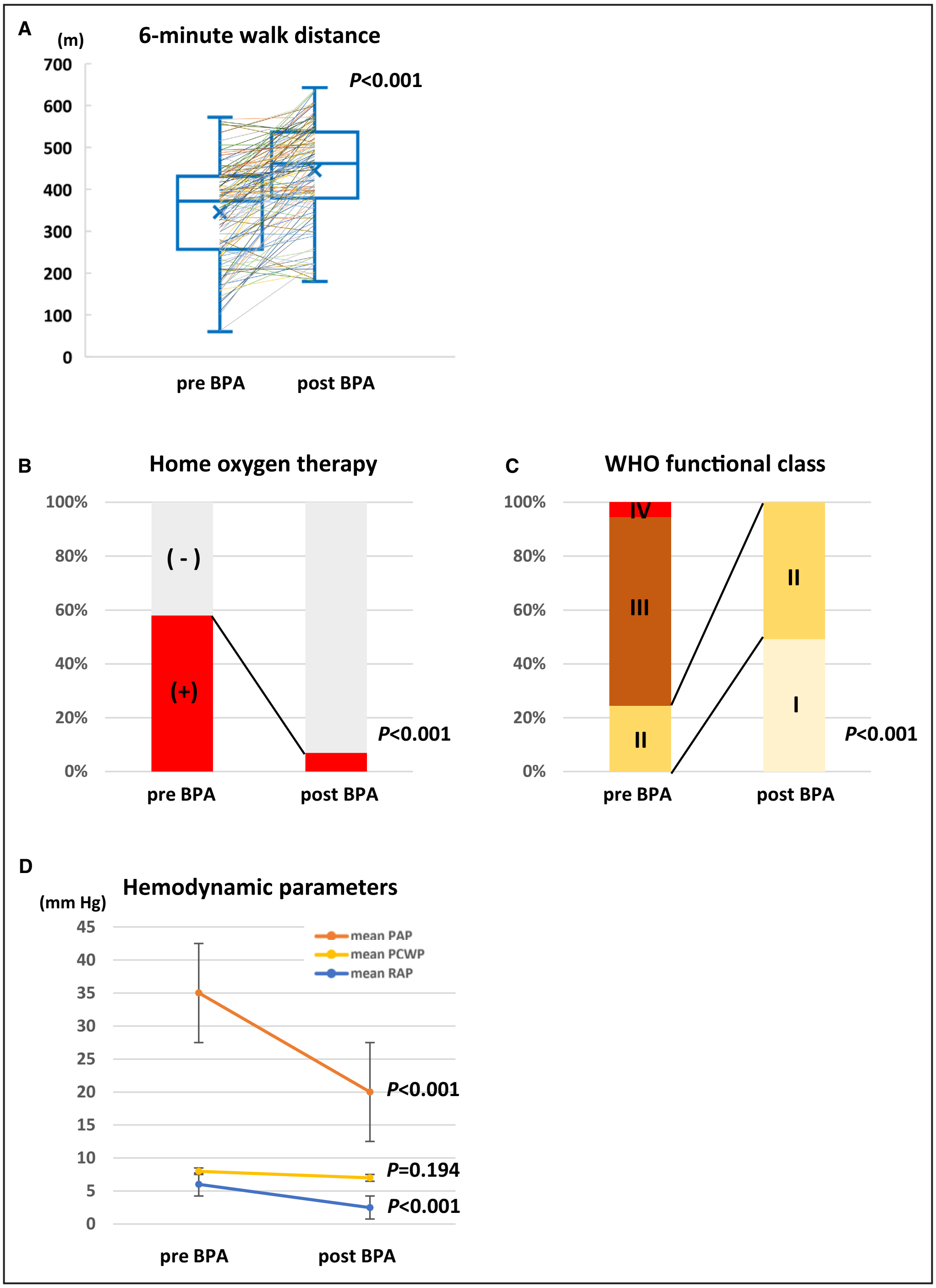

Figure 2. Improvement after balloon pulmonary angioplasty in (A) 6-minute walk distance, (B) use of home oxygen therapy, (C) WHO functional class, and (D) hemodynamic parameters.
McNemar test for (**C**) and Wilcoxon signed-rank test for others, were used. BPA indicates balloon pulmonary angioplasty; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; and WHO, World Health Organization.

lack of a combined exercise program. Vasodilators and diuretics were used similarly both at baseline and follow-up. Soluble guanylate cyclase stimulator was the drug used more frequently after BPA. This might be because it was the only drug approved for the treatment of CTEPH in Japan in 2014 based on a randomized controlled trial.[26] Although the use of soluble guanylate cyclase stimulator increased, the use of total vasodilators was similar before and after BPA, which might have minimal influence on the

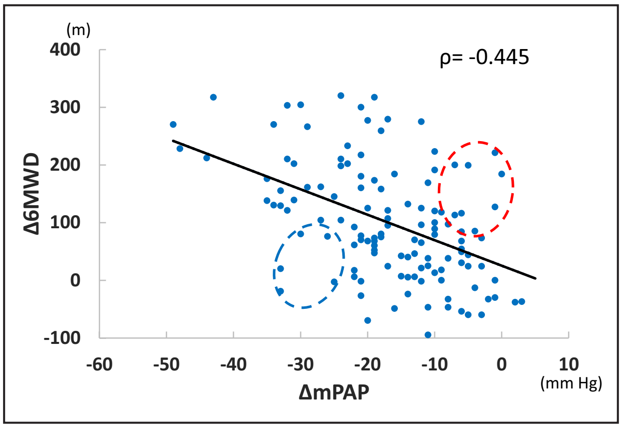

Figure 3. Scatterplot of Δ6MWD and ΔmPAP.
The red dotted circle indicates those who exhibit good improvement in Δ6MWD despite poor improvement in ΔmPAP, and the blue dotted circle, vice versa. 6MWD indicates 6-minute walk distance; mPAP, mean pulmonary artery pressure; Δ6MWD, post-6MWD minus pre-6MWD; ΔmPAP, post-mPAP minus pre-mPAP; and ρ, Spearman rank correlation coefficient.

investigation of improvement of exercise tolerance. However, further analysis matched for the use of each medication is warranted to evaluate the efficacy of BPA on exercise tolerance.

Age, Height, 6MWD, mPAP, and %VC at Baseline Were Associated With Amelioration of the 6MWD

There was a good correlation between Δ6MWD and ΔmPAP, suggesting that amelioration of exercise tolerance may be influenced by hemodynamics. However, some cases exhibited good 6MWD improvement despite the poor improvement of hemodynamics and vice versa. This implied that improvement of exercise tolerance was regulated not only by hemodynamic improvements but also by other factors. Correlation and simple regression analyses revealed that patient characteristics before BPA were associated with improvement in 6MWD after BPA without an exercise program. Multivariable regression analysis was performed with 10 independent variables that were thought to clinically contribute to improvements in exercise tolerance: age; height; 6MWD at baseline; mPAP at baseline; left ventricular ejection fraction, TAPSE, and cardiac index as left or right ventricular function parameters; and %VC, forced expiratory volume in 1 sec, and carbon monoxide diffusing capacity as pulmonary function parameters. The results revealed that age, height, 6MWD, mPAP, and %VC at baseline predicted good improvement in 6MWD after BPA. Taller patients might have

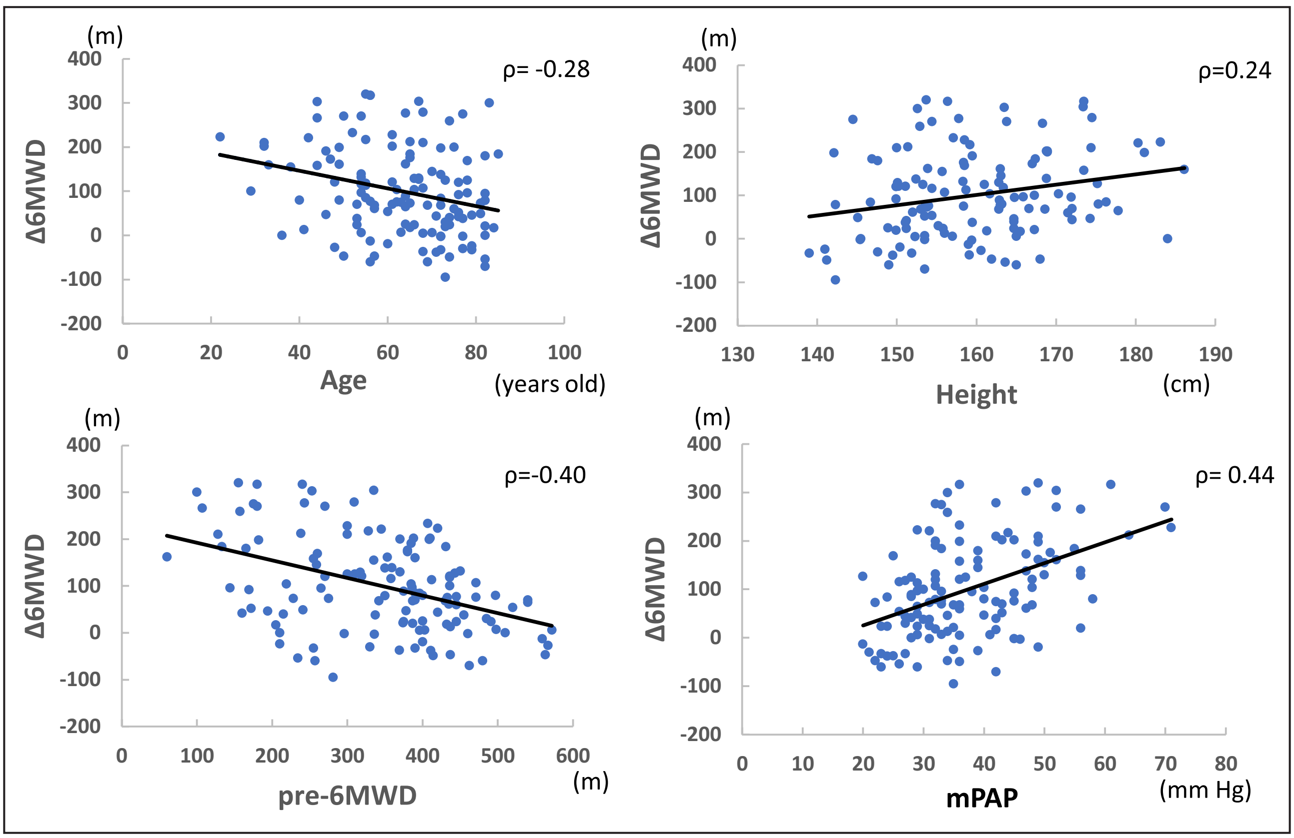

Figure 4. Scatter plot of Δ6MWD and age, height, pre-6MWD, and mPAP.
6MWD indicates 6-minute walk distance; mPAP, mean pulmonary artery pressure; and ρ, Spearman rank correlation coefficient.

Table 3. Results of the Multivariable Linear Regression Analysis

	Coeff. (95% CI)	Standardized partial regression coefficient	*P* value
Age	−2.8 (−4.0 to −1.5)	−0.39	<0.001*
Height	2.1 (0.58 to 3.6)	0.22	0.007*
pre-6MWD	−0.54 (−0.68 to −0.40)	−0.62	<0.001*
Left ventricular ejection fraction	…	…	…
Tricuspid annular plane systolic excursion	…	…	…
Mean pulmonary artery pressure	1.8 (0.4 to 3.2)	0.19	0.011*
Cardiac index	…	…	…
Forced expiratory volume in 1 sec	…	…	…
Lung capacity	1.6 (0.70 to 2.6)	0.25	<0.001*
Carbon monoxide diffusing capacity	…	…	…

Dependent variable: Δ6MWD, defined as post-6MWD minus pre-6MWD. A stepwise selection method was used with the independent variables listed above. 6MWD indicates 6-minute walk distance.

*If <0.05.

longer steps, resulting in greater improvement in the 6MWD. In addition, the 6MWD and mPAP at baseline represented the severity of CTEPH at the time of diagnosis. Therefore, patients with more severe illnesses showed greater benefits from treatment. Younger patients exhibited better improvement in the 6MWD after BPA. A possible explanation was that they were physically more active and had better preserved skeletal muscle function than older adults. Interestingly, in the multiple regression analysis, the Δ6MWD was greater in patients with higher baseline lung capacity (%VC). In this model, mPAP was simultaneously included as an independent variable, suggesting that in patients with higher mPAP, that is, the more severe hemodynamic PH, the more preserved the lung capacity, the better the exercise tolerance could be expected after BPA. Conversely, in patients with reduced lung capacity, a combination of respiratory rehabilitation may contribute to an improvement in exercise tolerance.

In a prospective randomized controlled trial, exercise training improved peak oxygen consumption and hemodynamics in patients with severe PH and inoperable CTEPH.[27] In a randomized controlled trial that enrolled patients with CTEPH or pulmonary arterial hypertension, exercise training in addition to medical therapy was reported to achieve better improvement of 6MWD than medical therapy alone.[28] Cardiac rehabilitation combined with BPA has been reported to further ameliorate exercise capacity.[29] Therefore, the current European Society of Cardiology and European Respiratory Society statement on CTEPH mentions that a low-dose rehabilitation program after PEA or BPA might be considered the standard of care.[30] A recent study reported that pulmonary vascular intervention increased oxygen delivery but had no effect on peripheral oxygen uptake.[31] In this study, some patients have a poor improvement in exercise tolerance despite hemodynamic amelioration, which implies that the other intervention is the key to improve exercise tolerance. We have also identified the patients' characteristics that predict improvement in exercise tolerance after BPA for CTEPH, and our findings suggest that exercise and pulmonary rehabilitation may provide them with better outcomes regarding exercise tolerance. In particular, the improvement in exercise tolerance was less effective in older patients, whose peripheral skeletal muscle function was suggested to be impaired, indicating that in addition to improving hemodynamics with BPA, maintaining and improving peripheral skeletal muscle function are essential for improving exercise tolerance. Further discussion is pivotal to confirm the clinical impact of rehabilitation on such patients and the timing of the introduction of exercise or pulmonary rehabilitation.

This study had several limitations. First, because of the observational study design, we cannot deny the influence of selection bias and unmeasured confounders on the effect of exercise tolerance, such as depression, frailty, and economic status, which might explain the improvement in exercise tolerance in some patients. In particular, parameters that represent skeletal muscle strength should have been included because it plays an important role in assessing exercise tolerance. Second, this study included a relatively small number of patients. Further randomized studies with larger sample sizes are required to overcome these limitations. Third, 6MWD was analyzed as an index of exercise capacity. It has been reported to be influenced by sex, age, height, body weight, corridor length, and motivation.[32,33] Therefore, these might have become confounding factors. In this respect, cardiopulmonary exercise testing may be a better method to assess exercise tolerance. Finally, we retrospectively analyzed data from a single department in Japan. Therefore, the interpretation of this result may be context dependent, and the exact accuracy of the prediction model remains to be further investigated by multicenter prospective studies.

CONCLUSIONS

In conclusion, our data suggest that young age, tall stature, short 6MWD, high mPAP, and high %VC at the time of diagnosis can predict improvement in exercise tolerance after BPA for CTEPH. To predict the efficacy of BPA on exercise tolerance, it is necessary to assess physical activity, respiratory function, and severity of PH before BPA.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Table S1–S4

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SUPPLEMENTAL MATERIAL

Table S1. Comparison of analysis cohort (N=126) and lost to follow-up cohort (N=13).

	Analysis cohort (N=126)	Lost to follow-up (N=13)	*P* value
Age, years	63.1 ± 13.6	63.6 ± 19.0	0.901
Height, cm	159.6 ± 10.1	159.0 ± 12.1	0.834
pre-6MWD, m	372.0 (256.5 – 431.3)	367.5 (268.8 – 412.3)	0.889
Mean PAP, mmHg	35.0 (29.0 – 45.0)	36 (27.5 – 46.0)	0.962
CI, L/min・m^2	2.2 (1.9 – 2.8)	2.3 (2.2 – 2.6)	0.175
FEV1%	70.8 ± 9.0	66.4 ± 8.5	0.137
%VC	93.2 ± 14.8	92.1 ± 11.7	0.810
%DLco	48.1 ± 13.0	52.7 ± 14.3	0.278

6MWD, 6-minute walk distance; PAP, pulmonary artery pressure; CI, cardiac index; FEV1%, forced expiratory volume in one second; %VC, lung capacity; % DLco, carbon monoxide diffusing capacity.

Table S2. Newly introduced or dosage-increased medications within a month before BPA.

	Medications	Baseline	Newly introduced or dosage increased
	Vasodilators (%)	83 (65.9%)	11 (8.7%)
Vasodilators	Soluble guanylate cyclase stimulator (%)	22 (17.5%)	5 (4.0%)
Vasodilators	Phosphodiesterase type 5 inhibitor (%)	51 (40.5%)	4 (3.2%)
Vasodilators	Prostaglandin I2 analog (%)	36 (28.6%)	1 (0.8%)
Vasodilators	Endothelin receptor antagonist (%)	41 (32.5%)	1 (0.8%)
	Diuretics (%)	81 (64.3%)	4 (3.2%)

Table S3. Comparison of medication use between baseline and follow-up.

		Baseline	Follow-up
Vasodilators (%)		83 (65.9%)	84 (66.7%)
Vasodilators	Soluble guanylate cyclase stimulator (%)	22 (17.5%)	61 (48.4%)
	Phosphodiesterase type 5 inhibitor (%)	51 (40.5%)	21 (16.7%)
	Prostaglandin I2 analog (%)	36 (28.6%)	1 (0.8%)
	Endothelin receptor antagonist (%)	41 (32.5%)	17 (13.5%)
Diuretics (%)		81 (64.3%)	88 (69.8%)

Table S4. Results of the simple linear regression analysis.

	Coeff. (95%CI)	*P* value
Age	-2.0 (-3.3, -0.75)	0.002*
Height	2.4 (0.65, 4.1)	0.007*
BMI	1.5 (-2.9, 5.8)	0.503
BNP	0.061 (0.019, 0.104)	0.005*
Pre-6MWD	-0.38 (-5.2, -2.4)	<0.001*
FEV1%	0.61 (-1.4, 2.6)	0.547
%VC	0.026 (-1.2, 1.2)	0.967
%DLco	0.084 (-1.3, 1.5)	0.904
Mean RAP	10.4 (5.7, 15.1)	<0.001*
Mean PAP	4.3 (2.8, 5.8)	<0.001*
Mean PCWP	6.0 (0.003, 11.9)	0.050
SvO_2	-2.0 (-4.0, -0.014)	0.048*
SpO_2	-1.5 (-5.7, 2.7)	0.488
CO	-5.5 (-18.7, 7.6)	0.406
CI	-23.1 (-46.9, 0.57)	0.056
PVR	0.045 (0.017, 0.074)	0.002*
LVEF	-0.061 (-2.7, 1.3)	0.500

E/e’	-0.085 (-8.8, 3.2)	0.355
TAPSE	-4.6 (-9.0, -0.2)	0.041*
RV-s’	-4.4 (-11.9, 3.1)	0.251

Dependent variable: Δ6MWD, defined as post-6 MWD minus pre-6 MWD. BMI, body mass index; BNP, brain natriuretic peptide; 6 MWD, 6-minute walk distance; FEV1%, forced expiratory volume in one second, %VC, lung capacity; %DLco, carbon monoxide diffusing capacity; RAP, right atrial pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; SvO_2, mixed venous oxygen saturation; SpO_2, percutaneous oxygen saturation; CO, cardiac output; CI, cardiac index; PVR, pulmonary vascular resistance; LVEF, left ventricular ejection fraction; E/e’, early mitral inflow velocity / mitral annular early diastolic velocity; TAPSE, tricuspid annular plane systolic excursion; RV-s’, tricuspid valve annulus - s’.