







ORIGINAL RESEARCH

# EmPHasis-10 Health-Related Quality of Life and Exercise Capacity in Chronic Thromboembolic Pulmonary Hypertension After Balloon Angioplasty

Hayato Sakamoto , PT; Ayumi Goda , MD, PhD; Kazuki Tobita, PT, PhD; Kaori Takeuchi , MD; Hanako Kikuchi, MD; Takumi Inami, MD, PhD; Yuichi Tamura , MD, PhD; Takashi Kohno, MD, PhD; Shin Yamada, MD, PhD; Kyoko Soejima , MD, PhD; Toru Satoh , MD, PhD

**BACKGROUND:** Whether pulmonary hemodynamic parameters and functional capacity are associated with quality of life in patients with chronic thromboembolic pulmonary hypertension remains unknown. This study aimed to evaluate disease-specific quality of life using the emPHasis-10 questionnaire and assess its determinants in patients with chronic thromboembolic pulmonary hypertension with normalized pulmonary hemodynamics.

**METHODS AND RESULTS:** This cross-sectional study included 187 health status assessments of 143 patients with chronic thromboembolic pulmonary hypertension (median age, 68 [58–75] years; men/women, 51/136; use of home oxygen therapy, 51 patients [27%]) after balloon pulmonary angioplasty with normalized mean pulmonary artery pressure <25 mmHg at rest. Right heart catheterization was performed, followed by assessment of 6-minute walk distance and the emPHasis-10 questionnaire. The median pulmonary artery pressure and pulmonary vascular resistance were 18 (15–21) mmHg and 2.2 (1.7–2.9) wood units, respectively. The median emPHasis-10 score was 14 (8–24), whereas the median 6-minute walk distance was 447 (385–517) m. Univariate linear regression analysis showed that the emPHasis-10 score was associated with 6-minute walk distance ( $\beta=-0.476$  [95% CI  $-0.604, -0.348$ ],  $P<0.001$ ) and home oxygen therapy ( $\beta=0.214$  [95% CI, 0.072, 0.356],  $P=0.003$ ) but not with hemodynamic parameters. Multiple regression analysis revealed that a higher emPHasis-10 score was associated with lower 6-minute walk distance ( $\beta=-0.475$  [95% CI,  $-0.631$  to  $-0.319$ ],  $P<0.001$ ).

**CONCLUSIONS:** Health-related quality of life was associated with exercise capacity and the use of home oxygen therapy, but not with hemodynamic parameters, in patients with chronic thromboembolic pulmonary hypertension and normalized hemodynamics after balloon pulmonary angioplasty. Improvements in exercise capacity may lead to further improvements in quality of life.

**Key Words:** angioplasty ■ exercise tolerance ■ hemodynamics ■ hypertension ■ pulmonary ■ pulmonary artery ■ quality of life

**C**hronic thromboembolic pulmonary hypertension (CTEPH) is an important cause of pulmonary hypertension (PH) and is associated with significant morbidity and mortality. Its main clinical manifestations include exertional dyspnea, accompanied by a marked

reduction in exercise capacity and quality of life (QOL).<sup>1–4</sup> While pulmonary endarterectomy (PEA) has traditionally served as the primary treatment for patients with CTEPH, therapeutic options have expanded with the development of balloon pulmonary angioplasty (BPA),

Correspondence to: Ayumi Goda, MD, PhD, Department of Cardiovascular Medicine, Kyorin University Hospital, 6-20-2 Shinkawa, Mitaka, Tokyo 181-8611, Japan. Email: [ayumix34@yahoo.co.jp](mailto:ayumix34@yahoo.co.jp)

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## CLINICAL PERSPECTIVE

### What Is New?

- The quality of life (QOL), as measured by emPHasis-10 scores, a unidimensional, disease-specific, patient-reported outcome assessment of QOL, remained impaired in patients with chronic thromboembolic pulmonary hypertension with normalized hemodynamics (mean pulmonary artery pressure <25 mmHg at rest) after balloon pulmonary angioplasty.
- The QOL score was associated with the 6-minute walk distance and the administration of home oxygen therapy, but not with hemodynamic parameters.

### What Are the Clinical Implications?

- Exercise capacity and the use of home oxygen therapy play important roles in QOL among patients with chronic thromboembolic pulmonary hypertension and normalized hemodynamics.
- Improvements in exercise capacity may lead to further improvements in QOL.

## Nonstandard Abbreviations and Acronyms

<b>BPA</b>	balloon pulmonary angioplasty
<b>CO</b>	cardiac output
<b>CTEPH</b>	chronic thromboembolic pulmonary hypertension
<b>HOT</b>	home oxygen therapy
<b>PAH</b>	pulmonary artery hypertension
<b>PAP</b>	pulmonary artery pressure
<b>PAWP</b>	pulmonary artery wedge pressure
<b>PEA</b>	pulmonary endarterectomy
<b>PH</b>	pulmonary hypertension
<b>WHO</b>	World Health Organization

leading to an improvement in prognosis.<sup>5-7</sup> However, even after BPA-mediated normalization of hemodynamics at rest, decrease in exercise capacity and QOL have been reported; hence, improvement in symptoms is considered the next treatment goal in the management of patients with CTEPH.<sup>8,9</sup> Recently, therapeutic decision-making for patients with CTEPH considers not only disease-specific outcomes (eg, improvement in prognosis and relief of PH) but also patient-centered outcomes (eg, improvement in QOL and alleviation of symptom burden).<sup>10</sup> In the 6th World Symposium on PH,<sup>11</sup> disease-specific measures of health-related QOL were highlighted as relevant and important end points in clinical trials. These measures should also be integrated into daily clinical practice for the treatment of CTEPH, as

has been performed for other cardiovascular diseases such as heart failure.<sup>12</sup>

The emPHasis-10 questionnaire is a unidimensional disease-specific patient-reported outcome assessment of QOL in patients with PH,<sup>13</sup> that can be used in both clinical trials and routine care. It consists of 10 questions on the important components of PH such as breathlessness, fatigue, lack of energy, social restrictions, and concerns on the effect of the disease on the patient's family and friends. EmPHasis-10 scores have been correlated with exercise capacity and hemodynamics in the patient population with PH, including those with CTEPH.<sup>14,15</sup> A part of its utility in clinical care stems from its strong association with long-term prognosis. Despite the recent proposal to redefine PH by lowering the mean pulmonary artery pressure (PAP) threshold from 25 to 20 mmHg, it remains unknown whether pulmonary hemodynamic parameters and/or functional capacity are associated with QOL among patients with CTEPH with a mean PAP of <25 mmHg. This represents an important knowledge gap, as these modifiable determinants may be potential targets for interventions aiming to improve QOL among patients with CTEPH treated with BPA.

We recently reported that impaired functional capacity was common in patients with CTEPH with improved hemodynamics after BPA.<sup>8</sup> Furthermore, we found that the 6-minute walk distance (6MWD), a widely used parameter of functional capacity in daily life, was mainly defined by peripheral factors but not pulmonary hemodynamics at rest.<sup>16</sup> In addition, some patients still struggled to wean from home oxygen (O<sub>2</sub>) therapy (HOT), even after hemodynamic normalization; this may have adversely affected QOL. The purpose of this study was to evaluate disease-specific QOL with emPHasis-10 and assess its determinants in patients with CTEPH with normalized pulmonary hemodynamics after BPA.

## METHODS

### Availability of Data and Materials

The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Study Design and Patient Recruitment

This study aimed to evaluate disease-specific QOL with emPHasis-10 and assess its determinants in patients with CTEPH with normalized pulmonary hemodynamics after BPA.

This retrospective study included patients with CTEPH at Kyorin University Hospital who underwent BPA >6 months previously. The inclusion criteria were as follows: Admission for routine follow-up at our hospital between June 2018 and August 2020 and PAP

<25 mm Hg by right heart catheterization. The 6-minute walk test (6MWT), right heart catheterization, and emPHasis-10 QOL assessment were performed at least 6 months after the patients' BPA session.

### Ethics Approval and Consent to Participate

This study was approved by the Committee for Clinical Studies and Ethics of Kyorin University School of Medicine, Tokyo, Japan. Because of the observational nature of the study and the provision of usual care, written informed consent was waived.

### Right Heart Catheterization

Right heart catheterization was performed using a 6-F double-lumen balloon-tipped flow-directed Swan-Ganz catheter (Harmac Medical Products, Inc., Buffalo, NY) via the transjugular approach. Baseline hemodynamic data were recorded; the zero-reference level (midchest) was adjusted at the start of pressure measurement, and the pulmonary artery wedge pressure (PAWP) was obtained as the mean value of the arterial trace during occlusion. Measurements were obtained at the end of a normal expiration, with the patients in the supine position in the resting state, to assess the right chamber, right atrial pressure, PAP (mean PAP, systolic PAP, and diastolic PAP), and PAWP. O<sub>2</sub> saturation in arterial blood in the radial or femoral artery and O<sub>2</sub> saturation in the pulmonary artery were measured. Cardiac output (CO) was determined by the Fick method using the following formula: CO (L/min)=Oxygen consumption (VO<sub>2</sub>)/1.34 hemoglobin×(arterial oxygen saturation–mixed venous oxygen saturation). Pulmonary vascular resistance (PVR) (wood units) was determined via (mean PAP–PAWP)/CO.

### Six-Minute Walk Test

The 6MWT was performed according to the guidelines published by the American Thoracic Society and the European Respiratory Society.<sup>17</sup> Participants were instructed to walk as fast and as far as possible for 6 minutes and to take as many breaks as possible for 6 minutes without O<sub>2</sub> supplementation. Each participant went through the 6MWT in a quiet hospital corridor with a 20-m marked track; chairs were used instead of cones to support turning if needed. The total distance walked was recorded as the 6MWD (to the nearest meter). To ensure adequate risk management, participants were constantly monitored with an ECG and peripheral O<sub>2</sub> saturation was assessed using a finger pulse oximeter. HOT was started when peripheral O<sub>2</sub> saturation was <90% and withdrawn when it did not fall <90% at rest and during exercise after BPA.

### QOL Assessment

The self-administered emPHasis-10 questionnaire was distributed to the patients after the 6MWT. Each patient completed the questionnaire after any queries they had were addressed.

The emPHasis-10 is a PH-specific health-related QOL questionnaire developed through joint research by the University of Manchester and the PH Association UK.<sup>13</sup> EmPHasis-10 consists of 10 items, each scored on a scale of 0 to 5; the total maximum score is 50, with a higher score indicating a poorer health status and QOL. Translation into several languages is currently underway, which will facilitate international comparisons of this QOL metric. The Japanese version was generated via translation, followed by back translation, and validated in a cohort that included patients with CTEPH. The final version was approved by the developers of the original English version and published in 2018.<sup>14</sup>

### Statistical Analysis

Data are presented as median (interquartile range) for continuous variables, whereas categorical variables are presented as absolute counts and percentages (%). The correlation between emPHasis-10 score and functional (6MWD) and hemodynamic parameters (mean right atrial pressure, mean PAP, PAWP, arterial oxygen saturation, mixed venous oxygen saturation, CO, and PVR) were determined using Spearman rank correlation. Univariate linear regression analysis was used to explore the linear correlation between the emPHasis-10 score and functional variables (6MWD), sociodemographic variables (age, sex, and body mass index), use of HOT, and hemodynamic parameters (mean PAP, PAWP, and CO). A multiple regression analysis was then performed to determine the standardized regression coefficients using variables of clinical importance, including age, sex, body mass index, use of HOT, and hemodynamic parameters (mean PAP, PAWP, and CO). A subanalysis was conducted in which patients with and without HOT were compared using the Mann–Whitney *U* test or Chi-square test, as appropriate. Statistical significance was set at *P*<0.05. Data were analyzed using Easy R version 1.41.

## RESULTS

### Patient Characteristics

Patient demographics are presented in [Table 1](#). A total of 187 health status assessments were performed in 143 patients with CTEPH. The median age of the patients was 68 (interquartile range, 58–75) years, and 73% were women. HOT was used in 51 (27%) patients, and the time interval since the last BPA was 26 (11–48) months. Hemodynamic

**Table 1. Baseline Characteristics of the Study Patients**

	187 health status assessments
Age, y	68 (58–75)
Sex (men/women), n	51/136
BMI, kg/m <sup>2</sup>	24.1 (21.5–26.7)
BNP level, pg/mL	17.0 (9.0–34.0)
Hemoglobin level, g/dL	13.2 (12.5–14.1)
HOT, n (%)	51 (27)
Time interval from final BPA, mo	26 (11–48)
Medical treatment	
SGCS, n (%)	43 (23)
Prostacyclin analogue, n (%)	23 (12)
ERA, n (%)	19 (10)
PDE5i, n (%)	16 (9)
Comorbidities	
Dyslipidemia, n (%)	46 (25)
Hypertension, n (%)	45 (24)
Diabetes, n (%)	10 (5)
Atrial fibrillation, n (%)	7 (4)
Hyperuricemia, n (%)	7 (4)
Hemodynamics	
Mean RAP, mmHg	3 (3–5)
Systolic PAP, mmHg	31 (26–35)
Diastolic PAP, mmHg	8 (6–11)
Mean PAP, mmHg	18 (15–21)
PAWP, mmHg	8 (6–9)
SaO <sub>2</sub> , %	94 (93–96)
SvO <sub>2</sub> , %	71 (68–73)
CO, L/min	4.4 (3.5–5.4)
PVR, wood unit	2.2 (1.7–2.9)
6MWD, m	447 (385–517)
emPHasis-10, score	14 (8–24)

Values are presented as median (interquartile range). 6MWD indicates 6-minute walk distance; BMI, body mass index; BNP, B-type natriuretic peptide; BPA, balloon pulmonary angioplasty; CO, cardiac output; ERA, endothelin receptor antagonist; HOT, home oxygen therapy; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PDE5i, phosphodiesterase type V inhibitor; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SaO<sub>2</sub>, arterial oxygen saturation; SGCS, soluble guanylate cyclase stimulator; and SvO<sub>2</sub>, mixed venous oxygen saturation.

parameters were as follows: Mean PAP, 18 (15–21) mmHg; CO, 4.4 (3.5–5.4) L/min; and PVR, 2.2 (1.7–2.9) wood units. The 6MWD was 447 (385–517) m. Soluble guanylate-cyclase stimulator and oral prostacyclin analogue were present in 43 (23%) and 23 (12%) patients, respectively. All patients were taking anticoagulants. The emPHasis-10 total score was 14 (8–24) points, which corresponded to the mid-point between the World Health Organization (WHO) functional Classes I and II reported in previous studies.<sup>13,14</sup> Figure 1 shows the distribution of each of the subitems of the emPHasis-10 as a violin plot. There was no extreme bias among the subitems.

## Relationship Between EmPHasis-10 Total Score and Functional/Hemodynamic Parameters

A significant moderate correlation was found between the emPHasis-10 total score and the 6MWD ( $\rho=-0.454$ ,  $P<0.001$ ). However, no correlations were observed between the emPHasis-10 total score and mean PAP ( $\rho=0.007$ ,  $P=0.929$ ) or PVR ( $\rho=0.080$ ,  $P=0.275$ ) (Figure 2).

## Factors Influencing the EmPHasis-10 Total Score

The items that showed a significant association with the emPHasis-10 total score in the univariate linear regression analysis were age ( $\beta=0.165$  [95% CI, 0.022–0.308],  $P=0.024$ ), use of HOT ( $\beta=0.214$  [95% CI, 0.072–0.356],  $P=0.003$ ), and 6MWD ( $\beta=-0.476$  [95% CI, -0.604 to -0.348],  $P<0.001$ ). There were no significant associations between the emPHasis-10 total score and any medical treatment or comorbidities (Table S1). Multiple linear regression analysis showed a significant association between the emPHasis-10 total score and 6MWD, with a standardized partial regression coefficient of  $\beta=-0.475$  (95% CI, -0.631 to -0.319,  $P<0.001$ ) (Table 2).

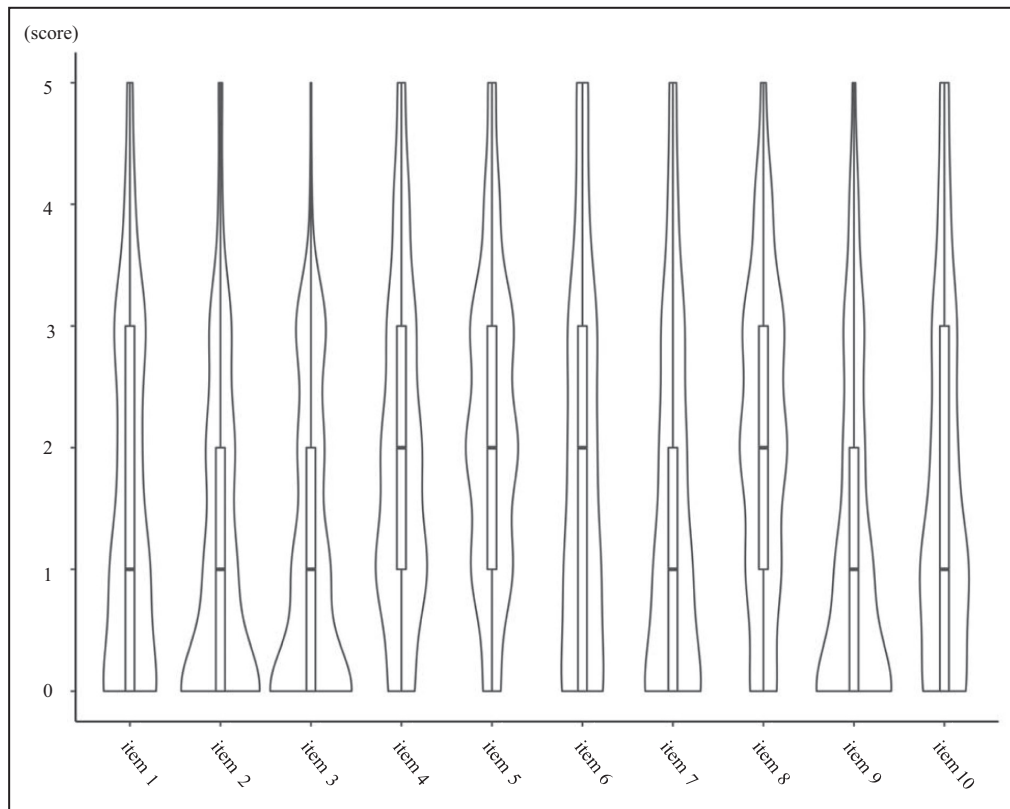
## Comparison Between Patients With and Without HOT

The baseline characteristics of patients with HOT ( $n=51$ ) and without HOT ( $n=136$ ) are shown in Table 3. Patients with HOT had a significantly higher mean PAP and PVR than those without HOT. Figure 3 shows the comparisons using a box plot between patients with and without HOT in the subitems and the total score of the emPHasis-10. EmPHasis-10 total scores were significantly higher in patients with HOT than in those without HOT (18 [9–28] versus 12 [7–21],  $P=0.005$ ). The subitems in items 1, 5, 6, 8, 9, and 10 were significantly higher in patients with HOT. Among the patients with HOT, 6MWD was also significantly associated with emPHasis-10 scores ( $\rho=-0.362$ ,  $P=0.020$ ).

## DISCUSSION

This study showed that QOL, as measured with the disease-specific scale emPHasis-10, remained impaired in patients with CTEPH with normalized hemodynamics (mean PAP <25 mmHg at rest) after BPA. While the QOL score was associated with 6MWD, it was not associated with hemodynamic parameters. The administration of HOT was also associated with impaired QOL. Among patients with HOT, the QOL score was associated with 6MWD.

To our knowledge, this is the first study to examine disease-specific QOL with emPHasis-10 in patients



**Figure 1. Violin plots showing the distribution of emPHasis-10 subitems.**

The shape of the violin is the mirrored frequency distribution of the data. Medians are marked by a black rectangle, the interquartile range is marked with a vertical white bar, and thin black lines denote the lower and upper range. Item 1 (I am not/very frustrated by my breathlessness); Item 2 (Being breathless never/always interrupts my conversations); Item 3 (I do not/always need to rest during the day); Item 4 (I do not/always feel exhausted); Item 5 (I have no/lots energy at all); Item 6 (When I walk up one flight of stairs I am not/very breathless); Item 7 (I am/not confident out in public places/ crowds despite my pulmonary hypertension); Item 8 (Pulmonary hypertension does not/completely control my life); Item 9 (I am independent/completely dependent); Item 10 (I never/always feel like a burden).

with CTEPH after BPA. With the current advances in the treatment, the prognosis of CTEPH has markedly improved. To improve post-treatment QOL has become more important as a goal of treatment.

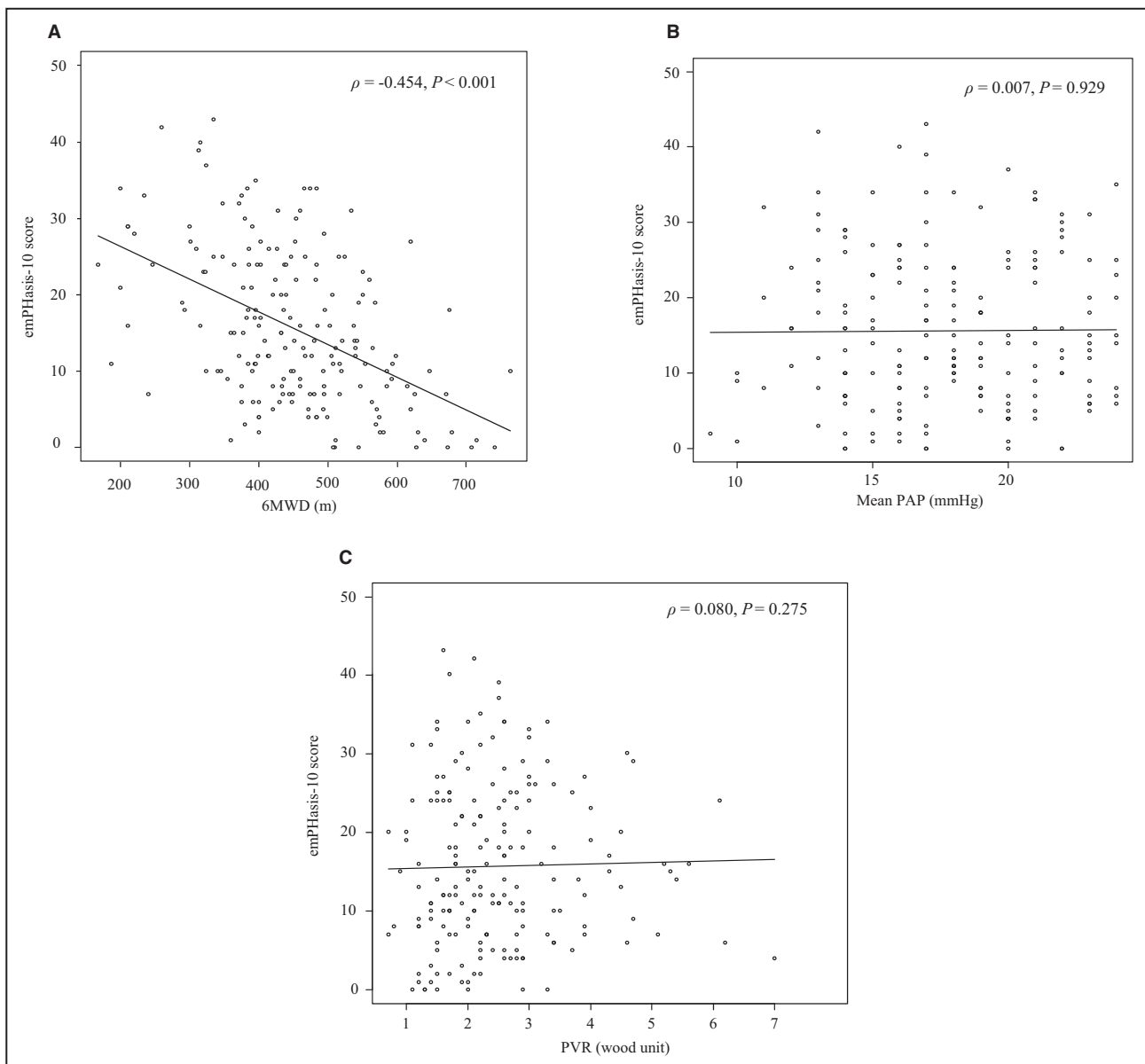
### EmPHasis-10 in Patients With PH

A previous validation study of emPHasis-10, which included patients with CTEPH, was conducted by Takeyasu et al<sup>14</sup> in Japan. The emPHasis-10 total score was  $19.4 \pm 10.6$  points; scores were increased with higher WHO functional classes (I, 5.0; II,  $17.0 \pm 1.4$ ; III,  $24.1 \pm 2.2$ ; and IV,  $39.5 \pm 2.5$ ). These results were consistent with those of the original emPHasis-10 report by Yorke et al,<sup>13</sup> which was based on patients in the United Kingdom and Ireland. The median emPHasis-10 total score was 14 (8–24) points, which corresponded to the midpoint between WHO functional Classes I and II.<sup>13,14</sup> This implied that QOL was not completely equivalent to WHO functional Class I, despite hemodynamic improvement.

Recently, Lewis et al reported that emPHasis-10 was an independent prognostic marker in patients with either idiopathic pulmonary artery hypertension (PAH) or connective tissue disease-associated PAH, thus emphasizing the importance of emPHasis-10 assessment.<sup>18</sup> There are limited reports on emPHasis-10 in patients with CTEPH.<sup>19</sup> While the majority can be treated by surgical and/or catheter interventions that do not apply to other patients with PH, the clinical progression and prognosis of these patients vary. Thus, further studies are needed to clarify the prognostic utility of emPHasis-10 in patients with CTEPH.

### Determinants of QOL in Patients With CTEPH

Studies using generic instruments have reported impaired QOL in patients with CTEPH with a mean PAP  $>25$  mmHg after treatment.<sup>4</sup> Halank et al<sup>20</sup> used the SF-36 questionnaire to assess QOL in patients with severe CTEPH and concluded that mental disorders, exercise



**Figure 2.** Correlations of the emPHasis-10 score with 6-minute walk distance (A), pulmonary artery pressure (B), and pulmonary vascular resistance (C).

6MWD indicates 6-minute walk distance; PAP, pulmonary artery pressure; and PVR, pulmonary vascular resistance.

capacity, long-term HOT, right heart failure, and age played more important roles in the impairment of QOL than hemodynamic parameters at rest. Kamenskaya et al<sup>21</sup> also used the SF-36 questionnaire and reported impaired QOL even after 1 year of PEA. Urushibara et al<sup>22</sup> found that QOL was also impaired after PEA and medical treatment; physical function items were especially associated with PVR and 6MWD. Using the EuroQoL-5 dimensions questionnaire, Minatsuki et al<sup>23</sup> observed impaired QOL after BPA and medical treatment; they also reported a significant correlation with mean PAP and 6MWD.

Generic QOL assessment scales may be unable to assess specific conditions inherent to patients with PH.

Therefore, it is necessary to use disease-specific QOL scales that assess factors directly affected by disease pathology and symptoms.<sup>24</sup> Several observational cohort studies have demonstrated that hemodynamics and exercise capacity are related to disease-specific QOL in patients with moderate-to-severe PH. In the original report, which included patients with varying types and severity of PH, emPHasis-10 was shown to have a moderate correlation with 6MWD.<sup>13</sup> Among patients with severe PH, including those with CTEPH, the emPHasis-10 score was moderately correlated with both 6MWD and mean PAP.<sup>15</sup> Lewis et al<sup>18</sup> reported that the emPHasis-10 score was modestly correlated

**Table 2. Association Between Hemodynamic Variables and Physical Function With emPHasis-10**

	Univariate		Multiple ( $R^2=0.21$ ; $P<0.001$ )	
	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value
Age	0.165 (0.022, 0.308)	0.024	0.010 (-0.141, 0.162)	0.892
Female sex	0.098 (-0.046, 0.243)	0.181	-0.019 (-0.161, 0.124)	0.796
BMI	0.08 (-0.064, 0.226)	0.271	-0.004 (-0.182, 0.174)	0.962
Use of HOT	0.214 (0.072, 0.356)	0.003	0.088 (-0.056, 0.231)	0.230
Mean PAP	0.024 (-0.121, 0.169)	0.745	-0.118 (-0.281, 0.046)	0.156
PAWP	-0.044 (-0.189, 0.101)	0.548	0.037 (-0.125, 0.198)	0.653
CO	0.054 (-0.091, 0.199)	0.460	0.062 (-0.117, 0.241)	0.494
6MWD	-0.476 (-0.604, -0.348)	<0.001	-0.475 (-0.631, -0.319)	<0.001

6MWD indicates 6-minute walk distance; BMI, body mass index; CO, cardiac output; HOT, home oxygen therapy; PAP, pulmonary artery pressure; and PAWP, pulmonary artery wedge pressure.

with 6MWD and weakly correlated with pulmonary hemodynamics in a large cohort with severe PAH of various etiologies. In severe PH, QOL is associated with hemodynamics, but it would be meaningful to investigate whether this association is eliminated in near-normal pulmonary hemodynamics. Recently, Borgese et al<sup>25</sup> analyzed 565 patients with PAH and revealed

strong associations of 6MWD and WHO-functional class with the emPHasis-10 score. This finding suggests that the emPHasis-10 score can potentially aid in clinical practice by serving as a quantitative measure of a patient's functional ability; emPHasis-10 implicitly considers their overall perception of the impact PAH has on their life. To our knowledge, the present study is the first to evaluate disease-specific QOL and its determinants among patients with CTEPH with a mean PAP <25 mmHg treated with BPA. Despite normalization of hemodynamics, exercise capacity remains abnormal in two-thirds of patients with CTEPH after PEA.<sup>26</sup> Ruigrok et al<sup>26</sup> demonstrated by multivariate analysis that a lower preoperative transfer factor for carbon monoxide was the only predictor of exercise intolerance after PEA. Additionally, our data showed that peripheral factors were the determinants of exercise intolerance after BPA. More recently, Howden et al<sup>27</sup> reported that patients with CTEPH displayed important dysfunction of peripheral O<sub>2</sub> extraction, as evidenced by reduced skeletal muscle diffusion capacity after PEA or BPA. We demonstrated that the emPHasis-10 score was related to the 6MWD but not to hemodynamic parameters. The reason of no association between QOL and hemodynamics in our cohort might be because of the improvement in subjective symptoms by improved hemodynamics, such as shortness of breath. These findings suggest that exercise capacity plays a more important role in QOL among patients with CTEPH with normalized hemodynamics.

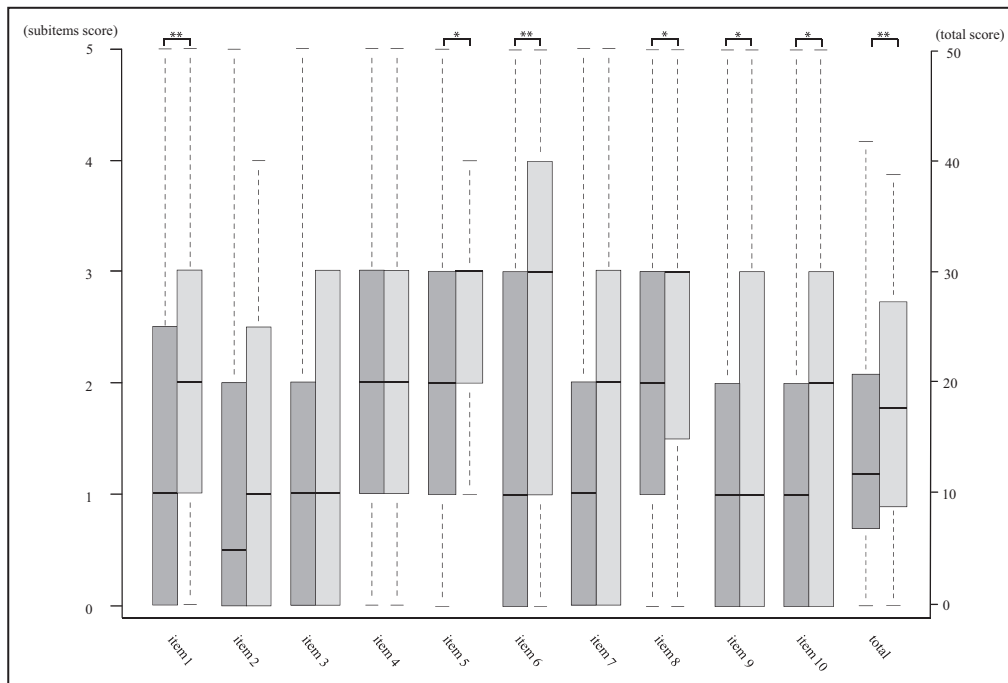
### Improvement in QOL

Exercise training has been reported to improve exercise capacity and QOL in patients with PH. Randomized

**Table 3. Comparison Between Patients With and Without Home Oxygen Therapy**

	Without HOT (n=136)	With HOT (n=51)	P value
Age, y	67 (55–75)	70 (65–77)	<0.001
Sex (men/women), n	40/96	11/40	0.357
BMI, kg/m <sup>2</sup>	24.1 (21.7–26.5)	24.4 (21.5–27.9)	0.761
BNP level, pg/dL	16.0 (8.0–26.0)	27.0 (11.3–51.3)	0.004
Time interval from final BPA, mo	27 (12–48)	24 (11–46)	0.563
Hemodynamics			
Mean PAP, mmHg	17 (14–20)	20 (17–22)	<0.001
PAWP, mmHg	7 (6–9)	8 (6–9)	0.434
SaO <sub>2</sub> , %	95 (93–96)	94 (92–95)	0.066
SvO <sub>2</sub> , %	71 (68–74)	70 (68–73)	0.109
CO, L/min	4.4 (3.5–5.3)	4.4 (3.5–5.4)	0.936
PVR, wood unit	2.2 (1.6–2.8)	2.5 (2.0–3.5)	0.007
6MWD, m	467 (396–545)	400 (340–445)	<0.001
emPHasis-10, score	12 (7–21)	18 (9–28)	0.005

Values are presented as median (interquartile range). 6MWD indicates 6-minute walk distance; BMI, body mass index; BNP, B-type natriuretic peptide; BPA, balloon pulmonary angioplasty; CO, cardiac output; HOT, home oxygen therapy; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; SaO<sub>2</sub>, arterial oxygen saturation; and SvO<sub>2</sub>, mixed venous oxygen saturation.



**Figure 3.** Box plot comparing each emPHasis-10 sub-item in patients with and without home oxygen therapy.

Home oxygen therapy is indicated by light gray bars. The absence of home oxygen therapy is indicated by dark gray bars. \* $P < 0.05$  and \*\* $P < 0.01$ .

controlled trials<sup>28–30</sup> evaluating the efficacy of individually tailored interventions, including exercise therapy and respiratory training, in patients with PH (who were on stable medications) have reported improved exercise capacity, health-related QOL, and cardiopulmonary parameters. A study that prospectively recruited 35 consecutive patients with confirmed invasive and inoperable CTEPH or residual CTEPH<sup>31</sup> found that exercise training was associated with improvements in exercise capacity and QOL. Notably, in a recent prospective cohort study of patients with CTEPH after BPA,<sup>32</sup> exercise training improved QOL and exercise capacity. Based on our data, it is plausible that exercise training can contribute to an improvement in QOL in patients with CTEPH with more normalized hemodynamics; this needs to be evaluated in further studies.

### QOL in Patients With HOT

The use of HOT was associated with impaired QOL. The following emPHasis-10 subitems were found to be significantly lower among patients treated with HOT: Frustration because of shortness of breath, vitality, shortness of breath on stairs, lack of control over life events because of PH, independent living, and burden on family and friends. This was unexpected as HOT prevents the progression of PH and improves hypoxemia.<sup>33,34</sup> However, it is consistent with previous

results reporting that HOT decreases QOL.<sup>20,35</sup> Yorke et al<sup>35</sup> showed that HOT had a significant impact on QOL assessed by emPHasis-10 in various types of PH. Possible factors related to impaired QOL may have included the patients' perceived restrictions on their daily activities, embarrassment about using O<sub>2</sub> with a nasal cannula in public, distress at losing their independence, and worry because of the possibility that their O<sub>2</sub> supply would be completely depleted if they were to leave their house.<sup>36</sup> We need to be cautious about the unnecessary use of HOT in patients with CTEPH with hemodynamic improvement. The use of HOT was associated with impaired hemodynamics, even among patients with a mean PAP <25 mmHg. This highlights the need for further study on whether additional treatment with BPA and/or medication adjustments could facilitate the discontinuation of HOT and lead to further improvement in QOL and physical function.

### Study Limitations

This study has some limitations. Our study adopted a cross-sectional observational design without a control group. While QOL was assessed, we were unable to verify the patients' psychological status, housing circumstances, family support, or other social aspects of their daily lives. The potential influence of these factors should be considered in future studies. The prevalence



of coronary artery disease and chronic obstructive pulmonary disease is lower in Japan and East Asian countries, and hence, our finding of no associations between QOL and comorbidities might have limited generalizability.

## CONCLUSIONS

In patients with CTEPH who underwent BPA with hemodynamic normalization, disease-specific QOL was suboptimal and related to exercise capacity and the use of HOT but not pulmonary hemodynamics.

## ARTICLE INFORMATION

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### Affiliations

Department of Rehabilitation (H.S., K.T., S.Y.) and Department of Cardiovascular Medicine (A.G., K.T., H.K., T.I., T.K., K.S., T.S.), Kyorin University Hospital, Tokyo, Japan; and Pulmonary Hypertension Center, International University of Health and Welfare Mita Hospital, Tokyo, Japan (Y.T.).

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### Disclosures

The authors declare that they have no conflicts of interest.

### Supplemental Material

Table S1

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## **SUPPLEMENTAL MATERIAL**

**Table S1. Association between Medical Treatment/Comorbidities and emPHasis-10**

	Univariate	
	Coefficient (95% CI)	P-value
SGCSs	0.141 (-0.003, 0.284)	0.055
Prostacyclin analogue	0.077 (-0.067, 0.222)	0.292
ERA	0.132 (-0.017, 0.276)	0.072
PDE5i	0.086 (-0.059, 0.230)	0.244
Dyslipidemia	0.006 (-0.139, 0.151)	0.931
Hypertension	0.028 (-0.117, 0.173)	0.702
Diabetes mellitus	0.106 (-0.039, 0.250)	0.150
Atrial fibrillation	-0.123 (-0.267, 0.021)	0.093
Hyperuricemia	0.044 (-0.101, 0.189)	0.551

CI, confidence interval; ERA, endothelin receptor antagonist; PDE5i, phosphodiesterase type V inhibitor; SGCSs, soluble guanylate cyclase stimulator