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# Beneficial effects of riociguat on hemodynamic responses to exercise in CTEPH patients after balloon pulmonary angioplasty – A randomized controlled study

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ABSTRACT

*Background:* Although balloon pulmonary angioplasty (BPA) improves symptoms and pulmonary hemodynamics in patients with chronic thromboembolic pulmonary hypertension (CTEPH), the effects of riociguat on hemodynamics and exercise capacity in patients after BPA remain to be elucidated.

*Methods and Results:* This study was a single-center, prospective, randomized, open-label trial. From November 2015 to November 2018, we prospectively examined 21 patients with CTEPH (65 ± 9 years old, M/F 2/19) who showed hemodynamic improvement with mean pulmonary arterial pressure (mPAP) < 30 mmHg after BPA without any vasodilators. We performed hemodynamic evaluation and expired gas analysis both at rest and during exercise in supine position using cycle ergometer. After right heart catheterization during exercise, they were randomly assigned to 2 groups with minimized method, using age, sex, and resting mPAP; riociguat (N = 10) and control (N = 11) groups. After 6 months, exercise capacity evaluated by 6-min walk distance and cardiopulmonary exercise testing, and resting hemodynamic parameters were comparable in both groups. However, cardiac output (CO) (6.0 ± 1.7–7.4 ± 1.6, P < 0.01) and pulmonary vascular resistance (4.8 ± 1.8–3.2 ± 0.7 Wood units, P = 0.02) at peak workload were significantly improved in the riociguat group as compared with the control group. The slope of linearized mPAP-CO relationship was significantly decreased in the riociguat group [14.5 (7.8, 14.7) to 6.41 (5.1, 11.4), P < 0.01] but not in the control group.

*Conclusions:* These results indicate that riociguat exerts beneficial effects on hemodynamic response to exercise in CTEPH patients even after hemodynamic improvement by BPA.



## 1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by persistent pulmonary arterial obstruction due to organized thrombus and fibrous tissue [1]. Although pulmonary endarterectomy (PEA) is an established surgical therapy for CTEPH patients, approximately 40% of them is inoperable [2], because stenotic lesion is localized in distal of pulmonary arteries. Furthermore, some patients who undergo PEA have persistent or recurrent pulmonary hypertension after the surgery [3]. We have recently reported that balloon pulmonary angioplasty (BPA) improves resting hemodynamics and long-term prognosis in patients with inoperable CTEPH [4]. In CTEPH, riociguat, a soluble guanylate cyclase stimulator, is the only drug indicated for the disorder [5]. The CHEST-1 study revealed that riociguat significantly improves exercise capacity and hemodynamics in patients with inoperable CTEPH and those with persistent or recurrent pulmonary hypertension [5]. Based on these results, the current guidelines on pulmonary hypertension recommended to use riociguat in those patients [6]. Furthermore, it was reported that

*Abbreviations:* BPA, Balloon pulmonary angioplasty; BP, Arterial blood pressure; CI, Cardiac index; CO, cardiac output; CTEPH, Chronic thromboembolic pulmonary hypertension; HR, heart rate; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PAWP, pulmonary arterial wedge pressure; PEA, pulmonary endarterectomy; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVEF, right ventricular ejection fraction; 6MWD, 6-min walk distance.

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combination therapy with BPA and riociguat significantly improves exercise capacity and hemodynamics in CTEPH patients [7]. Thus, riociguat is a key drug for treatment of CTEPH patients, however, it remains to be elucidated whether riociguat is required to maintain hemodynamic improvement by BPA.

In the proceeding of the 6th World Symposium on Pulmonary Hypertension in 2018, exercise right heart catheterization was evaluated as an useful procedure to detect minor pulmonary vascular lesions [8]. In healthy controls, PAP is raised along with increase in CO during exercise, however, exercise causes pulmonary vasodilation to increase pulmonary blood flow, resulting in reduction of pulmonary vascular resistance [9]. Thus, when evaluating hemodynamic response to exercise, mPAP and CO during exercise should be evaluated simultaneously. In this regard, evaluation of mPAP-CO relationship is recommended to examine hemodynamic response to exercise [8]. In a previous study, mPAP-CO relationship was evaluated in CTEPH patients who underwent PEA, in which steeper mPAP-CO slope was associated with exercise intolerance [10]. Furthermore, another study showed that steeper mPAP-CO slope is associated with poorer prognosis in patients with CTEPH or pulmonary arterial hypertension (PAH) [11]. Thus, evaluation of hemodynamic response to exercise is important not only to detect minor pulmonary vascular disorder but also to predict long-term prognosis of patients with pulmonary hypertension (PH).

In this study, we thus performed a randomized controlled study to examine the effects of riociguat on exercise capacity and hemodynamic response to exercise in CTEPH patients who achieved hemodynamic improvement by BPA. For this purpose, we simultaneously measured CO and mPA during exercise and examined the CO-mPA relationship in response to exercise.

## 2. Methods

The protocols of the present study were approved by the institutional review board of the Tohoku University Hospital (No. 2014-2-250). We obtained a written informed consent for participation from all patients. This study protocol was registered to the UMIN Clinical Trial Registry (UMIN000019599).

### *2.1. Study subjects*

This study is a single-center prospective randomized open-label trial. From November 2015 to November 2018, we prospectively enrolled 21 consecutive patients with CTEPH who showed improvements of symptom (WHO functional class I or II) and pulmonary hemodynamics (mPAP < 30 mmHg) after BPA without any vasodilators (Fig. 1). The values of age and mPAP used for randomization were median determined from our cohort including CTEPH patients who completed BPA in our hospital [4]. Our BPA procedures were previously reported in detail [4]. Average number of BPA procedure was 4.9 ± 1.3 times per patient. The patients were randomly assigned into 2 groups with minimization method using age (66 year-old), sex, and resting mPAP (23 mmHg); riociguat (N = 10) and control (N = 11) groups [12,13]. In the riociguat group, the dose was increased in a stepwise manner as much as possible (maximum dose, 7.5 mg per day). In the control group, usual medical therapy including anticoagulation therapy was continued but without any vasodilators. At baseline and 6 months later, we evaluated the effects of riociguat on hemodynamics at rest and hemodynamic response to exercise.

### *2.2. Evaluation of hemodynamic response to exercise by right heart catheterization*

At baseline and follow-up (6 months later), we evaluated the effects of riociguat on hemodynamics at rest and during exercise.

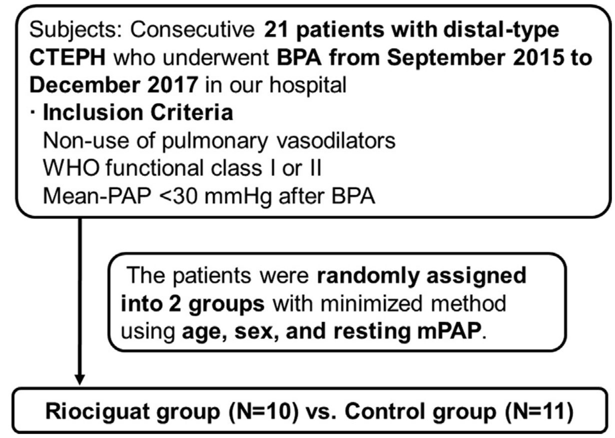


**Fig. 1.** Study flow chart. From September 2015 to November 2018, we prospectively enrolled 21 consecutive patients with chronic thromboembolic pulmonary hypertension (CTEPH) who underwent balloon pulmonary angioplasty (BPA) in our hospital. Inclusion criteria were as follows; (1) WHO functional class I or II, and (2) mean pulmonary arterial pressure (mPAP) < 30 mmHg without any vasodilators. The patients were randomly assigned to 2 groups with minimized method using age, sex, and resting mPAP; riociguat group (N = 10) and control group (N = 11).

We performed hemodynamic evaluation by right heart catheterization and ventilatory gas analysis both at rest and during exercise. Ventilatory gas analysis was performed using an expired gas analyzer (AE-100i; Minato Medical Science, Osaka, Japan) [14]. Swan-Ganz catheter (Edwards Life Science, Irvine, CA, USA) was inserted from the right internal jugular vein and placed in the right pulmonary artery. An arterial line was placed in the right radial artery. Exercise was performed with bicycle ergometer in supine position. Resting hemodynamics was evaluated with feet on bicycle pedals before exercise. Exercise protocol consisted of 1 min of unloaded cycling followed by graded 10-watt increments in workload at 1-min interval until self-reported exhaustion (peak workload) [15,16]. At peak workload, acquisition of all measurements was done within another 1 min at the same workload. In each patient, the same maximum work load was set at follow-up set as in baseline. Before exercise and at peak workload, hemodynamic parameters were measured as follows; PAP, pulmonary arterial wedge pressure (PAWP), right atrial pressure (RAP), arterial blood pressure (BP), heart rate (HR), cardiac output (CO), and pulmonary vascular resistance (PVR). Cardiac output was calculated by direct Fick method using the results of expired gas analysis and arterial/mixed venous blood gas analysis, and was corrected for body surface area (cardiac index, CI). PAWP and RAP were measured at end-expiration, and mPAP was calculated using average systolic and diastolic PAP of consecutive 10 beats. The slope of linearized mPAP-CO relationship was calculated using the 2-point method $[(mPAP_{peak} - mPAP_{rest}) / (CO_{peak} - CO_{rest})]$ [11]. It was previously reported that multipoint acquisition of mPAP and CO showed significant and strong positive linear increment by increase in work load ($r^2$ = 0.92 in PH patients) [17,18].

### *2.3. Evaluation of exercise capacity and right ventricular function*

Exercise capacity was evaluated by peak $VO_2$, VE vs. $VCO_2$ slope obtained from cardio-pulmonary exercise testing and 6-min walk distance (6MWD) [10,19]. These tests to evaluate right ventricular function and exercise capacity were performed within a week after the right heart catheterization with exercise. To evaluate right ventricular systolic function, all patients underwent repeated cardiac magnetic resonance at baseline and 6 months follow-up. Right ventricular function was evaluated using the images derived from cardiac magnetic resonance as previously described [20].

### 2.4. Statistical analysis

Continuous variables are expressed as mean ± SD or median [inter-quartile range (IQR)]. Change in each parameter was compared using paired *t*-test or Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical data, as appropriate. Randomization was performed by a statistician, one of the co-authors [S.M]. A P value of <0.05 was considered to be statistically significant. All analyses were performed using JMP 14 (SAS Institute, Cary, NC, USA) and R 3.3.2 (R Foundation for Statistical Computing, Vienna; http://www.R-project.org/).

## 3. Results

### 3.1. Baseline patient characteristics

Baseline patient characteristics are shown in Table 1. Mean daily dose of riociguat was 4.3 mg. Two of 10 patients in the riociguat group were able to reach the full dose (7.5 mg per daily). There were no adverse events related to riociguat that required its discontinuation. All parameters were comparable between the 2 groups. Mean age was 66 ± 8 and 64 ± 11 years-old in the control and riociguat group, and male prevalence was 9% and 10%, respectively (Table 1). Average period from last BPA session to enrollment in the present study was 22 ± 8 and 27 ± 15 months, respectively (Table 1). In the present study, 90% of the patients received pulmonary vasodilators before completion of the BPA procedures (Table 1). After completion of the BPA procedures, all patients continued anticoagulation therapy with warfarin but did not use any pulmonary vasodilators, and were randomized to control and riociguat groups (Table 1). Average periods from withdrawal of pulmonary vasodilators to enrollment in the present study was 20 ± 7 and 16 ± 8 months in the control and riociguat groups, respectively (Table 1). In both groups, average of mPAP was 25 mmHg at baseline (Table 1). Also, other hemodynamic parameters, including PAWP, PVR, *trans*-pulmonary pressure gradient and CO, were comparable between the 2 groups (Table 1). Furthermore, 6MWD, peak $VO_2$, VE vs. $VCO_2$ slope and right ventricular ejection fraction (RVEF) by cardiac magnetic resonance were comparable between the 2 groups (Table 1). Thus, at baseline, the CTEPH patients had mild pulmonary hypertension, preserved exercise capacity, and normal right ventricular systolic function.

**Table 1**
Baseline patient characteristics.

| Patient characteristics | Control (N = 11) | Riociguat (N = 10) | P value |
|---|---|---|---|
| Age | 66 ± 8 | 64 ± 11 | 0.50 |
| Gender (M/F) | 1/10 (9%) | 1/9 (10%) | 0.15 |
| Final BPA to enrollment (months) | 22 ± 8 | 27 ± 15 | 0.40 |
| Use of pulmonary vasodilators in the course of BPA | 10 (91%) | 9 (90%) | 1.00 |
| Elapsing time from withdrawal of pulmonary vasodilators (months) | 20 ± 7 | 16 ± 8 | 0.29 |
| Anticoagulation therapy | 11/11 (100%) | 10/10 (100%) | 1.00 |
| WHO functional class (I/II) | 7/4 | 5/5 | 0.67 |
| mPAP (mmHg) | 25 ± 4 | 25 ± 5 | 0.94 |
| PAWP (mmHg) | 11 ± 3 | 12 ± 4 | 0.31 |
| CO (L/min) | 4 ± 1 | 3.9 ± 1.1 | 0.75 |
| CI (L/min) | 2.7 ± 0.5 | 2.5 ± 0.6 | 0.45 |
| TPG (mmHg) | 14 ± 4 | 12 ± 3 | 0.27 |
| PVR (Wood units) | 3.8 ± 1.9 | 3 ± 1.3 | 0.23 |
| sBP (mmHg) | 148 ± 16 | 133 ± 19 | 0.08 |
| dBP (mmHg) | 69 ± 6 | 74 ± 17 | 0.31 |
| HR (/min) | 64 ± 8 | 63 ± 6 | 0.84 |
| 6MWD (m) | 527 ± 65 | 589 ± 94 | 0.10 |
| peak $VO_2$ (ml/min/kg) | 14.9 ± 3.3 | 15.9 ± 3 | 0.45 |
| VE vs. $VCO_2$ slope | 37.4 ± 5.2 | 36.2 ± 4.8 | 0.57 |
| RVEF (%) | 58 ± 9 | 57 ± 8 | 0.89 |

Continuous variables are expressed as mean ± SD.
BP, blood pressure; BPA, balloon pulmonary angioplasty; CI, cardiac index; CO, cardiac output; HR, heart rate; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVEF, right ventricular ejection fraction; TPG, *trans*-pulmonary pressure gradient; $VCO_2$, carbon dioxide production; $VO_2$, oxygen uptake; VE, minute ventilation; 6MWD, 6-min walk distance.

### 3.2. Effects of riociguat on resting hemodynamics

In the riociguat group, CO at rest trended to be increased at follow-up compared with the control group (3.9 ± 1.1–4.8 ± 0.8, P = 0.08) (Table 2). In the riociguat group, as compared with the control group, significant decrease in diastolic pressure and increase in heart rate were noted (both P = 0.03) (Table 2). There were no significant changes in other parameters in the 2 groups.

### 3.3. Effects of riociguat on exercise capacity and right ventricular function

At follow-up, no additional improvement of exercise capacity or right ventricular function was noted in both groups (Table 3).

### 3.4. Effects of riociguat on hemodynamics during exercise

In both groups, peak workload was comparable at baseline and follow-up (Table 4). In the riociguat group, one patient discontinued exercise during hemodynamic evaluation due to knee joint pain. Therefore, this patient was excluded from the present analysis on the effects of riociguat on hemodynamic response to exercise. Although mPAP at peak workload tended to decrease in the riociguat group (48 ± 7–44 ± 9 mmHg), the change was statistically insignificant (Table 4). In the riociguat group, CO at peak workload was significantly increased (6.0 ± 1.7–7.4 ± 1.6 L/min), resulting in significant decrease in PVR at peak workload (4.8 ± 1.8–3.2 ± 0.7 Wood units) (Table 4). Also, decrease in $SaO_2$ by exercise was comparable between the 2 groups (Table 4). Fig. 2 shows the change in mPAP-CO slope from baseline to follow-up. At baseline, the slope in the control and riociguat groups was 7.2 (6.4, 16.9) and 14.5 (7.8, 14.7), respectively. The slope in the riociguat group was greater than that in the control group, however, the difference was statistically insignificant (P = 0.46). Importantly, while the slope in the control group remained unchanged [7.2 (6.4, 16.9) to 8.4 (6.8, 12.0), P = 0.64] (Fig. 2A), it was significantly decreased in the riociguat group [14.5 (7.8, 14.7) to 6.41 (5.1, 11.4), P < 0.01] (Fig. 2B).

## 4. Discussion

The novel finding of the present study was that in CTEPH patients with hemodynamic improvement by BPA, riociguat significantly improved cardiac output and pulmonary vascular resistance during exercise as evidenced by significant decrease in mPAP-CO slope.

### 4.1. Effects of riociguat on resting hemodynamics, exercise capacity, and right ventricular function

A previous study showed that riociguat significantly increases 6-min walk distance (+46 m) and improves resting hemodynamics (mPAP, −4 mmHg) in patients with inoperable CTEPH or persistent or recurrent PH after pulmonary endarterectomy [5]. We have recently demonstrated that BPA dramatically improves

**Table 2**
Changes in resting hemodynamics.

| | Control (N = 11) | | | Riociguat (N = 10) | | | P value |
|---|---|---|---|---|---|---|---|
| | Baseline | Follow-up | P value | Baseline | Follow-up | P value | |
| mPAP (mmHg) | 25 ± 4 | 25 ± 3 | 0.51 | 25 ± 5 | 27 ± 5 | 0.23 | 0.43 |
| PAWP (mmHg) | 11 ± 3 | 13 ± 3 | <0.01 | 12 ± 4 | 16 ± 5 | 0.16 | 0.51 |
| CO (L/min) | 4.0 ± 1.0 | 3.7 ± 1.4 | 0.40 | 3.9 ± 1.1 | 4.8 ± 0.8 | 0.08 | 0.05 |
| TPG (mmHg) | 14 ± 4 | 12 ± 4 | 0.06 | 12 ± 3 | 10 ± 5 | 0.31 | 0.89 |
| PVR (Wood units) | 3.8 ± 1.9 | 3.8 ± 2.1 | 0.98 | 3 ± 1.3 | 2.5 ± 0.6 | 0.29 | 0.25 |
| sBP (mmHg) | 148 ± 16 | 156 ± 11 | 0.04 | 133 ± 19 | 138 ± 25 | 0.85 | 0.51 |
| dBP (mmHg) | 69 ± 6 | 71 ± 7 | 0.39 | 74 ± 17 | 67 ± 13 | 0.08 | 0.03 |
| HR (/min) | 64 ± 8 | 62 ± 7 | 0.10 | 63 ± 6 | 66 ± 8 | 0.13 | 0.03 |
| $SatO_2$ (%) | 95 ± 1.2 | 95 ± 1.4 | 0.98 | 95 ± 3 | 95 ± 2 | 0.88 | 0.87 |

Continuous variables are expressed as mean ± SD.
BP, blood pressure; CO, cardiac output; HR, heart rate; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; $SatO_2$, arterial oxygen saturation; TPG, *trans*-pulmonary pressure gradient.

**Table 3**
Changes in exercise capacity and RV function.

| | Control (N = 11) | | | Riociguat (N = 10) | | | P value |
|---|---|---|---|---|---|---|---|
| | Baseline | Follow-up | P value | Baseline | Follow-up | P value | |
| WHO functional class (I/II) | 7/4 | 7/4 | 1 | 5/5 | 6/4 | 1 | – |
| 6MWD (m) | 527 ± 65 | 535 ± 62 | 0.29 | 589 ± 95 | 595 ± 72 | 0.08 | 0.06 |
| peak $VO_2$ (ml/min/kg) | 14.9 ± 3.3 | 14.6 ± 2.6 | 0.69 | 15.9 ± 3 | 14.5 ± 2.1 | 0.12 | 0.27 |
| VE vs. $VCO_2$ slope | 37.4 ± 5.2 | 32.7 ± 4.2 | 0.01 | 36.2 ± 4.8 | 34.5 ± 4.1 | 0.20 | 0.14 |
| RVEF (%) | 57.6 ± 8.8 | 56.2 ± 4.7 | 0.65 | 57.1 ± 8.2 | 57.4 ± 11.1 | 0.85 | 0.61 |

Continuous variables are expressed as mean ± SD.
RVEF, right ventricular ejection fraction; $VCO_2$, carbon dioxide production; $VO_2$, oxygen uptake; VE, minute ventilation; 6MWD, 6-min walk distance.

**Table 4**
Changes in hemodynamics at peak workload.

| | Control (N = 11) | | | Riociguat (N = 9) | | | P value |
|---|---|---|---|---|---|---|---|
| | Baseline | Follow-up | P value | Baseline | Follow-up | P value | |
| Peak work load (Watt) | 38 ± 14 | 37 ± 11 | 0.59 | 38 ± 12 | 40 ± 12 | 0.35 | 0.34 |
| mPAP (mmHg) | 43 ± 7 | 43 ± 7 | 0.80 | 48 ± 7 | 44 ± 9 | 0.17 | 0.18 |
| PAWP (mmHg) | 20 ± 5 | 20 ± 5 | 0.93 | 22 ± 5 | 21 ± 7 | 0.66 | 0.74 |
| CO (L/min) | 6.2 ± 1.9 | 5.6 ± 2 | 0.24 | 6.0 ± 1.7 | 7.4 ± 1.6 | <0.01 | <0.01 |
| TPG (mmHg) | 23 ± 4 | 23 ± 6 | 0.88 | 26 ± 7 | 23 ± 7 | 0.30 | 0.30 |
| PVR (Wood units) | 4.1 ± 1.4 | 4.4 ± 1.5 | 0.28 | 4.8 ± 1.8 | 3.2 ± 0.7 | 0.02 | <0.01 |
| sBP (mmHg) | 193 ± 42 | 190 ± 28 | 0.72 | 174 ± 21 | 193 ± 30 | 0.09 | 0.11 |
| dBP (mmHg) | 77 ± 12 | 82 ± 10 | 0.13 | 87 ± 15 | 77 ± 11 | 0.05 | <0.01 |
| HR (/min) | 113 ± 19 | 107 ± 20 | 0.18 | 110 ± 16 | 116 ± 18 | 0.49 | 0.19 |
| $SatO_2$ (%) | 92.1 ± 3.1 | 91.9 ± 2.7 | 0.72 | 91.6 ± 3.7 | 91.8 ± 3.8 | 0.61 | 0.54 |
| mPAP-CO slope | 7.2 [6.4, 16.9] | 8.4 [6.8, 12.0] | 0.64 | 14.5 (7.8, 14.7) | 6.41 (5.1, 11.4) | <0.01 | 0.09 |

Continuous variables are expressed as mean ± SD.
BP, blood pressure; CO, cardiac output; HR, heart rate; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; SatO2, arterial oxygen saturation; TPG, *trans*-pulmonary pressure gradient.

hemodynamics (mPAP, −13 mmHg), exercise capacity (6MWD, +106 m), and long-term prognosis in the same population [4]. Although it has been reported that combination therapy with riociguat and BPA is effective in inoperable CTEPH patients [7], the separate role of riociguat remains to be clarified in patients who achieved improvement of hemodynamics and exercise capacity by BPA. In the present study, the use of riociguat was not associated with additional improvement of exercise capacity or resting hemodynamics. The patients enrolled in CHEST-1 showed reduced exercise capacity and severe pulmonary hypertension [5], whereas the patients in the present study showed normal exercise capacity and mild pulmonary hypertension after BPA without any vasodilators, indicating that riociguat may not improve resting hemodynamics or exercise capacity in CTEPH patients with mild PH after BPA. Furthermore, riociguat did not show additional improvement of right ventricular systolic function, which may be attributable to normal right ventricular systolic function at baseline.

### *4.2. Hemodynamic response to exercise in CTEPH patients after BPA*

Recently, hemodynamic response to exercise in CTEPH patients has gained attention to evaluate the functional state of the pulmonary vasculature. Previously, "exercise-induced PH" was defined as mPAP > 30 mmHg during exercise [16,21]. However, PAP usually rises in response to increase in CO during exercise. Thus, when evaluating hemodynamic response to exercise, not only mPAP but also CO should be examined simultaneously [22]. In the proceeding of pH World Symposium, the importance of evaluation of mPAP-CO slope by exercise right heart catheterization was emphasized to detect mild disorder of the pulmonary vasculature [8]. It has been reported that healthy subjects usually show mild mPAP-CO slope (mPAP-CO slope <3) compared with those having pulmonary vasculature disorders [22,23]. However, only a few studies addressed the hemodynamic response to exercise in CTEPH patients. A previous study showed that mPAP-CO slope

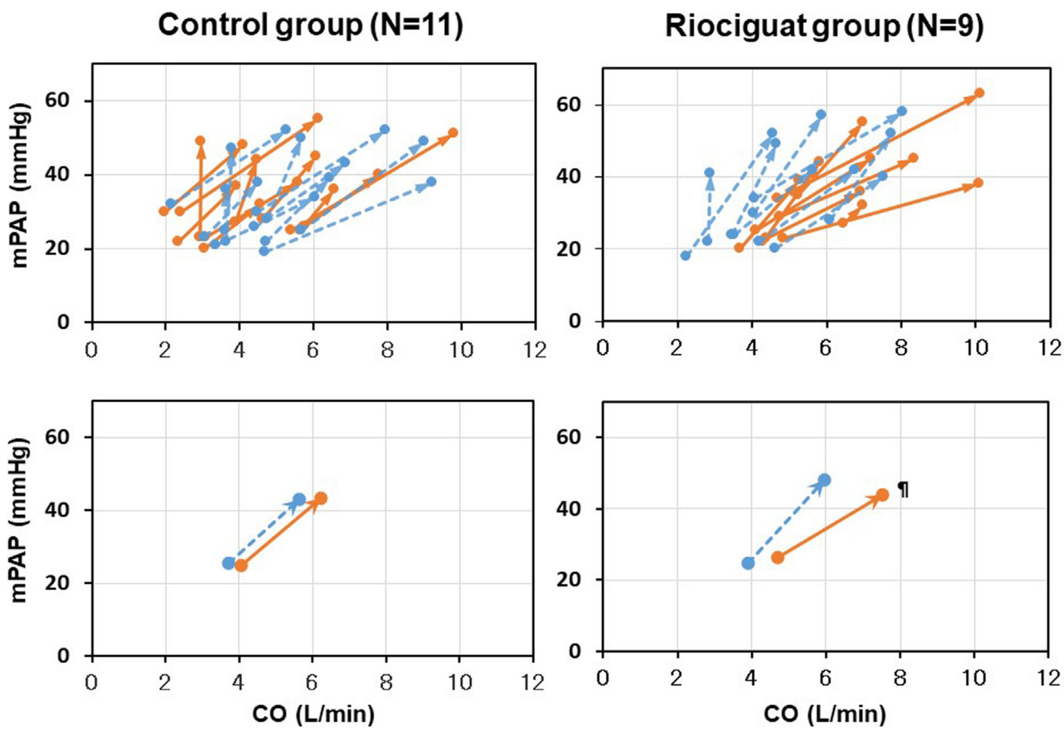


**Fig. 2.** mPAP-CO slope in the control and riociguat groups. The relationship between cardiac output (CO) and mean pulmonary arterial pressure (mPAP) is shown in individual patient in the control (A) and the riociguat (B) groups. Blue arrows indicate the values obtained at baseline, and orange ones at 6 months follow-up. Arrows in the upper panel show mPAP-CO relationship in each patient. A start point of each arrow represents CO and mPAP at rest, and an endpoint CO and mPAP at peak workload. In the lower panel, mPAP-CO relationship are shown as average CO and mPAP. (A) The slope in the control group showed no change from baseline to follow-up [7.2 (6.4, 16.9) to 8.4 (6.8, 12.0)]. (B) The slope in the riociguat group was significantly decreased at follow-up [14.5 (7.8, 14.7) to 6.41 (5.1, 11.4), $P < 0.01$]. In the riociguat group, a patient discontinued exercise during hemodynamic evaluation due to knee joint pain. Thus, this patient was excluded from the analysis of the effects of riociguat on hemodynamic response to exercise. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

was significantly improved by PEA from 6.7 to 4.7 [10]. Supplemental Table shows that BPA significantly improved hemodynamics and exercise capacity. Furthermore, no recurrence of pulmonary hypertension was noted at mid-term follow-up (26 ± 12 months after last BPA). The hemodynamic parameters before exercise indicate those obtained before exercise protocol in supine position (before putting feet on bicycle pedals). Although mPAP-CO slope before BPA was not evaluated in the present study, the slope after BPA was still steeper than that of CTEPH patients after PEA, suggesting that CTEPH patients have remaining pulmonary vascular lesions even after successful BPA.

### *4.3. Beneficial effects of riociguat on hemodynamics during exercise*

The present study demonstrates that riociguat significantly increases CO without significant reduction in mPAP at peak workload, resulting in significant reduction in PVR at peak workload in CTEPH patients with successful BPA. In the riociguat group, mPAP-CO slope was significantly decreased at follow-up, while it remained unchanged in the control group. These results suggest that riociguat has no additional effect on resting hemodynamics but works on pulmonary arteries in response to increased CO by exercise. Previous studies showed that sildenafil significantly improved mPAP-CO slope in CTEPH patients both before and after PEA [10,24], where it improved resting hemodynamic response to exercise but not resting hemodynamics as in the present study [10]. Previous experimental studies showed that increase in pulmonary vascular distensibility improved mPAP-CO slope, suggesting that pulmonary vasodilators improve hemodynamic response to exercise by dilating pulmonary vessels [18,25]. As mentioned above, CTEPH patients with remaining mild PH after BPA showed abnormal hemodynamic response to exercise, which may be related to remaining pulmonary arterial lesions, and riociguat may dilate pulmonary vessels and subsequently ameliorate the abnormal response to exercise. However, we found no association between this beneficial effect of riociguat and improvement of exercise capacity, as there was no additional improvement of 6-min walk distance, peak $VO_2$, or VE vs. $VCO_2$ slope in the present study. In PH patients, exercise capacity is determined by several factors, including remodeling of pulmonary vasculature, and cardiac and skeletal muscle functions [8,26,27]. A previous study showed that recovery of exercise capacity requires not only hemodynamic improvements but also peripheral adaptations, such as enhanced quadriceps muscle capillary density and oxidative enzyme activities [28]. Indeed, a previous report demonstrated the importance of peripheral vascular adaptations in CTEPH patients after PEA [29]. Thus, in CTEPH patients who achieved improvement of exercise capacity by BPA, riociguat, which mainly works on pulmonary vasculature, may show less impact on exercise capacity. However, a recent study showed that PH patients with steeper mPAP-CO slope have poorer prognosis than those with mild slope [11], suggesting that lowering mPAP-CO slope may improve long-term prognosis of pH patients. Further studies are needed in terms of the prognostic effects of riociguat in CTEPH patients after successful BPA.

### *4.4. Study limitations*

Several limitations should be mentioned for the present study. First, the present study is a single center study with a relatively small number of patients. Thus, the present findings need to be confirmed in future multicenter studies with a large number of patients. Second, the average dose of riociguat in the present study (4.3 mg daily) was lower than its maximum dose (7.5 mg daily). Although there were no severe adverse events that required discontinuation of riociguat, the decision to increase the dose was made by each attending doctors, which may have have resulted in the relatively lower dose. It is possible that underdose of riociguat might have reduced the expected effects of the drug. Finally, although mPAP-CO relationship was approximated by a straight line based on the previous report [17], it is known that the relationship shows slight curvilinearity [18].

## 5. Conclusions

In the present study, we were able to demonstrate that riociguat exerts beneficial effects on hemodynamic response to exercise in CTEPH patients even after hemodynamic improvement by BPA.

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## 7. Disclosures

None.

## CRediT authorship contribution statement

**Tatsuo Aoki:** Conceptualization, Methodology, Formal analysis, Writing - original draft. **Koichiro Sugimura:** Investigation, Writing - review & editing. **Yosuke Terui:** Investigation. **Shunsuke Tatebe:** Investigation. **Shigefumi Fukui:** Investigation. **Masanobu Miura:** Investigation. **Saori Yamamoto:** Investigation. **Nobuhiro Yaoita:** Investigation. **Hideaki Suzuki:** Investigation. **Haruka Sato:** Investigation. **Katsuya Kozu:** Investigation. **Ryo Konno:** Investigation. **Satoshi Miyata:** Formal analysis. **Kotaro Nochioka:** Investigation. **Kimio Satoh:** Investigation. **Hiroaki Shimokawa:** Project administration, Writing - review & editing, Supervision.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2020.100579.

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