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 are 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
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 worse 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. 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 symptoms (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, sex, and resting mPAP; riociguat group (N = 10) and control group (N = 11).

![Subjects: Consecutive 21 patients with distal-type CTEPH who underwent BPA from September 2015 to December 2017 in our hospital](Fig. 1).

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.

2.3. Evaluation of exercise capacity and right ventricular function

Exercise capacity was evaluated by peak VO2, VE vs. VCO2 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 VO₂, VE vs. VCO₂ 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.

3.2. Effects of riociguat on resting hemodynamics

In the riociguat group, CO at rest tended 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 SaO₂ 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...
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

| Table 2 | Changes in resting hemodynamics. |
|---------|---------------------------------|
| Control (N = 11) | Riociguat (N = 10) |
| 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 ± 69 | 156 ± 11 | 0.04 | 133 ± 17 | 138 ± 13 | 0.08 | 0.03 |
| 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 |
| SatO2 (%) | 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; SatO2, arterial oxygen saturation; TPG, trans-pulmonary pressure gradient.

| Table 3 | Changes in exercise capacity and RV function. |
|---------|---------------------------------|
| Control (N = 11) | Riociguat (N = 10) |
| 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 V̇O2 (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. V̇C02 slope | 37.4 ± 5.2 | 32.7 ± 4.2 | 0.01 | 36.2 ± 4.8 | 34.5 ± 4.4 | 0.20 | 0.14 |
| RVFE (%) | 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.
RVFE, right ventricular ejection fraction; V̇C02, carbon dioxide production; V̇O2, oxygen uptake; VE, minute ventilation; 6MWD, 6-min walk distance.

| Table 4 | Changes in hemodynamics at peak workload. |
|---------|---------------------------------|
| Control (N = 11) | Riociguat (N = 9) |
| 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 |
| SatO2 (%) | 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.
was significantly improved by PEA from 6.7 to 4.7 [10]. Supple-
mental Table shows that BPA significantly improved hemodynam-
ic 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 indi-
cate those obtained before exercise protocol in supine position (be-
fore 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, sug-
gestng 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 signifcantly
increases CO without signifcant reduction in mPAP at peak work-
load, resulting in signifcant reduction in PVR at peak workload in
CTEPH patients with successful BPA. In the riociguat group, mPAP-
CO slope was signifcantly 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 signifcantly
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 pul-
monary vascular distensibility improved mPAP-CO slope, suggest-
ing 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 benefcial efect of riociguat and improvement of
exercise capacity, as there was no additional improvement of 6-
min walk distance, peak VO2, or VE vs. VCO2 slope in the present
study. In PH patients, exercise capacity is determined by several
factors, including remodeling of pulmonary vasculature, and car-
diac and skeletal muscle functions [8,26,27]. A previous study
showed that recovery of exercise capacity requires not only hemo-
dynamic 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 exer-
cise 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 Yaaota: Investigation. Hideaki Suzuki: Investigation. Hiroaki Shimokawa: Investigation. Shunsuke Tatebe: Investigation. Yosuke Terui: Investigation. Katsuya Kozu: Investigation. Ryo Konno: Investigation. Satoshi Miyata: Formal analysis. Kotaro Noshioka: 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.jjica.2020.100579.

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