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ORIGINAL ARTICLE

Residual high intrapulmonary shunt fraction limits exercise capacity in patients treated with balloon pulmonary angioplasty

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Abstract

Balloon pulmonary angioplasty (BPA) has emerged as a new treatment strategy for patients with chronic thromboembolic pulmonary hypertension (CTEPH). Improvements in hemodynamic parameters after BPA have been reported, but some patients continue to suffer from reduced exercise tolerance even after the normalization of hemodynamic parameters following BPA. As the amelioration of hemodynamic parameters is reportedly achieved via BPA, we hypothesized that the limiting factors for exercise tolerance in these patients are related to respiratory function. Therefore, we investigated the associations between respiratory function and exercise tolerance, and the mechanisms underlying respiratory dysfunction in patients after BPA. We analyzed 62 patients with CTEPH who underwent 1-year follow-up after BPA. Predictors for reduced exercise tolerance after BPA determined with six-minute walk test were sought from pulmonary hemodynamic and respiratory parameters using logistic regression analysis. After multivariate adjustments, high mean right atrium pressure (mRAP) and high alveolar-arterial oxygen gradient (A-aDO_2) were significant predictors for reduced exercise tolerance. Next, we analyzed factors associated with high A-aDO2. Among the pathophysiological causes of high A-aDO2, including ventilation, diffusing capacity, and low ventilation-perfusion ratio, only low ventilation-perfusion ratio caused by high intrapulmonary shunt fraction was associated with high A-aDO_2. Impaired oxygenation due to residual high intrapulmonary shunt fraction was associated with reduced exercise tolerance in patients with CTEPH, after receiving BPA.

Keywords Chronic thromboembolic pulmonary hypertension · Balloon pulmonary angioplasty · Respiratory function · Exercise tolerance

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a disease caused by the chronic accumulation of organized thrombi in pulmonary arteries, and has a poor prognosis due to associated right sided heart failure if left untreated [1].

Pulmonary endarterectomy (PEA) is an established treatment strategy for patients with CTEPH, however a considerable proportion of such patients cannot tolerate the procedure due to its invasiveness [2]. Recently, balloon pulmonary angioplasty (BPA), also known as percutaneous transluminal pulmonary angioplasty has emerged as a new therapeutic option for patients with CTEPH. As it is relatively less invasive, BPA is now becoming a promising treatment choice for patients with CTEPH who cannot tolerate PEA [3–7]. Clinical studies have consistently shown improvements in pulmonary hemodynamic functions after BPA. However, some patients exhibit limited exercise tolerance even after apparent normalization of hemodynamic parameters following BPA. Of reported major determinants of exercise tolerance in patients with CTEPH, respiratory factors and hemodynamic factors, hemodynamic factors are thought to be ameliorated to a degree, thus we investigated the association between respiratory function—specifically impaired oxygenation—and exercise tolerance in these patients. We

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also analyzed the mechanisms underlying impaired oxygenation in patients after BPA.

Materials and methods

Study subjects

Data from subjects who received BPA at a single Japanese center for pulmonary hypertension (PH) were retrospectively analyzed. The center is a regional university hospital and referral center for PH. All patients analyzed were Japanese. The present study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki. All patients provided written informed consent.

We retrospectively analyzed 74 patients with CTEPH who completed BPA sessions and 1-year follow-up at Keio University Hospital in Japan from January 2012 to November 2016. CTEPH was diagnosed in accordance with the standard definition. Since we planned to analyze the association between the reduced exercise tolerance and oxygenation, we excluded total of 12 patients from the study, 2 who could not perform the 6-min walk test (6MWT) due to comorbidities other than CTEPH, and 10 requiring oxygen supplementation during right heart catheterization, in whom we were not able to calculate exact alveolar-arterial oxygen gradient (A-aDO_2). The remaining 62 patients were enrolled in the study (22 men and 40 women). All patients underwent right heart catheterization to obtain pulmonary arterial pressure (PAP), cardiac index (CI), and pulmonary vascular resistance (PVR) before the first BPA session, after the final BPA session, and 1 year after the final BPA session. The 6MWT was performed by each patient before the first BPA session and 1 year after the final BPA session. Seven patients did not undergo a pulmonary function test before the first BPA session, and one patient did not undergo a pulmonary function test at the 1-year follow-up after BPA. We were not able to ascertain the reasons for the lack of pulmonary function testing from their medical records.

Balloon pulmonary angioplasty

BPA was performed with staged sessions as previously described [3, 5–7]. Briefly, a 6-Fr long sheath was advanced through an 8-Fr indwelling sheath inserted from either jugular or femoral vein to main pulmonary artery trunk using a 5-Fr pig-tail catheter and 0.035-in. hydrophilic wire. A 6-Fr Judkins right, Amplatz left, or multipurpose guiding catheter was then advanced to the target vessels. After engaging the guiding catheter to the target vessel, the target lesion was crossed with a 0.014-in. guidewire, then dilated with an appropriate balloon. After ballooning, vessel dilatation was confirmed via angiography, intravascular ultrasonography, or optimal coherence tomography. Several BPA sessions were performed for each patient until a target mean PAP below 25 mmHg was achieved.

Pulmonary function testing

Each patient underwent pulmonary function testing to assess vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in the first 1 s (FEV1), residual volume (RV), and diffusing capacity for carbon monoxide (DLCO) divided by alveolar volume (VA) within 1 week of the corresponding right heart catheterization. Measurements were conducted in accordance with the American Thoracic Society recommendations, using a Multi-Functional Spirometer HI-801 and CHESTAC-9800 (CHEST Inc. Tokyo, Japan) [8, 9]. FEV1 was recorded as both percentage of the predicted value and percentage of forced vital capacity (FVC). Other parameters were recorded as percentage of the predicted value based on Global Lung Initiative equations. A-aDO_2 was calculated according to the results of blood gas testing.

Evaluation of Qs/Qt

To elucidate the effect of low ventilation/perfusion on impaired oxygenation, we estimated intrapulmonary shunt fraction (Qs/Qt). Qs/Qt was calculated using the following equation [10]:

$$\mathrm{Qs/Qt} = \frac{\mathrm{CcO_2} - \mathrm{CaO_2}}{\mathrm{CcO_2} - \mathrm{CvO_2}},$$

where CcO_2, CaO_2, and CvO_2 are the O_2 content of pulmonary capillary blood, systemic arterial blood, and pulmonary arterial blood, respectively. The O_2 content of arterial and pulmonary arterial blood were calculated using the following formula:

$$\mathrm{O_2\ content} = \mathrm{PO_2} \times 0.0031 + \text{serum hemoglobin concentration (g/dl)} \times 1.34 \times \mathrm{SO_2}/100.$$

where PO_2 and SO_2 are the partial pressure of oxygen (mmHg) and oxygen saturation of hemoglobin, respectively.

CaO_2 and CvO_2 were calculated using blood samples obtained during right heart cathetarization. CcO_2 was evaluated from alveolar O_2 tension (PAO_2) estimated with the alveolar air equation as follows:

$$\mathrm{PAO_2} = \mathrm{FIO_2} \times (\mathrm{PB} - \mathrm{PH_2O}) - (\mathrm{PaCO_2}/R).$$

where FIO_2 is the fractional inspired oxygen concentration (assumed to be 0.21), PB is barometric pressure, PH_2O is the water vapor pressure of saturated air (47 mmHg at 37 °C), $PaCO_2$ is the arterial partial pressure of carbon dioxide, and *R* is the respiratory quotient (assumed to be 0.8). Oxygen saturation of hemoglobin of pulmonary capillary blood was estimated with the equation of J. W. Severinghaus shown below [11].

$$SO_2 = ((23,400 \times ((PAO_2)^3 + 150 \times PAO_2)^{-1}) + 1)^{-1}.$$

Evaluation of exercise tolerance

The 6MWT is an established method for evaluating exercise tolerance, and it was conducted following current recommendations [12]. Briefly, patients walked along an enclosed, level, measured course on the floor. They were instructed to walk as far as possible at their own pace, in 6 min. Minimum percutaneous oxygen saturation during each test was measured.

Statistical analysis

As the current study involved a relatively small number of cases, continuous variables are reported as median (25th to 75th percentiles), and categorical variables are summarized as percentages. Changes in hemodynamic parameters, respiratory parameters, and exercise tolerance before and after BPA were analyzed with Wilcoxon's signed-rank test. Univariate and multivariate logistic regression analyzes were performed to investigate factors associated with reduced exercise tolerance after BPA and high A-aDO_2. For the analysis for 6MWT, we defined patients with 6MWT distances below 440 m as reduced exercise tolerance group based on previous reports in patients with PH [13]. Cut off value for high A-aDO_2 (25 mmHg) was defined with receiver operator curve predicting reduced exercise tolerance. All statistical analyzes were performed usingSPSS® ver. 21 (IBM, Armonk, New York, USA). A two-tailed *P* value of < 0.05 was considered statistically significant.

Results

Study population

Table 1 shows the baseline characteristics of the 62 patients enrolled. All patients were treated with comprehensive therapy including anti-coagulant therapy and home-oxygen therapy. Over 85% (53/62) of the patients were WHO functional class III or IV at baseline, suggesting that most of this study population had clinically severe CTEPH.

Table 1 Baseline characters of patients with BPA

	BPA (*N* = 62)
Characteristics	
Age (years)	65 (53–77)
Female	40 (68)
WHO-FC, I/II/III/IV	0/9/47/6
Medications	
PDEV inhibitors	40 (65)
ERAs	27 (44)
Oral PGI2	20 (32)
Intravenous PGI2	0 (0)
sGC stimulators	3 (5)

Data are presented *n* (%) or median (25th–75th percentile)

BPA balloon pulmonary angioplasty, *ERA* endothelin receptor antagonist, *PDEV* phospho diesterase V, *PGI2* prostaglandin I2, *sGC* soluble guanylate cyclase, *WHO-FC* World Health Organization Functional Class

Effect of BPA on exercise tolerance, hemodynamic parameters, and respiratory functions

6MWT results, WHO functional classifications, and pulmonary hemodynamic parameters remained improved 1 year after BPA. With regard to respiratory function parameters, we observed a significant but small increase in VC after BPA. Although oxygen saturation at rest showed significant improvement, lowest oxygen saturation during 6MWT remain unchanged. An index of oxygenation, A-aDO_2, also remained improved (Table 2).

Predictors of exercise tolerance after BPA

Table 3 shows the predictors of reduced exercise tolerance defined as a 6MWT result of < 440 m ($n = 26$, 42%). In single variable logistic regression analysis, mRAP, brain natriuretic peptide (BNP), DLCO/VA and A-aDO_2 were significant predictors of reduced exercise tolerance. We conducted multivariate logistic regression analysis with these parameters. As 26 patients were unable to achieve a 6MWT distance of > 440 m, we devised three models including A-aDO_2 to investigate associations between high A-aDO_2 and reduced exercise tolerance. A-aDO_2 remained a significant predictor of reduced exercise tolerance in two models, but not in the model including BNP and DLCO/VA (Supplemental Table 1).

Predictors of high A-aDO_2 after BPA

We then tried to clarify the mechanisms accounting for high A-aDO_2 after BPA. To divide patients into high and low A-aDO_2 groups, we generated a receiver-operating curve predicting reduced exercise tolerance (6MWT < 440 m)

Table 2 Effect of BPA on exercise tolerance, hemodynamic parameters, and respiratory functions

	Before BPA	1 Year after BPA	*P* value
Exercise tolerance			
6MWD (meters)	339 (224–397)	475 (378–540)	< 0.001
WHO-FC, I/II/III/IV	0/9/47/6	36/26/0/0	
Hemodynamic parameters			
mPAP (mmHg)	38 (31–47)	20 (17–23)	< 0.001
mRAP (mmHg)	7 (5–9)	3 (1–5)	< 0.001
PVR (dyne*s/cm^5)	670 (446–1003)	235 (166–311)	< 0.001
CI (l/m^2)	2.0 (1.8–2.6)	2.4 (2.1–3.0)	0.005
BNP (pg/ml)	68 (22–317)	26 (11–47)	< 0.001
Respiratory function ($n = 54$)			
VC (% predicted)	93 (85–101)	95 (88–107)	< 0.001
FVC (% predicted)	96 (87–106)	100 (91–110)	< 0.001
FEV1/FVC (%)	73 (68–79)	73 (69–79)	0.69
FEV1 (% predicted)	86 (75–92)	90 (78–97)	< 0.001
DLCO/VA (% predicted)	55 (45–63)	52 (46–61)	0.053
A-aDO$_2$ (mmHg)	45.9 (37.1–53.0)	26.5 (18.3–34.7)	< 0.001
Oxygen saturation at rest (%)	89 (87–91)	93 (91–95)	0.31
Minimum oxygen saturation during 6MWT (%)	89 (86–92)	89 (86–93)	< 0.001

Data are presented as median (25th–75th percentile)

6MWD 6 min walk distance, *6MWT* 6 min walk test, *A-aDO$_2$* alveolar-arterial oxygen difference, *BNP* brain natriuretic peptide, *CI* cardiac index, *DLCO/VA* diffusing capacity for carbon monoxide/alveolar volume, *FEV1* forced expiratory volume at 1 s, *FVC* forced vital capacity, *mPAP* mean pulmonary artery pressure, *mRAP* mean right atrium pressure, *PVR* pulmonary vascular resistance, *RV* residual volume, *TLC* total lung capacity, *VC* vital capacity, *WHO-FC* World Health Organization Functional Class

Table 3 Factors predicting poor exercise tolerance at 1 year after BPA

	OR (95% CI)	*P* value
Hemodynamic parameters		
mPAP, per 1 mmHg increase	1.09 (0.97–1.23)	0.15
mRAP, per 1mmHg increase	1.61 (1.19–2.19)	0.002
PVR, per 1 dyne*s/cm^5 increase	1.00 (0.99–1.00)	0.07
CI, per 1 l/m^2 increase	1.25 (0.55–2.86)	0.59
BNP, per 1 pg/ml increase	0.98 (0.97–1.00)	0.04
Respiratory function		
VC, per 1% predicted increase	0.98 (0.95–1.02)	0.38
FEV1/FVC, per 1% increase	1.06 (0.99–1.12)	0.08
FEV1, per 1% predicted increase	0.98 (0.95–1.01)	0.21
DLCO/VA, per 1% predicted increase	1.07 (1.02–1.13)	0.01
A-aDO$_2$, per 1 mmHg increase	0.93 (0.89–0.99)	0.01

Single variable logistic regression models predicting 6 min walk distance < 440m ($n = 26$, 42%)

A-aDO$_2$ alveolar-arterial oxygen difference, *BNP* brain natriuretic peptide, *CI* cardiac index, *DLCO/VA* diffusing capacity for carbon monoxide/alveolar volume, *FEV1* forced expiratory volume at 1 s, *FVC* forced vital capacity, *mPAP* mean pulmonary artery pressure, *mRAP* mean right atrium pressure, *PVR* pulmonary vascular resistance, *RV* residual volume, *TLC* total lung capacity, *VC* vital capacity, *WHO-FC* World Health Organization Functional Class

with A-aDO$_2$. The cut-off value derived from the curve was 25 mmHg, which yielded 80% sensitivity and 56% specificity for predicting reduced exercise tolerance (Supplemental Fig. 1). High A-aDO$_2$ ($n = 37$, 60%)was not associated with pulmonary hemodynamic parameters, VC, or FEV1/FVC, while reduced DLCO/VA, FEV1 as a percentage of the predicted value, and Qs/Qt were significant predictors of high A-aDO$_2$ (Table 4). After multivariate adjustments including DLCO/VA, FEV1 as a percentage of the predicted value, and Qs/Qt, only Qs/Qt remained a significant predictor of high A-aDO$_2$ after BPA (Supplemental Table 2).

Effect of pulmonary vascular selective vasodilators on Qs/Qt

Drugs used for pulmonary hypertension reportedly exacerbate Qs/Qt in some cases. We analyzed the associations between pulmonary vascular selective vasodilators and high A-aDO$_2$ and Qs/Qt. Patients prescribed with endothelin receptor antagonists were more likely to have higher Qs/Qt (Supplemental Tables 3 and 4).

Table 4 Factors predicting high A-aDO$_2$at 1 year after BPA

	OR (95% CI)	*P* value
Parameters before BPA		
mPAP, per 1 mmHg increase	1.01 (0.96–1.06)	0.77
mRAP, per 1 mmHg increase	0.93 (0.79–1.09)	0.36
PVR, per 1 dyne s/cm^5 increase	1.00 (1.00–1.00)	0.13
CI, per 1 l/m^2 increase	0.63 (0.30–1.36)	0.24
BNP, per 1 pg/ml increase	1.00 (1.00–1.00)	0.26
VC, per 1% predicted increase	1.03 (0.99–1.08)	0.20
FEV1/FVC, per 1% increase	0.97 (0.92–1.04)	0.40
FEV1, per 1% predicted increase	1.04 (1.00–1.09)	0.07
DLCO/VA, per 1% predicted increase	0.97 (0.93–1.02)	0.27
Qs/Qt, per 1% increase	1.02 (0.97–1.08)	0.43
Parameters 1 year after BPA		
mPAP, per 1 mmHg increase	1.03 (0.92–1.16)	0.62
mRAP, per 1 mmHg increase	1.04 (0.84–1.28)	0.75
PVR, per 1 dyne*s/cm^5 increase	1.00 (1.00–1.00)	0.41
CI, per 1 l/m^2 increase	1.19 (0.52–2.73)	0.40
BNP, per 1 pg/ml increase	1.02 (1.00–1.04)	0.06
VC, per 1% predicted increase	1.03 (0.99–1.07)	0.12
FEV1/VC, per 1% increase	0.99 (0.94–1.05)	0.74
FEV1, per 1% predicted increase	1.05 (1.01–1.09)	0.02
DLCO/VA, per 1% predicted increase	0.95 (0.91–1.00)	0.04
Qs/Qt, per 1% increase	1.52 (1.23–1.87)	< 0.001

Single variable logistic regression analysis predicting A-aDO$_2$ > 25mmHg (n = 37, 60%)

A-aDO$_2$ alveolar-arterial oxygen difference, *BNP* brain natriuretic peptide, *CI* cardiac index, *DLCO/VA* diffusing capacity for carbon monoxide/alveolar volume, *FEV1* forced expiratory volume at 1 s, *FVC* forced vital capacity, *mPAP* mean pulmonary artery pressure, *mRAP* mean right atrium pressure, *PVR*:pulmonary vascular resistance, *Qs/Qt* shunt fraction, *VC* vital capacity

Discussion

We found that the major limiting factor for exercise tolerance in patients with CTEPH after BPA was impaired oxygenation in the lungs due to high Qs/Qt. Favorable effects of BPA on pulmonary hemodynamics and exercise tolerance were increasingly recognized, however, some patients still exhibited reduced exercise tolerance after BPA. BPA will gain more attention as its use becomes more widespread, thus it is important to pay attention to quality of life (QOL) in patients who have already been treated with BPA. The results of the current study suggesting that residual high Qs/Qt after BPA exacerbates exercise intolerance may shed some light on this important issue.

Comparison with prior studies

Improvements in pulmonary hemodynamics and exercise tolerance after BPA have been reported by several institutions [3, 14, 15]. To our knowledge however, the maintenance of these improvements in pulmonary hemodynamics and exercise tolerance over 1 year have never been reported. In addition, we analyzed potential predictors of exercise tolerance 1 year after BPA. In the current study, high A-aDO$_2$—mainly caused by high Qs/Qt—was a significant predictor of reduced exercise tolerance after BPA, independent of hemodynamic parameters. Aoki et al. [16] reported that improvement of high Qs/Qt was associated with improvement of oxygenation in patients treated with BPA. That result is consistent with those of the current study, in that high intrapulmonary shunts are an ineligible factor with regard to impaired oxygenation in patients with CTEPH.

Oxygenation as a limiting factor for exercise tolerance

The importance of measuring exercise tolerance in patients with PH has been established, as reduced exercise tolerance predicts a poor prognosis in patients with PH [13]. Reported major determinants of exercise intolerance in these patients are respiratory factors, hemodynamic factors, and impaired oxygen utilization in skeletal muscles. Of these, we evaluated respiratory and hemodynamic parameters. Alveolar gas exchange efficiency as determined via A-aDO$_2$ was a predictor of reduced exercise tolerance in patients treated with BPA, whereas CI, mPAP, and PVR were not. With regard to hemodynamic parameters, mRAP and BNP were associated with exercise tolerance, which was likely related to sustained chronic right ventricular overload remaining even after pulmonary hemodynamic normalization at rest. In one multivariate model including DLCO/VA and BNP, the association between reduced exercise tolerance and A-aDO$_2$ did not reach statistical significance, likely due to the relatively small number of cases included, and multicollinearity between A-aDO$_2$ and DLCO/VA.

High Qs/Qt impaired oxygenation

We investigated the mechanisms potentially responsible for impaired oxygenation in patients after BPA. As our primary objective was to identify an intervention point to use to improve exercise capacity in patients after BPA, we set the cut-off value for A-aDO$_2$ at 25 mmHg using a receiver-operating curve for predicting reduced exercise tolerance. Pathophysiological determinants of impaired oxygenation include hypoventilation, shunt, decreased diffusion capacity, and ventilation-perfusion mismatch. We investigated the effects of these elements using surrogate markers, i.e., VC, FEV1

as a percentage of the predicted value, and FEV1/FVC for hypoventilation, DLCO/VA for diffusion capacity, and Qs/Qt for lowventilation / perfusion. After multivariate analysis, only high Qs/Qt was associated with elevation of A-aDO_2. High Qs/Qt in patients with CTEPH is thought to reflect a low ventilation/perfusion caused by blood redistribution to patent pulmonary arteries. Although BPA improved Qs/Qt, residual low ventilation/perfusion area was associated with impaired oxygenation, thus limiting exercise tolerance.

Clinical implications

Because the amelioration of pulmonary hypertension with BPA is now possible, our next aim is to improve QOL in patients with CTEPH after BPA, and exercise tolerance is an important component of QOL. In our analysis, impaired oxygenation caused by high Qs/Qt was the main cause of the reduced exercise tolerance observed in the patients in the current study. Although there is currently no treatment strategy for improving high Qs/Qt, it is at least reasonable to pay attention to it as a marker for poor exercise tolerance.

Limitations

The present study has some limitations. First, it was based on data from an observational registry. Although the number of cases was relatively large compared with previous studies investigating BPA, the small number of patients limited the statistical power of the findings. Prospective confirmation and analysis of a larger and more diverse population are needed. Second, we estimated the elevation of Qs/Qt via a physiological equation, however, its pathological mechanisms remain unclear. Further clarification of the mechanisms leading to high Qs/Qt may yield clues to new treatment strategies. Third, to determine changes in ventilation-perfusion inequality, the multiple inert gas elimination technique (MIGET) is an essential method. However, the resources required for the clinical application of the MIGET are not readily available to the majority of institutions. Thus, we evaluated reduced ventilation/perfusion ratio via Qs/Qt. Lastly, we did not analyze the effect of dead space ventilation. Dead space ventilation is reportedly associated with reduced exercise tolerance in patients with CTEPH [10]. However, dead space ventilation does not cause impaired oxygenation. Therefore, the main finding in the current study that impaired oxygenation caused by high Qs/Qt was associated with reduced exercise tolerance in patients after BPA was not thought to have been affected by this limitation.

Conclusion

Impaired oxygenation due to residual high Qs/Qt was associated with reduced exercise tolerance in patients with CTEPH, after receiving BPA.

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Compliance with ethical standards

Conflict of interest The authors have nothing to declare regarding the contents of this manuscript.

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