Exercise intolerance in chronic thromboembolic pulmonary hypertension after pulmonary angioplasty

Hanako Kikuchi, Ayumi Goda, Kaori Takeuchi, Takumi Inami, Takashi Kohno, Konomi Sakata, Kyoko Soejima and Toru Satoh

Affiliation: Dept of Cardiovascular Medicine, Kyorin University Hospital, Tokyo, Japan.

Correspondence: Ayumi Goda, Dept of Cardiovascular Medicine, Kyorin University Hospital, 6-20-2 Shinkawa, Mitaka, Tokyo 181-8611, Japan. E-mail: ayumix34@yahoo.co.jp

@ERSpublications
Impaired exercise capacity and ventilatory efficiency were observed in patients with chronic thromboembolic pulmonary hypertension after BPA who had normalised pulmonary arterial pressure at rest but exercise pulmonary hypertension https://bit.ly/2JujDh1

Cite this article as: Kikuchi H, Goda A, Takeuchi K, *et al*. Exercise intolerance in chronic thromboembolic pulmonary hypertension after pulmonary angioplasty. *Eur Respir J* 2020; 56: 1901982 [https://doi.org/10.1183/13993003.01982-2019].

ABSTRACT

Introduction: Exercise pulmonary hypertension is common in patients with chronic thromboembolic pulmonary hypertension (CTEPH) who experience shortness of breath during exercise and reduced exercise capacity despite normalised pulmonary arterial pressure (PAP) at rest; however, the relationship between exercise pulmonary hypertension and exercise capacity remains unclear. Here we aimed to determine whether exercise pulmonary hypertension is related to exercise capacity and ventilatory efficiency in CTEPH patients with normalised resting haemodynamics after pulmonary balloon angioplasty (BPA).

Patients and methods: In total, 249 patients with CTEPH treated with BPA (mean±SD age 63±14 years; male:female 62:187) with normal mean PAP (mPAP) (<25 mmHg) and pulmonary arterial wedge pressure (⩽15 mmHg) at rest underwent cardiopulmonary exercise testing with right heart catheterisation. mPAP–cardiac output (CO) during exercise was plotted using multipoint plots. Exercise pulmonary hypertension was defined by a mPAP–CO slope >3.0.

Results: At rest, pulmonary vascular resistance was significantly higher in the exercise pulmonary hypertension group (n=116) than in the non-exercise pulmonary hypertension group (n=133). Lower peak oxygen consumption (13.5±3.8 *versus* 16.6±4.7 $mL \cdot min^{-1} \cdot kg^{-1}$; p<0.001) was observed in the former group. The mPAP–CO slope was negatively correlated with peak oxygen consumption (r=−0.45, p<0.001) and positively correlated with the minute ventilation *versus* carbon dioxide output slope (r=0.39, p<0.001).

Conclusions: Impaired exercise capacity and ventilatory efficiency were observed in patients with CTEPH who had normalised PAP at rest but exercise pulmonary hypertension.

Received: 10 Oct 2019 | Accepted after revision: 26 March 2020

Introduction

With advancements in the treatment of chronic thromboembolic pulmonary hypertension (CTEPH), including balloon pulmonary angioplasty (BPA), an increasing number of patients gradually achieve normal haemodynamics and mean pulmonary arterial pressure (mPAP) [1–4]. However, after BPA, some patients still have shortness of breath during exercise and a reduced exercise capacity despite an improved prognosis and normalisation of PAP at rest. Exercise capacity improvement immediately after BPA remains insufficient despite remarkably improved resting haemodynamics. Thus, exercise intolerance and symptoms on effort are also important issues for CTEPH after BPA [5]. In these patients, an abnormal response to PAP during exercise is observed after BPA, as well as after pulmonary endarterectomy (PEA) [6–8].

Recently, exercise pulmonary hypertension, defined as mPAP >30 mmHg at cardiac output (CO) 10 L·min^{-1} during exercise, has been considered a mild degree of pulmonary hypertension with mPAP <25 mmHg at rest. Exercise pulmonary hypertension may be indicative of pulmonary vasculopathy [9–11].

The prognosis, natural history and clinical characteristics of patients with CTEPH and exercise pulmonary hypertension after BPA have yet to be clarified. There are only a few reports on exercise capacity and ventilatory efficiency in patients with CTEPH and normalised haemodynamics after BPA [5].

This study aimed to determine whether exercise pulmonary hypertension among CTEPH patients with normalised resting haemodynamics after BPA is related to exercise capacity and ventilatory efficiency.

Patients and methods

This study was approved by the Committee for Clinical Studies and Ethics of Kyorin University School of Medicine, Tokyo, Japan (approval 490).

Study patients

Consecutive patients who underwent cardiopulmonary exercise testing with right heart catheterisation (RHC) at Kyorin University Hospital between May 2012 and August 2019 with CTEPH after treatment with BPA were considered eligible for this study.

Patients with high mPAP (⩾25 mmHg) and/or pulmonary arterial wedge pressure (PAWP) elevation (>15 mmHg) at rest were excluded. Those whose data during exercise could not be used due to technical or mechanical difficulty were excluded. Patients who exhibited poor effort on the exercise test were also excluded.

Among patients with normal PAP and PAWP at rest, those with exercise PAWP elevation were excluded from the analysis. PAWP 25 mmHg at peak exercise was considered definite exercise-induced post-capillary pulmonary hypertension.

The purposes and risks of the study were explained to the patients, each of whom provided informed consent prior to participating.

RHC and cardiopulmonary exercise testing

RHC was performed using a 6-Fr double-lumen balloon-tipped flow-directed Swan–Ganz catheter (Harmac Medical Products, Buffalo, NY, USA) *via* the transjugular approach.

Baseline haemodynamic data were recorded; the zero reference level (mid-chest) was adjusted at the start of pressure measurement and 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 at the resting state to assess the right chamber, PAP (mPAP, systolic PAP and diastolic PAP) and PAWP [12].

An incremental symptom-limited exercise test was performed in the supine position using an electromagnetically braked cycle ergometer (Nuclear Imaging Table with Angio Ergometer; Lode, Groningen, Netherlands) according to the ramp protocol. For cycling, the legs were elevated. The test consisted of a 3-min rest period, followed by a 3-min warm-up at an ergometer setting of 10 W (60 revolutions·min^{-1}) and testing with a 1 W increase in exercise load every 6 s (totalling 10 W·min^{-1}).

During exercise, oxygen consumption (V'_{O_2}), carbon dioxide output (V'_{CO_2}) and minute ventilation (V'_E) were measured using a metabolic cart (Cpex-1; Inter Reha, Tokyo, Japan). Prior to calculating the parameters from the respiratory gas analysis, an eight-point moving average of the breath-by-breath data was obtained. Peak V'_{O_2} was defined as the average value obtained during the last 30 s of exercise. The anaerobic threshold point was determined using the V' slope method in addition to the following conventional criteria: increased V'_E/V'_{O_2} after registering as flat or decreasing and constant or decreased V'_E/V'_{CO_2} [13, 14]. The V'_E *versus* V'_{CO_2} slope was calculated from the start of the incremental exercise to the respiratory compensation point using least-squares linear regression [15, 16].

Heart rate, arterial blood pressure directly recorded in the radial artery and electrocardiographic findings were monitored continuously during the test. PAP and PAWP during RHC were also measured every minute. We used average mPAP and mean PAWP during several-second periods rather than end-expiratory measurements during the exercise testing.

Arterial oxygen saturation (S_{aO_2}), partial pressure of arterial oxygen (P_{aO_2}), partial pressure of arterial carbon dioxide (P_{aCO_2}) in the radial artery and mixed venous oxygen saturation (S_{vO_2}) in the pulmonary artery were measured at rest, anaerobic threshold and peak exercise. CO was determined *via* the Fick method using the following formula: CO ($L \cdot min^{-1}$)=V'_{O_2}/(1.34×haemoglobin level×($S_{aO_2}-S_{vO_2}$)). The arterial mixed venous oxygen content difference (C_{a-vO_2}) was calculated as: 1.34×haemoglobin level×($S_{aO_2}-S_{vO_2}$)/1000. Pulmonary vascular resistance (PVR) was calculated as: PVR (Wood Units (WU))= (mPAP−PAWP)/CO. All measurements during exercise testing were performed without supplemental oxygen.

The slope of the mPAP–flow relationship (mPAP–CO slope) was calculated from multipoint plots of mPAP and CO using least-squares linear regression. Exercise pulmonary hypertension was defined as a mPAP–CO slope >3 and/or mPAP >30 mmHg at CO 10 $L \cdot min^{-1}$.

Echocardiography

Transthoracic Doppler echocardiography at rest was performed within 3 months from the RHC and the results were stored digitally on the Artida (Toshiba, Tokyo, Japan) or EPIQ (Philips Healthcare, Cambridge, MA, USA) ultrasound system. On echocardiography, each patient was provided with a unique identification number to ensure the blind analysis of the images and patient characteristics. The frame rate was kept at a minimum of 60 frames$\cdot s^{-1}$. For Doppler recordings, the average of three to five consecutive beats was measured using a horizontal sweep of 75–100 $cm \cdot s^{-1}$.

Left ventricular dimensions and left atrial diameter were measured from the parasternal long-axis view. Left ventricular ejection fraction was calculated using Simpson's biplane method from the apical four- and two-chamber views.

Mitral inflow was assessed in the apical four-chamber view with the pulsed-wave Doppler sample volume placed at the tips of the mitral valve leaflets during diastole. From the pulsed-wave Doppler mode positioned at the tip of the mitral valve, the early (E) and late (A) peak diastolic velocities of the mitral inflow and the E-wave deceleration time were measured. Mitral annular motion was assessed using pulsed-wave tissue Doppler with the sample volume placed in the septal (e′ septal) and lateral (e′ lateral) mitral annuli. The E/e′ ratio was then calculated.

Right ventricular systolic function was assessed by measuring tricuspid annular plane systolic excursion (TAPSE). Right ventricular end-diastolic area ($RVED_{area}$) and end-systolic area ($RVES_{area}$) were assessed *via* manual planimetry in the apical four-chamber view, and right ventricular fractional area change (RVFAC) was derived using: RVFAC=(($RVED_{area}-RVES_{area}$)/$RVED_{area}$)×100. Systolic tricuspid valve lateral annular velocity was measured using an analogous method over the anterior leaflet in the long-axis view of the right ventricle [17].

Statistical analysis

Data are presented as mean with standard deviation or median (interquartile range) as appropriate; categorical variables are expressed as numbers and percentages. The Shapiro–Wilk test was used to assess the normality of the data distribution. All continuous variables, except for brain natriuretic peptide level and interval from BPA, were distributed normally. The correlations between the mPAP–CO slope and cardiopulmonary exercise parameters were assessed using Pearson's correlation analysis. Statistical comparisons were considered significant at $p<0.05$. All analyses were performed using SPSS version 11.0 (SPSS, Chicago, IL, USA).

Results

Baseline data

The patient flowchart is shown in figure 1. Among the 375 patients who underwent exercise testing, 47 were excluded due to high PAP and/or PAWP at rest, 17 due to mechanical and technical difficulties, and 12 due to poor effort. Among the 299 patients with normal PAP and PAWP at rest, 50 showed PAWP elevation at peak exercise and were excluded. Finally, 249 patients (mean±SD age 63±14 years; male:female 62:187) were analysed. There were 116 patients in the exercise pulmonary hypertension group and 133 patients in the non-exercise pulmonary hypertension group. The baseline characteristics of the study groups classified by the presence or absence of exercise pulmonary hypertension are shown in table 1.

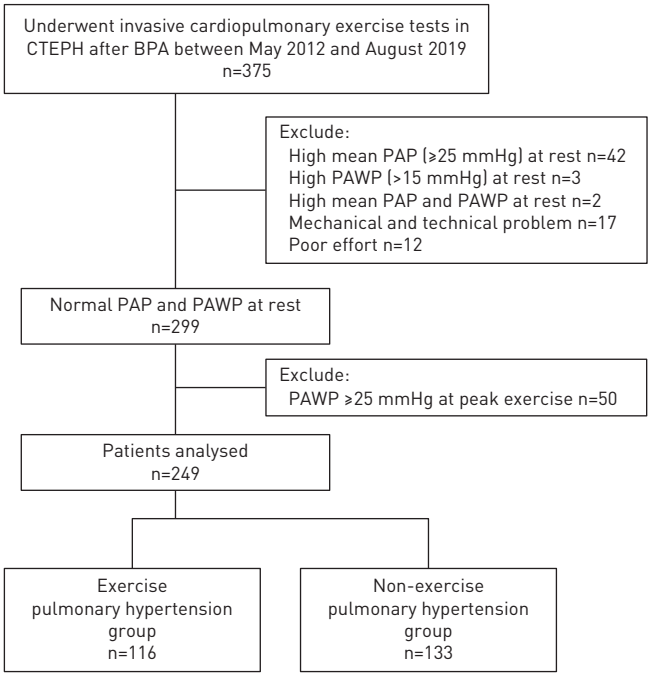

FIGURE 1 Flowchart of patients with chronic thromboembolic pulmonary hypertension (CTEPH) after balloon pulmonary angioplasty (BPA) who underwent cardiopulmonary exercise testing with right heart catheterisation. PAP: pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure.

The patients with good haemodynamics at rest but dyspnoea on exertion and abnormal haemodynamics on exercise underwent an additional BPA session when the flow-limiting pulmonary artery had a treatable anatomy. 32 patients in our cohort received the additional BPA.

The distributions of mPAP by group are shown in figure 2.

The exercise pulmonary hypertension group patients (n=116) were older and had higher brain natriuretic peptide levels, lower CO (4.6±1.3 *versus* 5.1±1.6 L·min^{-1}; p=0.002) and higher PVR (2.5±1.0 *versus* 2.0±0.9 WU; p<0.001) at rest than the non-exercise pulmonary hypertension group patients (n=133).

More patients in the exercise pulmonary hypertension than non-exercise pulmonary hypertension group required ambulatory oxygen therapy (34% *versus* 20%; p=0.012) and prior PEA (15% *versus* 4%; p=0.003). The number of BPA sessions and interval from BPA did not differ significantly between the two groups. World Health Organization Functional Class was significantly higher and 6-min walk distance was significantly lower (432±102 *versus* 462±105 m; p=0.024) in the exercise pulmonary hypertension group. The prescription rate of soluble guanylate cyclase stimulators (SGCSs) was significantly lower in the exercise pulmonary hypertension group than in the non-exercise pulmonary hypertension group (34% *versus* 20%; p=0.012). All study patients were taking anticoagulants.

Exercise data

The exercise test responses at rest (after leg raise), anaerobic threshold and peak exercise are listed in table 2. Mean peak V'_{O_2} was 14.4±3.9 mL·min^{-1}·kg^{-1}, with a respiratory quotient of 1.06±0.10, consistent with near-maximal effort.

The relationship of mPAP according to CO in each group is shown in figure 3. mPAP was higher in the exercise pulmonary hypertension group during exercise than in the non-exercise pulmonary hypertension group (anaerobic threshold: 40±8 *versus* 34±6 mmHg; p<0.001; peak: 44±8 *versus* 37±7 mmHg; p<0.001). CO was significantly lower during exercise in the exercise pulmonary hypertension group than in the non-exercise pulmonary hypertension group (anaerobic threshold: 8.2±2.1 *versus* 10.9±3.2 L·min^{-1}; p<0.001; peak: 9.0±2.4 *versus* 12.6±3.8 L·min^{-1}; p<0.001). C_{a-vO_2} in the exercise pulmonary hypertension group was also more impaired than in the non-exercise pulmonary hypertension group.

Absolute V'_E during exercise in the exercise pulmonary hypertension group was lower; however, V'_E at any given CO in the exercise pulmonary hypertension group was increased. The plot of V'_E/V'_{CO_2} as a function of P_{aCO_2} measured at anaerobic threshold is shown in figure 4. V'_E/V'_{CO_2} at anaerobic threshold was significantly increased in the exercise pulmonary hypertension group (42.7±8.3 *versus* 39.3±7.1; p=0.001), whereas P_{aCO_2} at anaerobic threshold was similar between both groups.

Lower peak V'_{O_2} (13.5±3.8 *versus* 16.6±4.7 mL·min^{-1}·kg^{-1}; p<0.001) and higher V'_E *versus* V'_{CO_2} slope (39.7±9.0 *versus* 35.2±7.5; p<0.001) were observed in the exercise pulmonary hypertension group.

TABLE 1 Baseline characteristics of the study patients at rest

	Exercise pulmonary hypertension group	Non-exercise pulmonary hypertension group	p-value
Subjects	116	133	
Age years	67±11	60±15	<0.001
Male:female	23:93	39:94	0.106
BMI kg·m^{-2}	23.2±3.6	24.1±4.3	0.076
BNP pg·dL^{-1}	28 (14–56)	19 (11–31)	<0.001
Hb g·dL^{-1}	12.6±1.5	12.5±1.7	0.505
HOT	40 (34)	27 (20)	0.012
Prior PEA	17 (15)	5 (4)	0.003
BPA sessions	4.0±1.9	3.8±1.6	0.541
Interval from BPA months	12 (6–23)	12 (6–20)	0.857
WHO FC I/II/III	47/67/2	90/43/0	<0.001
6MWD m	432±102	462±105	0.024
Treatment			
PDE5i	42 (36)	59 (44)	0.191
SGCS	8 (7)	30 (23)	0.001
ERA	47 (41)	52 (39)	0.819
PCA	38 (33)	37 (28)	0.397
Mean RAP mmHg	3±2	4±2	0.017
Systolic PAP mmHg	34±6	32±6	0.179
Diastolic PAP mmHg	8±4	7±4	0.220
Mean PAP mmHg	19±3	18±3	0.011
PAWP mmHg	8±3	8±3	0.393
S_{aO_2} %	95±3	95±3	0.317
S_{vO_2} %	71±5	73±5	0.005
CO L·min^{-1}	4.6±1.3	5.1±1.6	0.002
PVR WU	2.5±1.0	2.0±0.9	<0.001

Data are presented as n, mean±SD, median (interquartile range) or n (%), unless otherwise stated. BMI: body mass index; BNP: brain natriuretic peptide; Hb: haemoglobin; HOT: home oxygen therapy; PEA: pulmonary endarterectomy; BPA: balloon pulmonary angioplasty; WHO FC: World Health Organization Functional Class; 6MWD: 6-min walk distance; PDE5i: phosphodiesterase type V inhibitor; SGCS: soluble guanylate cyclase stimulator; ERA: endothelin receptor antagonist; PCA: prostacyclin analogue; RAP: right atrial pressure; PAP: pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; S_{aO_2}: arterial oxygen saturation; S_{vO_2}: mixed venous oxygen saturation; CO: cardiac output; PVR: pulmonary vascular resistance.

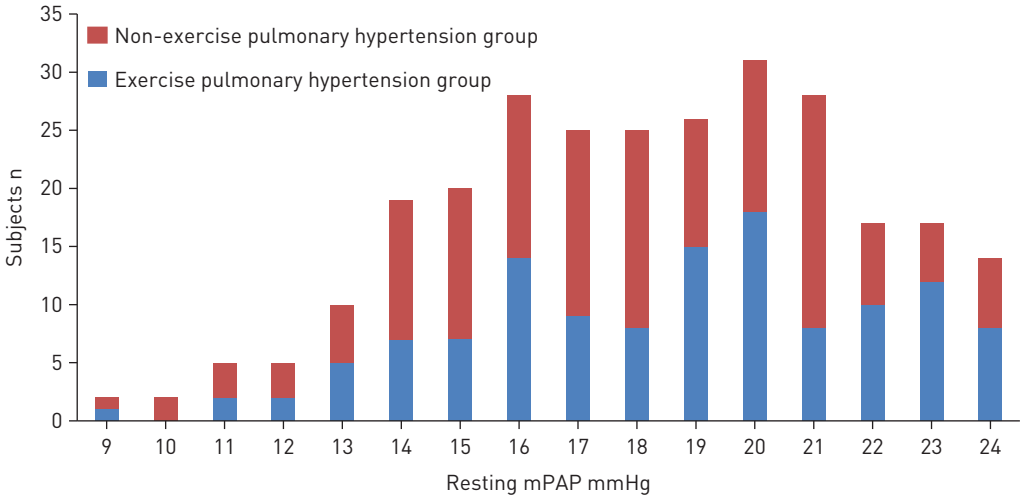

FIGURE 2 Distribution of resting mean pulmonary arterial pressure (mPAP) and exercise pulmonary hypertension.

TABLE 2 Exercise parameters

	Exercise pulmonary hypertension group	Non-exercise pulmonary hypertension group	p-value
Subjects	116	133	
Rest after leg raise			
HR beats·min^{-1}	71±11	69±11	0.242
Systolic BP mmHg	149±24	141±21	0.005
Diastolic BP mmHg	73±13	71±10	0.287
Mean BP mmHg	102±18	97±13	0.020
Systolic PAP mmHg	43±10	39±9	<0.001
Diastolic PAP mmHg	10±6	10±5	0.186
Mean PAP mmHg	25±6	23±5	0.002
PAWP mmHg	11±4	11±4	0.995
CO L·min^{-1}	4.9±1.7	5.7±1.9	0.002
PVR WU	3.2±1.7	2.3±1.3	<0.001
P_{aO_2} mmHg	73±11	77±12	0.011
P_{aCO_2} mmHg	41±5	41±4	0.730
S_{aO_2} %	94±3	95±3	0.025
S_{vO_2} %	68±5	71±5	0.002
C_{a-vO_2} mL·dL^{-1}	4.4±0.9	4.1±0.8	0.008
V'_{O_2} mL·min^{-1}	206±51	224±68	0.024
V'_{CO_2} mL·min^{-1}	172±45	185±64	0.077
R	0.83±0.08	0.81±0.08	0.227
V'_E L·min^{-1}	8.2±1.9	8.3±2.3	0.733
V'_E/V'_{O_2}	42.0±11.4	39.1±10.2	0.034
V'_E/V'_{CO_2}	50.8±11.8	48.0±11.2	0.057
Anaerobic threshold			
HR beats·min^{-1}	104±17	104±15	0.917
Mean PAP mmHg	40±8	34±6	<0.001
PAWP mmHg	16±5	15±4	0.067
CO L·min^{-1}	8.2±2.1	10.9±3.2	<0.001
PVR WU	3.1±1.3	1.9±1.0	<0.001
P_{aO_2} mmHg	67±11	70±12	0.041
P_{aCO_2} mmHg	40±4	41±4	0.270
S_{aO_2} %	92±4	93±4	0.087
S_{vO_2} %	48±8	52±6	<0.001
R	0.95±0.20	0.95±0.08	0.745
V'_E L·min^{-1}	23.6±7.0	26.1±7.4	0.008
V'_E/V'_{CO_2}	42.7±8.3	39.3±7.1	0.001
Peak			
Work rate watts	67±21	80±29	<0.001
HR beats·min^{-1}	121±19	125±18	0.103
Systolic BP mmHg	188±41	181±33	0.172
Diastolic BP mmHg	86±15	84±16	0.444
Mean BP mmHg	124±20	120±20	0.159
Systolic PAP mmHg	73±13	63±11	<0.001
Diastolic PAP mmHg	19±6	14±6	<0.001
Mean PAP mmHg	44±8	37±7	<0.001
PAWP mmHg	16±5	15±5	0.123
CO L·min^{-1}	9.0±2.4	12.6±3.8	<0.001
PVR WU	3.3±1.2	1.9±0.8	<0.001
P_{aO_2} mmHg	64±11	68±11	0.023
P_{aCO_2} mmHg	40±5	40±4	0.680
S_{aO_2} %	91±4	92±4	0.285
S_{vO_2} %	41±7	44±7	0.005
C_{a-vO_2} mL·dL^{-1}	8.5±1.7	8.0±1.7	0.030
V'_{O_2} mL·min^{-1}	775±268	1014±382	<0.001
V'_{CO_2} mL·min^{-1}	830±312	1083±436	<0.001
R	1.06±0.10	1.06±0.11	0.810
V'_E L·min^{-1}	34.7±10.9	40.9±13.7	<0.001
V'_E/V'_{O_2}	46.5±8.8	42.0±7.9	<0.001

Continued

TABLE 2 Continued

	Exercise pulmonary hypertension group	Non-exercise pulmonary hypertension group	p-value
V'_E/V'_{CO_2}	44.0±8.4	39.8±6.7	<0.001
Peak V'_{O_2} mL·kg^{-1}·min^{-1}	13.5±3.8	16.6±4.7	<0.001
V'_E *versus* V'_{CO_2} slope	39.7±9.0	35.2±7.5	<0.001

Data are presented as n or mean±SD, unless otherwise stated. HR: heart rate; BP: blood pressure; PAP: pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; CO: cardiac output; PVR: pulmonary vascular resistance; WU: Wood Units; P_{aO_2}: partial pressure of arterial oxygen; P_{aCO_2}: partial pressure of arterial carbon dioxide; S_{aO_2}: arterial oxygen saturation; S_{vO_2}: mixed venous oxygen saturation; C_{a-vO_2}: arterial mixed venous oxygen content difference; V'_{O_2}: oxygen consumption; V'_{CO_2}: carbon dioxide output; R: respiratory exchange ratio; V'_E: minute ventilation.

Relationship between the mPAP–CO slope and exercise capacity and ventilatory efficiency

The correlations between the mPAP–CO slope and peak V'_{O_2} and between the mPAP–CO slope and the V'_E *versus* V'_{CO_2} slope are shown in figure 5. Peak V'_{O_2} was negatively correlated with the mPAP–CO slope (r=−0.45, p<0.001), while the V'_E *versus* V'_{CO_2} slope was positively correlated with the mPAP–CO slope (r=0.39, p<0.001).

Echocardiographic parameters

Echocardiographic data were obtained from 208 patients. The echocardiographic parameters of the two groups are shown in table 3. TAPSE in the exercise pulmonary hypertension group was significantly shorter than in the non-exercise pulmonary hypertension group (21.0±4.0 *versus* 22.4±4.0 mm; p=0.013).

Discussion

The present study revealed that impaired exercise capacity and ventilatory efficiency are observed in patients with CTEPH after BPA who have a normalised PAP at rest but have exercise pulmonary hypertension.

Definition of exercise pulmonary hypertension

Recently, exercise pulmonary hypertension, defined as mPAP >30 mmHg at CO 10 L·min^{-1} on exercise, has been recognised as a mild degree of pulmonary hypertension with mPAP <25 mmHg at rest [9–11]. Additionally, mPAP–CO slopes >3.0, which are defined as being linearly correlated based on serial

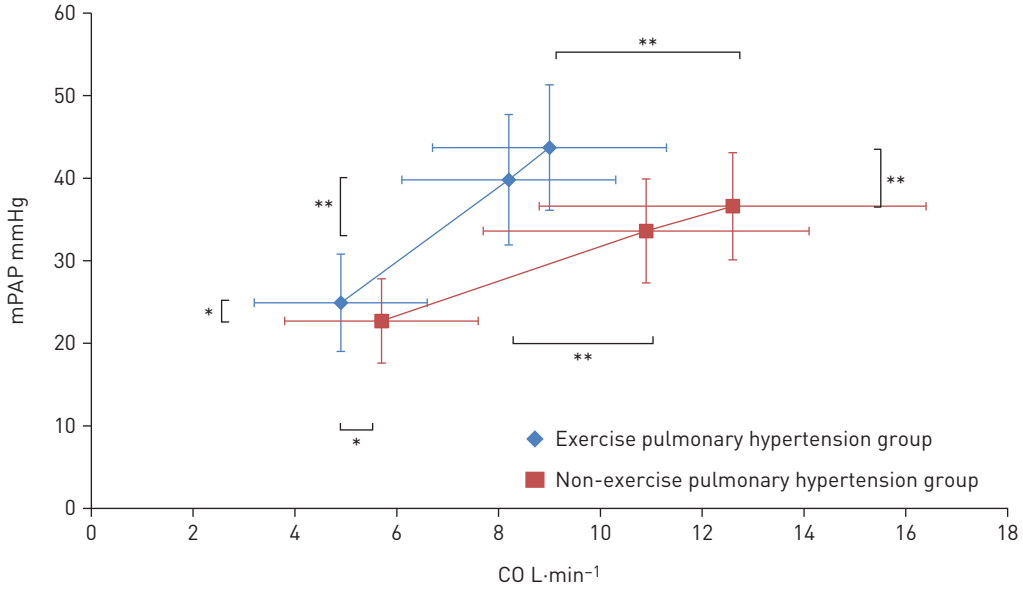

FIGURE 3 Relationship of cardiac output (CO) with mean pulmonary arterial pressure (mPAP) during exercise. *: p<0.05; **: p<0.001 (exercise pulmonary hypertension group *versus* non-exercise pulmonary hypertension group).

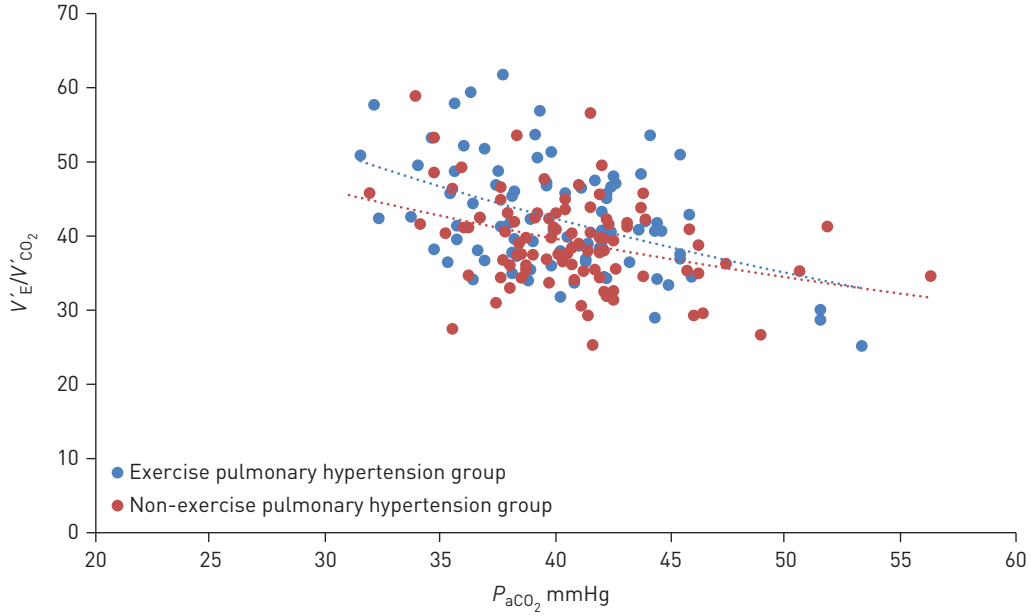

FIGURE 4 Plot of minute ventilation (V'_E)/carbon dioxide output (V'_{CO_2}) as a function of arterial carbon dioxide tension (P_{aCO_2}) measured at anaerobic threshold. V'_E/V'_{CO_2} at anaerobic threshold was significantly increased in the exercise pulmonary hypertension group, whereas P_{aCO_2} at anaerobic threshold was similar between both groups.

measurements of mPAP and CO during incremental exercise, reflect an abnormal pulmonary vascular response to exercise [18]. Exercise pulmonary hypertension screened by echocardiography can detect early pulmonary hypertension in patients with connective tissue disease [19]. In patients with pulmonary arterial hypertension (PAH) or CTEPH, the pressure–flow relationship during exercise predicted survival and was correlated with the established markers of disease severity and outcome [20]. Thus, exercise pulmonary hypertension may be indicative of pulmonary vasculopathy.

According to the 2015 European Society of Cardiology/European Respiratory Society guideline, pulmonary hypertension is defined as an elevation of mPAP to ⩾25 mmHg [21]. However, the physiological upper limit of normal mPAP is considered 20 mmHg [22]. Douschan *et al.* [23] reported that a mildly increased mPAP to 17–20 mmHg is associated with decreased physical capacity and increased mortality, whereas an elevation of mPAP to 21–24 mmHg is an independent predictor of mortality *versus* normal mPAP. In our cohort, the average mPAP in the exercise pulmonary hypertension group was 19 mmHg. We speculate that

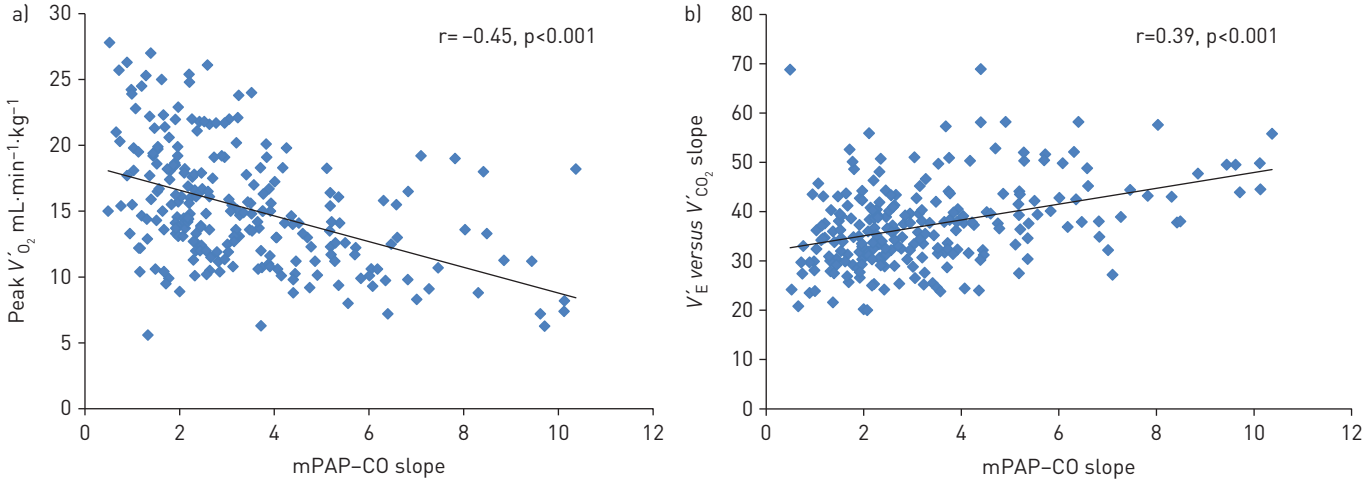

FIGURE 5 Correlation of the mean pulmonary arterial pressure (mPAP)–cardiac output (CO) slope with a) peak oxygen consumption (V'_{O_2}) and b) the minute ventilation (V'_E) *versus* carbon dioxide output (V'_{CO_2}) slope. Peak V'_{O_2} was negatively correlated with the mPAP–CO slope, while the V'_E *versus* V'_{CO_2} slope was positively correlated with the mPAP–CO slope.

TABLE 3 Resting echocardiographic parameters

	Exercise pulmonary hypertension group	Non-exercise pulmonary hypertension group	p-value
Subjects	101	107	
LVEF %	67±6	68±7	0.312
LV mass index g·m^{-2}	88±18	89±19	0.634
LAD mm	35±5	35±6	0.344
E cm·s^{-1}	64.3±16.2	67.6±15.8	0.131
A cm·s^{-1}	82.7±19.5	77.7±15.2	0.042
E/A	0.81±0.31	0.92±0.33	0.023
DcT cm·s^{-1}	202±54	196±48	0.420
E′ septal cm·s^{-1}	6.8±1.8	7.5±2.0	0.009
E/e′ septal cm·s^{-1}	9.9±3.2	9.5±2.9	0.358
E′ lateral cm·s^{-1}	9.4±2.4	10.3±3.2	0.022
E/e′ lateral cm·s^{-1}	7.2±2.4	7.0±2.6	0.662
TAPSE mm	21.0±4.0	22.4±4.0	0.013
RVFAC %	42±7	43±6	0.771
TVs′ cm·s^{-1}	12.8±2.4	13.4±3.1	0.142

Data are presented as n or mean±SD, unless otherwise stated. LVEF: left ventricular ejection fraction; LV: left ventricle; LAD: left atrial diameter; DcT: deceleration time; TAPSE: tricuspid annular plane systolic excursion; RVFAC: right ventricular fractional area change; TVs′: systolic tricuspid valve lateral annular velocity.

the exercise pulmonary hypertension group showed a lower mPAP because, even at the same value of resting mPAP, CO varies and must be evaluated with the consideration of PVR. In our study patients, the resting PVR in the exercise pulmonary hypertension group was significantly higher than in the non-exercise pulmonary hypertension group.

Cause of residual shortness of breath after CTEPH treatment

BPA and PEA significantly improve the prognosis and quality of life of patients with CTEPH [1, 3]. However, some operated patients continue to experience limited exercise capacity despite normalisation of resting PAP and PVR [7]. Bonderman *et al.* [6] reported that, after successful PEA, patients with persistent exertional dyspnoea displayed an abnormal pulmonary haemodynamic response to exercise characterised by an increased PVR and decreased pulmonary compliance. Richter *et al.* [8] examined the haemodynamics before and after PEA, and reported that a flattened mPAP–CO slope indicated an increased capacity of the pulmonary vasculature for a higher CO after PEA. Thus, exercise-induced pulmonary hypertension is one factor related to exercise intolerance in patients with a normalised CTEPH after PEA.

The 6th World Symposium on Pulmonary Hypertension in 2018 included exercise pulmonary hypertension in its definition of chronic thromboembolic disease (CTED) [24]. van Kan *et al.* [25] reported that patients with CTED showed an abnormal pulmonary vascular response to exercise and decreased ventilator efficiency. Exercise capacity was reduced by 29% and 57% in patients with CTED and CTEPH, respectively, compared with control subjects [26]. The clinical phenotype of CTED in terms of exercise tolerance and cardiac reserve is considered to be between normal and CTEPH.

We previously reported that BPA for CTED positively impacts exercise tolerance and ventilation efficiency [27]. This may suggest the possible significance of BPA for CTED with exercise pulmonary hypertension. If patients with CTEPH after BPA or PEA have exercise pulmonary hypertension, additional treatment might be considered in terms of improving their exercise tolerance and ventilatory efficiency.

Mechanism of exercise capacity and ventilatory efficiency

Pulmonary vascular diseases cause haemodynamic resistance in the central circulation, making it difficult for the right ventricle to deliver blood to the left atrium at a sufficient rate to meet the increased CO needed for exercise. Because the CO increase in response to exercise is reduced, anaerobic threshold and peak V'_{O_2} are impaired in patients with pulmonary vascular diseases [28, 29]. Even in patients with pulmonary hypertension only, the increase in CO during exercise is thought to be hindered.

Pulmonary vascular diseases are associated with hypoperfusion of the ventilated alveoli, particularly during exercise. Consequently, the alveoli with non-occluded capillaries must accept a greater than normal

perfusion and be ventilated to a proportionately greater degree than normal to remove carbon dioxide and to maintain P_{aCO_2}, P_{aO_2} and pulmonary hypertension at appropriate values. Because of the increase in physiological dead space ventilation, V'_E is increased in patients with pulmonary vascular diseases at rest and to a greater degree during exercise [29–31]. The increased dead space ventilation results in a higher V'_E *versus* V'_{CO_2} slope.

An additional reason for the increased ventilator drive during exercise in patients with pulmonary vascular diseases is arterial hypoxaemia, which worsens during exercise. In the presence of pulmonary vascular diseases, the functional capillary bed is destroyed and the capillary bed reserved for recruitment during exercise is already recruited at rest. This is considered the cause of arterial hypoxaemia. The decrease in P_{aO_2} stimulates chemoreceptors that stimulate ventilation. Even in our cases, exercise pulmonary hypertension showed greater hypoxaemia, which may be attributed to the mechanism of hyperventilation and ventilation–perfusion mismatch. Ulrich *et al.* [32] reported that the oxygen supply in PAH/CTEPH patients increased in exercise performance and reduced the excessive ventilatory response to exercise. This finding is consistent with that of our study. Plots of V'_E/V'_{CO_2} as a function of P_{aCO_2} measured at anaerobic threshold are reportedly useful in determining whether the ventilatory inefficiency was due to increased dead space ventilation or increased chemosensitivity [33]. From our plots between V'_E/V'_{CO_2} and P_{aCO_2} at anaerobic threshold, the breathlessness in patients with exercise pulmonary hypertension is thought to be contributed to by the increase in physiological dead space ventilation compared with non-exercise pulmonary hypertension.

Effects of right ventricle function

Regarding resting right ventricle function measured on echocardiography, except for TAPSE, there were no significant intergroup differences. This finding is consistent with those of previous reports. If the right ventricle function at peak exercise was measured, a difference might have been observed [7, 26].

There are no data showing that patients with a normalised PAP but with exercise pulmonary hypertension have worse outcomes. The benefit of PAH-specific drugs in patients with a normalised pressure and CTEPH would be for exercise capacity and ventilator efficiency, but supporting data are lacking. In this observational study, the prescription rate of SGCSs was significantly lower in the exercise pulmonary hypertension group. SGCSs may be effective in residual small vessel disease that are not dilated by BPA and might be beneficial for haemodynamic response to exercise in patients with stronger small vessel disease. Our data would actually support the premise that PAH-specific drugs may improve the response to exercise, which is linked to improved symptoms. In cases where exercise pulmonary hypertension and symptoms persist, but where it is difficult to perform BPA, SGCSs might be a therapeutic option. Thus, future randomised controlled trials are needed to elucidate this point.

Study limitations

Our study population did not include patients with high mPAP at rest or completely normal pulmonary vascular function.

Age is an important confounder of the pulmonary vascular response to exercise. It was reported that resting PAP also increases in the elderly [22]. PAP during exercise may also increase in the elderly. Age would have slightly affected exercise tolerance and echocardiographic parameters.

Respiratory function test data are also lacking; thus, the effect of respiratory function on exercise pulmonary hypertension is unknown.

Conclusions

Impaired exercise capacity and ventilatory efficiency are observed in patients with CTEPH after BPA, normalised PAP at rest and exercise pulmonary hypertension.

Author contributions: A. Goda and H. Kikuchi designed the study, analysed the data and wrote the manuscript. T. Kohno, K. Sakata, T. Satoh and K. Soejima reviewed the data and edited the manuscript. K. Takeuchi, H. Kikuchi, A. Goda and T. Inami performed the exercise tests and BPA.

Conflict of interest: None declared.

References

1 Inami T, Kataoka M, Yanagisawa R, *et al.* Long-term outcomes after percutaneous transluminal pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. *Circulation* 2016; 134: 2030–2032.
2 Kataoka M, Inami T, Hayashida K, *et al.* Percutaneous transluminal pulmonary angioplasty for the treatment of chronic thromboembolic pulmonary hypertension. *Circ Cardiovasc Interv* 2012; 5: 756–762.
3 Mahmud E, Madani MM, Kim NH, *et al.* Chronic thromboembolic pulmonary hypertension: evolving therapeutic approaches for operable and inoperable disease. *J Am Coll Cardiol* 2018; 71: 2468–2486.

4 Wiedenroth CB, Olsson KM, Guth S, *et al.* Balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic disease. *Pulm Circ* 2018; 8: 2045893217753122.
5 Fukui S, Ogo T, Goto Y, *et al.* Exercise intolerance and ventilatory inefficiency improve early after balloon pulmonary angioplasty in patients with inoperable chronic thromboembolic pulmonary hypertension. *Int J Cardiol* 2015; 180: 66–68.
6 Bonderman D, Martischnig AM, Vonbank K, *et al.* Right ventricular load at exercise is a cause of persistent exercise limitation in patients with normal resting pulmonary vascular resistance after pulmonary endarterectomy. *Chest* 2011; 139: 122–127.
7 Claessen G, La Gerche A, Dymarkowski S, *et al.* Pulmonary vascular and right ventricular reserve in patients with normalized resting hemodynamics after pulmonary endarterectomy. *J Am Heart Assoc* 2015; 4: e001602.
8 Richter MJ, Sommer N, Gall H, *et al.* Pulmonary hemodynamic response to exercise in chronic thromboembolic pulmonary hypertension before and after pulmonary endarterectomy. *Respiration* 2015; 90: 63–73.
9 Naeije R, Vanderpool R, Dhakal BP, *et al.* Exercise-induced pulmonary hypertension: physiological basis and methodological concerns. *Am J Respir Crit Care Med* 2013; 187: 576–583.
10 Kovacs G, Herve P, Barbera JA, *et al.* An official European Respiratory Society statement: pulmonary haemodynamics during exercise. *Eur Respir J* 2017; 50: 1700578.
11 Simonneau G, Montani D, Celermajer DS, *et al.* Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J* 2019; 53: 1801913.
12 Hoeper MM, Bogaard HJ, Condliffe R, *et al.* Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol* 2013; 62: Suppl. 25, D42–D50.
13 Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* 1986; 60: 2020–2027.
14 Sue DY, Wasserman K, Moricca RB, *et al.* Metabolic acidosis during exercise in patients with chronic obstructive pulmonary disease. Use of the V-slope method for anaerobic threshold determination. *Chest* 1988; 94: 931–938.
15 Chua TP, Ponikowski P, Harrington D, *et al.* Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol* 1997; 29: 1585–1590.
16 Koike A, Itoh H, Kato M, *et al.* Prognostic power of ventilatory responses during submaximal exercise in patients with chronic heart disease. *Chest* 2002; 121: 1581–1588.
17 Rudski LG, Lai WW, Afilalo J, *et al.* Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010; 23: 685–713.
18 Lewis GD, Bossone E, Naeije R, *et al.* Pulmonary vascular hemodynamic response to exercise in cardiopulmonary diseases. *Circulation* 2013; 128: 1470–1479.
19 Kusunose K, Yamada H, Hotchi J, *et al.* Prediction of future overt pulmonary hypertension by 6-min walk stress echocardiography in patients with connective tissue disease. *J Am Coll Cardiol* 2015; 66: 376–384.
20 Hasler ED, Muller-Mottet S, Furian M, *et al.* Pressure-flow during exercise catheterization predicts survival in pulmonary hypertension. *Chest* 2016; 150: 57–67.
21 Galiè N, Humbert M, Vachiery JL, *et al.* 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Respir J* 2015; 46: 903–975.
22 Kovacs G, Berghold A, Scheidl S, *et al.* Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. *Eur Respir J* 2009; 34: 888–894.
23 Douschan P, Kovacs G, Avian A, *et al.* Mild elevation of pulmonary arterial pressure as a predictor of mortality. *Am J Respir Crit Care Med* 2018; 197: 509–516.
24 Kim NH, Delcroix M, Jais X, *et al.* Chronic thromboembolic pulmonary hypertension. *Eur Respir J* 2019; 53: 1801915.
25 van Kan C, van der Plas MN, Reesink HJ, *et al.* Hemodynamic and ventilatory responses during exercise in chronic thromboembolic disease. *J Thorac Cardiovasc Surg* 2016; 152: 763–771.
26 Claeys M, Claessen G, La Gerche A, *et al.* Impaired cardiac reserve and abnormal vascular load limit exercise capacity in chronic thromboembolic disease. *JACC Cardiovasc Imaging* 2019; 12: 1444–1456.
27 Inami T, Kataoka M, Kikuchi H, *et al.* Balloon pulmonary angioplasty for symptomatic chronic thromboembolic disease without pulmonary hypertension at rest. *Int J Cardiol* 2019; 289: 116–118.
28 Sun XG, Hansen JE, Oudiz RJ, *et al.* Exercise pathophysiology in patients with primary pulmonary hypertension. *Circulation* 2001; 104: 429–435.
29 Yasunobu Y, Oudiz RJ, Sun XG, *et al.* End-tidal P_{CO2} abnormality and exercise limitation in patients with primary pulmonary hypertension. *Chest* 2005; 127: 1637–1646.
30 Hansen JE, Ulubay G, Chow BF, *et al.* Mixed-expired and end-tidal CO_2 distinguish between ventilation and perfusion defects during exercise testing in patients with lung and heart diseases. *Chest* 2007; 132: 977–983.
31 Charalampopoulos A, Gibbs JS, Davies RJ, *et al.* Exercise physiological responses to drug treatments in chronic thromboembolic pulmonary hypertension. *J Appl Physiol* 2016; 121: 623–628.
32 Ulrich S, Hasler ED, Saxer S, *et al.* Effect of breathing oxygen-enriched air on exercise performance in patients with precapillary pulmonary hypertension: randomized, sham-controlled cross-over trial. *Eur Heart J* 2017; 38: 1159–1168.
33 Naeije R, Faoro V. The great breathlessness of cardiopulmonary diseases. *Eur Respir J* 2018; 51: 1702517.