ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Early View

Original article

Response to exercise in patients with pulmonary arterial hypertension treated with combination therapy

Mari Nishizaki, Aiko Ogawa, Hiromi Matsubara

Please cite this article as: Nishizaki M, Ogawa A, Matsubara H. Response to exercise in patients with pulmonary arterial hypertension treated with combination therapy. *ERJ Open Res* 2020; in press (https://doi.org/10.1183/23120541.00725-2020).

Response to exercise in patients with pulmonary arterial hypertension treated with combination therapy

Mari Nishizaki, MD[1], Aiko Ogawa, MD, PhD[2], Hiromi Matsubara, MD, PhD[2,3]

1 Department of Rehabilitation, National Hospital Organization Okayama Medical Center, Okayama, Japan

2 Department of Clinical Science, National Hospital Organization Okayama Medical Center, Okayama, Japan

3 Department of Cardiology, National Hospital Organization Okayama Medical Center, Okayama, Japan

Correspondence: Hiromi Matsubara,

Department of Cardiology and Department of Clinical Science,

National Hospital Organization Okayama Medical Center,

1711-1 Tamasu, Kita-ku, Okayama 701-1192, Japan.

Tel: +81-86-294-9911

Fax: +81-86-294-9255

E-mail: matsubara.hiromi@gmail.com

Introduction

Pulmonary arterial hypertension (PAH) is characterized by pulmonary haemodynamic dysfunction, leading to elevation of pulmonary arterial pressure and progressive right heart failure [1]. However, PAH-specific therapy, which includes selective pulmonary vasodilators, improves pulmonary haemodynamics at rest, exercise capacity, quality of life, and prognosis [2-4]. Currently, combination therapy is the most widely utilized strategy, and randomized controlled trials have shown its efficacy on the improvement of exercise capacity and the reduction of time to clinical worsening [5]. We demonstrated that pulmonary haemodynamics at rest was remarkably improved and survival was good in Japanese patients with idiopathic/heritable PAH patients, most of whom were receiving combination therapy [6]; however, exertional dyspnoea remained in some patients. It was reported that there was no improvement in Borg Dyspnoea Score even after combination therapy [7]. Exertional dyspnoea in patients with PAH can be related to ventilation/perfusion mismatching due to hypoperfusion of ventilated alveoli during exercise [8]. We hypothesized that pulmonary haemodynamic response to exercise was impaired in patients with PAH even after pulmonary haemodynamics at rest was improved with combination therapy, and that it related to ventilatory efficiency and hypoxemia during exercise. We also hypothesized that the impairment of pulmonary haemodynamic response would depend on pulmonary haemodynamics at rest.

Material and methods

Study participants

From June 2009 to April 2018, 141 patients with PAH consecutively underwent haemodynamic studies with right-heart catheterization during follow-up at the National Hospital Organization Okayama Medical Center, Okayama, Japan. The diagnosis of PAH was established using standard criteria [9]. The exclusion criteria for cardiopulmonary exercise

testing (CPET) with right-heart catheterization were as follows: monotherapy; treatment with PAH-specific therapy in other hospitals for more than 1 year; mild PAH (mean pulmonary arterial pressure (mPAP) <30 mmHg) at the initiation of PAH-specific therapy at our hospital; under optimization of treatment regimen of PAH-specific therapy; concomitant treatment with surgery (e.g., closure of shunt); World Health Organization (WHO) functional class IV; six-minute walk distance ≤200 m; comorbid arthritis or musculoskeletal disorder; tachyarrhythmia; and enrolment in another clinical study. After providing informed consent, 34 patients underwent CPET with right-heart catheterization (Figure 1). This study was approved by the institutional review board at National Hospital Organization Okayama Medical Center (RINKEN 2018-028). All patients were referred from other hospitals with or without PAH-specific therapy. Clinical parameters had been evaluated at the initiation of PAH-specific therapy in our hospital, indicated as baseline. The parameters were also evaluated when CPET was performed, indicated as study enrolment. Blood samples were drawn from a peripheral vein and brain natriuretic peptide levels were measured. Pulmonary functions were tested using a spirometer (CHESTAC-3000, CHEST, Tokyo, Japan, or FUDAC-77, FUKUDA DENSHI, Tokyo, Japan). Vital capacity, forced expiratory volume in the first second, and diffusing capacity of the lungs for carbon monoxide (DL_{CO}) were evaluated. The six-minute walk test was performed according to the guidelines [10].

Cardiopulmonary exercise test with right-heart catheterization

A Swan–Ganz catheter (AK-09903-J, Arrow Teleflex medical, PA, USA) was inserted via the internal jugular vein into the pulmonary artery, and haemodynamic parameters were assessed at rest in the supine position in the catheterization laboratory. The mPAP, pulmonary artery wedge pressure, and cardiac output (CO) were evaluated using the Fick method during right-heart catheterization. Cardiac index (CI) was calculated as CO divided by body surface

area. After preparation within 30 minutes, CPET with right-heart catheterization was performed to evaluate pulmonary haemodynamic and respiratory response to exercise. Patients were carefully assisted onto a semi-supine cycle ergometer (Strength Ergo 240 BK-ERG-003, Mitsubishi Electric Engineering, Tokyo, Japan), which was set at an angle of 40° with legs comfortably positioned. After resting for 3 minutes, the patients started warm-up cycling at 0 watt for 2 minutes. The workload during exercise was increased by 1 watt every 12 seconds. They were instructed to maintain cycling at the speed of 50–55 rotations per minute. Cardiac activity and peripheral arterial oxygen saturation (SpO_2) were continuously monitored using a standard 12-lead electrocardiogram and pulse oximeter, respectively, and non-invasive systolic blood pressure at the brachial artery with a sphygmomanometer was measured every minute. Because mPAP and mean right atrial pressure are easily influenced by breathing, the values measured during expiration were recorded. CI and mixed venous oxygen saturation were monitored using continuous CO monitoring (Vigilance monitor, Edwards Lifesciences LLC, Irvine, CA, USA). CI was measured using the thermodilution method every minute, and three consecutive values were averaged. All these parameters were recorded per minute. Patients performed submaximal symptom-limited exercise. According to the guidelines, the criteria for the CPET termination were as follows: dizziness, chest pain, ischemic electrocardiographic changes, significant arrhythmia, fall in systolic blood pressure (>20 mmHg from the highest value during the test), hypertension (systolic blood pressure >220 mmHg), severe elevation in mPAP (>70 mmHg), desaturation (SpO_2 <88%), and reaching targeted heart rate, which was calculated as (220-age) × 0.8 [11]. The CPET was performed by several medical staff trained for emergencies. Total pulmonary resistance (TPR) was calculated as mPAP divided by CO. The mPAP/workload slope was calculated as the change in mPAP from rest to peak exercise divided by peak workload, and the SpO_2/workload slope was calculated as the change in SpO_2 from rest to peak exercise divided by peak workload. The mPAP/CO slope, a parameter of

pulmonary haemodynamic response to exercise, was calculated as the change in mPAP from rest to peak exercise divided by the change in CO from rest to peak exercise.

The levels of respiratory gases were also measured breath-by-breath using an aero monitor (AE-300S, Minato Medical Science Co., Ltd, Osaka, Japan, or Cpex-1, Inter Reha Co., Ltd, Osaka, Japan) during exercise. Oxygen uptake ($V'O_2$), carbon dioxide output ($V'CO_2$), and minute ventilation (V'E) were monitored continuously. Anaerobic threshold was determined by V-slope method or ventilatory equivalents method [12]. As a parameter of ventilatory efficiency, $V'E/V'CO_2$ slope was evaluated. It was determined by linear regression of V'E versus $V'CO_2$ from start of exercise to the ventilatory compensation point for metabolic acidosis.

Statistical Analysis

All parameters were expressed as mean ± standard deviation. Because brain natriuretic peptide levels were not normally distributed, median values were exceptionally adopted. The WHO functional class was expressed as the median, and the changes in the number of patients in each class were evaluated using the Wilcoxon signed rank test. The changes in the number of PAH-specific therapy were evaluated using the McNemar test. The parameters between the two groups were compared using the paired t-test. Linear regression analysis (Pearson's correlation) was used to calculate the correlations among parameters. All analyses were performed using IBM SPSS Statistics 20 (IBM corp., Armonk, NY, USA). P-values <0.05 were considered statistically significant.

Results

Patient Characteristics

We performed CPET with right-heart catheterization for 34 patients with PAH undergoing combination therapy. After two patients with poor recording during CPET were excluded, 32 patients were enrolled in this study (Figure 1). The patient characteristics are shown in Table 1. The study population included 29 women (91%). Twenty-two patients had idiopathic/heritable PAH. Seven patients had PAH associated with connective tissue disease; three had systemic lupus erythematosus, three had mixed connective tissue disease, and one had systemic sclerosis. PAH was associated with congenital heart disease in two patients and portal hypertension in one patient. At baseline, PAH-specific therapy was already induced in 17 patients (53%) at the previous hospitals; however, only six patients (19%) were undergoing combination therapy. After being referred to our hospital, PAH-specific drugs were initiated or added, and all patients were undergoing combination therapy at study enrolment: dual therapy: 13 (41%); triple therapy: 19 (59%). At study enrolment, 26 patients (81%) were treated with intravenous epoprostenol (61.1 ± 47.3 months, 66.4 ± 32.9 $ng \cdot kg^{-1} \cdot min^{-1}$). Most patients had been classified in the WHO functional class III or IV at baseline; however, after 55.2 ± 45.2 months of PAH-specific therapy at our hospital, all patients improved to class I or II at study enrolment. Brain natriuretic peptide levels significantly improved. DL_{CO} at baseline were not available for two patients. DL_{CO} significantly improved at study enrolment; however, the values were not within the normal limits. Haemodynamic impairment of mPAP, CI, and pulmonary vascular resistance (PVR) had been moderate-to-severe at baseline; however, remarkable improvement was seen with the combination therapy at study enrolment. The mPAP at rest <25 mmHg was obtained in 13 patients. The six-minute walk distance also significantly improved.

Pulmonary haemodynamic and respiratory response during exercise

All 32 patients underwent successful CPET, and no adverse events during the test. The endpoint was leg fatigue in 11 patients, dyspnoea in eight patients, both leg fatigue and dyspnoea in 10 patients, and severe elevation of mPAP in three patients. Workload at peak exercise was 37.7 ± 11.3 watt. Haemodynamic and oxygen parameters during CPET are shown in Table 2 and Figure 2. The mPAP significantly increased from 27.9 ± 10.7 to 45.9 ± 16.7 mmHg (Figure 2A). CI inadequately increased from 3.72 ± 0.85 to 5.35 ± 1.20 $L \cdot min^{-1} \cdot m^{-2}$ (Figure 2B). As a result, TPR increased from 5.74 ± 3.42 to 6.58 ± 3.82 Wood units (Figure 2C). SpO_2 decreased from 97.0 ± 1.2 to 94.0 ± 2.7% (Figure 2D). SpO_2 at rest was ≥95% in all 32 patients; however, SpO_2 at peak exercise was <90% in four patients. The mPAP/workload slope significantly correlated with mPAP at rest ($r = 0.78$, $p<0.01$) (Figure I in Data Supplement). The mPAP/CO slope was 10.0 ± 6.7 $mmHg \cdot L^{-1} \cdot min$, and it was >3 $mmHg \cdot L^{-1} \cdot min$ in 28 patients (Figure 3). This result indicated that the pulmonary haemodynamic response to exercise was impaired in most of the patients despite remarkable improvement in pulmonary haemodynamics at rest with combination therapy. On the other hand, 10 out of 13 patients whose mPAP at rest was <25 mmHg met the criterion of mPAP at peak exercise ≤30 mmHg or TPR at peak exercise ≤3 Wood units (normalized resting pulmonary hypertension (PH) without exercise-induced PH), although their pulmonary haemodynamic impairment at baseline was severe (mPAP: 52.2 ± 9.5 mmHg, PVR: 17.8 ± 4.9 Wood units).

Respiratory parameters during CPET are indicated in Table 3. Peak $V'O_2$/weight and $V'O_2$ at anaerobic threshold/weight moderately decreased compared with predicted values. Peak $V'O_2$/weight did not significantly correlate with the mPAP/CO slope ($r = -0.09$, $p = 0.62$); however, it correlated with CI at peak exercise ($r = 0.39$, $p = 0.03$). The $V'E/V'CO_2$ slope increased, as compared with that of normal subjects [13].

Correlation between pulmonary haemodynamic response and parameters at rest and during exercise

The mPAP/CO slope significantly correlated with the V'E/V'CO_2 slope (r = 0.51, p <0.01) (Figure 4A), and it negatively correlated with the SpO_2/workload slope (r = − 0.41, p = 0.02) (Figure 4B). The mPAP/CO slope tended to shift upward and become steeper as mPAP at rest (Figure 3). We investigated the correlation between the mPAP/CO slope and parameters at rest and during exercise (Table 4). The mPAP/CO slope significantly correlated with mPAP at rest (r = 0.73, p<0.01) and TPR at rest (r = 0.64, p<0.01); however, it did not correlate with other haemodynamic, oxygen, and respiratory parameters at rest.

Discussion

Pulmonary haemodynamic and respiratory response during exercise

Pulmonary circulation is a lower-pressure and lower-vascular resistance system compared with systemic circulation due to the high compliance of the right ventricular-pulmonary vascular bed unit under normal conditions. Pulmonary circulation also has a large reserved capacity, that is, pulmonary vessels could be distended and recruited when blood flow increases [14]. For these reasons, PVR decreases during exercise and it leads to slight increase in pulmonary arterial pressure even with increased CO. This physiology was confirmed in the systematic review based on the right-heart catheterization in 1187 healthy participants from 47 studies in 13 countries, and mPAP during exercise was dependent on exercise level and age [15]. Tolle et al. demonstrated that mPAP increased from 13.9 to only 27.4 mmHg, and PVR decreased from 154 to 62 dyne·s·cm^{-5} (from 1.9 to 0.8 Wood units) at the maximal workload under the stress of incremental cycling exercise in 16 normal participants [16]. According to the review by Lewis et al., invasive or non-invasive studies in healthy participants showed that the mPAP/CO slope ranged from 0.9 to 2.5 mmHg·L^{-1}·min [17]. However, this response could be impaired in

patients with PAH due to pulmonary vascular remodelling. Decreased reserved capacity in pulmonary vascular bed would bring remarkable increase in mPAP and PVR, resulting in the steeper mPAP/CO slope. Although the data on PAH patients are limited, Blumberg et al. indicated that the constant exercise on a 45°-upright cycle ergometer increased mPAP from 45 to 70 mmHg and PVR from 904 to 1013 dyne·s·cm^{-5} (from 11.3 to 12.7 Wood units) in 16 patients with PH including PAH [18]. In the review by Lewis et al., the mPAP/CO slope in patients with PAH, whose mPAP at rest was over 40 mmHg, ranged from 6.1 to 11.9 mmHg·L^{-1}·min [17]. Another study reported that the steep mPAP/CI slope existed in PAH patients, whose mPAP at rest was still high despite of PAH-specific therapy [19, 20]. In the present study, even though mPAP at rest was much lower, the mPAP/CO slopes in most of the patients remained steep. This result suggests that reserved capacity in pulmonary vascular bed did not recover sufficiently. Recently, combining mPAP >30 mmHg and TPR >3 Wood units during exercise has been proposed as the criterion for diagnosis of exercise PH [21]. Ten patients in the present study met the criteria of mPAP at rest <25 mmHg and mPAP at peak exercise ≤30 mmHg or TPR at peak exercise ≤3 Wood units (normalized resting PH without exercise-induced PH), although their pulmonary haemodynamic impairment before treatment was severe. Exercise capacity was moderately reduced. The subjective exercise limitation in most patients was leg fatigue and/or dyspnoea. The objective exercise limitation was not mPAP/CO slope but cardiac output.

Correlation between pulmonary haemodynamic response and parameters at rest and during exercise

It has been shown that the steep V'E/V'CO_2 slope was related to both resting and exercise PVR in patients with Group II PH [22]. V'E/V'CO_2 is determined by two factors: ratio of dead space to tidal volume and arterial CO_2 tension [23]. In patients with idiopathic PAH, the ventilation

of underperfused alveoli causes an increase in dead space ventilation, manifested by a hyperbolic increase in V'E relative to the V'CO_2 increase during exercise [8]. In the present study, we demonstrated that the mPAP/CO slope significantly correlated with the V'E/V'CO_2 slope. This suggests the possibility that hypoperfusion of ventilated alveoli due to impaired pulmonary haemodynamic response to exercise increased dead space, resulting in steep V'E/V'CO_2 slope. We further found that the mPAP/CO slope significantly correlated with the SpO_2/workload slope. This result suggests that reduced pulmonary capillary bed due to impaired pulmonary haemodynamic response would also influence hypoxemia during exercise. Exertional dyspnoea in patients with PAH can be attributed to at least three mechanisms that increased ventilatory drive: the first is ventilation/perfusion mismatching, resulting in an increased ratio of dead space to tidal volume due to hypoperfusion of ventilated alveoli; the second is the increased hydrogen ion stimulus to ventilation resulting from a low workload lactic acidosis, and the third is arterial hypoxemia due to reduced pulmonary capillary bed or to right to left shunt through a patent foramen ovale [8]. We demonstrated the possibility of hypoperfusion of ventilated alveoli and hypoxemia in the present study. These factors might cause residual exertional dyspnoea.

In a previous study, it was shown that the mPAP/CO slope significantly correlated with mPAP at rest in several patients with PAH [24]. We investigated the correlation between the mPAP/CO slope and parameters at rest and during exercise in more patients with PAH. The mPAP/CO slope significantly correlated with mPAP and TPR at rest. This result suggests that the impairment of pulmonary haemodynamic response could be predicted by the severity of pulmonary haemodynamics at rest.

We recommend investigation of the pulmonary and respiratory response by CPET with right-heart catheterization before a rehabilitation program can be started for all PAH patients; however, it is difficult when haemodynamic impairment is severe. Based on the findings of a

steep mPAP/CO slope in patients with higher mPAP and TPR at rest, patients with severe PAH should avoid excessive exercise training, because the right ventricular overload during exercise would be much higher in these patients, even if exercise load is the same.

Study Limitations

This study has some limitations. First, the size of the patient population was small. Second, patients with mPAP <30 mmHg at the initiation of PAH-specific therapy at our hospital were not included and it is unknown if our results apply to patients with mild PAH. Third, we evaluated vascular resistance using TPR and not PVR because pulmonary artery wedge pressure as an estimate of left atrial pressure was technically difficult to evaluate at peak exercise. The left atrial pressure could increase during exercise due to impaired filling of the left ventricle by left-shift of intraventricular septum. Fourth, the CPET with right-heart catheterization could not be performed at baseline because of disease severity (PVR >18 Wood units). A comparison with the haemodynamic data during exercise before therapy might have strengthened the conclusion on the effect of combination therapy on haemodynamics during exercise. Fifth, we could not evaluate arterial CO_2 tension and hydrogen ion because we did not collect blood samples during exercise.

Conclusions

Even after pulmonary haemodynamics at rest was remarkably improved with PAH-specific combination therapy, pulmonary haemodynamic response to exercise remained impaired in most of the PAH patients and it related to decreased ventilatory efficiency and the severity of hypoxemia. The impairment of pulmonary haemodynamic response depended on higher mPAP and TPR at rest.

Acknowledgements

We are grateful to physical therapists Tatsuya Yasukawa, Kaori Ando, Noriko Takehara, Tetsushi Nakaji, and Ayano Nakano (National Hospital Organization Okayama Medical Center) for their assistance in performing CPET with right-heart catheterization.

References

1. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M; ESC Scientific Document Group. 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 Heart J 2016; 37: 67-119.
2. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, Groves BM, Tapson VF, Bourge RC, Brundage BH, Koerner SK, Langleben D, Keller CA, Murali S, Uretsky BF, Clayton LM, Jöbsis MM, Blackburn SD, Shortino D, Crow JW; Primary Pulmonary Hypertension Study Group. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med 1996; 334: 296-301.
3. Monaco TJ, Davila CD. Safety, efficiency, and clinical utility of macitentan in the treatment of pulmonary arterial hypertension. Drug Design, Development and Therapy 2016; 10: 1675-1682.
4. Sastry BKS, Narasimhan C, Reddy NK, Raju BS. Clinical efficacy of Sildenafil in primary

pulmonary hypertension: A randomized, placebo-controlled, double-blind, crossover study. J Am Coll Cardiol 2004; 43: 1149-1153.

5. Galiè N, Palazzini M, Manes A. Pulmonary arterial hypertension: from the kingdom of the near-dead to multiple clinical trial meta-analyses. Eur Heart J 2010; 31: 2080-2086.
6. Ogawa A, Satoh T, Tamura Y, Fukuda K, Matsubara H. Survival of Japanese Patients With Idiopathic/Heritable Pulmonary Arterial Hypertension. (Am J Cardiol 2017; 119: 1479-1484.
7. McLaughlin VV, Benza RL, Rubin LJ, Channick RN, Voswinckel R, Tapson VF, Robbins IM, Olschewski H, Rubenfire M, Seeger W. Addition of Inhaled Treprostinil to Oral Therapy for Pulmonary Arterial Hypertension: A Randomized Controlled Clinical Trial. J Am Coll Cardiol 2010; 55: 1915–1922.
8. Sun X-G, Hansen JE, Oudiz RJ, Wasserman K. Exercise Pathophysiology in Patients With Primary Pulmonary Hypertension Circulation 2001; 104: 429-435
9. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, Gomez Sanchez MA, Krishna Kumar R, Landzberg M, Machado RF, Olschewski H, Robbins IM, Souza R. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013; 62, Suppl D: D34-D41.
10. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS Statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166: 111-117.
11. American Thoracic Society/American College of Chest Physicians. ATS/ACCP Statement on Cardiopulmonary Exercise Testing. Am J Respir Crit Care Med 2003; 167: 211-277.
12. Binder RK, Wonisch M, Corra U, Cohen-Solald A, Vanhees L, Saner H, Schmid J-P. Methodological approach to the first and second lactate threshold in incremental cardiopulmonary exercise testing. Eur J Cardiovasc Prev Rehabil 2008, 15: 726–734.

13. Sun X-G, Hansen JE, Garatachea N, Storer TW, Wasserman K. Ventilatory efficiency during exercise in healthy subjects. Am J Respir Crit Care Med 2002; 166: 1443-1448
14. West JB, Luks AM. West's Respiratory Physiology. The essentials. 10th edition. Wolters Kluwer, 2016; pp. 41-62.
15. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. Eur Respir J 2009; 34: 888-894.
16. Tolle JJ, Waxman AB, Van Horn TL, Pappagianopoulos PP, Systrom DM. Exercise-induced pulmonary arterial hypertension. Circulation 2008; 118: 2183-2189.
17. Lewis GD, Bossone E, Naeije R, Grünig E, Saggar R, Lancellotti P, Ghio S, Varga J, Rajagopalan S, Oudiz R, Rubenfire M. Pulmonary vascular hemodynamic response to exercise in cardiopulmonary diseases. Circulation 2013; 128: 1470-1479.
18. Blumberg FC, Riegger G. J, Pfeifer M. Hemodynamic effects of aerosolized iloprost in pulmonary hypertension at rest and during exercise. Chest 2002; 121: 1566-1571.
19. Provencher S, Hervé P, Sitbon O, Humbert M, Simonneau G, Chemla D. Changes in exercise haemodynamics during treatment in pulmonary arterial hypertension. Eur Respir J 2008; 32: 393-398.
20. Castelain V, Chemla D, Humbert M, Sitbon O, Simonneau G, Lecarpentier Y, Hervé P. Pulmonary artery pressure-flow relations after Prostacyclin in Primary Pulmonary Hypertension. Am J Respir Crit Care Med 2002; 165: 338-340.
21. Herve P, Lau EM, Sitbon O, Savale L, Montani D, Godinas L, Lador F, Jaïs X, Parent F, Günther S, Humbert M, Simonneau G, Chemla D. Criteria for diagnosis of exercise pulmonary hypertension. Eur Respir J 2015; 46: 728-737.
22. Lewis GD, Shah RV, Pappagianopolas PP, Systrom DM, Semigran MJ. Determinants of ventilatory efficiency in heart failure: The role of right ventricular performance and pulmonary vascular tone. Circ Heart Fail 2008; 1: 227-233.

23. Johnson RL. Gas Exchange Efficiency in Congestive Heart Failure. Circulation 2000; 101: 2774-2776.
24. Janicki JS, Weber KT, Likoff MJ, Fishman AP. The pressure-flow response of the pulmonary circulation in patients with heart failure and pulmonary vascular disease. Circulation 1985; 72: 1270-1278.

Tables:

Table 1 Patient characteristics

	baseline	study enrolment	p-value
Sex (male/female), n	3/29		—
Age, years	28.5 ± 10.3	33.0 ± 10.1	<0.01
Body mass index, $kg \cdot m^{-2}$	20.7 ± 3.0	19.8 ± 2.6	0.09
WHO-functional class * (I/II/III/IV), n	3 (0/6/14/12)	2 (7/25/0/0)	<0.01
Pulmonary arterial hypertension-specific therapy			
intravenous epoprostenol, n (%)	1 (3%)	26 (81%)	<0.01
beraprost, n (%)	11 (34%)	5 (16%)	0.18
endothelin receptor antagonist, n (%)	9 (28%)	30 (94%)	<0.01
phosphodiesterase type 5 inhibitor, n (%)	6 (19%)	21 (66%)	<0.01
soluble guanylate cyclase stimulator, n (%)	0 (0%)	1 (3%)	—
combination therapy			
dual therapy, n (%)	2 (6%)	13 (41%)	<0.01
triple therapy, n (%)	4 (13%)	19 (59%)	<0.01
Laboratory parameters			
BNP**, $pg \cdot mL^{-1}$	334.45 (8.7-1687.6)	10.25 (5.8-131.7)	<0.01
Respiratory parameters			
%VC, % predicted	89.9 ± 17.2	93.7 ± 14.4	0.03
FEV_1/FVC, %	84.1 ± 7.3	82.5 ± 7.2	0.24
$\%DL_{CO}$, % predicted	58.5 ± 12.6	66.3 ± 10.8	<0.01
Pulmonary hemodynamic parameters			
PAWP, mmHg	8.3 ± 3.4	7.9 ± 3.2	0.57

mPAP, mmHg	61.8 ± 18.3	28.7 ± 12.2	<0.01
CI, $L \cdot min^{-1} \cdot m^{-2}$	2.17 ± 0.66	3.59 ± 0.89	<0.01
PVR, Wood units	18.3 ± 8.0	4.3 ± 2.9	<0.01
Exercise capacity			
6MWD, m	287.3 ± 117.1	449.7 ± 69.2	<0.01

Data are presented as mean ± standard deviation, unless stated otherwise.

* median (number); ** median (range)

WHO: World Health Organization; BNP: brain natriuretic peptide; VC: vital capacity; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; DL_{CO}: diffusing capacity of the lungs for carbon monoxide; PAWP: pulmonary artery wedge pressure; mPAP: mean pulmonary arterial pressure; CI: cardiac index; PVR: pulmonary vascular resistance; 6MWD: six-minute walk distance.

Table 2 Hemodynamic and oxygen parameters during cardiopulmonary exercise test

	rest	peak exercise	change (%)	p-value
sBP, mmHg	104.0 ± 10.4	127.8 ± 19.4	+ 23	<0.01
HR, bpm	82.4 ± 12.0	121.9 ± 14.7	+ 50	<0.01
mRAP, mmHg	3.6 ± 2.0	6.4 ± 2.2	+ 121	<0.01
mPAP, mmHg	27.9 ± 10.7	45.9 ± 16.7	+ 67	<0.01
CI, $L \cdot min^{-1} \cdot m^{-2}$	3.72 ± 0.85	5.35 ± 1.20	+ 46	<0.01
TPR, Wood units	5.74 ± 3.42	6.58 ± 3.82	+ 17	<0.01
SpO_2, %	97.0 ± 1.2	94.0 ± 2.7	- 3.1	<0.01
SvO_2, %	76.8 ± 4.2	53.5 ± 7.6	- 30	<0.01

Data are presented as mean ± standard deviation.

sBP: systolic blood pressure; HR: heart rate; mRAP: mean right atrial pressure; mPAP: mean pulmonary arterial pressure; CI: cardiac index; TPR: total pulmonary resistance; SpO_2: peripheral arterial oxygen saturation; SvO_2: mixed venous oxygen saturation.

Table 3 Respiratory parameters during cardiopulmonary exercise test

Peak $V'O_2$, $mL \cdot min^{-1}$	658.5 ± 147.8
Peak $V'O_2$/weight, $mL \cdot min^{-1} \cdot kg^{-1}$	14.3 ± 3.7
%peak $V'O_2$/weight, % predicted	53.8 ± 13.5
$V'O_2$ at AT, $mL \cdot min^{-1}$	533.3 ± 106.0
$V'O_2$ at AT/weight, $mL \cdot min^{-1} \cdot kg^{-1}$	11.6 ± 2.5
%$V'O_2$ at AT/weight, % predicted	70.8 ± 15.4
$V'E/V'CO_2$ slope, $mL \cdot mL^{-1}$	31.7 ± 5.2

Data are presented as mean ± standard deviation.

$V'O_2$: oxygen uptake; AT: anaerobic threshold; V'E: minute ventilation; $V'CO_2$: carbon dioxide output.

Table 4 Correlation between the mPAP/CO slope and parameters at rest and during the exercise

	r	p-value
At rest		
mPAP	0.73	<0.01
CI	− 0.15	0.41
TPR	0.64	<0.01
SpO_2	− 0.03	0.89
SvO_2	− 0.15	0.42
%VC	0.33	0.07
FEV_1/FVC	− 0.15	0.42
$\%DL_{CO}$	0.05	0.78
During exercise		
mPAP at peak	0.70	<0.01
CI at peak	− 0.60	<0.01
TPR at peak	0.80	<0.01
SpO_2 at peak	− 0.19	0.29
SvO_2 at peak	− 0.15	0.40

mPAP: mean pulmonary arterial pressure; CI: cardiac index; TPR: total pulmonary resistance; SpO_2: peripheral arterial oxygen saturation; SvO_2: mixed venous oxygen saturation; VC: vital capacity; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; DL_{CO}: diffusing capacity of the lungs for carbon monoxide.

Figure 1

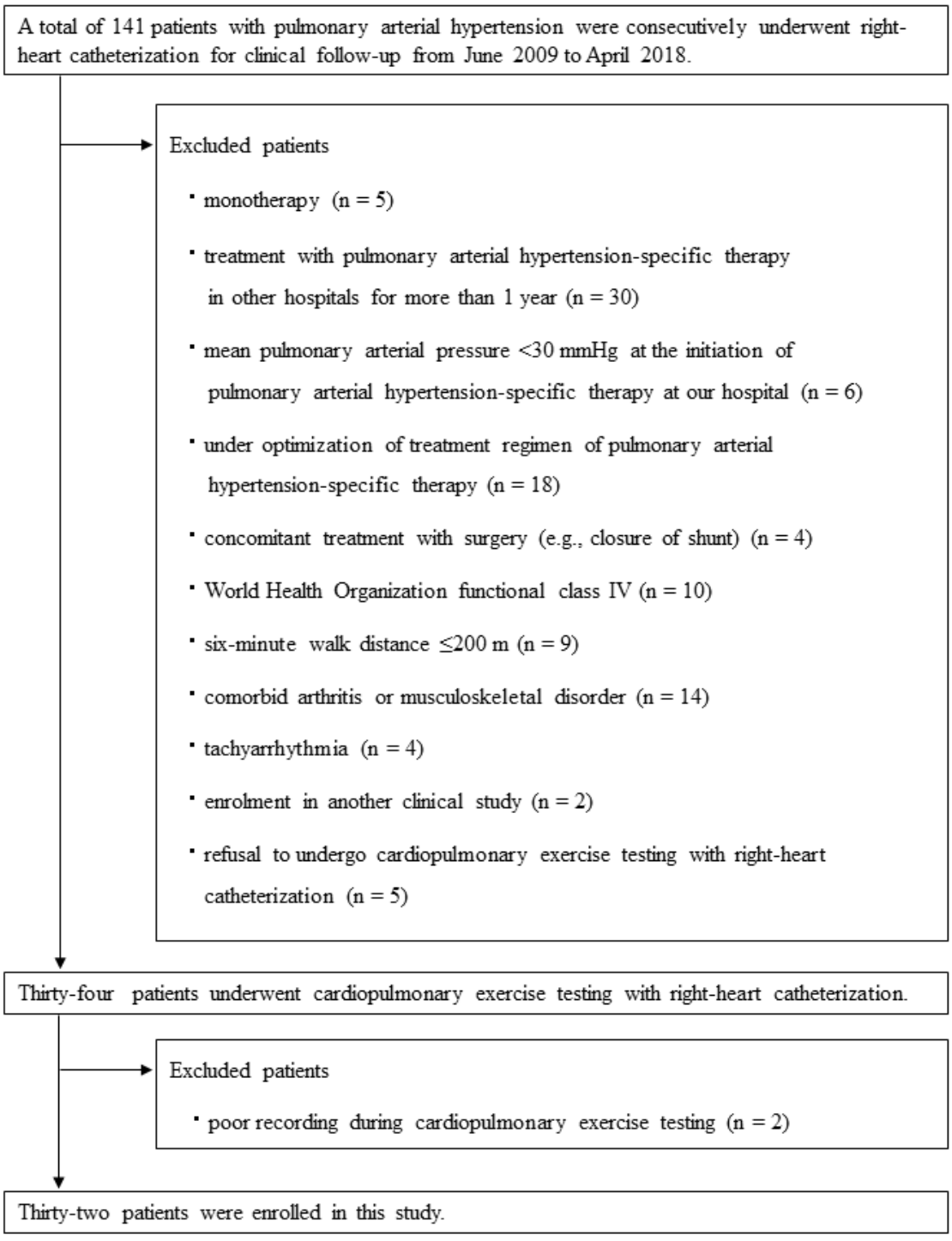

Figure 1 Flow diagram of patient population for study inclusion

Figure 2

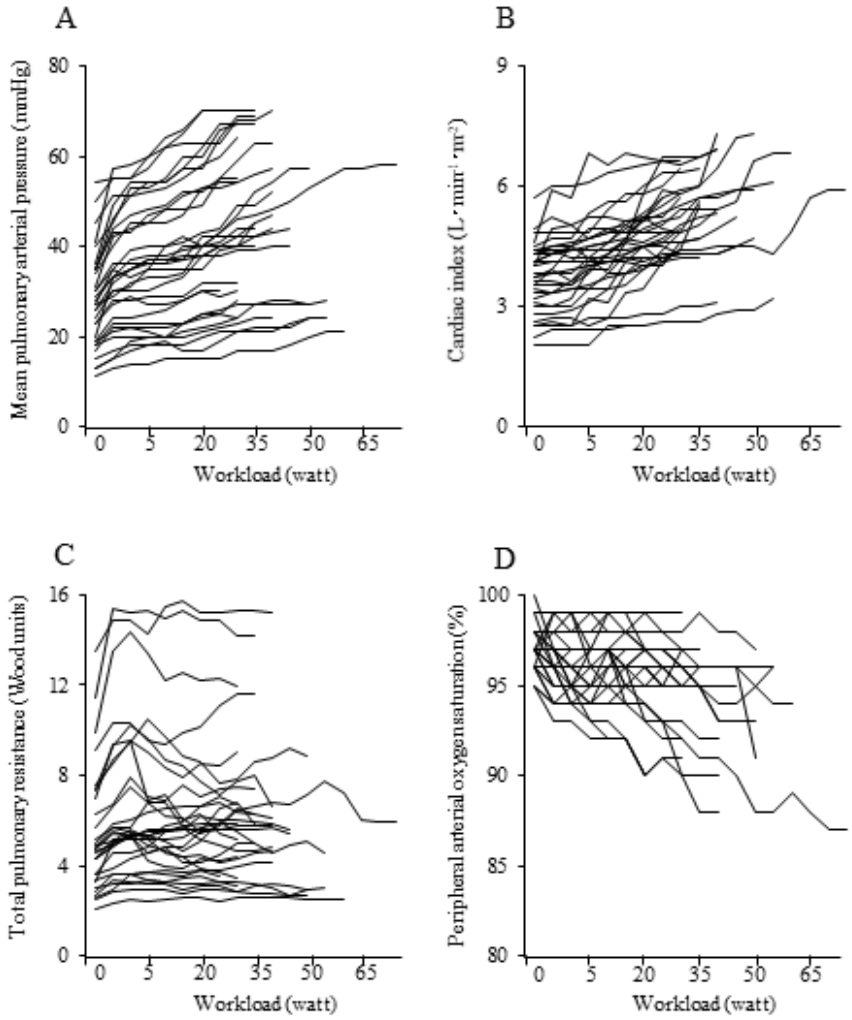

Figure 2 Haemodynamic and oxygen parameters during cardiopulmonary exercise testing in patients with pulmonary arterial hypertension. A - mean pulmonary arterial pressure; B - cardiac index; C - total pulmonary resistance; D - peripheral arterial oxygen saturation

Figure 3

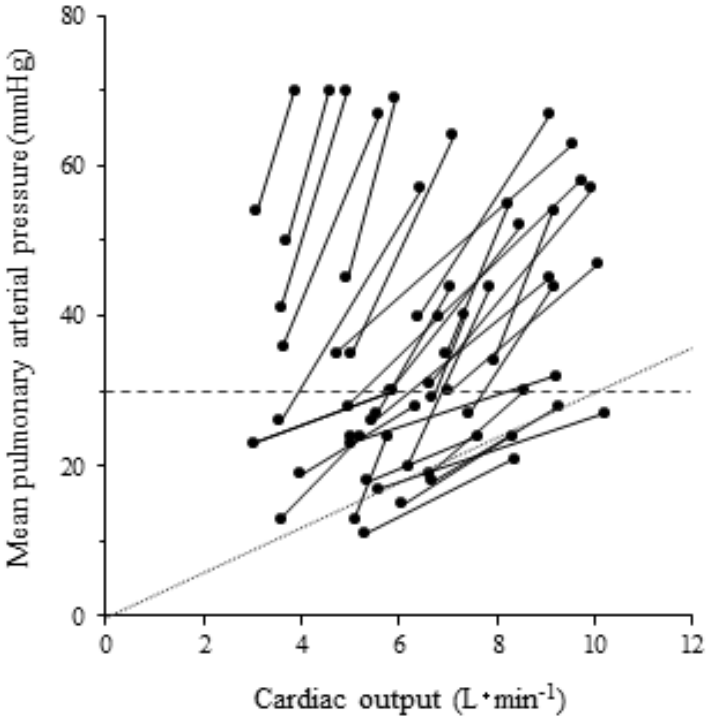

Figure 3 The mean pulmonary arterial pressure (mPAP)/cardiac output (CO) slope during cardiopulmonary exercise testing in patients with pulmonary arterial hypertension. The broken line represents mPAP at rest of 30 mmHg and the dotted line represents the mPAP/CO slope of 3 mmHg·L-1·min.

Figure 4

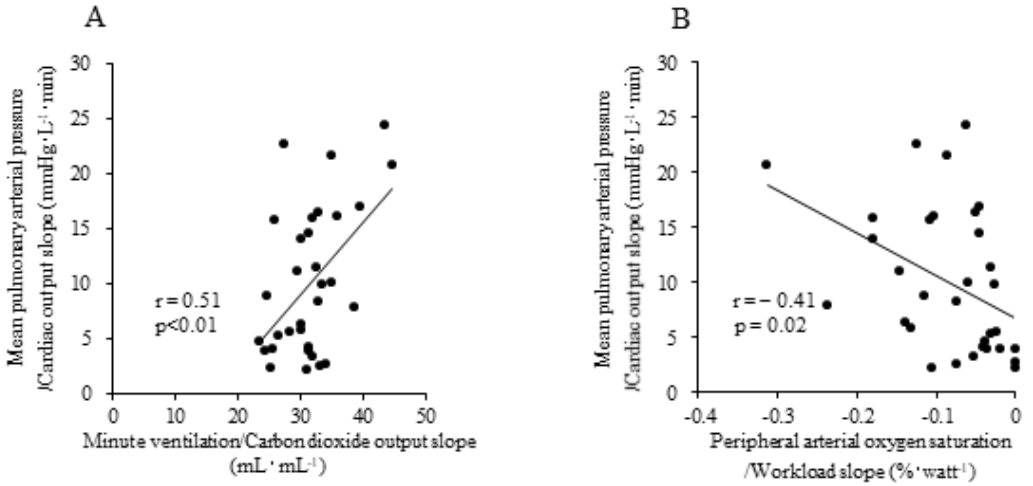

Figure 4 Correlation between the mean pulmonary arterial pressure/cardiac output slope and parameters during cardiopulmonary exercise testing in patients with pulmonary arterial hypertension. A - minute ventilation/carbon dioxide output slope; B - peripheral arterial oxygen saturation/workload slope The continuous lines indicate the regression lines.

Supplementary Data

Response to exercise in patients with pulmonary arterial hypertension treated with combination therapy

Mari Nishizaki, MD[1], Aiko Ogawa, MD, PhD[2], Hiromi Matsubara, MD, PhD[2,3]

1 Department of Rehabilitation, National Hospital Organization Okayama Medical Center, Okayama, Japan

2 Department of Clinical Science, National Hospital Organization Okayama Medical Center, Okayama, Japan

3 Department of Cardiology, National Hospital Organization Okayama Medical Center, Okayama, Japan

Correspondence: Hiromi Matsubara,

Department of Cardiology and Department of Clinical Science,

National Hospital Organization Okayama Medical Center,

1711-1 Tamasu, Kita-ku, Okayama 701-1192, Japan.

Tel: +81-86-294-9911

Fax: +81-86-294-9255

E-mail: matsubara.hiromi@gmail.com

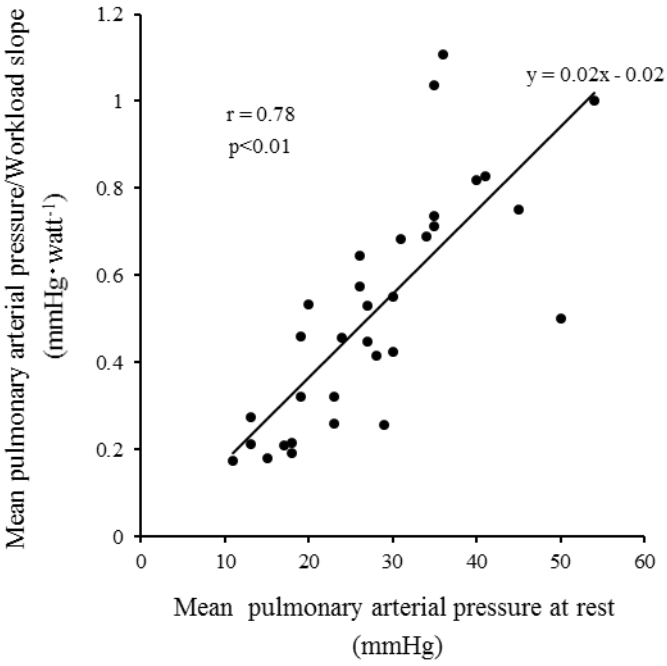

Figure I in Data Supplement Correlation between mean pulmonary arterial pressure (mPAP) at rest and the mPAP/workload slope during cardiopulmonary exercise testing in patients with pulmonary arterial hypertension.

The continuous line indicates the regression line. The mPAP/workload slope significantly correlated with mPAP at rest. The equation to predict mPAP at peak exercise was (mPAP at rest) + 0.02 × [(mPAP at rest) − 1] × (workload at peak exercise).