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Associations of Exercise Tolerance with Hemodynamic Parameters for Pulmonary Arterial Hypertension and for Chronic Thromboembolic Pulmonary Hypertension

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Structured Abstract

INTRODUCTION: Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are the main subgroups of pulmonary hypertension (PH). Despite differences in their etiologies, both diseases are characterized by vascular remodeling resulting in progressive right heart failure. The noninvasive periodic evaluation of exercise tolerance has become increasingly important as well as hemodynamic assessment by right heart catheterization (RHC). Cardiopulmonary exercise testing (CPX) and 6-minute walking test (6MWT) are now both recommended for evaluating exercise tolerance, but there is insufficient knowledge about possible differences in the associations of exercise tolerance with RHC data for PAH and for CTEPH patients.

METHODS: A retrospective study was performed of 57 PH patients, 24 with PAH and 33 with CTEPH, all of whom underwent echocardiography, CPX, 6MWT, and RHC.

RESULTS: For both PAH and CTEPH patients, peak HR resulting from CPX was significantly higher than that from 6MWT, while minimum SpO_2 resulting from CPX and 6MWT was similar. For PAH patients, significant correlations were observed between peak VO_2 and cardiac index (CI) ($r=0.59$; $p=0.002$) and between VE/VCO_2 slopes and CI ($r=-0.46$, $p=0.02$), as well as a correlative tendency, although not statistically significant, for peak VO_2 and PVR or for VE/VCO_2 and PVR ($r=-0.39$; $p=0.05$ and $r=0.39$; $p=0.06$, respectively). For CTEPH patients, however, significant correlation was observed only between VE/VCO_2 slopes and CI ($r=-0.38$; $p=0.02$).

CONCLUSION: PH etiology should be taken into consideration when assessing exercise tolerance, while CPX can be effective in addition to hemodynamic assessment by means of RHC for periodic evaluation during follow-up.

Condensed Abstract

We studied 57 pulmonary hypertension (PH) patients 24 with pulmonary arterial hypertension (PAH) and 33 with chronic thromboembolic PH (CTEPH). Associations between exercise tolerance and hemodynamic parameters were different for PAH and CTEPH patients despite similar disease characteristics. Exercise tolerance should thus be assessed while taking PH etiology into consideration.

Key Words: Pulmonary arterial hypertension; Chronic thromboembolic pulmonary hypertension; Cardiopulmonary exercise testing

Introduction

Pulmonary hypertension (PH) is a clinical syndrome characterized by progressive obstructive pulmonary vasculopathy leading to increased pulmonary vascular resistance (PVR), elevated pulmonary artery pressure, and right ventricular failure[1, 2]. Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are the main subgroups of this disorder. Although recent advances in theoretic options have improved symptoms and survival of both PAH and CTEPH patients[3, 4], prognosis remains poor while individual risk stratification is important for establishing the appropriate treatment strategy. In line with improved prognosis for PH patients, periodic noninvasive therapeutic evaluation has become increasingly important in addition to hemodynamic assessment by means of right heart catheterization (RHC) for assessing exercise tolerance. Cardiopulmonary exercise testing (CPX) and the 6-minute walking test (6MWT) are both recommended for evaluating exercise tolerance of both PAH and CTEPH patients[5, 6], Previous clinical trials reported that endothelin receptor antagonist therapy improved hemodynamic parameters and exercise tolerance for PAH, but improved only exercise tolerance for CTEPH[7, 8]. In addition, it was recently reported that riociguat therapy as pulmonary vasodilator improved hemodynamic parameters and exercise tolerance for both PAH and CTEPH[3, 4]. On the other hand, exercise tolerance was assessing by 6MWT in these clinical trials, previous study showed that CPX is more useful for maximum exercise test in children PH patients[9], but it is not clear which of CPX and 6MWT are more useful for maximum exercise test in PAH and CTEPH patients. Furthermore there is insufficient knowledge about possible differences in the associations of exercise tolerance with RHC data for PAH and for CTEPH patients.

Accordingly, the objective of our study was to evaluate that which is more useful as maximum exercise test for PAH and CTEPH patients by means of CPX or 6MWT. We also tested the hypothesis that there are differences in the associations of exercise tolerance with RHC data for PAH and CTEPH patients.

Methods

Study Populations

Of a total of 97 consecutive PH patients classified as Dana Point classification group 1 or 4 who visited or were admitted to Kobe University Hospital between June 2010 and December 2014. 57 PH patients of whose underwent echocardiography, CPX, 6MWT, and RHC were analyzed retrospectively. PH was defined as mean pulmonary arterial pressure (PAP) > 25mmHg at rest determined by means of RHC. All patients were in World Health Organization (WHO) functional class II or III, and none with musculoskeletal disease were included in this study. The patients excluded from the study were those with: (1) atrial fibrillation; (2) coronary artery disease, defined as a single coronary artery stenosis of >50 % of the diameter of a major epicardial vessel or a previous history of myocardial infarction; (3)

congenital heart disease; (4) more than mild aortic and/or mitral valvular heart disease. All patients were in clinically stable condition at the time of enrollment. This study was approved by the local ethics committee of our institution, and written informed consent was obtained from all patients.

Cardiopulmonary Exercise Testing

CPX using a cycle-ergometer (Strength Ergo 8; Mitsubishi Electric Engineering, Tokyo, Japan) in accordance with the American Thoracic Society guidelines was performed within 1 week following RHC[10]. One minute of upright rest was followed by 4 minutes of unloaded pedaling (0 W) and then progressive increments in the workload (5 or 10 W/min) to symptom-limited maximum tolerance. The rate of increase in the workload was empirically determined by the supervising physical therapist and physician on the basis of the patient's medical history and clinical data. Test duration was between 7 and 14 min (from unloaded pedaling to peak exercise capacity) for all patients. Oxygen consumption (VO_2), carbon dioxide production (VCO_2), and minute ventilation (VE) were measured continuously on a breath-by-breath basis (Cpex-1; Inter-Reha, Tokyo, Japan). Peak VO_2 was defined as the VO_2 measured during the last 30 seconds of peak exercise[7]. Ventilatory efficiency during exercise was expressed as the slope of VE versus VCO_2 over the linear component of the plot of VE versus VCO_2[11]. Pulse oximetry O_2 saturation (SpO_2) was measured continuously with a finger probe (Smart Pulse, Fukuda Denshi, Tokyo, Japan).

6-Minute Walking Test

6MWT was performed in accordance with the American Thoracic Society guidelines[10]. 6MWT was performed in a 30-meter long, straight corridor under the guidance of physical therapist or physician. For this test, participants were instructed to walk at a self-selected pace with the aim of covering as much distance as possible in six minutes. At the end of the test, the 6-minute walking distance (6MWD) was recorded. SpO_2 was measured continuously with a finger probe (Smart Pulse, Fukuda Denshi).

Hemodynamic Measurements

A Swan-Ganz catheter was used for hemodynamic measurements at rest. mPAP, PCWP, PVR and cardiac index (CI) were estimated according to the Fick principle. An investigator blinded to the echocardiographic, CPX, and 6MWT data measured the pressure.

Statistical Analysis

Continuous variables were expressed as mean values ± standard deviation or percentages, while categorical data were summarized as frequencies and percentages. All group data were compared by using the 2-tailed Student's *t* test for unpaired data. Univariate linear correlation analysis was used for comparison of RHC and CPX data. For all tests, a p value of <0.05 was considered statistically significant. All analyses were performed with commercially available software (MedCalc software version 12.1; MedCalc Software, Inc., Mariakerke, Belgium).

Results

Baseline Characteristic of PH Patients

The baseline clinical, echocardiographic, and hemodynamic data of the 57 PH patients are summarized in Table 1. Twenty-four patients (42%) were found to have PAH and the remaining 33 (58%) CTEPH. Twenty-four patients (42 %) took PH-specific drugs at the time of enrollment. Compared with the CTEPH patients, the PAH patients were more likely to be younger, and have higher heart rate (HR), lower tricuspid annular plane systolic excursion, and higher prevalence of administration of diuretics. CPX and 6MWT were successfully performed for all patients, and the data are summarized in Table 2. At peak exercise capacity, PAH patients were more likely to show lower blood pressure, workload, and VE/VCO_2 slope than did CTEPH patients. 6MWT results, on the other hand, were similar for the two groups.

Comparison of CPX and 6MWT Data for PAH and CTEPH Patients

Figure 1 shows peak HR and minimum SpO_2 as assessed by means of CPX and 6MWT for PAH and CTEPH patients. For PAH patients, CPX-assessed peak HR was significantly higher than 6MWT- assessed HR (132.1±20.6 bpm vs. 109.5±17.1 bpm; $p<0.0001$), while minimum SpO_2 as assessed by means of CPX and 6MWT was similar (86.5±8.6 % vs. 86.6±6.0 %; $p=0.93$). Similarly for CTEPH patients, CPX-assessed peak HR was significantly higher than 6MWT-assessed HR (131.4±20.0 bpm vs. 106.8±15.3 bpm; $p<0.0001$), and minimum SpO_2 as assessed by means of CPX and 6MWT proved to be similar (88.5±4.1 % vs. 88.2±3.9 %; p=0.75).

Comparisons of Associations of Exercise Tolerance with RHC Data for PAH and CTEPH Patients

Associations of exercise tolerance with RHC data for PAH and CTEPH patients are shown in Figures 2 and 3. For PAH patients, significant correlations were observed between peak VO_2 and CI (r=0.59, p=0.002) and between VE/VCO_2 slopes and CI (r=-0.46, p=0.02). Moreover, PAH patients had a trend for a significant correlation between peak VO_2 and PVR tended to be significant (r=-0.39, p=0.05), but not statistically significant between VE/VCO_2 and PVR (r=0.39, p=0.06). For CTEPH patients, on the other hand, significant correlation was observed only between VE/VCO_2 slopes and CI (r=-0.38, p=0.02).

Discussion

The findings of our study demonstrate that peak CPX-assessed HR was significantly higher than 6MWT-assessed HR while minimum SpO_2 assessed by means of CPX and 6MWT was similar for PAH and CTEPH patients. A noteworthy difference in associations was observed between exercise tolerance and RHC data for PAH and CTEPH patients despite similar baseline characteristics of the two disorders.

Assessment of Exercise Tolerance for PAH and CTEPH

CPX-assessed peak HR was significantly higher than 6MWT-assessed HR, while minimum SpO_2 assessed by means of CPX and 6MWT was similar for PAH and CTEPH patients in this study. Most investigations of PAH and CTEPH patients have focused on cardiac function at rest. In addition, the therapeutic effects on exercise capacity for such patients have been commonly based on results for 6MWT. However, in a recent meta-analysis of 6MWT findings for PAH patients, improvement in 6MWT results did not reflect benefits in terms of clinical outcomes[12]. The findings of our study confirm those previously reported that CPX is more effective than 6MWT for measuring maximum exercise tolerance for PH patients[13,14]. On the other hand, Lammers et al reported that 6MWT reflects symptomatic maximum exercise test compared with CPX using bicycle ergometry in PH children with a 6MWD below 300m[9]. Although this study and ours produced the different findings, our study used 57 elderly PH patients with a mean 6MWD of 349m.

Peak VO_2 and VE/VCO_2 slopes correlated with CI and PVR for all PH patients, whether PAH or CTEPH[15-17], because an increase in PVR produces a decrease in blood flow to the left side of the heart, thus resulting in a lower CI. Our study found that hemodynamic parameters including CI and PVR were associated with CPX-derived parameters including peak VO_2 and VE/VCO_2 slope for PAH patients, but no such findings were observed for CTEPH patients. The differences in correlations between exercise tolerance and hemodynamic parameters may reflect differences in the pathophysiology of PAH and CTEPH. Zhai et al reported that physiologic ventilatory dead space fraction (V_D/V_Tphys) measured at peak exercise by using arterial blood gas analysis and VE/VCO_2 slopes were higher for CTEPH than PH patients[18]. They suggested that common prognostic end points determined by means of CPX cannot be applied to all forms of PH. Furthermore, a previous study has shown that abnormal pulmonary vascular and right ventricular reserve during CPX was observed in CTEPH patients with normalized resting mPAP after pulmonary endarterectomy compared with healthy control[19]. This may support our findings of the differences in hemodynamic parameters during CPX for PAH and CTEPH.

Clinical Implications

PAH is a main subgroup of PH, which encompasses disease processes that lead to increased right ventricular load, while CTEPH is another PH subgroup with symptoms and a clinical picture that are partly similar to those of PAH. Despite the differences in etiologies between PAH and CTEPH, both are primarily characterized by vascular remodeling that results in progressive right heart failure and death[20-22]. However, several treatment options have become available for patients with various forms of PH, especially PH-specific vasodilators for PAH patients, and balloon pulmonary angioplasty or pulmonary endarterectomy for CTEPH patients. Given the poor prognosis for both diseases, treatment compliance and follow-up are thus very important. As described above, the associations of exercise tolerance with hemodynamic parameters are different for PAH and CTEPH patients because of differences in their pathophysiology. CPX may therefore constitute a better noninvasive management procedure for PAH and CTEPH patients, so that evaluation of exercise tolerance during follow-up has become increasingly important in view of the etiology of PH.

Study Limitation

This study covered a small number of patients in a single-center retrospective study, so that future studies of larger patient populations are necessary to validate our findings. Furthermore, since only patients who could pedal a cycle-ergometer were enrolled in this study, there is a possibility of some selection bias.

Conclusion

CPX is more useful than 6MWT as maximum exercise test for PAH and CTEPH patients. Peak VO_2 and VE/VCO_2 slopes correlated with CI for PAH patients, VE/VCO_2 slopes only correlated with CI for CTEPH patients. These differences might be represented by pathophysiology of PAH and CTEPH patients. Thus, PH etiology should be taken into consideration when assessing exercise tolerance, and CPX may therefore be useful in addition to hemodynamic assessment by means of RHC for periodic evaluation during follow-up.

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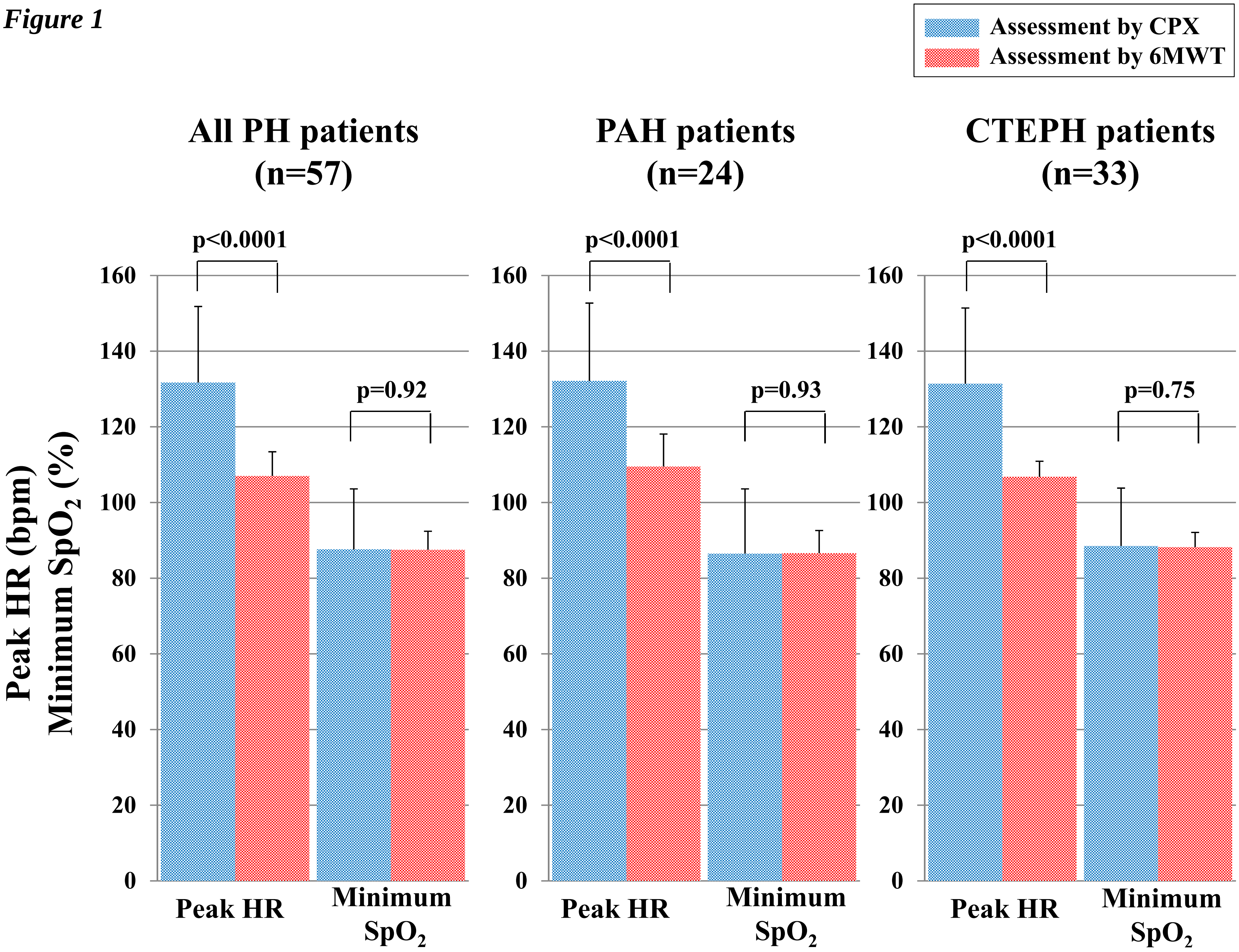
Figure Legends

Figure 1: Comparison of peak heart rate (HR) and minimum SpO_2 as assessed by means of cardiopulmonary exercise testing (CPX) and 6-minute walk test (6MWT) for all pulmonary hypertension (PH), pulmonary arterial hypertension (PAH) and chronic thromboembolic PH (CTEPH) patients.

Figure 2: Associations of hemodynamic parameters including cardiac index (CI) and pulmonary vascular resistance (PVR) with cardiopulmonary exercise testing (CPX)-derived parameters including peak oxygen consumption (VO_2) and ventilation/carbon dioxide production ratio (VE/VCO_2) slope of pulmonary arterial hypertension (PAH) patients.

Figure 3: Associations of hemodynamic parameters including cardiac index (CI) and pulmonary vascular resistance (PVR) with cardiopulmonary exercise testing (CPX)-derived parameters including peak oxygen consumption (VO_2) and ventilation/carbon dioxide production ratio (VE/VCO_2) slope of chronic thromboembolic pulmonary hypertension (CTEPH) patients.

Figure 1



Assessment by CPX
Assessment by 6MWT
All PH patients (n=57)
PAH patients (n=24)
CTEPH patients (n=33)
p<0.0001
p=0.92
p<0.0001
p=0.93
p<0.0001
p=0.75
Peak HR (bpm)
Minimum SpO2 (%)
0
20
40
60
80
100
120
140
160
Peak HR
Minimum SpO2

Figure 2

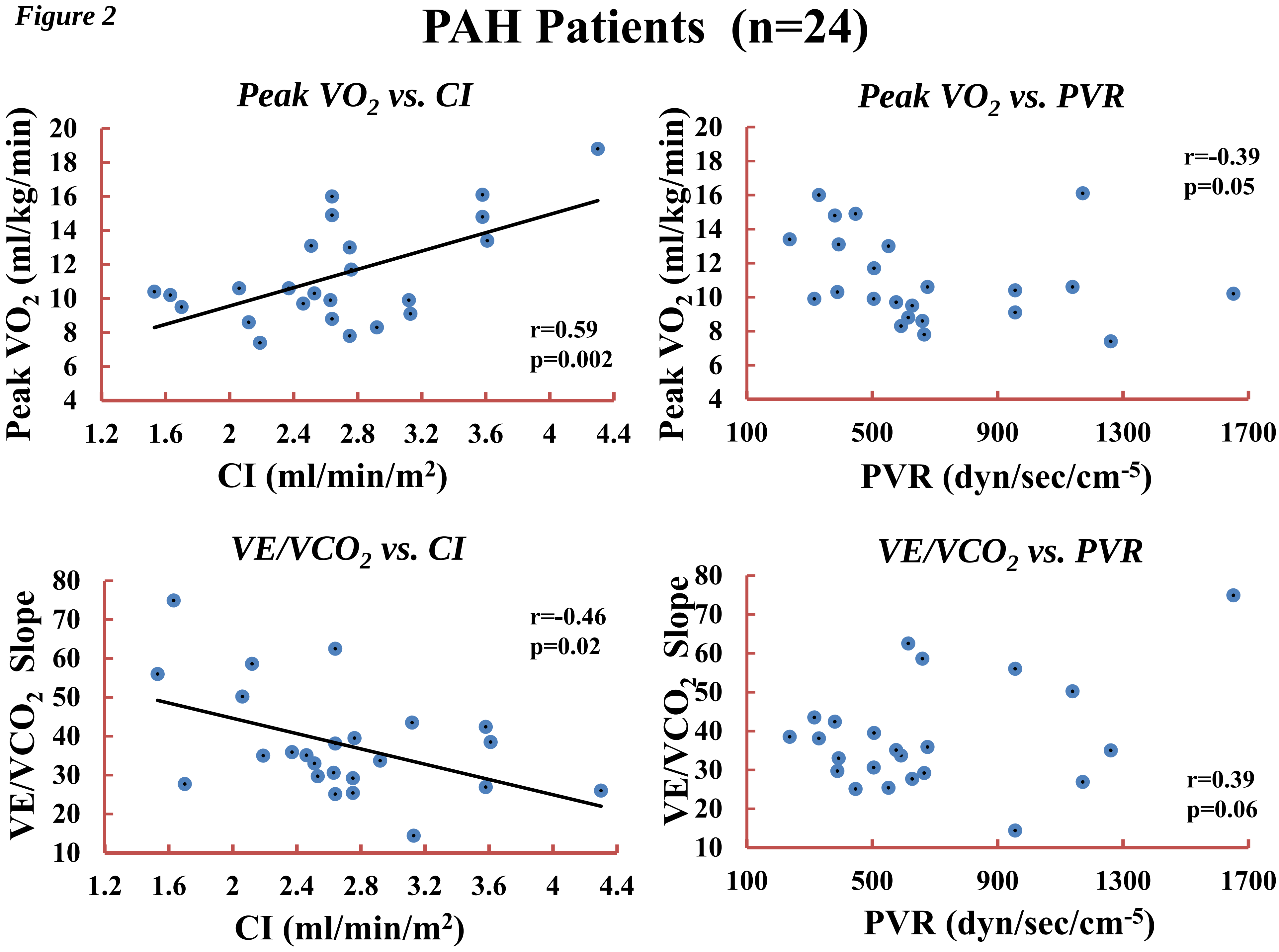

PAH Patients (n=24)
Peak VO2 vs. CI
Peak VO2 (ml/kg/min)
CI (ml/min/m2)
r=0.59
p=0.002
Peak VO2 vs. PVR
PVR (dyn/sec/cm-5)
r=-0.39
p=0.05
VE/VCO2 vs. CI
VE/VCO2 Slope
r=-0.46
p=0.02
VE/VCO2 vs. PVR
r=0.39
p=0.06

Figure 3

CTEPH Patients (n=33)

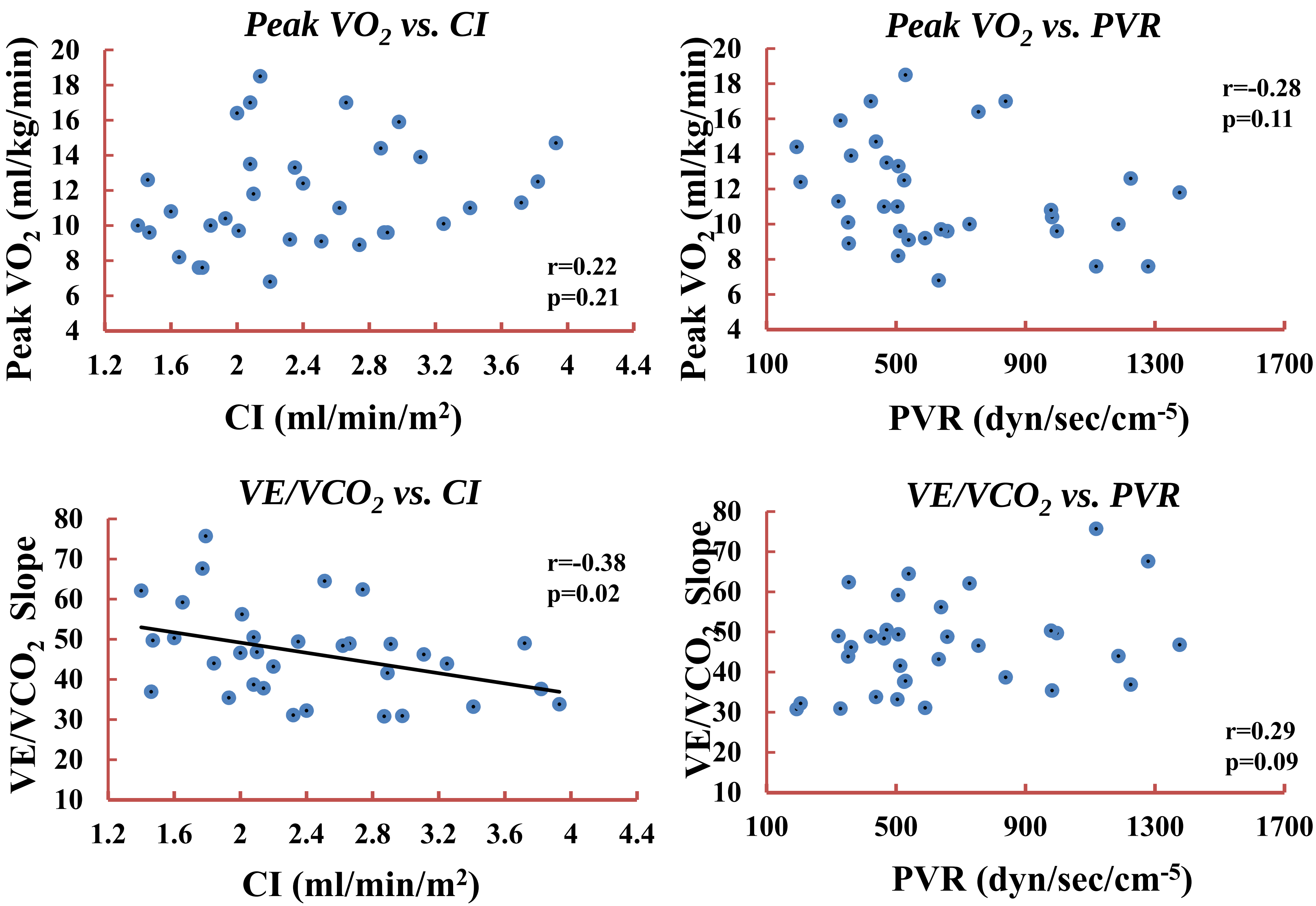


Table 1
Characteristic of Patients

	All PH Patients (n=57)	PAH Patients (n=24)	CTEPH Patients (n=33)	p value
Age, y	58 ± 15	52 ± 17	63 ± 12	0.003
Female, n (%)	39 (68)	18 (75)	21 (64)	0.36
Height, m	1.58 ± 0.08	1.57 ± 0.07	1.59 ± 0.09	0.33
Weight, kg	56.4 ± 12.1	54.4 ± 12.7	57.9 ± 11.7	0.28
Body mass index, kg/m^2	23.2 ± 7.8	23.9 ± 11.4	22.7 ± 3.5	0.56
Systolic blood pressure, mmHg	110±19	110 ± 16	113 ± 21	0.20
Diastolic blood pressure, mmHg	67± 13	65 ± 13	68 ± 12	0.31
Heart rate, beats per minute	80±14	85 ± 17	75 ± 11	0.007
World Health Organization functional class, n (%)				
I	0 (0)	0 (0)	0 (0)	1.0
II	0 (0)	8 (33)	10 (30)	0.80
III	0 (0)	16 (67)	23 (70)	0.80
IV	0 (0)	0 (0)	0 (0)	1.0
Laboratory data				
Brain natriuretic peptide, pg/ml	95 ± 116	100 ± 107	92 ± 124	0.80
pH	7.43 ± 0.03	7.42 ± 0.03	7.43 ± 0.03	0.53
PaO_2, mmHg	68.2 ± 10.6	69.2 ± 10.0	67.5 ± 11.1	0.55
$PaCO_2$, mmHg	36.8 ± 6.1	37.1 ± 8.2	36.6 ± 4.0	0.77
Echocardiographic data				
Left ventricular end-diastolic diameter, mm	41.7 ± 5.4	40.7 ± 5.5	42.5 ± 5.3	0.22
Left ventricular end-systolic diameter, mm	25.3 ± 4.9	24.9 ± 5.3	25.7 ± 4.7	0.55
Left ventricular ejection fraction	67.8 ± 7.9	65.6 ± 7.2	69.4 ± 8.1	0.07
Tricuspid annular plane systolic excursion, mm	18.1 ± 4.2	16.4 ± 4.5	19.4 ± 3.6	0.01
Right heart catheterization data				
Cardiac index, $L/min/m^2$	2.5 ± 0.7	2.7 ± 0.7	2.4 ± 0.7	0.18
Pulmonary capillary wedge pressure;, mmHg	7.9 ± 3.5	8.2 ± 3.9	7.7 ± 3.1	0.59
Mean pulmonary arterial pressure, mmHg	37.0 ± 11.4	39.1 ± 14.4	35.5 ± 8.6	0.24
Pulmonary vascular resistance, $dyn/sec/cm^{-5}$	653 ± 338	654 ± 306	652 ± 322	0.98
Medications, n (%)				
Endothelin receptor antagonist	19 (33)	9 (38)	10 (30)	0.56
Phosphodiesterase type 5 inhibitors	11 (19)	6 (25)	5 (15)	0.35
Oral prostayclin analogs	10 (18)	4 (17)	6 (18)	0.88

Epoprostenol	1 (2)	1 (4)	0 (0)	0.23
Diuretics	17 (30)	11 (46)	6 (18)	0.02

Data are shown as n (%) or mean ± SD.

Table 2
Exercise Tolerance Data of the Patients

	PH Patients (n=57)	PAH Patients (n=24)	CTEPH Patients (n=33)	p value
Cardiopulmonary exercise testing parameters				
At peak exercise				
Systolic blood pressure, mmHg	157.6 ± 32.3	142.8 ± 27.5	168.4 ±31.5	0.002
Heart rate, beats per minute	131.7 ± 20.1	132.1 ± 20.6	131.4 ± 20.0	0.88
Pulse oximeter oxygen saturation, %	87.6 ± 6.4	86.5 ± 8.6	88.5 ± 4.1	0.24
Respiratory exchange ratio	1.30 ± 0.11	1.31 ± 0.12	1.30 ± 0.09	0.61
Borg scale	16.1 ± 2.0	15.9 ± 2.3	16.3 ± 1.8	0.47
Workload, W	62.2 ± 21.2	54.9 ± 21.2	67.4 ± 19.8	0.02
VO_2, ml/kg/min	11.5 ± 3.0	11.4 ± 3.0	11.6 ± 3.0	0.73
VE/VCO_2 slope	42.9 ± 13.1	38.0 ± 13.9	46.5 ± 11.4	0.01
6 minutes walking test parameters				
6 minutes walking distance, m	349.4 ± 108.7	347.2 ± 127.2	350.9 ± 95.1	0.90
Peak Heart rate, beat per minute	107.9 ± 16.0	109.5 ± 17.1	106.8 ± 15.3	0.53
Lowest pulse oximeter oxygen saturation, %	87.5 ± 4.9	86.6 ± 6.0	88.2 ± 3.9	0.22

Data are shown as mean ± SD

VO_2, oxygen uptake; VE, ventilation; VCO_2, carbon dioxide prodution.