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ORIGINAL ARTICLE

Sex-specific cardiopulmonary exercise testing parameters as predictors in patients with idiopathic pulmonary arterial hypertension

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Cardiopulmonary exercise testing (CPET) has been used for prognosis in idiopathic pulmonary arterial hypertension (IPAH). We explored whether sex differences had an impact on prognostic assessments of CPET in IPAH. Data were retrieved from 21 male and 36 female incident IPAH patients who underwent both right heart catheterization and CPET from 2010 to 2016 at Shanghai Pulmonary Hospital. Cox proportional hazards analysis was used to assess the prognostic value of CPET. The mean duration of follow-up was 22 ± 15 months. Nine men and 15 women had an event. The differences in clinical parameters in the whole population were not the same as the inter-subgroup differences. Event-free women had significantly higher cardiac output, lower pulmonary vascular resistance and percentage of predicted FVC compared with event men (all $P<0.05$). Event-free men had significantly higher end-tidal partial pressure of CO_2 ($P_{ET}CO_2$) at anaerobic threshold (AT), peak workload, $P_{ET}CO_2$, maximum oxygen consumption (VO_2)/minute ventilation (VE), and oxygen uptake efficiency slope and lower end-tidal partial pressure of O_2 ($P_{ET}O_2$) at AT, peak $P_{ET}O_2$, and lowest VE/VCO_2 compared with event men. Event-free women had dramatically higher peak VO_2, VCO_2, VE and O_2 pulse than event women (all $P<0.05$). Peak $P_{ET}CO_2$ was the independent predictor of event-free survival in all patients and males, whereas peak O_2 pulse was the independent predictor of event-free survival in females. Men with peak $P_{ET}CO_2 \geqslant 20.50$ mm Hg, women with peak O_2 pulse $\geqslant 6.25$ ml per beat and all patients with peak $P_{ET}CO_2 \geqslant 27.03$ mm Hg had significantly better event-free survival. Sex-specific CPET parameters are predictors of poor outcomes. Decreased peak $P_{ET}CO_2$ in men and peak O_2 pulse in women were associated with lower event-free survival in IPAH.
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INTRODUCTION

Sex differences exist in the prevalence, diagnosis, treatment and survival of patients with idiopathic pulmonary arterial hypertension (IPAH).[1–5] Although the incidence in females is higher, several authors have reported that male sex is associated with decreased survival.[6–10] In the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL), male PAH patients were categorized as New York Heart Association Functional Classification I-II (NYHA FC I-II) and had higher mean pulmonary arterial pressure, mean right atrial pressure and cardiac output (CO), as measured by right heart catheterization and 6-min walk distance (6MWD) at diagnosis.[3] Swift *et al.*[11] indicated that men had a proportionally lower right ventricular ejection fraction, right ventricular stroke volume and left ventricular (LV) stroke volume than females, as measured by cardiac MRI, suggesting that the female myocardium exhibits superior adaptation to elevated afterload in IPAH patients.[12] However, there are very few reports about sex differences in IPAH with regard to other diagnostic, screening or assessment methods, for example, cardiopulmonary exercise testing (CPET).

It has already been reported that CPET with gas exchange measurements has the potential to noninvasively grade the severity of exercise limitations, quantifying the hypoperfusion of the lungs and systemic circulation, and assessing responses to therapy in IPAH.[13–17] Most IPAH patients have hypoperfusion of the lungs and systemic circulation, resulting in ventilation and gas exchange abnormalities along with exercise limitations.[18–20] Therefore, CPET can be used to assess functional capacity and treatment efficacy in patients with

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IPAH. However, there are various differences in CPET parameters between healthy male and female subjects. Whether these sex differences in CPET parameters are also seen in IPAH patients with different grades of severity remains unclear.

Therefore, we sought to characterize the sex differences in CPET parameters in IPAH patients with different severity and to attempt to determine whether sex differences are associated with clinical outcomes in these patients.

METHODS

Study sample

Fifty-seven (21 males, 36 females) incident IPAH patients over 18 years old were recruited from Shanghai Pulmonary Hospital from May 2010 to April 2016. The diagnosis of IPAH was established according to the updated NICE clinical classification.[21] Patients with PAH associated with a definite cause such as connective tissue disease and congenital heart disease, and those with porto-pulmonary hypertension, chronic pulmonary obstruction, chronic pulmonary thromboembolism or pulmonary hypertension due to left heart disease were excluded. We also excluded patients with acute or chronic illnesses that might influence hormonal metabolism (that is, acute or chronic infections, chronic autoimmune diseases, previously established primary endocrine disorders) and patients receiving any treatment with hormones (thyroid hormones, anabolic steroids, corticosteroids) or drugs that markedly inhibit hormone production, either at the time of the study or in the past. The local ethics committee approved the study, and all patients gave written informed consent.

Clinical assessment

The demographic information, body mass index (BMI), 6MWD, World Health Organization (WHO) functional classification (FC), N-terminal pro-brain natriuretic peptide (NT pro-BNP), hemodynamic, pulmonary function test (PFT) and CPET parameters were determined at baseline during hospitalization. Right heart catheterization was performed as described in a previous study.[22] The 6MWD test was performed according to American Thoracic Society (ATS) guidelines,[23] and a Borg dyspnea score was determined immediately after the 6MWD test. Immediately prior to their CPET studies, patients underwent standard pulmonary function tests. Patients underwent right heart catheterization and CPET within 3 months.

Each patient underwent resting measurements of forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), maximum voluntary ventilation (MVV), diffusing capacity for carbon monoxide (DLCO) and total lung capacity (TLC) using standard methodology and equipment (Masterscreen-PFT, Jaeger, Hoechberg, Germany; Masterscreen-plethysmography, Jaeger). All PFT values were reported in absolute terms and normalized to the percentage of predicted (%pred). Predicted spirometry values, TLC and DLCO were calculated using accepted equations for Chinese adults.[17]

Under physician supervision, all patients performed a standard, progressively increasing work rate CPET to maximum tolerance on an electromagnetically braked cycle ergometer. Pulse oximetry, heart rate and 12-lead ECG were monitored and recorded. The exercise protocol consisted of 3 min of rest and 3 min of unloaded cycling at 60 rpm, followed by a uniform increase in resistance of 5–15 W min^{-1} for patients and 20–25 W min^{-1} for normal subjects up to maximal tolerance.[24] The rate of workload increment depended on the estimated exercise capacity of the subjects. Subjects were encouraged to exercise to the limits of their functional capacities or until the physician stopped the test because of severe adverse events such as chest pain, lightheadedness, potentially life-threatening arrhythmias, ST segment changes or marked systolic hypotension.[17] Maximum oxygen consumption (VO_2), carbondioxide output (VCO_2), minute ventilation (VE) and other exercise variables were computer-calculated breath by breath, interpolated second by second and averaged over 10-s intervals.[24,25] The anaerobic threshold (AT) ratio of oxygen pulse (O_2 pulse) was determined as previously described.[24] Exercise and metabolic capacity were expressed as workload and VO_2, respectively. Ventilatory efficiency during exercise was expressed as VCO_2, VE, the ratio of VO_2/VE and VE/VCO_2, oxygen uptake efficiency plateau and oxygen uptake efficiency slope.[16] Cardiovascular capacity was expressed as O_2 pulse and heart rate. Gas exchange efficiency was expressed as end-tidal partial pressure of CO_2 ($P_{ET}CO_2$) and end-tidal partial pressure of O_2 ($P_{ET}O_2$).[26]

Outcomes

The primary outcome was clinical worsening, including death, hospitalization or initiation of new active therapy because of worsening PAH. Event-free survival was estimated from the date of confirmation to 5 April 2016. Patients lost to follow-up were censored as alive on the last day of contact.

Statistical analysis

All data are expressed as the mean ± s.d. or medians (and interquartile range) for continuous variables and as the absolute number for categorical variables. Comparisons were performed using *t*-tests or the Mann–Whitney *U*-test for continuous variables and the χ^2-test for categorical variables. Correlations were assessed using the rho coefficient of Spearman. Univariate Cox proportional hazards analysis was performed using baseline values of CPET parameters to assess the prognostic value of each variable and event-free survival. Using a forward stepwise multivariate model, the prognostic power of CPET parameters was compared with that of other significant CPET parameters with univariate analysis. We forced age, BMI and WHO FC into the models to adjust the multivariate analysis. Receiver-operating characteristic curves for independent parameters were drawn, and the areas under the curves were calculated. For a specific parameter, the cutoff level that resulted in the highest product of sensitivity and specificity was considered the optimal cutoff for prognostication. Event-free survival grouped by the cutoff value of independent predictors of CPET parameters was estimated using the Kaplan–Meier method and analyzed with the log-rank test. A P-value < 0.05 was considered significant. The main analysis was performed using SPSS (Statistic Package for Social Science, Chicago, IL, USA) version 19.0.

RESULTS

Characteristics of the studies

A total of 57 IPAH patients matched the inclusion criteria, and 36 (63%) were women. The mean duration of follow-up was 22 ± 15 months. Nine men and 15 women had an event (defined as cardiopulmonary death, hospitalization for right heart failure, addition of another active therapy due to clinical worsening or a switch from oral PAH-active therapy to parenteral for clinical worsening). Seven men and 12 women switched to another active therapy or added target therapy because of adverse effects of the compound itself. Overall, two men and two women died. Only the first event was used in the analysis in seven patients with more than one event. No patient was lost to follow-up, giving us a follow-up rate of 100%. The demographic and hemodynamic data are presented in Table 1. The mean ± s.d. age was 38.3 ± 16.1 for all patients with an event, 40.7 ± 13.0 for event-free patients, 43.9 ± 22.0 for men with an event, 41.6 ± 13.8 for event-free men, 34.9 ± 10.8 for women with an event and 40.2 ± 12.8 for event-free women.

There were no differences in the age, BMI, WHO FC and 6MWD between the event and event-free groups in all patients. Event patients had significantly higher NT pro-BNP levels than the event-free group. There were no differences in the hemodynamic parameters except pulmonary vascular resistance (PVR) at diagnosis between event and event-free patients. The event-free group had significantly lower PVR compared with the event group (Table 1). In the subgroup analysis, there were no differences in age, BMI, WHO FC, 6MWD and NT pro-BNP between the event and event-free groups in men or in women. The two subgroups of men had similar baseline clinical parameters as the two subgroups of women. There were no differences in most hemodynamic parameters at diagnosis between the event group and the event-free group in the whole population, as well as between the subgroups of men and women. However, the event-free

Table 1 Baseline characteristics of all patients with IPAH

	All patients		*Male patients*		*Female patients*	
	Event[a] (n = *24*)	*Event*[a]*-free* (n = *33*)	*Event*[a] (n = *9*)	*Event*[a]*-free* (n = *12*)	*Event*[a] (n = *15*)	*Event*[a]*-free* (n = *21*)
Clinical variables						
Age, y	38.3 ± 16.1	40.7 ± 13.0	43.9 ± 22.0	41.6 ± 13.8	34.9 ± 10.8	40.2 ± 12.8
BMI, kg m^{-2}	22.0 ± 2.9	23.0 ± 3.2	22.9 ± 3.4	23.6 ± 3.3	21.5 ± 2.5	22.7 ± 3.1
WHO FC, n (%)						
I–II	18 (75.0)	20 (60.6)	7 (77.8)	7 (58.3)	11 (73.3)	13 (61.9)
III–IV	6 (25.0)	13 (39.4)	2 (22.2)	5 (41.7)	4 (26.7)	8 (38.1)
6 MWD, m	417.5 ± 108.8	385.5 ± 97.5	465.7 ± 98.4	357.4 ± 104.9	391.2 ± 109.2	402.0 ± 92.1
NT pro-BNP, pg ml^{-1}	665 (187, 1555)	182 (35, 639)[b]	796 (133, 2290)	91 (36, 489)	620 (219, 1516)	183 (34, 649)
Hemodynamics						
mRAP, mm Hg	6.0 ± 3.9	5.4 ± 4.7	7.6 ± 4.4	6.0 ± 5.7	5.33 ± 3.3	4.9 ± 4.0
mPAP,mm Hg	57.9 ± 11.5	53.2 ± 13.5	60.3 ± 10.8	53.0 ± 14.1	57.8 ± 12.4	53.0 ± 13.0
mPAWP,mm Hg	6.6 ± 3.0	7.6 ± 3.6	8.0 ± 1.9	7.4 ± 2.6	6.2 ± 3.3	7.4 ± 4.2
PVR, Wood units	14.0 ± 4.4	10.3 ± 4.5*	14.3 ± 4.2	10.0 ± 4.7	14.7 ± 4.3	10.3 ± 4.5**
CO, l min^{-1}	2.9 ± 0.5	3.0 ± 0.6	3.9 ± 0.9	4.9 ± 1.7	3.9 ± 0.9	4.7 ± 1.1*
SVO_2, %	63.9 ± 12.6	66.5 ± 9.3	58.0 ± 7.0	64.9 ± 12.2	66.9 ± 14.7	68.0 ± 6.2
Specific medications						
PDE- 5 inhibitors, %	11 (45.8)	15 (45.5)	2 (22.2)	7 (58.4)	9 (60.0)	8 (38.1)
ERAs, %	3 (12.5)	8 (24.2)	0 (0.0)	3 (25.0)	3 (20.0)	5 (23.8)
Prostacyclin analog, %	0 (0.0)	3 (9.1)	0 (0.0)	1 (8.3)	0 (13.0)	2 (9.5)
Combination, %	9 (37.5)	6 (18.2)	7 (77.8)	1 (8.3)	2 (13.3)	5 (23.8)
No specific medication	1 (4.2)	1 (3.0)	0 (0.0)	0 (0.0)	1 (6.7)	1 (4.8)

Abbreviations: 6MWD, 6- min walk distance; BMI, body mass index; CO, cardiac output; ERAs, endothelial receptor antagonist; IPAH = idiopathic pulmonary arterial hypertension; mPAP, mean pulmonary arterial pressure; mPAWP, mean pulmonary capillary wedge pressure; mRAP, mean right atrial pressure; NT pro-BNP, N-terminal pro-brain natriuretic peptide; PDE-5, phosphodiesterase type 5; PVR, pulmonary vascular resistance; SVO_2, mixed venous O_2 saturation; WHO FC, World Health Organization functional class.
[a]Event defined as cardiopulmonary death, hospitalization for right heart failure, addition of another active therapy.
*$P<0.05$ and **$P<0.01$, event -free vs. event.
Values are mean (s.d.) or median (interquartile range) for clinical worsening or a switch from oral PAH-active therapy to parenteral for clinical worsening.

women had significantly lower PVR and higher CO compared with event men (Table 1).

Targeted PAH medication included inhaled iloprost, i.v. iloprost, oral beraprost, oral bosentan, oral ambrisentan, oral sildenafil, oral vadenafil and oral tadalafil. Both sexes used phosphodiesterase type 5 inhibitors (9 men and 17 women), endothelin receptor antagonists (3 men and 8 women) and prostacyclin analogs (1 man and 2 women) therapy with a similar frequency. There were no apparent differences in the use of combination therapy (8 men and 7 women) or non-specific medications. Two women had no targeted PAH medication. There were no differences in specific medications between the event and event-free groups in all patients or in the inter-subgroup patients (Table 1).

Sex differences in PFT parameters in patients with IPAH

In all patients, no significantly different PFT parameters were found between the event group and event-free group (Table 2). There were no significant differences in FVC, FEV1, FEV1/FVC, MVV, DLCO, TLC and their percentage of predicted values between the event and event-free groups in the men and women (Table 2). The event and event-free female patients had significantly lower FVC, FVC %pred, FEV1, MVV and TLC compared with the event and event-free male patients (Table 2).

Sex differences in CPET parameters in patients with IPAH

The five aspects of CPET parameters are summarized in Table 3. There were many differences in metabolic, ventilation, cardiovascular and gas exchange parameters between the two groups in the whole population. The event group had lower $P_{ET}CO_2$ at AT, peak VO_2, peak VCO_2, peak $P_{ET}CO_2$, peak VO_2/VE, and peak O_2 pulse and higher $P_{ET}O_2$ at AT, peak $P_{ET}O_2$ and lowest VE/VCO_2 compared with the event-free group. There were also many differences in exercise capacity, ventilation and gas exchange parameters between the event and event-free groups in male patients. The event-free men had a significantly higher peak workload, peak VO_2/VE, oxygen uptake efficiency slope, peak $P_{ET}CO_2$ and $P_{ET}CO_2$ at AT, and lower lowest VE/VCO_2, peak $P_{ET}O_2$ and $P_{ET}O_2$ at AT than the event men. Compared with the event female patients, significant differences were mainly manifested in the metabolic, ventilation and cardiovascular parameters. The event-free group had dramatically higher peak VO_2, peak VCO_2, peak VE and peak O_2 pulse than the event group. The event female patients and event male patients had many differences in ventilatory and gas exchange parameters between them. The event female patients had significantly lower peak VCO_2, lowest VE/VCO_2, and peak $P_{ET}O_2$ and higher peak VO_2/VE and peak $P_{ET}CO_2$ compared with event male patients. There were no significant differences in CPET parameters between the event-free male and event-free female patients.

Factors influencing even-free survival

In the univariate Cox proportional hazards analysis, peak O_2 pulse, peak $P_{ET}O_2$, peak $P_{ET}CO_2$ and $P_{ET}CO_2$ at AT values were related to event-free survival in all patients with IPAH. Peak VO_2/VE and peak $P_{ET}CO_2$ levels were related to event-free survival in male patients

Table 2 Comparison of PFT parameters between event and event-free patients with IPAH

	All patients		*Male patients*		*Female patients*	
	Event (n = 24)	*Event-free (n = 33)*	*Event (n = 9)*	*Event-free (n = 12)*	*Event (n = 15)*	*Event-free (n = 21)*
FVC, l	3.0 ± 0.7	3.0 ± 0.7	3.8 ± 0.4	3.7 ± 0.7	2.5 ± 0.4[a]	2.6 ± 0.4[b]
FVC %Pred	83.4 ± 13.6	85.2 ± 12.8	92.1 ± 13.9	93.1 ± 14.2	78.8 ± 11.4[a]	80.5 ± 9.4[b]
FEV1, l	2.4 ± 0.6	2.4 ± 0.6	3.0 ± 0.5	2.9 ± 0.6	2.1 ± 0.5[a]	2.1 ± 0.3[b]
FEV1 %Pred	80.0 ± 16.3	81.4 ± 11.2	88.8 ± 18.7	86.4 ± 14.1	75.0 ± 13.2	78.4 ± 7.9
FEV1/FVC, %	78.0 ± 17.8	78.4 ± 15.6	69.9 ± 26.5	78.7 ± 8.7	82.3 ± 9.6	78.3 ± 18.8
MVV, l min^{-1}	72.9 ± 33.0	74.4 ± 22.3	96.5 ± 35.6	89.5 ± 26.3	60.1 ± 24.1[a]	65.4 ± 13.5[b]
MVV %Pred	78.5 ± 31.5	80.4 ± 18.8	92.4 ± 35.9	87.0 ± 20.2	71.1 ± 27.3	76.5 ± 17.1
DLCO, ml mm Hg^{-1} min^{-1}	17.1 ± 5.3	17.5 ± 4.4	18.4 ± 8.2	19.7 ± 5.3	16.5 ± 3.2	16.2 ± 3.2
DLCO %Pred	80.0 ± 17.5	83.6 ± 13.1	72.8 ± 21.3	82.5 ± 15.3	83.6 ± 14.6	84.3 ± 11.9
TLC, l	5.0 ± 1.0	4.9 ± 1.0	6.1 ± 0.3	5.9 ± 0.7	4.5 ± 0.7[a]	4.3 ± 0.5[b]
TLC %Pred	97.8 ± 15.2	95.8 ± 12.6	100.9 ± 11.2	101.4 ± 15.5	96.2 ± 17.0	92.4 ± 9.4

Abbreviations: %Pred, percentage of predicted value; DLCO, diffusing capacity for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; IPAH, idiopathic pulmonary arterial hypertension; MVV, maximum voluntary ventilation; PFT, pulmonary function test; TLC, total lung capacity.
[a]$P<0.05$, event in women *vs.* event in men.
[b]$P<0.05$, event-free in women *vs.* event-free in men.
Values are mean (s.d.).

Table 3 Comparison of CPET parameters between event and event-free patients with IPAH

	All patients		*Male patients*		*Female patients*	
	Event (n = 24)	*Event-free (n = 33)*	*Event (n = 9)*	*Event-free (n = 12)*	*Event (n = 15)*	*Event-free (n = 21)*
Exercise capacity parameters						
Peak workload, Watt	67.1 ± 28.6	76.5 ± 29.6	66.9 ± 28.3	87.9 ± 37.3*	58.9 ± 17.3	74.5 ± 27.9
Metabolic parameters						
Peak VO2, ml min^{-1} kg^{-1}	13.4 ± 3.3	15.7 ± 4.1*	13.8 ± 4.0	15.8 ± 4.7	12.7 ± 2.9	15.6 ± 3.7*
VO_2 at AT, ml min^{-1} kg^{-1}	9.8 ± 2.2	11.2 ± 2.7	10.4 ± 2.2	11.8 ± 3.0	9.1 ± 1.8	11.0 ± 2.6
Ventilatory parameters						
Peak VCO_2, ml min^{-1}	819.3 ± 256.3	993.3 ± 290.1*	889.5 ± 271.0	1077.4 ± 359.6	708.4 ± 163.4[aa]	969.5 ± 247.7**
Peak VE, l min^{-1}	45.9 ± 16.8	44.6 ± 10.8	60.3 ± 15.2	49.3 ± 13.0	34.4 ± 7.3	43.2 ± 9.6**
Peak VO_2/VE	17.7 ± 5.2	20.7 ± 4.9*	13.8 ± 4.0	15.80 ± 4.70**	20.4 ± 4.0[aa]	20.7 ± 5.0
OUEP, ml l^{-1}	25.4 ± 5.1	29.0 ± 5.4*	23.0 ± 6.0	27.3 ± 4.2	26.6 ± 4.2	29.8 ± 5.6
OUES, l min^{-1} log^{-1}	1.0 ± 0.3	1.2 ± 0.4	1.0 ± 0.4	1.4 ± 0.5*	1.0 ± 0.3	1.1 ± 0.3
Lowest VE/VCO_2	49.8 ± 12.4	42.3 ± 9.0*	57.9 ± 15.5	45.5 ± 13.9*	45.7 ± 7.2[a]	41.3 ± 8.1
Cardiovascular parameters						
Peak O_2 pulse, ml per beat	5.4 ± 1.0	6.8 ± 2.1**	5.8 ± 1.3	7.4 ± 2.7	5.1 ± 0.6	6.5 ± 1.6**
Peak HR, beats per minute	144.0 ± 26.9	139.6 ± 23.6	145.9 ± 32.9	137.7 ± 27.3	139.7 ± 23.4	142.8 ± 22.1
Gas exchange parameters						
Peak $P_{ET}O_2$, mm Hg	127.6 ± 6.1	124.1 ± 6.0*	132.3 ± 5.9	125.0 ± 5.7**	124.2 ± 4.4[aa]	124.1 ± 6.2
$P_{ET}O_2$ at AT, mm Hg	121.5 ± 7.2	117.0 ± 7.7*	126.7 ± 6.0	119.4 ± 5.8*	118.3 ± 6.5	125.9 ± 8.1
Peak $P_{ET}CO_2$, mm Hg	22.1 ± 6.7	27.8 ± 6.7**	17.5 ± 6.9	27.3 ± 5.7**	24.8 ± 5.4[a]	27.9 ± 7.0
$P_{ET}CO_2$ at AT, mm Hg	25.2 ± 7.1	30.2 ± 6.3**	22.1 ± 8.3	28.6 ± 5.0*	26.6 ± 6.1	30.9 ± 6.6

Abbreviations: AT, anaerobic threshold; CPET, cardiopulmonary exercise testing; HR, heart rate; IPAH, idiopathic pulmonary arterial hypertension; OUEP, oxygen uptake efficiency plateau; OUES, oxygen uptake efficiency slope; $P_{ET}CO_2$, end-tidal partial pressure of CO_2; $P_{ET}O_2$, end-tidal partial pressure of O_2; PVR, pulmonary vascular resistance; VCO_2, carbon dioxide output; VE, minute ventilation; VO_2, oxygen uptake.
*$P<0.005$ and **$P<0.01$, event-free *vs.* event. [a]$P<0.05$ and [aa]$P<0.01$, event in women *vs.* event in men.
Values are mean (s.d.) or median (interquartile range).

($P<0.05$), while peak O_2 pulse was related to event-free survival in female patients ($P<0.05$). However, age, sex, BMI and hemodynamic variables were not predictors of event-free survival in all patients, male or female subgroups.

In the multivariate forward stepwise Cox proportional hazards analysis, model 1 was adjusted by age, sex, BMI and WHO FC-associated peak O_2 pulse, peak $P_{ET}O_2$, peak $P_{ET}CO_2$ and $P_{ET}CO_2$ at AT; only the peak $P_{ET}CO_2$ level was an independent predictor of event-free survival in all patients (Table 4). In male IPAH patients, model 2 was adjusted by age, BMI and WHO FC-associated peak VO_2/VE and peak $P_{ET}CO_2$; only peak $P_{ET}CO_2$ was an independent predictor of event-free survival. In female

patients, peak O_2 pulse was the sole independent predictor of event-free survival (Table 4).

Receiver-operating characteristic

Receiver-operating characteristic curves for 22 ± 15 months were plotted for peak $P_{ET}CO_2$ in all patients and male subgroups, and for peak O_2 pulse in female patients (Table 5). Peak $P_{ET}CO_2 < 27.03$ mm Hg had a sensitivity of 57.6% and specificity of 75.0% in predicting an event in all patients. A peak $P_{ET}CO_2 < 20.50$ mm Hg during exercise had a high sensitivity of 91.7% and specificity of 77.8% in male patients. Peak O_2 pulse < 6.25 ml per beat in female patients had a sensitivity of 57.1% and high specificity of 93.3% to predict event-free survival.

Kaplan–Meier event-free survival analysis

Kaplan–Meier event-free survival curves according to the cutoff values of peak $P_{ET}CO_2$ and peak O_2 pulse by receiver-operating characteristic analysis. In the analysis of all patients, patients with a peak $P_{ET}CO_2 \geqslant 27.03$ mm Hg had a significantly better prognosis (1-year event-free survival, 81% *vs.* 96%; 2-year event-free survival, 65% *vs.* 84%; 3-year event-free survival, 45% *vs.* 80%, respectively; $P = 0.043$) than those with a peak $P_{ET}CO_2 < 27.03$ mm Hg. Male patients with $P_{ET}CO_2 \geqslant 20.50$ mm Hg had a significantly better event-free survival rate than male patients with a peak $P_{ET}CO_2 < 20.50$ mm Hg (1-year event-free survival, 57% *vs.* 100%; 2-year event-free survival, 29% *vs.* 92%; 3-year event-free survival, 14% *vs.* 85%, respectively; $P < 0.001$). Female patients with peak O_2 pulse < 6.25 ml per beat had significantly worse event-free survival (1-year event-free survival, 83% *vs.* 100%; 2-year event-free survival, 65% *vs.* 92%; 3-year event-free survival, 43% *vs.* 92%, respectively; $P = 0.034$) (Figures 1a–c).

Discussion

This study suggests that sex might influence values of CPET parameters in IPAH, thereby influencing the grading of clinical severity and prognosis in such patients. We note that peak $P_{ET}CO_2$ was independently related to event-free survival in male patients with IPAH and that decreased peak $P_{ET}CO_2$ levels were associated with lower event-free survival rates in these patients. However, peak O_2 pulse was an independent predictor of event-free survival in female patients with IPAH. Women with increased peak O_2 pulse had better event-free survival. In addition, although the proportion of men was less than that of women, peak $P_{ET}CO_2$ as an independent predictor for event-free survival in all patients was similar in male patients; the only difference was the different cutoff value as analyzed by the receiver-operating characteristic.

In our study, the differences in clinical parameters in all patients as a single group were not similar to the differences in subgroup patients. Event women had significantly higher PVR and lower CO compared with event-free women, which indicates that event women had a more severe clinical status at the time of diagnosis. Although we did not see these differences in male patients, trends of increased PVR and decreased CO in event men were seen, suggesting that event men might already have had a poor clinical condition. We are cautious in interpreting these results because of the small sample of male patients. In addition, there were no sex differences in WHO FC, 6MWD, NT pro-BNP or hemodynamics at the time of diagnosis and target treatment in our study. However, a critique of the REVEAL Registry by Shapiro *et al.*[3] indicated that men had higher mean pulmonary arterial pressure, mean right atrial pressure, CO and 6MWD at diagnosis. One possible reason for the inconsistency with our results is that the REVEAL Registry was a large sample study and included a variety of different subtypes of PAH. Another possible reason is the hemodynamics measured by right heart catheterization at rest in our study, which cannot completely reflect sex differences in cardiac[12] and pulmonary function in our patients.

The present study indicates that sex differences in PFT parameters are seen in IPAH patients. Event female patients had significantly lower FVC, FVC %pred, FEV1, MVV and TLC compared with event male patients. Similar sex differences were seen in event-free patients. The sex difference in FVC %pred might indicate that these female patients with IPAH have poorer pulmonary function. However, FVC, FEV1, MVV and TLC are the actual values; therefore, these results are unable to directly demonstrate that female patients have more severe respiratory disease in the resting state. The precise reason for sex differences in FVC %pred in IPAH patients requires further studies for confirmation. Obstructive lung alterations may be a manifestation of pulmonary congestion,[27] which offers a reasonable explanation for the association between increased preload and decreased FEV1/FVC and FEV1/FVC ratios.[28] Subjects in the present study were incident patients with a confirmed diagnosis of IPAH based on recommended criteria, and COPD patients were excluded. IPAH can also cause obstructive ventilatory deficits. We consider that it would be very useful to do a follow-up PFT after the patients were under optimal management. There were no significant differences in DLCO and DLCO% pred between the men and women, indicating that there was no difference in pulmonary vascular flow and gas exchange. On the basis of the present difference in CPET findings in the two sexes, further studies could enlighten us more regarding specific mechanisms.

We chose to observe the sex differences in CPET parameters because CPET with gas exchange measurements noninvasively grades the severity of exercise limitations, quantifies hypoperfusion of the

Table 4 Parameters predictive of event-free survival in forward multivariate Cox proportional hazards analysis

Populations studied	*Model*	*Variables*	*HR*	*95% CI*	P-*value*
All patients ($n=57$)	Model 1	Peak $P_{ET}CO_2$	0.931	0.881 ~ 0.984	0.012
Male patients ($n=21$)	Model 2	Peak $P_{ET}CO_2$	0.894	0.816 ~ 0.978	0.015
Female patients ($n=36$)	Model 2	Peak O_2 pulse	0.555	0.313 ~ 0.985	0.044

Abbreviations: BMI, body mass index; CI, confidence interval; FC, functional classification; HR, heart rate; Model 1, adjusted for age, sex, BMI and WHO FC; Model 2, adjusted for age, BMI and WHO FC; $P_{ET}CO_2$, end tidal partial pressure of CO_2; WHO, World Health Organization.

Table 5 Receiver-operating characteristics

Populations studied	*Variables*	*Cutoff value*	*Sensitivity*	*Specificity*	*AUC*	*95% CI*
All patients ($n=57$)	Peak $P_{ET}CO_2$	27.33	0.576	0.750	0.722	0.591–0.853
Male patients ($n=21$)	Peak $P_{ET}CO_2$	20.50	0.917	0.778	0.870	0.000–1.000
Female patients($n=36$)	Peak O_2 pulse	6.25	0.571	0.933	0.733	0.568–0.898

Abbreviations: AUC, area under the curve; CI, confidence interval; $P_{ET}CO_2$, end tidal partial pressure of CO_2.

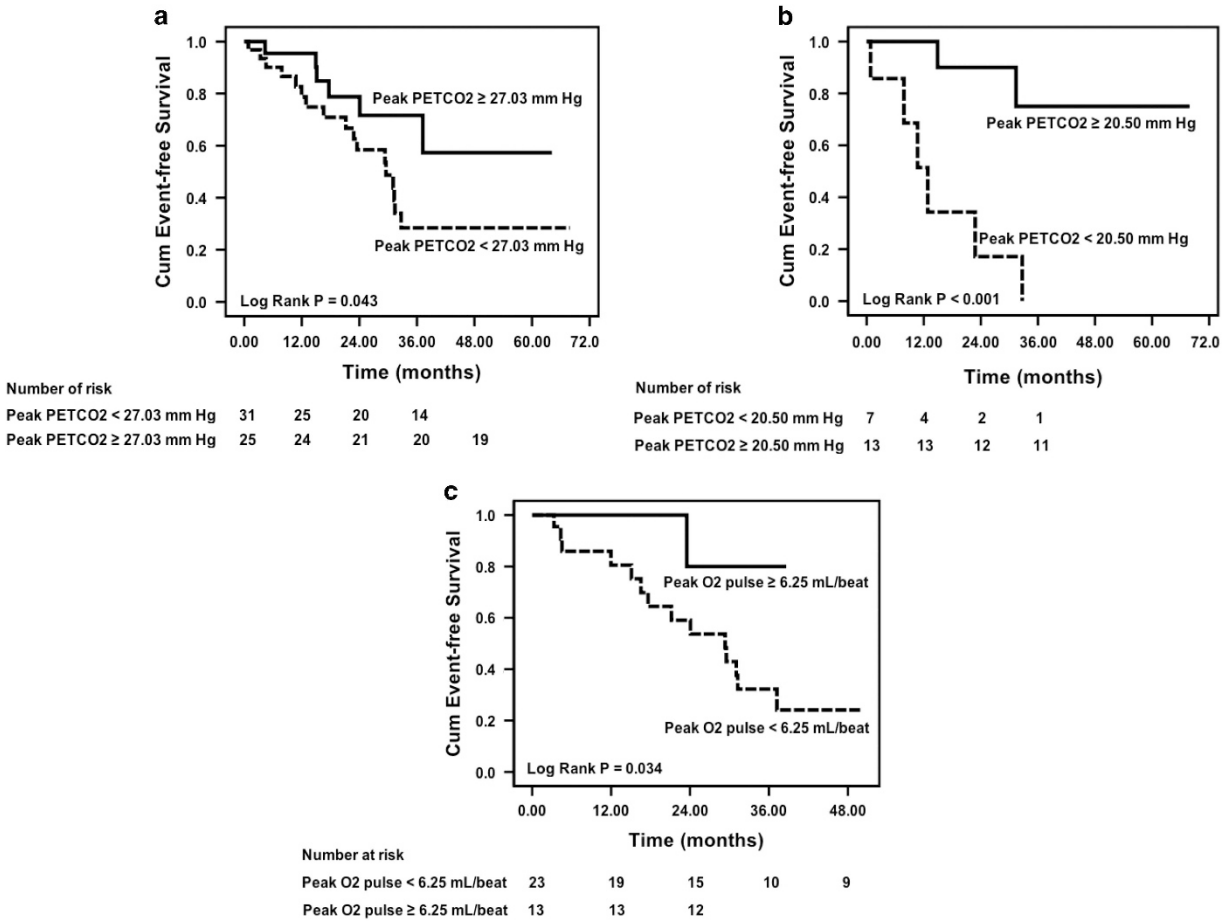

Figure 1 Kaplan–Meier cumulative event-free survival curves of patients with IPAH by sex. (**a**) All patients with peak $P_{ET}CO_2$ exercise of <27.03 mm Hg *vs.* $\geqslant 27.03$ mm Hg. (**b**) Male patients with a peak $P_{ET}CO_2$ exercise of <20.50 mm Hg *vs.* $\geqslant 20.50$ mm Hg. (**c**) Female patients with a peak O_2 pulse exercise of <6.25 ml per beat *vs.* $\geqslant 6.25$ ml per beat. IPAH, idiopathic pulmonary arterial hypertension; $P_{ET}CO_2$, end-tidal partial pressure of CO2.

lung and systemic circulation, and assesses responses to therapy before overt right ventricular failure and PAH are evident even at rest.[15–17,20,29] However, CPET results were not consistent with PFT results. The present study demonstrated that event men had exercise, ventilatory and gas exchange limitations compared to those of event-free men in the exercising state. Men with an event had a lower breathing reserve resulting from increased ventilatory demand due to worse ventilation and gas exchange inefficiency, that is, lower peak VO_2/VE, oxygen uptake efficiency slope, lowest VE/VCO_2 and peak $P_{ET}CO_2$. The unequal sample size between the male and female groups in the present study might have contributed more toward the unequal $P_{ET}CO_2$ result. Nevertheless, factors such as sexual dimorphism[30] in alveolar structure have been reported in animal models, and differences with cardiac and pulmonary remodeling between the two sexes[28,31] including fibrosis and pulmonary obstruction possibly contributed to such a finding. We think that differences in ventilation and gas exchange inefficiency might have a greater impact on peak exercise capacity. Valli *et al.*[32] also reported that this was one reason why they saw a correlation between 6MWD and VE/VCO_2 in PAH. Nonetheless, event women had worse peak VO_2, peak VCO_2, peak VE and peak O_2 pulse in our study, and because O_2 pulse is dependent on effective coupling between the cardiopulmonary systems, the difference in interaction between lung and cardiovascular remodeling by sex influenced this parameter as well.[28,33] Therefore, event women might have worse cardiovascular dysfunction and ventilatory inefficiency resulting in a lower CO, peak VCO_2, peak VE and peak O_2 pulse with exercise. Peak VO_2 was one of the most powerful prognosticators in chronic heart failure and IPAH, and was also an independent predictor of CO decline in such patients,[14,34] and event women had lower peak VO_2 in our study. In addition, event men had worse ventilator and gas exchange inefficiency than event women. These sex differences demonstrated that men with IPAH might have worse ventilatory and gas exchange abnormalities, while women with IPAH might have worse cardiovascular abnormalities in the exercising state. There have been concerns that different sex hormones might be factors in causing or potentiating or ameliorating IPAH. Animal studies in female and male mice have demonstrated acute vasodilator effects of estrogen in vascular rings from both sexes, and estrogen level variations have been observed with menstruation, with less vasodilation found prior to ovulation at lower estrogen levels.[35]

A marked sex difference in the independent predictors of event-free survival was confirmed by a follow-up of ~22 months. Peak $P_{ET}CO_2$ and peak O_2 pulse independently predicted event-free survival in men and women, respectively, which could be a possible reason why men might have worse pulmonary ventilation and gas exchange abnormalities, while women might have worse cardiovascular dysfunction. One previous study indicated that $P_{ET}CO_2$ at AT is a non-invasive indicator of ventilatory and gas exchange efficiency.[36] The diagnosis of IPAH becomes more likely if $P_{ET}CO_2$ progressively decreases from rest to AT.[37] Another study showed that values of $P_{ET}CO_2 < 20$ mm Hg

were unusual in other diseases and that the likelihood of diagnosis of IPAH was even more suspected in patients with exercise intolerance of unknown cause.[36,38] Our study had similar results whereby men with peak $P_{ET}CO_2 < 20.50$ mm Hg had a worse prognosis. Although the peak O_2 pulse independently predicted event-free survival in women and the number of women was 1.7 times that of men in the present study, peak $P_{ET}CO_2$ was an independent predictor of event-free survival in all patients. Patients with a peak $P_{ET}CO_2 < 27.30$ mm Hg had a worse event-free survival rate, which suggested that all patients could have more severe ventilatory and gas exchange inefficiency like male patients than cardiovascular abnormalities. These findings showed interesting implications for understanding the reasons for poor prognosis in men compared with women with PAH from the REVEAL Registry.[8] Previous studies have suggested that female sex is associated with a lower prevalence and a better outcome of adult patients with heart failure.[39] One possible reason is that LV stroke volume is significantly better in female patients with IPAH; this measurement has been strongly linked to adverse outcomes in patients with IPAH in previous studies, emphasizing that only the changes in the right ventricle are important.[40,41] Luchner *et al.*[37] reported that myocardial adaptations to increased afterload differ between sexes, with male subjects possessing a greater tendency to develop left ventricular dilatation and hypertrophy during the course of left ventricular dysfunction. Therefore, male and female IPAH patients with different results on multivariate analyses need to be further evaluated for altered structure in the heart and lungs. Additionally, whether sex hormones contribute to this finding in IPAH also needs further research.

There are limitations in the present study. Sufficient numbers of patients with more severe disease were not included in this study. There were also difficulties in obtaining optimal CPET data from WHO FC III–IV patients as compared to WHO FC I–II patients with IPAH. Although we could compare CPET data in just a single WHO FC, that is, WHO FC II, we determined that combining WHO classes would be better given the difference in the sample size between the classes due to the limited number of subjects. We feel it is important to evaluate the data on those patients. Furthermore, we do not have long-term follow-up data, so we could not analyze the survival rate and only used the event-free survival to reflect the prognosis. In addition, the focus of this analysis was patients with IPAH being managed at a single center; therefore, we need a larger sample, multicenter, long-term follow-up, along with a full cohort of patients with PAH, to explore the mechanism and role of sex differences in CPET parameters.

Although the number of patients in this study was limited, the data suggested that sex could influence CPET parameters for predicting the clinical severity of IPAH. The peak $P_{ET}CO_2$ and peak O_2 pulse were independent predictors for event-free survival in male and female patients with IPAH, respectively. Peak $P_{ET}CO_2$ was also an independent predictor for event-free survival in all patients with IPAH. A decreased peak $P_{ET}CO_2$ value was associated with a lower event-free survival rate in all patients and in the male subgroup. Women with decreased peak O_2 pulse values had a worse event-free survival. While these findings need further research to be confirmatory, they suggested that men could have worse pulmonary ventilatory and gas exchange abnormalities, while women might have worse cardiovascular dysfunction. Therefore, our data might provide new clues for different sex patients with different pathogenesis as well as new evidence and guidelines for the prognosis and treatment of patients of both sexes with IPAH.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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