Exercise pathophysiology differs between connective tissue diseases-associated pulmonary arterial hypertension and idiopathic pulmonary arterial hypertension

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Abstract

Objective

Previous studies demonstrated that connective tissue diseases-associated pulmonary arterial hypertension (CTD-PAH) had a worse prognosis than idiopathic pulmonary arterial hypertension (IPAH), although the former one had better haemodynamic profiles and right heart function. To find potential explanations for this contradictory phenomenon, we compared the exercise pathophysiology of CTD-PAH with that of IPAH using cardiopulmonary exercise testing (CPET).

Methods

Ninety-three CTD-PAH patients were retrospectively enrolled and matched 1:1 with 93 IPAH patients according to age, gender, body mass index, and body surface area. Multiple linear regression analysis was performed to adjust confounding factors.

Results

CTD-PAH had higher rest heart rate (HR@Rest) and lower rest oxygen uptake/HR (VO_2/HR@Rest) than IPAH. During exercise, the peak power (Power@Peak), VO_2@Peak, peak metabolic equivalents (METS@Peak), peak minute ventilation (VE@Peak), peak tidal volume (VT@Peak), HR@Peak, peak systolic blood pressure (SBP@Peak) and peak diastolic blood pressure (DBP@Peak) of CTD-PAH were lower than those of IPAH. After adjustment, CTD-PAH still had lower values of Power@Peak, VO_2@Peak, METS@Peak, VT@Peak, VO_2/HR@Rest, DBP@Peak and had higher HR@Rest than IPAH.

Conclusion

CTD-PAH had more impaired ventilation, cardiac function and muscular strength (reflected by CPET-derived parameters) than IPAH, in despite of better haemodynamic profiles and comparable heart structure (assessed by echocardiography) and functional status (indicated by World Health Organisation functional class, N-terminal pro-brain natriuretic peptide and six-minute walk distance).

Key words

connective tissue disease, pulmonary arterial hypertension, exercise test

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Received on June 6, 2020; accepted in revised form on September 14, 2020.

Funding: this research article was supported by National Natural Science Foundation of China [81370326, 81641005]; Beijing Municipal Science and Technology Project [Z181100001718200]; Beijing Municipal Natural Science Foundation [7202168] and National Precision Medical Research Program of China [2016YFC0905602].

Competing interests: none declared.

Introduction

Pulmonary arterial hypertension (PAH) is a severe complication of connective tissue diseases (CTD). Systemic sclerosis (SSc) is the most common underlying disease of CTD-PAH in western countries (1-3), while systemic lupus erythematosus (SLE) in east Asian countries (4-6).

Both CTD-PAH and idiopathic PAH (IPAH) fall within the group 1 pulmonary hypertension (PH) (7). They also have similar histological changes (8), clinical presentation (7), prognostic predictors (9, 10) and treatment algorithms (7). Despite these similarities, differences do exist between these two distinct entities. Compared with IPAH, patients with CTD-PAH have better haemodynamic profiles and right heart function (1), but have less favourable responsiveness to treatment (11) and worse prognosis (1).

Six-minute walk distance (6MWD) is a widely used endpoint in clinical trials for PAH. However, exercise capacity of patients with CTD-PAH could also be affected by non-PAH factors such as concomitant musculoskeletal impairment. This implies exercise pathophysiology may differ between CTD-PAH and IPAH. In fact, the REVEAL study reported that CTD-PAH had lower 6MWD than IPAH (1). Cardiopulmonary exercise testing (CPET) is a useful tool to reveal aberrant physiology in PH, because it can objectively and non-invasively assess the independent and integrated exercise responses of the cardiovascular and pulmonary systems (12). Therefore, it may offer us useful information that could partially explain why CTD-PAH patients have worse prognosis while having better haemodynamic profiles and right heart function than IPAH. However, knowledge on the CPET characteristics of CTD-PAH is limited. Inspired by results from the REVEAL study (1), we performed further work using CPET to explore the differences in exercise pathophysiology between CTD-PAH and IPAH.

Materials and methods

This retrospective, single-centre study was carried out at Fuwai Hospital, China. The study protocol was approved by the Ethics Committee of Fuwai Hospital. Written informed consent was obtained from each patient.

Study sample

We retrospectively reviewed the medical records of patients diagnosed with CTD-PAH and IPAH from January 2012 to March 2019. We also collected data of echocardiography-suspected PH patients with normal invasive pulmonary arterial pressure during the same time interval. All included CTD-PAH patients were matched 1:1 with IPAH patients by age, gender, body mass index and body surface area (using SPSS v. 23.0). The classification of various CTDs were based on American Rheumatism Association criteria for SLE (13), SSc (14), rheumatoid arthritis (15), 2002 international classification criteria for primary Sjögren's syndrome (pSS) (16), and 1987 Sharp criteria for mixed CTD (17). The establishment of CTD-PAH and IPAH was based on the 2009 (before January 2016) or 2015 European Society of Cardiology/European Respiratory Society guideline for the diagnosis and treatment of PH (7, 18). Normal pulmonary arterial pressure was defined as mean pulmonary arterial pressure (mPAP) <25 mm Hg (7, 18). The disease course was defined as the time interval between the onset of PAH symptom (*e.g.* shortness of breath and syncope) and receiving right-sided heart catheterisation (RHC) at our centre. Exclusion criteria were: (a) patients with undifferentiated CTD; (b) patients without CPET data; (c) patients with interstitial lung disease (ILD) and mPAP ≤40 mm Hg (patients with ILD and mPAP >40 mm Hg was considered as group 1 dominant PH and included) (19) (d) patients with anaemia.

Data collection

The following clinical data were collected via electronic medical record system by two independent reviewers: (a) basic characteristics, including age, gender, body mass index, body surface area, disease course, respiratory impairment, cardiac impairment, pulmonary function test, World Health Organisation functional class (WHO FC),

6MWD, N-terminal pro-brain natriuretic peptide (NT-proBNP), co-morbidities, drug therapy, smoking and alcohol intake history; (b) echocardiographic and RHC variables; and (c) CPET variables. Any discordance was resolved by the supervisors (QL and ZHL). These data were compared between CTD-PAH and IPAH, CTD-PAH and patients with normal pulmonary arterial pressure, and within CTD-PAH subgroups.

Protocol of echocardiography, RHC and CPET

Transthoracic echocardiography was performed by experienced ultrasonologists in the department of echocardiography under the current guidelines (20). Details for the protocol of RHC and CPET have been well described in our previous publications (21, 22). One metabolic equivalent (MET) is defined as ≈3.5ml O_2/kg/min (23).

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range). Categorical variables are given as counts or percentages. Comparisons between variables of CTD-PAH and IPAH patients were made using paired-sample t-test, Wilcoxon signed rank test or McNemar's test, as appropriate. Comparisons between CTD-PAH and patients with normal pulmonary arterial pressure, and within CTD-PAH subgroups were made using independent-sample t-test, Mann-Whitney U-test or Chi-square test, as appropriate. To validate the differences in CPET parameters between CTD-PAH and IPAH groups, we performed multiple linear regression analysis (with "Enter" procedure) to adjust potential confounding factors. A selected CPET parameter entered as a dependent variable; PAH aetiology, forced vital capacity (FVC), smoking, mPAP, pericardial effusion and ILD entered as independent variables considering both *p*-values of the variables and their clinical significance. Each CPET parameter entering the regression shared a same set of independent variables. Systolic pulmonary arterial pressure (sPAP) (estimated by echocardiography) and WHO FC were excluded from the model for their collinearity with mPAP and pericardial effusion, respectively. No severe collinearity problem was found in our final model (variance inflation factor values <2). The same procedure was also performed within CTD-PAH subgroups. A selected CPET parameter entered as a dependent variable; CTD-PAH subtype, sPAP, pulmonary vascular resistance (PVR), mean right atrial pressure (mRAP) entered as independent variables considering both *p*-values of the variables and their clinical significance, and the collinearity was also checked. A two-sided *p*-value <0.05 was considered statistically significant. For multiple linear regression analysis, we used Bonferroni's correction (*p*-value <0.05/n, n=times of testing) to control the type I error rate (24). Data analysis was performed using SPSS v. 23.0 (IBM SPSS Corp.; Armonk, NY, USA).

Table I. Basic characteristics of all patients.

Variable	CTD-PAH (n=93)	IPAH (n=93)	Normal (n=38)	*p*-value[#]
Age, years	41.2 ± 12.1*	41 ± 12	48 ± 15.9	0.450
Female gender	89 (95.7%)**	89 (95.7%)	25 (65.8%)	1.000
BMI, kg/m^2	22.5 ± 3.8*	22.3 ± 3.1	24.2 ± 3.9	0.998
BSA, m^2	1.6 ± 0.2**	1.6 ± 0.1	1.7 ± 0.2	0.881
Disease duration, months	26.5 (5, 36)	33.6 (6, 36)	-	0.576
Respiratory impairment				
Interstitial lung disease	5 (5.4%)	0	0	**0.063**
Emphysema	2 (2.2%)	4 (4.3%)	0	0.625
Pulmonary infection	4 (4.3%)	1 (1.1%)	1 (2.6%)	0.375
chronic bronchitis	1 (1.1%)	2 (2.2%)	2 (5.3%)	1.000
Cardiac impairment				
tricuspid insufficiency	10 (10.8%)	13 (14.0%)	9 (23.7%)	0.648
left ventricular dysfunction	2 (2.2%)	3 (3.2%)	0	1.000
Pulmonary function test				
FVC, % predicted	83.2 ± 14**	87.7 ± 12	96.3 ± 15.5	**0.024**
FEV1, % predicted	76.6 ± 14.8**	79.5 ± 14	91.5 ± 16.6	0.174
FEV1/FVC ratio	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.487
WHO-FC				**0.097**
I–II	37 (39.8%)**	49 (52.7%)	34 (89.5%)	
III–IV	56 (60.2%**	44 (47.3%)	4 (10.5%)	
6MWD, m	401.4 ± 107.1**	420 ± 93.9	490.3 ± 90.8	0.628
NT-proBNP, pg/ml	1251 (434.8, 2536.5)**	1033.9 (450.3, 2184.5)	91.6 (37, 163.8)	0.384
Co-morbidities				
Systemic hypertension	11 (11.8%)**	12 (12.9%)	16 (42.1%)	1.000
Diabetes mellitus	8 (8.6%)	5 (5.4%)	4 (10.5%)	0.581
Hyperlipidaemia	9 (9.7%)	4 (4.3%)	4 (10.5%)	0.109
Smoking	9 (9.7%)	2 (2.2%)	6 (15.8%)	**0.065**
Alcohol intake	8 (8.6%)	3 (3.2%)	6 (15.8%)	0.344
Drug therapy[†]				
None	14 (15.1%)	8 (8.6%)	-	0.263
Mono therapy	53 (57%)	65 (69.9%)	-	0.120
Combination therapy	26 (28%)	20 (21.5%)	-	0.429

Data are presented as mean ± standard deviation, median (range) or number (percentage).
BMI: body mass index; BSA: body surface area; CTD-PAH; connective tissue disease-associated pulmonary arterial hypertension; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; IPAH: idiopathic pulmonary arterial hypertension; NT-proBNP: N-terminal pro-brain natriuretic peptide; WHO-FC: World Health Organisation functional class; 6MWD: 6-min walk distance.
[†]Including endothelin receptor antagonists, phosphodiesterase type-5 inhibitors, prostacyclins and calcium channel blockers. [#]CTD-PAH compared with IPAH.
*p<0.05, CTD-PAH compared with patients with normal pulmonary arterial pressure.
**p<0.001, CTD-PAH compared with patients with normal pulmonary arterial pressure.

Results

Basic characteristics

Ninety-three CTD-PAH patients, 93 IPAH patients and 38 patients with normal pulmonary arterial pressure were included in this study. Among CTD-PAH patients, the numbers of patients with SSc, mixed CTD, rheumatoid arthritis, pSS and SLE were 6, 9, 12, 33, and 33, respectively. Their basic characteristics are summarised in Table 1. Compared with IPAH group, CTD-PAH group had lower values of FVC (83.2±14 *vs*. 87.7±12 %predicted,

p=0.024). CTD-PAH group also tended to have higher prevalence of ILD (5.4 *vs*. 0 %, *p*=0.063), worse WHO FC (III–IV: 60.2 *vs*. 47.3 %, *p*=0.097) and more smokers (9.7 *vs*. 2.2 %, *p*=0.065). Other basic characteristics, including 6MWD and NT-proBNP, did not differ between these two groups. A subgroup analysis within CTD-PAH patients was also performed, yet the basic characteristics between pSS and SLE patients were comparable (see Supplementary Table S1).

Echocardiographic and haemodynamic parameters

Echocardiographic and haemodynamic parameters of all patients are presented in Table II. Compared with IPAH group, CTD-PAH group had lower values of sPAP (84.5±23 *vs*. 91.9±20.6 mm Hg, *p*=0.014) and mPAP (46.8±11.3 *vs*. 55±13.2 mm Hg, *p*<0.001); however, the proportion of patients with pericardial effusion was greater in CTD-PAH group (24.7% *vs*. 7.5%, *p*=0.001). Other parameters were comparable between these two groups. Additionally, subgroup analysis showed no difference in echocardiographic and haemodynamic parameters between pSS and SLE patients, but there was a trend toward higher values in sPAP (92.2±19.9 *vs*. 82.4±23.7 mm Hg, *p*=0.079) and PVR (876.1±384.6 *vs*. 701.7±263.1 dyn•s/cm^5, *p*=0.077) in pSS patients (Suppl. Table S2).

CPET parameters

As shown in Table III, most CPET parameters at rest were comparable between CTD-PAH and IPAH groups, except that CTD-PAH group had higher rest heart rate (HR@Rest) (85.2±13.3 *vs*. 78.4±12.6 beat/min, *p*<0.001) and lower rest oxygen uptake/HR (VO_2/HR@Rest) (3.3±0.6 *vs*. 3.6±0.1 mL/beat, *p*=0.005). During exercise, CTD-PAH group had lower values of Power@Peak (60.3±24.6 *vs*. 70.5±22.1 W, *p*=0.004), VO_2@Peak (12±3.8 *vs*. 13.4±3.3 mL/min/kg, *p*=0.007), peak METS (METS@Peak, 3.4±1.1 *vs*. 3.9±1, *p*=0.005), peak minute ventilation (VE@Peak, 34.4±12.7 *vs*. 39±9.9 L/min, *p*=0.005), peak tidal volume (VT@Peak, 1.1±0.3 *vs*. 1.3±0.3 L, *p*<0.001), HR@Peak (130.9±23.5 *vs*. 139.6±20.1 beat/min, *p*=0.004), peak systolic blood pressure (SBP@Peak, 127.5±28.5 *vs*. 136±31.5 mm Hg, *p*=0.049) and peak diastolic blood pressure (DBP@Peak, 81.1±16.5 *vs*. 92.8±26.2 mm Hg, *p*<0.001). Subgroup analysis indicated that most CPET parameters both at rest and during exercise were comparable between pSS and SLE patients, except that pSS patients had lower SBP@Peak (124.1±31.5 *vs*. 135±25.5 mm Hg, *p*=0.043) and seemed to have lower oxygen uptake efficiency slope [OUES, 778.2±301.4 *vs*. 945±361.6 L/mL/log(1/min), *p*=0.065] (Suppl. Table S3).

Table II. Echocardiographic and haemodynamic parameters of all patients.

Variable	CTD-PAH (n=93)	IPAH (n=93)	Normal (n=38)	*p*-value #
Echocardiography				
LVEF, %	65.1 ± 7.2	64.9 ± 6.1	64.1 ± 4.7	0.558
LA, mm	30.1 ± 4.3**	30 ± 4.2	34.6 ± 4.6	0.861
LVED, mm	36.9 ± 5.8**	36.2 ± 5.2	46.1 ± 5.6	0.358
RVED, mm	31.8 ± 6.4**	31.4 ± 6.9	24.7 ± 4.8	0.783
sPAP, mm Hg	84.5 ± 23**	91.9 ± 20.6	46.2 ± 9.4	**0.014**
Pericardial effusion	23 (24.7%)*	7 (7.5%)	0	**0.001**
RHC				
S_VO_2, %	69.6 ± 6**	68.8 ± 7.9	77 ± 4.3	0.579
mRAP, mm Hg	5 (1.8, 7)	4 (2, 7)	3 (2, 5)	0.344
mPAP, mm Hg	46.8 ± 11.3**	55 ± 13.2	16 ± 4.1	**<0.001**
CI, L/min/m^2	3.1 ± 0.7**	3.2 ± 1	4.1 ± 1.4	0.609
PVR, dyn•s/cm^5	798.7 ± 360.6**	933.7 ± 398	103.1 ± 43.5	0.135
PCWP, mm Hg	6 (4, 9)	7 (5, 9)	8 (6, 9)	1.000

Data are presented as mean ± standard deviation or median (range).
CI: cardiac index; CTD-PAH: connective tissue disease-associated pulmonary arterial hypertension; IPAH: idiopathic pulmonary arterial hypertension; LA: left atrium dimension; LVED: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; mRAP: mean right atrial pressure; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; PCWP: pulmonary capillary wedge pressure. RHC: right-sided heart catheterisation; RVED: right ventricular end-diastolic diameter; sPAP: systolic pulmonary arterial pressure; S_VO_2: mixed venous oxygen saturation.
#CTD-PAH compared with IPAH. *p=0.001, CTD-PAH compared with patients with normal pulmonary arterial pressure. **p<0.001, CTD-PAH compared with patients with normal pulmonary arterial pressure.

Multiple linear regression analysis

The conservative nature of Bonferroni's correction (*p*-value <0.05/n, n=times of testing) limited the amount of CPET parameters that could be tested. Thus, we selected only 10 CPET parameters for multiple linear regression analysis, *i.e*. Power@Peak, VO_2@Peak, METS@Peak, VE@Peak, VT@Peak, HR@Rest, HR@Peak, VO_2/HR@Rest, SBP@Peak and DBP@Peak (A two-sided *p*-value <0.005 was considered statistically significant for multiple linear regression analysis). Meanwhile, PAH aetiology, FVC, smoking, mPAP, pericardial effusion and ILD entered as independent variables considering both *p*-values of the variables and their clinical significance. Events per variable (EPV) is often used to estimate the sample size needed in multiple linear regression, and the lowest acceptable EPV is usually considered as 10. Given the sample size is 93 for both CTD-PAH and IPAH, it is relatively safe for us to put these 6 independent variables into regression.

Table IV only shows the *p*-value for aetiology of PAH in multiple linear regression analysis, and results for all independent variables are presented in Supplementary Table S4. After adjusting confounding factors, CTD-PAH group still had lower Power@Peak, VO_2@Peak, METS@Peak, VT@Peak, VO_2/HR@Rest, DBP@Peak and higher HR@Rest than IPAH group. There was also a trend towards lower VE@Peak (*p*=0.016) and HR@Peak (*p*=0.037) in CTD-PAH group. However, the etiology of PAH did not contribute to the differences in SBP@Peak between CTD-PAH and IPAH. The same regression procedure was also performed within CTD-PAH subgroups. We chose SBP@AT, SBP@Peak and OUES entered

Table III. CPET parameters of all patients.

Variable	CTD-PAH (n=93)	IPAH (n=93)	Normal (n=38)	*p*-value#
Power@AT, W	34.4 ± 14.4**	38.8 ± 12.8	64.1 ± 18	**0.022**
Power@Peak, W	60.3 ± 24.6**	70.5 ± 22.1	119.2 ± 36.9	**0.004**
VO_2@Rest, mL/min/kg	4.8 ± 0.9	4.9 ± 1.1	4.8 ± 0.7	0.985
VO_2@AT, mL/min/kg	9.2 ± 3**	10 ± 2.3	14 ± 2.9	**0.008**
VO_2@Peak, mL/min/kg	12 ± 3.8**	13.4 ± 3.3	21.2 ± 5.2	**0.007**
METS@Rest	1.4 ± 0.3	1.4 ± 0.3	1.4 ± 0.2	0.767
METS@AT	2.6 ± 0.9**	2.8 ± 0.7	4 ± 0.8	**0.011**
METS@Peak	3.4 ± 1.1**	3.9 ± 1	6.1 ± 1.5	**0.005**
RER@Rest	0.8 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	**0.051**
RER@AT	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 08	0.690
RER@Peak	1.1 ± 0.1*	1.1 ± 0.1	1.2 ± 0.1	0.175
VE@Rest, L/min	9.9 ± 2.1	10.2 ± 2.4	9.8 ± 2.7	0.365
VE@AT, L/min	19.8 ± 6.7*	20.7 ± 6.1	23.3 ± 5.9	0.488
VE@Peak, L/min	34.4 ± 12.7**	39 ± 9.9	46.7 ± 15.2	**0.005**
VT@Rest, L	0.6 ± 0.2	0.6 ± 0.1	0.6 ± 0.1	0.925
VT@AT, L	0.8 ± 0.3*	0.9 ± 0.2	1 ± 0.2	**0.096**
VT@Peak, L	1.1 ± 0.3**	1.3 ± 0.3	1.5 ± 0.4	**<0.001**
RF@Rest, 1/min	18.5 ± 4.2	19 ± 4.1	17.8 ± 4.1	0.457
RF@AT, 1/min	24.5 ± 5.7	23.7 ± 5.6	24.9 ± 5.4	0.338
RF@Peak, 1/min	31.3 ± 5.9	31.2 ± 5.6	32.1 ± 6.7	0.842
HR@Rest, beat/min	85.2 ± 13.2**	78.4 ± 12.6	73.3 ± 13.2	**<0.001**
HR@AT, beat/min	106.7 ± 17	104.9 ± 16.5	104.7 ± 17.3	0.425
HR@Peak, beat/min	130.9 ± 23.5*	139.6 ± 20.1	142.2 ± 19.6	**0.004**
VO_2/HR@Rest, mL/beat	3.3 ± 0.6**	3.6 ± 0.9	4.3 ± 0.9	**0.005**
VO_2/HR@AT, mL/beat	4.9 ± 1.5**	5.4 ± 1.3	8.7 ± 2.3	**0.020**
VO_2/HR@Peak, mL/beat	5.2 ± 1.5**	5.5 ± 1.4	9.8 ± 2.8	0.125
SBP@Rest, mm Hg	104.2 ± 14.4*	108.2 ± 15.6	115 ± 19.1	0.144
SBP@AT, mm Hg	117.6 ± 25.5*	123.6 ± 27.7	126.5 ± 24.4	0.144
SBP@Peak, mm Hg	127.5 ± 28.5*	136 ± 31.5	147.2 ± 35.9	**0.049**
DBP@Rest, mm Hg	71.9 ± 10.2	70.7 ± 12.6	71.8 ± 9.9	0.554
DBP@AT, mm Hg	77.6 ± 17.1	83.7 ± 21.2	83.2 ± 20.2	**0.041**
DBP@Peak, mm Hg	81.1 ± 16.5*†	92.8 ± 26.2†	90.1 ± 21.3†	**<0.001**
$P_{ET}CO_2$@Rest, mm Hg	28.4 ± 4**	28.7 ± 4.1	34.6 ± 4.1	0.705
$P_{ET}CO_2$@AT, mmHg	28.3 ± 5.2**	28.9 ± 4.9	39.9 ± 4.1	0.459
$P_{ET}CO_2$@Peak, mmHg	25.6 ± 5.6**	25 ± 5.3	39.4 ± 5.3	0.453
$P_{ET}O_2$@Rest, mmHg	113.8 ± 5.6**	114.1 ± 5.5	107.8 ± 6.5	0.764
$P_{ET}O_2$@AT, mmHg	116.2 ± 6.2**	115.5 ± 5.7	103 ± 5.3	0.456
$P_{ET}O_2$@Peak, mmHg	122.9 ± 5.3**	123.7 ± 5.4	111 ± 5.9	0.246
VE/VO_2@Rest	35.9 ± 5.8*	35.8 ± 6.2	32.9 ± 8.7	0.912
VE/VO_2@AT	38.8 ± 8.7**	36.8 ± 7.1	26.1 ± 3.7	0.104
VE/VO_2@Peak	50.6 ± 10.2**	52.6 ± 12.2	33.7 ± 5	0.223
VE/VCO_2@Rest	42.3 ± 5.9**	41.5 ± 6.4	36.5 ± 6.2	0.548
VE/VCO_2@AT	42.8 ± 10.1**	40.6 ± 7.7	29.3 ± 3.8	0.272
VE/VCO_2@Peak	47.3 ± 11**	47.6 ± 11	29.6 ± 3.9	0.853
SpO_2@Rest, %	95.1 ± 3.6**	96.2 ± 1.8	97.2 ± 1	0.231
SpO_2@AT, %	93.9 ± 4.7**	94.3 ± 3.8	96.9 ± 1.5	0.869
SpO_2@Peak, %	92.8 ± 5.7**	89.4 ± 10.9	95.5 ± 4.2	**0.052**
VE/VCO_2 slope, L/min/L/min	44.8 ± 16.6**	40.8 ± 11.6	25.8 ± 3.6	0.100
VO_2/WR slope, mL/(min•W)	3.9 (1, 5.4)**	4.7 (2.8, 6.2)	7.7 (6.8, 8.7)	0.596
Lowest VE/VCO_2, L/min	39.8 ± 7.2**	38 ± 6.4	22.5 ± 3.9	0.239
OUES, L/mL/log(1/min)	834.9 ± 312.2**	894.8 ± 315.3	1755.2 ± 470.4	0.259

Data are presented as mean ± standard deviation or median (range).
AT: anaerobic threshold; CPET: cardiopulmonary exercise testing; CTD-PAH: connective tissue disease-associated pulmonary arterial hypertension; DBP: diastolic blood pressure; HR: heart rate; IPAH: idiopathic pulmonary arterial hypertension; METS: metabolic equivalents; OUES: oxygen uptake efficiency slope; $P_{ET}CO_2$: end-tidal partial pressure of carbon dioxide; $P_{ET}O_2$: end-tidal partial pressure of oxygen; RER: respiratory exchange rate; RF: respiratory frequency; SBP: systolic blood pressure; SpO_2: oxygen saturation; VCO_2: carbon dioxide output; VE: minute ventilation; VO_2: oxygen uptake; VT: tidal volume; WR: work rate.
#CTD-PAH compared with IPAH. *p<0.05, CTD-PAH compared with patients with normal pulmonary arterial pressure. **p-0.001, CTD-PAH compared with patients with normal pulmonary arterial pressure. † p<0.001, compared with rest by using paired-sample t-test.

as dependent variables (A two-sided p-value <0.016 was considered statistically significant), and subtypes of CTD-PAH, sPAP, PVR, mRAP entered as independent variables considering both p-values of the variables and their clinical significance. After adjusting confounding factors, CTD-PAH subtypes did not contribute to the differences in CPET parameters between pSS and SLE patients (Suppl. Table S5).

Discussion

In the present study, the heart structure (indicated by echocardiography), functional status (indicated by WHO FC, NT-proBNP and 6MWD) were comparable between CTD-PAH and IPAH, whilst CTD-PAH even had better haemodynamic profiles. However, we found that CTD-PAH had worse CPET-derived parameters (both at rest and during exercise) than IPAH, indicating that CTD-PAH had more impaired ventilation, cardiac function and muscular strength.

Parameters associated with cardiopulmonary function

HR, VO_2/HR and DBP are parameters closely associated with cardiopulmonary function. VO_2/HR@Rest was lower in CTD-PAH group, reflecting less oxygen extracted per heart beat and stroke volume (25), which explained why HR@Rest was higher in CTD-PAH group, to compensate for decreased oxygen supply. This phenomenon implied that cardiopulmonary function differed between CTD-PAH and IPAH even at rest. On the contrary, HR@Peak tended to be lower in CTD-PAH group (p=0.026, p<0.005 was considered statistically significant for multiple linear regression analysis), which might indicate CTD-PAH had poorer chronotropic response to exercise than IAPH. The mechanisms behind the higher HR@Rest and the reduced chronotropic competence may be partially attributed to the abnormal diastolic function of both ventricles in CTD (26). Henkens *et al*. reported that higher HR@Rest was an independent predictor of adverse prognosis for IPAH (27). Moreover, chronotropic incompetence was an independent prognostic marker for patients with heart failure (28). We therefore suspect that higher HR@Rest and lower HR@Peak may indicate worse prognosis of CTD-PAH patients, but further studies are need to verify this hypothesis. In healthy sub-

Table IV. Contribution of aetiology of PAH to the differences in CPET parameters between CTD-PAH and IPAH.

Dependent variable	B*	SE*	β*	*p*-value*†
Power@Peak	-12.684	3.917	-0.259	**0.001**
VO_2@Peak	-1.766	0.587	-0.243	**0.003**
METS@Peak	-0.492	0.170	-0.236	**0.004**
VE@Peak	-4.711	1.936	-0.214	**0.016**
VT@Peak	-0.165	0.048	-0.263	**0.001**
HR@Rest	8.311	2.254	0.318	**<0.001**
HR@Peak	-8.287	3.940	-0.187	**0.037**
VO_2/HR@Rest	-0.451	0.133	-0.293	**0.001**
SBP@Peak	-8.495	5.542	-0.140	0.127
DBP@Peak	-13.131	3.940	-0.294	**0.001**

AT: anaerobic threshold; CPET: cardiopulmonary exercise testing; CTD: connective tissue disease; DBP: diastolic blood pressure; HR: heart rate; IPAH: idiopathic pulmonary arterial hypertension; METS: metabolic equivalents; PAH: pulmonary arterial hypertension; SBP: systolic blood pressure; VE: minute ventilation; VO_2: oxygen uptake; VT: tidal volume.
*Role of aetiology of PAH in multiple linear regression analysis (results for all independent variables are presented in Supplementary Table S4). †$p<0.005$ was considered statistically significant.

jects, exercise DBP usually remains unchanged or is moderately reduced due to vasodilatation of the vascular bed (29). Ha *et al*. (30) reported that excessive elevation in exercise DBP was associated with increased likelihood of coronary artery disease. We found that CTD-PAH, IPAH and patients with normal pulmonary arterial pressure all had elevated DBP during exercise, and CTD-PAH had the lowest DBP@Peak. Given that CTD-PAH group had the most unfavourable CPET-derived parameters, we tended to consider the relatively lower DBP@Peak in this study as an adverse signal, which is opposite to the results of Ha *et al*. (30). Although the present study could not elucidate the underlying mechanism of this phenomenon, we suspect that concomitant vasculitis may play an important role.

Parameters associated with ventilation

VT and VE (VT × respiratory frequency) are ventilation-related parameters. Herein, VT@Peak was lower in CTD-PAH group, while CTD-PAH and IPAH shared similar respiratory frequency. Consequently, VE@peak tended to be lower in CTD-PAH group ($p=0.012$, $p<0.005$ was considered statistically significant for multiple linear regression analysis). Meanwhile, these two groups had similar VE/VCO_2@AT, VE/VCO_2 slope and lowest VE/VCO_2, which indicated that their ventilation efficiency was comparable (31). Usually, patients with PAH require increased VE to compensate for ventilation-perfusion mismatch (32). Previous studies demonstrated that CTD-PAH had lower diffusion capacity for carbon monoxide (a marker of capillary surface area) than IPAH (1, 33). Moreover, Langleben *et al*. (34) found that CTD-PAH had a lower functional capillary surface area/body surface area ratio than IPAH for a given cardiac index. Theoretically, CTD-PAH were supposed to increase their VE to higher levels compared with IPAH to compensate for the extra loss of functional capillary surface area, but what we found was exactly the opposite. We suspected that lower VT@Peak in CTD-PAH may be attributed to systemic inflammation-impaired respiratory muscular strength and pulmonary elasticity. We also found that CTD-PAH had lower FVC than IPAH, consistent with previous studies (1, 33), which indicated that CTD-PAH had more sever restrictive problem. This further supported our hypothesis.

Parameters associated with exercise intensity

Power and METS, two parameters that reflect exercise intensity, were both worse in CTD-PAH group. Power@Peak is closely associated with muscular strength (35). Unfortunately, muscular pain and weakness are common in CTD, despite they might not be the major clinical manifestations in some subtypes (36, 37). Furthermore, Oliveira *et al*. (38) reported that SSc patients without pulmonary impairment have reduced exercise capacity. Besides, METS is also routinely utilised to provide a repertoire of activities that patients can safely participate in. Considering the wide range of functional classification (female patients with 2.8-4.4 METS could tolerate moderate exercise intensity) (23), the difference in METS@Peak between CTD-PAH and IPAH was quite small (3.4±1.1 *vs*. 3.9±1.0 METS, $p=0.003$). In other words, it may be hard for clinicians to tell the differences in exercise capacity between CTD-PAH and IPAH from the limitation of daily activities. In fact, the present study showed poorer exercise capacity in CTD-PAH than in IPAH, despite comparable WHO FC and 6MWD between the two groups.

VO_2@Peak

VO_2@Peak is a parameter closely associated with pulmonary, cardiac, haematologic, vascular, and mitochondrial function (39). Compared with IPAH, lower VO2@Peak in CTD-PAH group may be considered as an overall manifestation of more severe impairment of ventilation, cardiac function and muscular strength.

Interestingly, we found that CTD-PAH had worse CPET parameters both at rest and during exercise than IPAH, although CTD-PAH did have better haemodynamic profiles. We offer a hypothesis for this contradictory phenomenon. It is known that many CTDs directly affect the heart through direct connective tissue deposition and microvascular dysfunction (for example, the so-called systemic-sclerosis related cardiomyopathy). This direct heart involvement produces subclinical organ damage which mainly targets right ventricle (40) and could explain, through a reduced subclinical systolic function (41), the lower pressure in CTD-PAH group. Therefore, we strongly suggest doctors be vigilant against the "good" haemodynamic profiles of CTD-PAH when it comes to clinical decision-making. Another interesting part is that CTD-PAH patients included in the present study seemed to be younger than those in the REVEAL study (41.2±12.1

vs. 57.1±13.7 years) (1), which is consistent with a cohort study conducted in China (37.8±10.4 years) (42).

Subgroup analysis

We found that pSS patients tended to have higher sPAP and PVR than SLE, which is consistent with the work by Zhao *et al*. (42) They also reported that pSS had worse survival rate than SLE (42). In the first place, we observed that pSS patients had lower SBP@Peak and seemed to have lower OUES. After adjustment, subtypes of CTD-PAH did not contribute to the differences in CPET parameters between pSS and SLE patients. Given the limited information we can offer in the present study, more extensive work is needed to explain why pSS had a worse survival rate than SLE.

Limitations

Several limitations of this study should be noted. First, parameters of pulmonary function test like diffusion capacity for carbon monoxide were not available. Therefore, the clinical implications of lower VT@Peak and VE@Peak in CTD-PAH might not be thoroughly interpreted. Second, we failed to obtain follow-up information, which makes the prognostic value of CPET parameters such as HR@Rest and DBP@Peak remain unknown. Third, Bonferroni's correction is quite conservative, which limits the amount of CPET parameter we could test. Therefore, parameters at AT were not discussed in this study. Finally, the small sample size in the subgroup analysis may make our results less persuasive. Prospective studies with bigger sample sizes are encouraged to explore why pSS had a worse prognosis than SLE.

Conclusion

CTD-PAH had more impaired ventilation, cardiac function and muscular strength (reflected by CPET-derived parameters) than IPAH, although the heart structure (indicated by echocardiography), functional status (indicated by WHO FC, NT-proBNP and 6MWD) were comparable between these two groups, and CTD-PAH even had better haemodynamic profiles. In other words, CPET could detect impairment of ventilation, cardiac function and muscular strength earlier than echocardiography, WHO FC, 6MWD, NT-proBNP and RHC in patients with CTD-PAH. Our results highlighted the usefulness of CPET for the management of CTD-PAH.

Acknowledgements

This research article was supported by National Natural Science Foundation of China [81370326, 81641005]; Beijing Municipal Science and Technology Project [Z181100001718200]; Beijing Municipal Natural Science Foundation [7202168] and National Precision Medical Research Program of China [2016YFC0905602].

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