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Prognostic value of cardiopulmonary exercise testing in pediatric pulmonary arterial hypertension

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Abstract

RATIONALE: Pulmonary arterial hypertension (PAH) is a deadly disease occurring in both adults and children. Cardiopulmonary exercise testing (CPET) has been widely used in heart failure for many years and has recently been recommended in patients with PAH, especially in younger population. This could provide more objective information on exercise capacity and right ventricular performance than six minute walking distance. It is now well established that CPET parameters are prognostic in adult patients with PAH, however, there has been very little research investigating the prognostic value in children with PAH since CPET has been proved to be safe and practical in those patients.

METHODS: Thirty-seven children diagnosed with PAH were prospectively enrolled from those attending a national referral center between July 2013 and December 2015. Standard incremental CPET was performed in each participant under physician supervision. During follow-up, clinical worsening events including death, heart/lung transplantation, escalation of PAH targeted therapy, and hospitalization for PAH deterioration, were recorded. The final census date for the study was September 1, 2016.

RESULTS: Patients had a mean (SD) age of 14.9 (2.5) years old and 21 (57%) of them were female. Of the 37 patients, 17 were idiopathic PAH, and 20 were congenital heart disease associated PAH. The mean (SD) follow-up time was 19 (9) months, during which 1 patient died of right heart failure, 7 patients were hospitalized for PAH deterioration, and 5 patients had escalation of PAH targeted therapy (they were also hospitalized). CPET parameters such as anaerobic threshold (AT) and peak oxygen uptake per minute ($\dot{V}O_2$) negatively correlated, and the slope of ventilation per minute ($\dot{V}E$) to carbon dioxide output per minute ($\dot{V}CO_2$) ratio ($\dot{V}E/\dot{V}CO_2$ slope) positively correlated with with mean pulmonary artery pressure and pulmonary vascular resistance. Peak workload and peak systolic blood pressure (sBP) had negative relationships with pulmonary vascular resistance. In multivariate COX

regression analysis, peak sBP was identified as an independent prognostic factor for clinical worsening, with hazard ratio (95% confidence interval) of 0.791 (0.648-0.964). The best cutoff value generated from ROC curve was 119 mmHg (AUC area: 0.77, sensitivity: 75%, specificity: 76%, p =0.021) for peak sBP. In Kaplan-Meier analysis, patients with lower peak sBP had worse survival (p = 0.002).

CONCLUSIONS: CPET parameters are associated with disease severity in Children with PAH. Children with PAH incapable of achieving higher peak sBP during CPET are more likely to have clinical worsening events.

Key words: children; pediatric; pulmonary arterial hypertension; cardiopulmonary exercise testing; survival

Word count (396)

Abbreviations and Acronyms

PAH = pulmonary arterial hypertension

PVR = pulmonary vascular resistance

CPET = cardiopulmonary exercise testing

mPAP = pulmonary artery pressure

CPET = cardiopulmonary exercise testing

$\dot{V}O_2$ = oxygen uptake per minute

$\dot{V}E/\dot{V}CO_2$ = the ventilatory equivalent for carbon dioxide

sBP = systolic blood pressure

mPAP = mean pulmonary artery pressure

PAWP = pulmonary artery wedge pressure

RHC = right heart catheterization

$\dot{V}E$ = ventilation per minute

AT = anaerobic threshold

CW = clinical worsening

ERA = endothelin receptor antagonist

PDE-5i = phosphodiesterase type 5 inhibitor

CCB = calcium channel blocker

dBP = diastolic blood pressure

CO = cardiac output

Introduction

Pulmonary arterial hypertension (PAH) is a deadly disease occurring in both adults and children, characterized by progressively increase in pulmonary vascular resistance (PVR) which could lead to right heart failure and eventually death[1]. In the 1980s, patients with idiopathic PAH had a median survival of 2.8 years[2]. In the past two decades, many groundbreaking clinical trials have been conducted successfully and many targeted drugs have been approved in adult PAH, which have largely improved their survival[3, 4]. Those drugs have also been introduced in children with PAH based on expert consensus, although they have not been approved (except sildenafil in Europe and Canada)[5].

Since exercise intolerance is the main manifestation of patients with PAH, evaluating exercise capacity regularly plays a crucial role in the management of those patients. Cardiopulmonary exercise testing (CPET) has been widely used in heart failure for decades and now there is a growing body of literature that recognizes its value in PAH. Recently it has been recommended in adult patients with PAH, especially in younger population, which could provide more objective information on exercise capacity and right ventricular performance than six minute walking distance[1].

In children with PAH, there are much fewer studies on CPET than in adults mainly because of safety issues. However, a few studies have demonstrated that it is safe and practical to perform CPET in children with PAH, with low rates of arrhythmias and ST-segment depression, while an experienced team is needed [6, 7]. Also, in the latest guidelines for pediatric PAH, CPET was suggested to be performed, especially before the patient engages in any athletic activities[5, 8].

It is now well established that CPET parameters such as the peak minute oxygen uptake (peak $\dot{V}o_2$) [9-11], the ventilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}_{CO_2}$) [10], and peak systolic blood pressure (peak sBP) [9] are prognostic in adult patients with PAH. In children with PAH, it has been shown that CPET parameters correlate with disease

severity[12, 13], however, there has been very little research investigating the prognostic value of CPET in those patients. The aim of this study therefore was to investigate whether CPET parameters predict clinical outcomes in children with PAH.

Methods

Patients Enrollment

This study was approved by the Institutional Review Board of FuWai Hospital, Beijing, China and informed consent was obtained from all subjects prior to enrollment.
This study prospectively enrolled 37 children (< 18 years old at enrollment) diagnosed with PAH between July 2013 and December 2015 in a national referral center in China. PAH was defined as resting mean pulmonary artery pressure (mPAP) ≥ 25mmHg, pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg and PVR > 3 wood units measured by right heart catheterization (RHC), with other causes of pre-capillary pulmonary hypertension excluded[1]. Patients with WHO functional class of IV were excluded. The height limit for participant was ≥ 130 cm. Patients who were not able to or not willing to do CPET were excluded. All the patients recruited did standard incremental CPET to maximum tolerance on an upright cycle ergometer under physician supervision.
RHC and CPET were both performed during this admission for 33 patients, and another 4 patients had their RHCs performed over 1 year prior to this admission.

Protocol for exercise testing

CPET was performed in FuWai-UCLA CPET lab, FuWai Hospital, Beijing, China. The cycle ergometer CPET systems (COSMED, Schiller and MedGraphics) were calibrated everyday prior to the testing. As described in previous studies[14-17], gas exchange parameters were measured during 3 minutes of rest, 3 minutes of unloaded cycling, followed by progressively increasing workload of 10-30 watts/min in ramp pattern to maximum tolerance, and 2 minutes of recovery. Workload increases were individually selected so that subjects would reach their maximum tolerated workload within 6 to 10 minutes of exercise.

Gas Exchange Measurements

Breath-by-breath data were collected and interpreted second-by-second and sequentially averaged in 10-s bins. The peak $\dot{V}o_2$ was determined as the highest average value during a sequential 30-s period[14-17]. Peak HR was determined as concurrent 30-s averages[14-17]. The anaerobic threshold (AT) was measured by the V-slope method using 10-s averages[14-17]. The $\dot{V}_E/\dot{V}_{CO_2}$ slope was calculated by linear regression below the ventilatory compensation point[14]. Pulse oximetry, 12-lead ECG, and cuff blood pressure were also monitored and recorded. The participants were asked to describe the reason of stopping exercise after the testing.

Follow-up

During follow-up, clinical worsening (CW) events including death, heart/lung transplantation, escalation of PAH targeted therapy, and hospitalization for PAH deterioration, were recorded. The final census date for the study was September 1, 2016.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) or median (25th to 75th percentiles) of data not normally distributed, and categorical parameters are showed as ratio or percentage. For continuous data, either student *t* test or Mann-Whiney U test was conducted between two independent samples as appropriate. Chi-square test was used for categorical data. Association between peak sBP levels and other parameters was analyzed by Pearson correlation or Spearman correlation in data of non-normal distribution. In order to identify risk factors for clinical outcomes univariate and multivariate COX regression analyses were conducted. In the multivariate COX analysis, Forward LR model was used. Receiver operative characteristic (ROC) curves were used to determine the best cutoff values of predictors. Kaplan-Meier curve was carried out and log rank p value was

calculated in survival analysis. A p value < 0.05 was considered significant. All the analyses were performed using R version 3.2.3 (packages used: survival, pROC, ggplot2), and Graphpad Prism version 7.0.

Results

Baseline characteristics

Demographics, clinical characteristics, echocardiography and hemodynamic parameters, and treatment information were listed in **table 1**. Thirty-seven children with PAH were enrolled in this study with a median (25^{th} to 75^{th} percentiles) age of 15.7 (13.0 to 17.2) years old at enrollment. Just over half (57%) the population was female. Of the 37 patients, 17 were idiopathic PAH, and 20 were congenital heart disease associated PAH (CHD-PAH).

Before enrollment, 18 (48.6%) patients were treatment-naïve with PAH targeted therapies, 7 (18.9%) with phosphodiesterase type 5 inhibitor (PDE-5i), 5 (13.5%) with endothelial receptor antagonist (ERA), 4 (10.8%, responders in vasoreactivity testing) with calcium channel blocker (CCB), and 3 (8.1%) with combination therapy (ERA + PDE-5i). After discharge, 16 (43.2%) were on combination therapy (11 on ERA + PDE-5i, 5 on PDE-5i + beraprost), 2 were not on any targeted therapies because of economic reasons, and others were on monotherapy of ERA, PDE-5i or CCB.

The median (25^{th} to 75^{th} percentiles) follow-up time was 15.8 (12.5 to 26.8) months, during which CW events occurred in 8 (22%) patients, with 1 death of right heart failure, 7 hospitalizations for PAH deterioration, and 5 escalations of PAH targeted therapy (they were also hospitalized).

Cardiopulmonary exercise testing parameters

CPET parameters for patients with or without CW events were presented in **table 2**. Patients in CW group had lower peak sBP ($p < 0.001$), resting diastolic blood pressure (dBP) ($p = 0.024$), peak dBP ($p = 0.019$), and AT ($p = 0.016$) compared to patients

without CW events. There was only boarderline significance (p = 0.080) of peak $\dot{V}o_2$ between the two groups.

Survival analysis

Traditional markers for clinical worsening were all analyzed in univariate COX regression analysis (**supplement table 1**), and of all those, age, pericardial effusion, PVR, cardiac output (CO), peak wokload, peak dBP, peak sBP, and peak $\dot{V}o_2$ had potential prognostic value (with p < 0.1) (**table 3**). After adjustment in multivariate COX regression analysis, peak sBP was identified as an independent prognostic factor for clinical worsening, with hazard ratio (95% confidence interval) of 0.813 (0.674-0.981) (**table 3**).

The best cutoff value for predicting CW events generated from ROC curve was 119 mmHg (AUC area= 0.77, p =0.021) for peak sBP, with sensitivity of 75% and specificity of 76% (**figure 1**).

In Kaplan-Meier analysis, patients with peak sBP ≤ 119 mmHg had worse survival (p = 0.002) (**figure 2**), with 1 and 2 year event-free survival rate 75.5% and 25.2% respectively, while the figure was 95.8% and 88.5% respectively in patients with peak sBP > 119 mmHg. Peak sBP ≤ 119 mmHg was also strong independent predictor in multivariate COX analysis after adjustment for other risk factors identified in univariate COX analysis (HR = 10.467; 95% CI: 1.183, 58.176; p = 0.007).

Relationships between peak sBP and disease severity

Peak sBP correlated with traditional markers for disease severity such as NT-proBNP (r = -0.384, p =0.019), PVR (r = -0.450, p = 0.005), and CO (r = 0.568, p < 0.001) (**table 4**). Peak sBP also had relationships with other CPET markers indicating exercise capacity and gas exchange efficiency, including peak $\dot{V}o_2$ (r = 0.626, p < 0.001), AT (r = 0.646, p < 0.001), peak workload (r = 0.764, p < 0.001), and $\dot{V}_E/\dot{V}_{CO_2}$ slope (r = -0.349, p = 0.034) (**table 4**). When dividing patients into two groups by peak sBP of 119

mmHg, patients with lower peak sBP had significantly lower CO ($p < 0.001$) and higher PVR ($p = 0.001$) (**figure 3**).

Discussion

In this study we investigate for the first time the prognostic value of CPET parameters in children with PAH, which fills the gap in the literature. We found that lower peak sBP during CPET predicts CW in these patients, with every 5 mmHg lower yielding a 19% higher risk of CW.

It has been noted that peak sBP is a strong independent predictor of clinical outcomes in adults with PAH[9]. In a study of 86 idiopathic PAH patients, Wensel et. al showed that patients with peak sBP lower than 120 mmHg had significantly worse survival compared to patients with higher values (log rank $p < 0.001$ in Kaplan-Meier analysis), and that peak sBP ≤ 120 mmHg was independent predictor in a bivariate COX analysis adjusted for peak $\dot{V}o_2$ (HR = 5.9, $p < 0.0001$). In our study, the best cutoff value for peak sBP was 119 mmHg generated from ROC curve, which also significantly predicted survival (log rank $p = 0.002$ in Kaplan-Meier analysis). In multivariate COX analysis, data showed patients with peak sBP ≤ 119 mmHg had more than 10 times higher risk for CW ($p = 0.007$). Interestingly, when using Wensel et. al `s cutoff value 120 mmHg in our analysis, the result is consistent (log rank $p = 0.004$ in Kaplan-Meier analysis; HR = 8.525, $p = 0.014$ in multivariate COX analysis). So we suggest that peak sBP around 120mmHg can be used for predictor both in pediatric and adult PAH.

sBP normally rises during exercise along with the increase in cardiac output[18]. The reason why peak sBP during CPET predicts outcomes might be because to some degree it could reflect right ventricle function. Since CO during exercise could be noninvasively estimated from CPET parameters [19], we investigated the correlations between peak sBP and CO during exercise. Peak sBP was found to have strong

positive correlations with peak CO (r = 0.749, p < 0.001) and the increase of CO from baseline to peak (r = 0.733, p < 0.001), which indicated lower peak sBP was associated with worse right ventricle function during exercise. In addition, lower sBP might lower coronary perfusion, which could lead to right ventricular ischemia. In a study by Gomez et al.[20], right ventricular ischemia was found to be significantly related to right ventricular dysfunction. In our study mild ST-segment depression in ECG were detected in 5 (62.5%) patients with CW events compared to 6 (20.7%) patients without CW events (p = 0.007), which indicated patients in CW group might have worse right ventricular function during exercise.

Peak $\dot{V}o_2$ was identified as an independent predictor in several studies in adult PAH. In Wensel`s [9] and Grunig` s[11] studies, peak $\dot{V}o_2$ was predictor of mortality and in Deboeck`s study [10], peak $\dot{V}o_2$ predicted CW. In our study, peak $\dot{V}o_2$ (not adjusted by weight) had predictive potential in univariate analysis (p < 0.1) but failed to be predictive in the multivariate analysis.

In children with PAH, CPET was demonstrated to be safe and feasible and was recommended by the latest guideline [5-7]. In several studies, CPET parameters were found to be related to functional capacity [12, 21] and disease severity[12, 13]. In Lammer`s study, peak $\dot{V}o_2$ correlated positively with 6 minute walking distance and the relationship was more significant with 6 minute walking distance up to 300m[21]. Yetman et.al suggested significant negative correlation between peak $\dot{V}o_2$ and PVR (r = -0.6, p= 0.006)[13]. In our study, we also investigated the relationship between CPET parameters and hemodynamics. AT and peak $\dot{V}o_2$ had negative relationships with mPAP and PVR, and $\dot{V}_E/\dot{V}_{CO_2}$ positively correlated with mPAP and PVR (supplement table 2).

As for prognosis evaluation of CPET in children with PAH, Rausch et al. [12]found that $\dot{V}_E/\dot{V}_{CO_2}$ slope was significantly higher in patients with poor outcomes, however, survival analysis was not performed. But the prognostic value of CPET has been

investigated in children with heart failure caused by dilated cardiomyopathy[22]. Guimaraes et al. [22]reported that in multivariate analysis, of all the CPET parameters indicating exercise capacity and ventilator efficiency, only exercise time was predictive during follow-up. Our data showed that exercise time in patients with CW events was numerically lower than those without events but not statistically, and that it did not predict CW in survival analysis.

In our study, traditional markers targeted treatment and WHO functional class were not related to survival in univariate analysis. PVR and CO had borderline significance ($p < 0.1$) and pericardial perfusion was predictive ($p < 0.05$) in univariate analysis, but they were not predictive in multivariate analysis.

Limitations

Our study has several limitations. Firstly, due to safety issues, this study did not examine the invasive hemodynamic parameters during exercise. Secondly, patients were on different therapies at enrollment, but therapy seemed not to be related to survival in the COX regression analysis. Thirdly, the sample is relatively smaller than adult studies, partly because some children were too young to do CPET and some were not willing to. But we believe this study could still make an important contribution to the field of CPET study in children with PAH.

Conclusions

Peak sBP during CPET is associated with disease severity in Children with PAH. Children with PAH incapable of achieving higher peak sBP during CPET are more likely to have clinical worsening events.

Figure legends

Figure 1. Sensitivity and specificity of peak systolic blood pressure (peak sBP) in predicting clinical worsening events. Higher peak sBP (AUC area = 0.70, p = 0.021) predicted clinical worsening in children with PAH.

Figure 2. Event-free survival in children with pulmonary arterial hypertension (PAH) stratified by levels of peak systolic blood pressure (peak sBP).

Figure 3. Comparison of disease severity in patients with systolic blood pressure (peak sBP) ≤ and > 119 mmHg.

Tables

Tabel 1. Baseline characteristics of patients

	PAH (n = 37)
Demographics	
Age, yr	15.7 (13.0 to 17.2)
Women, %	21 (56.8)
BMI, kg/m^2	17.9 (16.9 to 20.4)
Clinical characteristics	
Idiopathic PAH, n (%)	17 (46)
CHD-PAH, n (%)	20 (54)
WHO FC, III/I-II	7/30
NT-proBNP, pg/ml	239.0 (78.0 to 833.3)
Echocardiography	
TAPSE	18.0 ± 3.8
Pericardial effusion, n (%)	1 (2.7)
Hemodynamics	
mRAP, mmHg	8.0 (4.8 to 11.3)
mPAP, mmHg	80.5 (55.8 to 90.0)
PAWP, mmHg	11.0 (9.0 to 12.0)
PVR, Wood Unit	15.2 ± 8.0
CO, L/min	4.28 (3.7 to 5.3)
PAH targeted therapy pre-admission	

Treatment naive, n (%)	18 (48.6)
PDE-5is, n (%)	7 (18.9)
ERA, n (%)	5 (13.5)
Prostanoids, n (%)	0 (0)
CCB, n(%)	4 (10.8)
Combination therapy, n (%)	3 (8.1)
PAH targeted therapy post-discharge	
none, n (%)	2 (5.4)
PDE-5is, n (%)	11 (29.7)
ERA, n (%)	4 (10.8)
Prostanoids, n (%)	0 (0)
CCB, n(%)	4 (10.8)
Combination therapy, n (%)	16 (43.2)

Values are expressed as n (%), ratio, mean ± SD, or median (25th to 75th percentiles). PAH: pulmonary arterial hypertension; BMI: body mass index; WHO FC: World Health Organization functional class; CHD-PAH: congenital heart disease associated PAH; NT-proBNP: N-terminal pro-brain natriuretic peptide; TAPSE: tricuspid annular plane systolic excursion; mRAP: mean artrial artery pressure; mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; CO: cardiac output; PDE-5is: phosphodiesterase type 5 inhibitors; ERA: endothelial receptor antagonist; CCB: calcium channel blocker.

Table 2. CPET parameters in patients with and without clinical worsening evens.

	All patients **n = 37**	**Patients without CW events** **n = 29**	**Patients with CW events** **n = 8**	**p value**
Peak workload, Watt	73 (58 to 100)	74 (61 to 104)	65 (40 to 76)	0.137
Exercise time, min	7.7 ± 1.3	7.7 ± 1.3	7.5 ± 1.0	0.741
Resting HR, bpm	88.1 ± 13.3	89.2 ± 13.9	83.6 ± 10.3	0.211
Peak HR, bpm	157.0 ± 17.0	156.3 ± 16.8	159.8 ± 18.9	0.479
Resting sBP, mmHg	102.5 ± 17.2	104.2 ± 17.3	96.0 ± 16.3	0.275
Peak sBP, mmHg	130.3 ± 21.0	134.7 ± 21.0	113.0 ± 8.4	0.007
Resting dBP, mmHg	68.0 ± 11.8	69.4 ± 12.7	62.4 ± 4.2	0.024
Peak dBP, mmHg	74.4 ± 12.3	77.0 ± 11.7	64.0 ± 9.5	0.019
Resting SpO_2 (%)	97 (95.5 to 98)	97 (95 to 98)	97.5 (97 to 98)	0.502
Peak SpO_2 (%)	93 (84.5 to 95)	90 (83.5 to 95)	94 (90 to 96.5)	0.266

Peak $\dot{V}_E$, L/min	36.0 (28.5 to 44.6)	38.5 (29.4 to 45.3)	31.5 (26.0 to 34.0)	0.251
AT				
L/min	0.63 ± 0.18	0.65 ± 0.19	0.54 ± 0.07	0.016
ml/min/kg	12.8 ± 3.0	12.9 ± 3.1	12.6 ± 2.9	0.698
Peak $\dot{V}_{O_2}$				
L/min	0.81 (0.64 to 0.98)	0.87 (0.65 to 1.02)	0.70 (0.51 to 0.79)	0.080
ml/min/kg	16.9 (13.5 to 19.8)	17.2 (14.5 to 20.7)	15.6 (12.3 to 19.8)	0.299
$\dot{V}_E/\dot{V}_{CO_2}$ slope	36.0 (31.0 to 45.0)	35.5 (30.5 to 44.1)	37.0 (33.0 to 47.0)	0.236

Values are expressed as mean ± SD or median (25th to 75th percentiles)

HR: heart rate; sBP: systolic blood pressure; dBP: diastolic blood pressure; $\dot{V}_E$: ventilation per minute; SpO_2: pulse oximetry; $\dot{V}_{O_2}$: oxygen uptake per minute; AT: anaerobic threshold; $\dot{V}_E/\dot{V}_{CO_2}$ slope: the slope of ventilatory equivalent for carbon dioxide

Table 3. Univariate and multivariate Cox regression analysis of risk factors for clinical worsening events

	Unadjusted Hazard Ratio (95% CI)	**p value**	**Adjusted Hazard Ratio (95% CI)**	**p value**
Age, per yr ↑	0.720 (0.532, 0.976)	< 0.05		
Pericardial effusion, presence vs none	11.135 (1.157, 107.132)	< 0.05		
PVR, per Wood Unit ↑	1.090 (0.992, 1.197)	< 0.1		
CO, per L/min ↑	0.473 (0.228, 0.981)	< 0.1		
Peak workload, per Watt ↑	0.971 (0.940, 1.003)	< 0.1		
Peak dBP, per 5 mmHg	0.713 (0.500, 1.016)	< 0.1		
Peak sBP, per 5 mmHg ↑	0.815 (0.682, 0.973)	< 0.05	0.813 (0.674, 0.981)	0.031
Peak $\dot{V}O_2$, per L/min ↑	0.038 (0.001, 1.510)	< 0.1		

PVR: pulmonary vascular resistance; CO: cardiac output; dBP: diastolic blood pressure; sBP: systolic blood pressure; $\dot{V}O_2$: oxygen uptake per minute; ↑: increase

Table 4. Correlations between peak sBP and markers of disease severity

	Peak sBP	
	Correlation Coefficient	**P value**
NT-proBNP, pg/ml	-0.384	0.019
PVR,Wood Unit	-0.450	0.005
CO, L/min	0.568	< 0.001
Peak workload, watt	0.764	< 0.001
Peak $\dot{V}O_2$, ml/min	0.626	< 0.001
AT, ml/min	0.646	< 0.001
$\dot{V}E/\dot{V}CO_2$ slope	-0.349	0.034

NT-proBNP: N-terminal pro-brain natriuretic peptide; PVR: pulmonary vascular resistance; CO: cardiac output; $\dot{V}O_2$: oxygen uptake per minute; AT: anaerobic threshold; $\dot{V}E/\dot{V}CO_2$ slope: the slope of ventilatory equivalent for carbon dioxide

Supplemental Table 1. Univariate Cox regression analysis of risk factors for clinical worsening events

	Unadjusted Hazard Ratio (95% CI)	**p value**
Age, per yr ↑	0.720 (0.532, 0.976)	< 0.05
Sex, female vs male	1.168 (0.279, 4.892)	> 0.1
WHO FC, III vs I-II	0.865 (0.105, 7.143)	> 0.1
PAH targeted therapy pre-admission		
Treatment-naïve	Preference	
PDE-5i	2.210 (0.375, 11.996)	> 0.1
ERA	1.290 (0.140, 11.847)	> 0.1
CCB	0.000 (0.000, 0.000)	> 0.1
Combination Therapy	1.853 (0.205, 16.781)	> 0.1

PAH targeted therapy post-discharge	0.874 (0.610, 1.253)	> 0.1
Combination Therapy	Preference	
None	0.000 (0.000, 0.000)	> 0.1
PDE-5i	1.707 (0.344, 8.477)	> 0.1
ERA	3.344 (0.556, 20.106)	> 0.1
CCB	0.000 (0.000, 0.000)	> 0.1
Pericardial effusion, presence vs none	11.135 (1.157, 107.132)	< 0.05
RV, per mm ↑	1.055 (0.967, 1.151)	> 0.1
TAPSE, per mm ↑	0.851 (0.674, 1.074)	> 0.1
NT-proBNP, per pg/ml ↑	1.000 (1.000, 1.001)	> 0.1
mRAP, per mmHg ↑	0.948 (0.778, 1.155)	> 0.1
mPAP, per mmHg ↑	0.999 (0.965, 1.036)	> 0.1
PVR, per Wood Unit ↑	1.090 (0.992, 1.197)	< 0.1

CO, per L/min ↑	0.473 (0.228, 0.981)	< 0.1
Peak workload, per Watt ↑	0.971 (0.940, 1.003)	< 0.1
Exercise time	1.001 (0.991, 1.012)	> 0.1
Resting sBP, per 5 mmHg ↑	0.881 (0.701, 1.109)	> 0.1
Peak sBP, per 5 mmHg ↑	0.815 (0.682, 0.973)	< 0.05
Resting dBP, per 5 mmHg	0.737 (0.470, 1.155)	> 0.1
Peak dBP, per 5 mmHg	0.713 (0.500, 1.016)	< 0.1
Resting HR, per 5 bpm ↑	1.077 (0.862, 1.345)	> 0.1
Peak HR, per 5 bpm ↑	1.105 (0.971, 1.061)	> 0.1
Resting SaO_2, per 5% ↑	2.354 (0.384, 14.426)	> 0.1
Peak SaO_2, per 5% ↑	1.321 (0.810, 2.156)	> 0.1
Peak $\dot{V}_E$, per L/min ↑	0.956 (0.886, 1.032)	> 0.1
Peak $\dot{V}_{O_2}$	0.784 (0.563, 1.091)	> 0.1

per L/min ↑	0.038 (0.001, 1.510)	< 0.1
per ml/min/kg ↑	0.974 (0.810, 1.170)	> 0.1
AT		
per L/min ↑	0.025 (0.000, 2.877)	> 0.1
per ml/min/kg ↑	0.976 (0.752, 1.265)	> 0.1
$\dot{V}_E/\dot{V}_{CO_2}$ slope, per unit ↑	1.021 (0.968, 1.076)	> 0.1

Values are expressed as n (%), ratio, mean ± SD, or median (25th to 75th percentiles). PAH: pulmonary arterial hypertension; BMI: body mass index; WHO FC: World Health Organization functional class; CHD-PAH: congenital heart disease associated PAH; NT-proBNP: N-terminal pro-brain natriuretic peptide; TAPSE: tricuspid annular plane systolic excursion; mRAP: mean artrial artery pressure; mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; CO: cardiac output; PDE-5is: phosphodiesterase type 5 inhibitors; ERA: endothelial receptor antagonist; CCB: calcium channel blocker; HR: heart rate; sBP: systolic blood pressure; dBP: diastolic blood pressure; $\dot{V}_E$: ventilation per minute; SpO_2: pulse oximetry; $\dot{V}_{O_2}$: oxygen uptake per minute; AT: anaerobic threshold; $\dot{V}_E/\dot{V}_{CO_2}$ slope: the slope of ventilatory equivalent for carbon dioxide; ↑: increase

Supplemental table 2 . Correlations between CPET parameters and markers of disease severity

	Peak $\dot{V}O_2$, L/min/kg		AT, L/min/kg		$\dot{V}e/\dot{V}co2$ slope	
	r	p value	r	p value	r	p value
NT-proBNP, pg/ml	-0.558	< 0.001	-0.638	< 0.001	0.299	0.072
PVR, Wood Unit	-0.591	< 0.001	-0.388	0.019	0.466	0.004
mPAP, mmHg	-0.477	0.003	-0.394	0.037	0.433	0.007
CO, L/min	0.411	0.012	0.144	0.402	-0.194	0.250

NT-proBNP: N-terminal pro-brain natriuretic peptide; PVR: pulmonary vascular resistance; mPAP: mean pulmonary artery pressure; CO: cardiac output; $\dot{V}O_2$: oxygen uptake per minute; AT: anaerobic threshold; $\dot{V}E/\dot{V}CO_2$ slope: the slope of ventilatory equivalent for carbon dioxide; r : correlation coefficient.

Figure 1

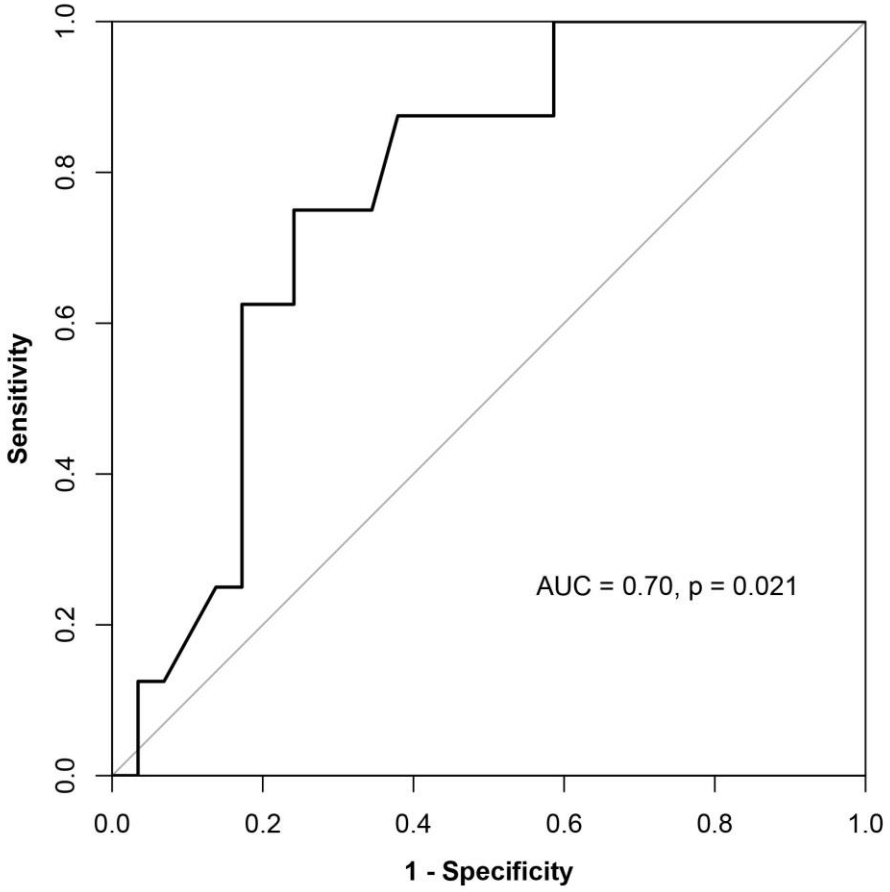
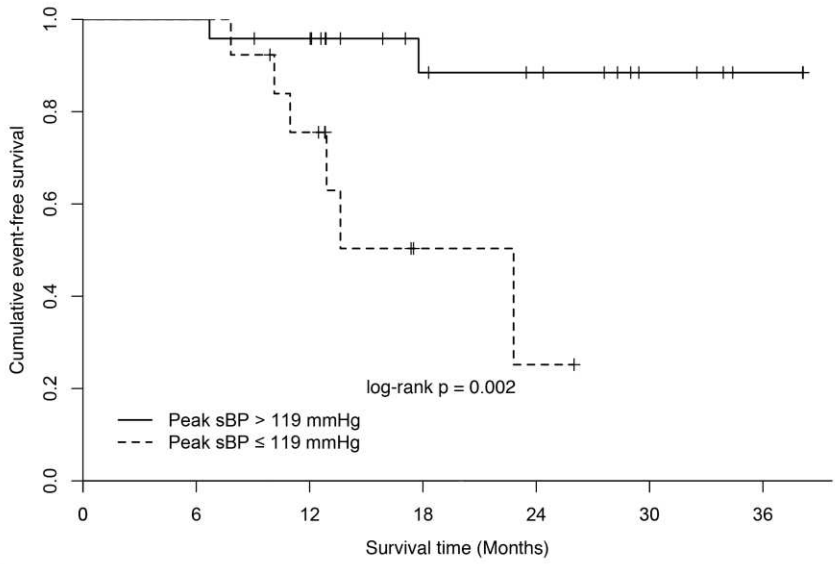
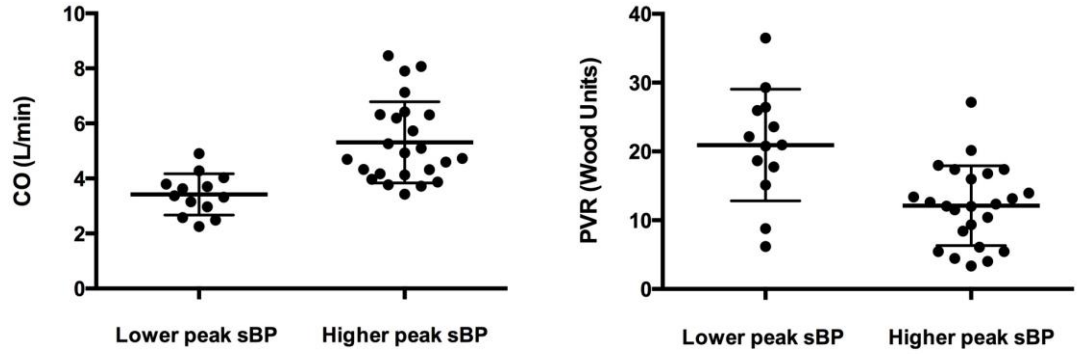


Figure 2



Numbers at risk:							
Peak sBP > 119 bpm	24	24	18	11	8	4	1
Peak sBP ≤ 119 bpm	13	13	7	2	1		

Figure 3


CO (L/min)
10
8
6
4
2
0
Lower peak sBP
Higher peak sBP
PVR (Wood Units)
40
30
20
10
0
Lower peak sBP
Higher peak sBP

References:

1. Galie 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, Aboyans V, Vaz Carneiro A, Achenbach S, Agewall S, Allanore Y, Asteggiano R, Paolo Badano L, Albert Barbera J, Bouvaist H, Bueno H, Byrne RA, Carerj S, Castro G, Erol C, Falk V, Funck-Brentano C, Gorenflo M, Granton J, Iung B, Kiely DG, Kirchhof P, Kjellstrom B, Landmesser U, Lekakis J, Lionis C, Lip GY, Orfanos SE, Park MH, Piepoli MF, Ponikowski P, Revel MP, Rigau D, Rosenkranz S, Voller H, Luis Zamorano J. 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). *European heart journal*. 2016;37:67-119
2. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Annals of internal medicine*. 1991;115:343-349
3. Humbert M, Lau EM, Montani D, Jais X, Sitbon O, Simonneau G. Advances in therapeutic interventions for patients with pulmonary arterial hypertension. *Circulation*. 2014;130:2189-2208
4. McLaughlin VV, Shah SJ, Souza R, Humbert M. Management of pulmonary arterial hypertension. *Journal of the American College of Cardiology*. 2015;65:1976-1997
5. Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, Hanna BD, Rosenzweig EB, Raj JU, Cornfield D, Stenmark KR, Steinhorn R, Thébaud B, Fineman JR, Kuehne T, Feinstein JA, Friedberg MK, Earing M, Barst RJ, Keller RL, Kinsella JP, Mullen M, Deterding R, Kulik T, Mallory G, Humpl T, Wessel DL. Pediatric pulmonary hypertension. *Circulation*. 2015;132:2037-2099
6. Smith G, Reyes JT, Russell JL, Humpl T. Safety of maximal cardiopulmonary exercise testing in pediatric patients with pulmonary hypertension. *Chest*. 2009;135:1209-1214
7. Abumehdi MR, Wardle AJ, Nazzal R, Charalampopoulos A, Schulze-Neick I, Derrick G, Moledina S, Giardini A. Feasibility and safety of cardiopulmonary exercise testing in children with pulmonary hypertension. *Cardiology in the young*. 2016;26:1144-1150
8. Lammers AE, Apitz C, Zartner P, Hager A, Dubowy KO, Hansmann G. Diagnostics, monitoring and outpatient care in children with suspected pulmonary hypertension/paediatric pulmonary hypertensive vascular disease. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The european paediatric pulmonary vascular disease network, endorsed by ishlt and dgpk. *Heart*. 2016;102 Suppl 2:ii1-13
9. Wensel R, Opitz CF, Anker SD, Winkler J, Hoffken G, Kleber FX, Sharma R, Hummel M, Hetzer R, Ewert R. Assessment of survival in patients with primary pulmonary hypertension: Importance of cardiopulmonary exercise testing. *Circulation*. 2002;106:319-324
10. Deboeck G, Scoditti C, Huez S, Vachiery JL, Lamotte M, Sharples L, Melot C, Naeije R. Exercise testing to predict outcome in idiopathic versus associated pulmonary arterial hypertension. *The European respiratory journal : official journal of the European Society for Clinical*

Respiratory Physiology. 2012;40:1410-1419

11. Grunig E, Tiede H, Enyimayew EO, Ehlken N, Seyfarth HJ, Bossone E, D'Andrea A, Naeije R, Olschewski H, Ulrich S, Nagel C, Halank M, Fischer C. Assessment and prognostic relevance of right ventricular contractile reserve in patients with severe pulmonary hypertension. *Circulation*. 2013;128:2005-2015
12. Rausch CM, Taylor AL, Ross H, Sillau S, Ivy DD. Ventilatory efficiency slope correlates with functional capacity, outcomes, and disease severity in pediatric patients with pulmonary hypertension. *Int J Cardiol*. 2013;169:445-448
13. Yetman AT, Taylor AL, Doran A, Ivy DD. Utility of cardiopulmonary stress testing in assessing disease severity in children with pulmonary arterial hypertension. *The American journal of cardiology*. 2005;95:697-699
14. Sun XG, Hansen JE, Beshai JF, Wasserman K. Oscillatory breathing and exercise gas exchange abnormalities prognosticate early mortality and morbidity in heart failure. *Journal of the American College of Cardiology*. 2010;55:1814-1823
15. Sun XG, Hansen JE, Garatachea N, Storer TW, Wasserman K. Ventilatory efficiency during exercise in healthy subjects. *American journal of respiratory and critical care medicine*. 2002;166:1443-1448
16. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. *Circulation*. 2001;104:429-435
17. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Gas exchange detection of exercise-induced right-to-left shunt in patients with primary pulmonary hypertension. *Circulation*. 2002;105:54-60
18. Garofano RP, Barst RJ. Exercise testing in children with primary pulmonary hypertension. *Pediatric cardiology*. 1999;20:61-64; discussion 65
19. Stringer WW, Hansen JE, Wasserman K. Cardiac output estimated noninvasively from oxygen uptake during exercise. *Journal of Applied Physiology*. 1997;82:908-912
20. Gomez A, Bialostozky D, Zajarias A, Santos E, Palomar A, Martinez ML, Sandoval J. Right ventricular ischemia in patients with primary pulmonary hypertension. *Journal of the American College of Cardiology*. 2001;38:1137-1142
21. Lammers AE, Diller GP, Odendaal D, Tailor S, Derrick G, Haworth SG. Comparison of 6-min walk test distance and cardiopulmonary exercise test performance in children with pulmonary hypertension. *Archives of disease in childhood*. 2011;96:141-147
22. Guimaraes GV, Bellotti G, Mocelin AO, Camargo PR, Bocchi EA. Cardiopulmonary exercise testing in children with heart failure secondary to idiopathic dilated cardiomyopathy. *Chest*. 2001;120:816-824