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Exercise testing to predict outcome in idiopathic *versus* associated pulmonary arterial hypertension

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ABSTRACT: We tested the ability of exercise testing to predict not only survival, but also time to clinical worsening (TTCW) in idiopathic *versus* associated pulmonary arterial hypertension (PAH).

136 patients with PAH (85 idiopathic and 51 with associated conditions) underwent cardiopulmonary exercise testing and a 6-min walk test. Death or transplantation, and clinical worsening events were recorded.

32 patients died and four had lung transplantation. In a univariate analysis, PAH patients survival was associated with oxygen uptake ($V'O_2$) at peak exercise and at the anaerobic threshold, ventilatory equivalent for carbon dioxide (minute ventilation ($V'E$)/carbon dioxide production ($V'CO_2$) at the anaerobic threshold (at)), $V'E/V'CO_2$ slope and distance walked. TTCW was associated with peak $V'O_2$ and $V'O_2$,at, $V'E/V'CO_2$,at, end-tidal carbon dioxide tension measured at the anaerobic threshold, peak oxygen pulse, increase in oxygen pulse and distance walked. In a multivariable analysis, distance walked and $V'E/V'CO_2$,at predicted survival, and only peak $V'O_2$ predicted TTCW. The receiver operating characteristic curve-derived cut-off values were 305 m for the 6-min walk distance, 54 for $V'E/V'CO_2$,at and 11.6 mL·kg^{-1}·min for peak $V'O_2$. In the subgroup with associated PAH, no variable independently predicted either survival or clinical worsening.

We conclude that several exercise variables predict survival and clinical stability in idiopathic PAH. Exercise variables are less accurate predictors of outcome in associated PAH.

KEYWORDS: Cardiopulmonary exercise testing, clinical worsening, pulmonary arterial hypertension, pulmonary hypertension, 6-min walk test, survival

The symptomatology of pulmonary arterial hypertension (PAH) is dominated by dyspnoea and fatigue induced by exercise until the final stages of the disease, when the patients are symptomatic at rest [1, 2]. Accordingly, a variety of variables measured during a cardiopulmonary exercise test (CPET) and, more simply the 6-min walk distance (6MWD) are used in clinical practice to estimate disease severity [3, 4].

The 6-min walk test (6MWT) has been shown to be an independent prognostic marker [5–10], and as such has served as a primary end-point in most randomised controlled trials of new therapies for PAH [11]. Peak oxygen uptake ($V'O_2$) and ventilatory responses during CPET also relate to survival in pulmonary hypertension. This has been shown in idiopathic PAH (IPAH) [12] and in a cohort of pulmonary hypertension patients composed of IPAH, PAH with associated conditions (APAH) and chronic thromboembolic pulmonary hypertension (CTEPH) patients [7].

Because PAH is still an incurable disease with limited survival, clinical stability is a desirable therapeutic goal, especially in patients who are not too severely ill, or still in New York Heart Association (NYHA) functional class II or early NYHA functional class III [1, 2]. Time to clinical worsening (TTCW) has emerged as an improved primary end-point in newly designed event-driven randomised controlled trials in PAH [11]. However, no study to date has addressed the question whether exercise capacity predicts the TTCW. Another incompletely answered question is whether the predictive value of exercise testing is equivalent in IPAH or APAH.

The purpose of the present study is to evaluate the prognostic value of CPET variables and 6MWT in IPAH *versus* APAH, and to determine their ability not only to predict survival, but also TTCW.

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METHODS

Protocol

Our study included the CPET and 6MWT data of 136 PAH patients from the pulmonary hypertension clinic of Erasmus University Hospital, Brussels, Belgium, between November 2001 and July 2010. The study was approved by the Erasmus Hospital Institutional Review Board. The mortality end-point was defined as all-cause mortality or lung transplantation, with the remaining cases designated as event-free survival. The clinical worsening (CW) end-point was defined as previously reported [11]: all causes of mortality; nonelective hospital stay for PAH (for initiation of prostanoids, lung transplantation or atrial septostomy); disease progression defined as a reduction from baseline in the 6MWD by 15% confirmed by two studies performed within 2 weeks plus worsening functional class.

Patients

The diagnosis of PAH rested on a right heart catheterisation with demonstration of an increase in mean pulmonary artery pressure (>25 mmHg), a normal pulmonary artery wedge pressure (<15 mmHg), no identifiable cardiac or pulmonary cause, and possibly associated with conditions such as appetite suppressant intake, connective tissue disease (CTD), liver cirrhosis, HIV infection and congenital left-to-right shunt (congenital heart disease; CHD) [1, 2]. 70 patients had IPAH and 66 patients had APAH that were previous to intake of anorexigen in 15 patients, CTD (all systemic sclerosis) without lung function impairment in 19, hepatic cirrhosis in 11, HIV infection in four, CHD in 16 patients or schistosomiasis in one patient. Patients with PAH associated with the intake of anorexigens were considered as IPAH patients, as recent studies have shown that anorexigens only trigger the disease, which is otherwise indiscernible [2, 13]. Thus, the study considered two subgroups of 85 patients with IPAH and 51 patients with APAH.

Exercise testing

CPET

Each patient underwent standard cycle ergometer incremental CPET until the symptom-limited maximum [14]. The CPET protocol consisted of pedalling at 0–20 W during the first 3 min and then an incremental increase in load from 5 to 15 $W \cdot min^{-1}$, aiming to obtain an exercise duration of between 8 and 12 min. Because of equipment renewal over the years, ventilation and gas analysis were performed using a CPX/D meter (Medical Graphics, St Paul, MN, USA) in 16 tests and a VMax meter (SensorMedics, Yorba Linda, CA, USA) in 120 tests. The gas analysers and pneumotachograph were calibrated prior to each test. Cardiac frequency (f_C)and blood pressure were obtained *via* automatic standard ECG and sphygmomanometer.

Peak V'_{O_2}, V'_{O_2} at the anaerobic threshold (V'_{O_2},at), the ventilatory equivalent for carbon dioxide (minute ventilation (V'_E)/carbon dioxide production (V'_{CO_2})) measured at anaerobic threshold (V'_E/V'_{CO_2},at) or as a slope from 1 min after the beginning of loaded exercise to the end of the isocapnic buffering period (V'_E/V'_{CO_2} slope), the end-tidal carbon dioxide tension (P_{ET,CO_2}) measured at the anaerobic threshold, the maximum–rest change in P_{ET,CO_2} ($\Delta P_{ET,CO_2}$), the oxygen pulse, calculated as the V'_{O_2}/f_C ratio, at peak exercise (O_2pulse), the difference in O_2 pulse between rest and peak exercise (ΔO_2pulse), the peak systolic blood pressures and the occurrence of a right-to-left exercise-induced shunt (EIS) through a patent foramen ovale following previously described criteria [15] were reviewed as potential prognostic markers. Peak V'_{O_2} was defined as the highest V'_{O_2} measured during a period of 20 s at the end of the CPET and anaerobic threshold was determined using the V-slope method [16]. In the case of uncertainty, the anaerobic threshold was counter checked using the nadir of ventilatory equivalents [14].

6MWT

Each patient underwent a 6MWT according to standardised protocol [17]. Time was given every 2 min without encouragement.

6MWD and 6-min walking work evaluated by the formula 6MWD × weight (kg) were considered as potential prognostic markers [18].

Statistics

Statistical analysis SPSS version 18.0.0 (SPSS Inc., Chicago, IL, USA) was performed, including the 136 PAH patients. The 85 IPAH and 51 APAH patients were also considered separately. PAH patients associated with CHD were removed from the analysis of the influence of EIS on survival and TTCW. Time of origin was the date of exercise to date of death or transplantation, the patient was censored at the end of the study if still alive.

Data are presented in mean ± SD. PAH, and IPAH and APAH subgroups were compared by unpaired t-tests. Proportion differences were tested by either Chi-squared or Fisher's exact tests depending of the number of patients in each group.

A Cox proportional hazards regression analysis was used to detect predictors associated with survival and with TTCW. Hazard ratio, 95% confidence intervals and p-values from the likelihood ratio test are given.

For the variables that were predictive of survival or TTCW, receiver operating characteristic (ROC) curves were plotted at 4 yrs for death and at 2 yrs for TTCW. The area under the curve (AUC) with 95% confidence interval and p-value was determined using the nonparametric method. When the lowest 95% confidence interval was >50% and the p-value <0.05, the optimal cut-off point for predicting survival was identified on the basis of the highest sum of sensitivity and specificity, and Kaplan–Meier cumulative survival plots constructed for pattern above and below the threshold were used to describe survival rates. The log rank test was used to compare survival curves (figs 1–4).

Multivariable Cox regression analysis with a forward selection procedure was used to determine independent predictors from the variables with $p<0.10$ in univariate analysis. In all analyses, a p-value <0.05 was considered significant.

RESULTS

Demographic, haemodynamic and clinical data, and pertinent exercise variables are given in tables 1 and 2. The diagnostic right heart catheterisations had been performed at the time of the exercise test in 82 patients, and otherwise 6 ± 11 months before. At the time of the exercise test, 37 patients received

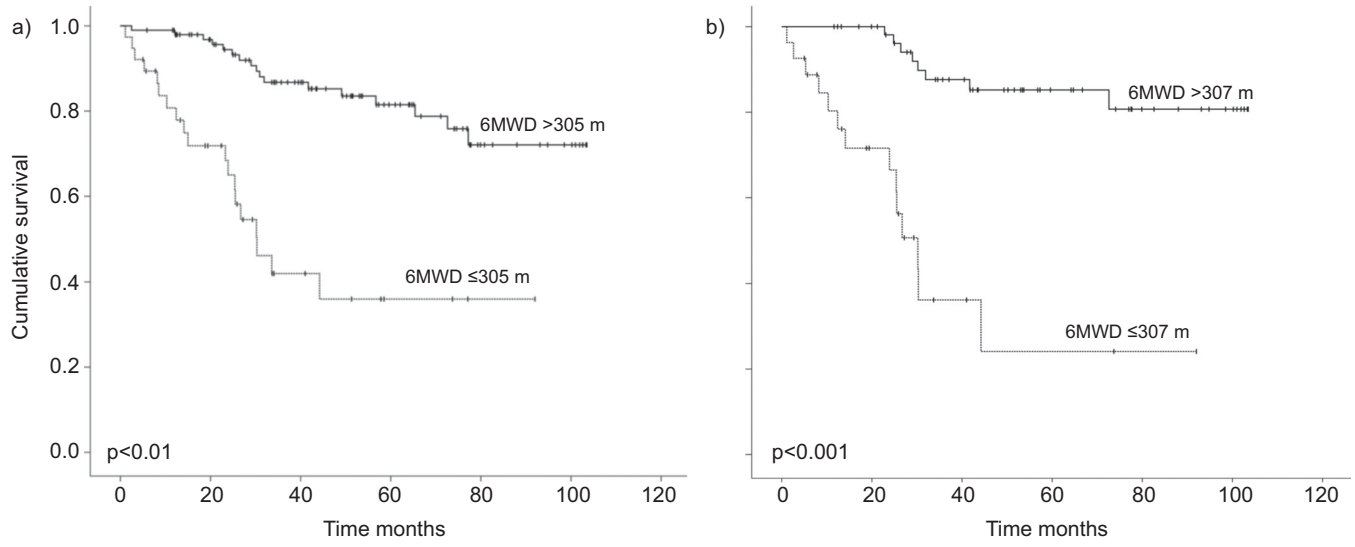

FIGURE 1. Kaplan–Meier cumulative survival curves for the 6-min walk distance (6MWD) in a) 136 patients with pulmonary arterial hypertension (PAH) and b) 85 patients with idiopathic PAH. Cut-off value determined by receiver-operating characteristic curve.

targeted treatment for PAH, such as endothelin receptor antagonists, phosphodiesterase-5 inhibitors or prostacyclins.

Survival

Of the 136 PAH patients followed (44.2±28.3 months), 32 died (at between 1.1 and 77.2 months) and four had lung transplantation (at between 14.1 and 72.6 months). PAH patients had a Kaplan–Meier survival rate at 1, 2, 3 and 4 yrs of 94, 86.5, 75.1 and 72.7%, respectively.

In the IPAH patients (followed over 45.3±30.4 months), 18 died (at between 1.1 and 41.7 months) and four benefited from a lung transplantation (at between 14.1 and 72.6 months); survival at 1, 2, 3 and 4 yrs was 94.0, 88.7, 73.4 and 69.4%, respectively.

In the APAH patients (followed over 42.3±24.6 months), 14 died (at between 2.5 and 77.2 months) and survival at 1, 2, 3 and 4 yrs was 94.1, 82.9, 77.9 and 77.9%, respectively.

As can be seen in table 1, nonsurvivors compared with survivors had similar sex distribution and were of the same age, functional state and haemodynamic severity of pulmonary hypertension (with exception of a lower mixed venous oxygen saturation (S_{v,O_2}) in PAH and APAH and a higher right atrial pressure (P_{ra}) in the APAH subgroups). Exercise capacity variables were more altered in the nonsurvivors PAH patients and this appeared to be driven entirely by the IPAH subgroup.

Univariate Cox analyses for prediction of survival are shown in table 3.

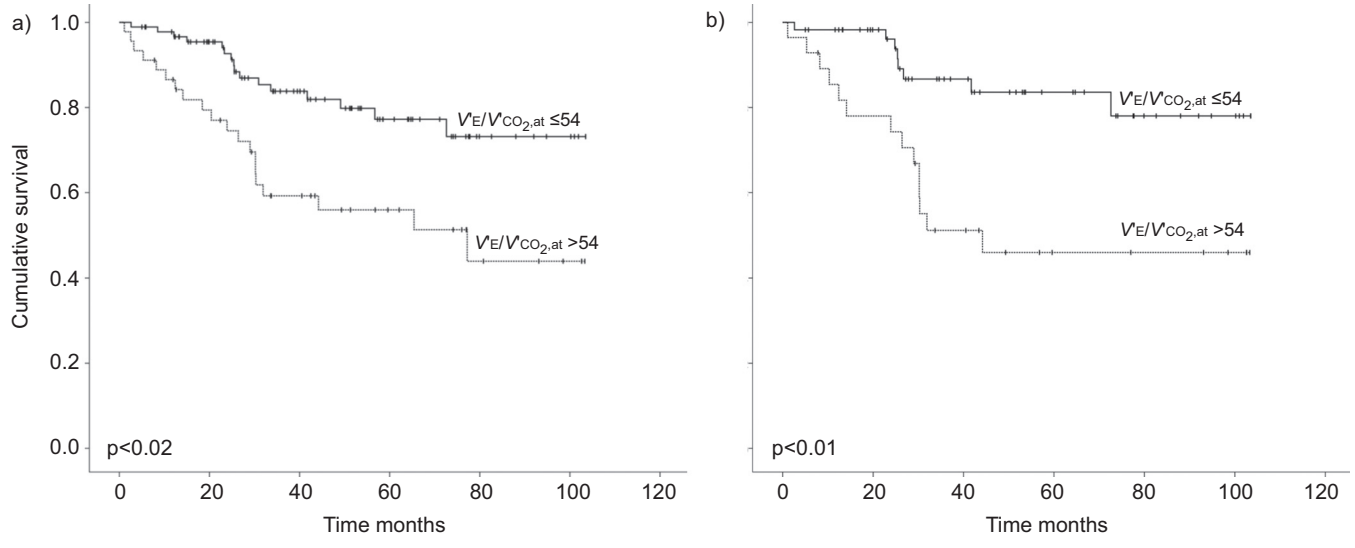

FIGURE 2. Kaplan–Meier cumulative survival curves for the ventilatory equivalent for carbon dioxide at the anaerobic threshold ($V'_E/V'_{CO_2,at}$) in a) 136 patients with pulmonary arterial hypertension (PAH) and b) 85 patients with idiopathic PAH. Cut-off value determined by receiver-operating characteristic curve.

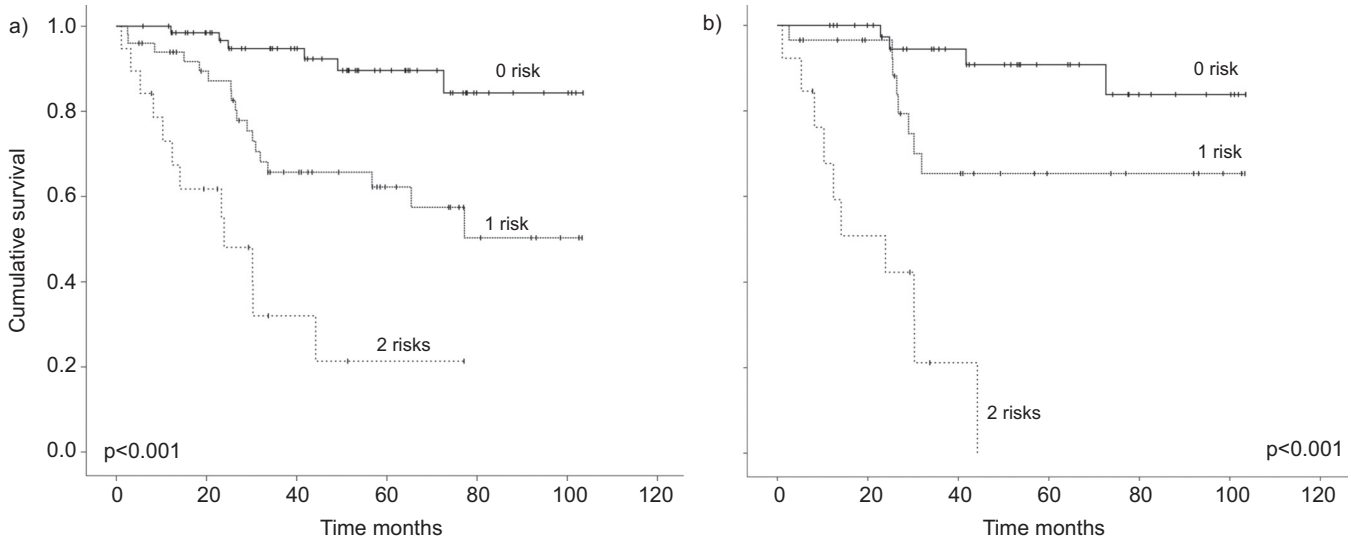

FIGURE 3. Kaplan–Meier cumulative survival curves for no, one or two additional risks factors being a 6-min walk distance <305 m in pulmonary arterial hypertension (PAH) and 307 m in idiopathic PAH (IPAH) and a ventilatory equivalent for carbon dioxide at the anaerobic threshold >54 in PAH and IPAH in a) 136 patients with PAH and b) 85 patients with IPAH.

Peak $V'O_2$, $V'O_2$,at, $V'E/V'CO_2$,at, $V'E/V'CO_2$ slope and 6MWD were predictive of survival in PAH and IPAH patients. No variable was associated with mortality in APAH patients. The 6MWD and $V'E/V'CO_2$,at predicted death independently in PAH and in IPAH patients. Correcting the 6MWD for bodyweight did not affect its predictive value.

Results for receiver operating characteristics analysis are shown in table 4. In the PAH patients, optimal cut-off values to predict survival were: 11.5 mL·kg^{-1}·min^{-1} for peak $V'O_2$; 8.8 mL·kg^{-1}·min^{-1} for $V'O_2$,at; 54 for $V'E/V'CO_2$,at (fig. 2a); 62 for $V'E/V'CO_2$ slope; and 305 m for 6MWD (fig. 1a).

In the IPAH patients, optimal cut-off values to predict survival were: 10.6 mL·kg^{-1}·min^{-1} for peak $V'O_2$; 9.8 mL·kg^{-1}·min for $V'O_2$,at; 54 for $V'E/V'CO_2$,at (fig. 2b); and 307 m for 6MWD (fig. 1b). No optimal cut-off point was determined for $V'E/V'CO_2$ slope as the ROC curve p-value was >0.05 and the lowest 95% confidence interval of the area under the curve was <0.5. Kaplan–Meier cumulative survival curves for 0, 1 or 2 additional independant risks factors are shown in fig. 3.

Clinical worsening

Of the 136 PAH patients followed, 88 encountered a clinical worsening (at between 1.0 and 101 months). The rate of CW after 1, 2, 3 and 4 yrs for the PAH group was 33.6, 51.6, 59.8 and 64.6%, respectively. Of the IPAH patients, 56 had a CW (at between 1.0 and 101 months) and rate of CW at 1, 2, 3 and 4 yrs was 41.9, 58.2, 67.3 and 73.1%, respectively. Of the APAH

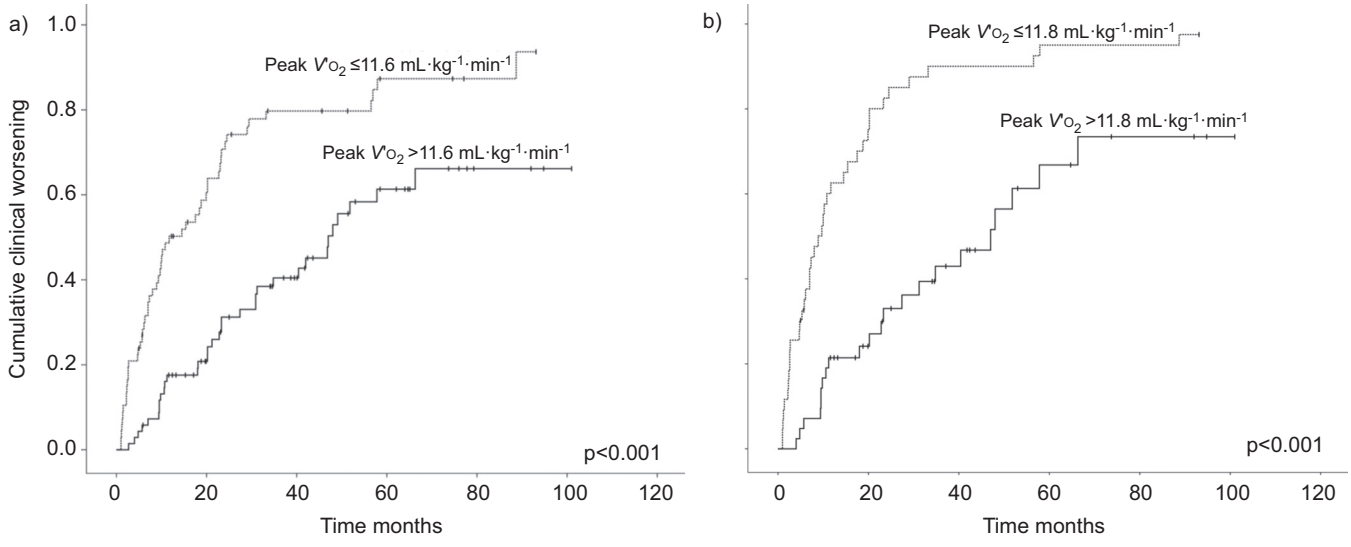

FIGURE 4. Kaplan–Meier cumulative curves for clinical worsening for peak oxygen uptake (peak $V'O_2$) in a) 136 patients with pulmonary arterial hypertension (PAH) and b) 85 patients with idiopathic PAH. Cut-off value determined by receiver-operating characteristic curve.

TABLE 1 Demographic and clinical data of survivors *versus* nonsurvivors in the pulmonary arterial hypertension (PAH) cohort and idiopathic PAH (IPAH) and PAH with associated conditions (APAH) subgroups

	PAH#		IPAH		APAH	
	Survivors	Nonsurvivors	Survivors	Nonsurvivors	Survivors	Nonsurvivors
Subjects	136		85		51	
Males/females	36/64	19/17	21/42	12/10	15/22	7/7
Age yrs	52±16	57±15	53±16	57±17	49±16	57±10
Weight kg	70±19	73±18	72±18	74±19	68±21	73±16
Height cm	166±9	168±11	166±9	169±12	167±22	167±9
Specific treatment yes/no	26/74	11/25	23/40	6/16	3/34	5/9*
NYHA I/II/III/IV	2.7±0.5	2.9±0.5	2.7±0.5	2.9±0.5	2.8±0.4	2.8±0.5
***P*ra mmHg**	8±5	9±5	8±5	9±4	7±5	10±6*
Mean *P*pa mmHg	51±15	50±14	49±11	49±9	52±19	53±21
PVR Wood units	11±6	11±4	11±6	11±4	10±6	11±5
***P*pcw mmHg**	10±3	10±3	9±4	10±4	10±3	11±3
CO L·min^{-1}	4.3±1.3	4±1	4.1±1.3	4±0.8	4.7±13	4±1.3
CI L·min^{-1}·m^{-2}	2.4±0.7	2.2±0.5	2.3±0.6	2.2±0.4	2.7±0.7	2.2±0.6
S_{v,O_2} %	63±11	57±9*	59±12	56±9	69±7	58±11*
6MWD m	416±119	330±141***	411±118	312±155***	424±124	359±115
Work rate Watts	56±20	41±28**	56±26	38±18**	56±31	45±22
***P*ET,CO$_2$,rest mmHg**	27±4	24±5**	26±5	24±5	27±3	25±4*
***P*ET,CO$_2$,at mmHg**	25±5	23±5*	25±4	23±5	26±6	23±4
Δ*P*ET,CO$_2$ mmHg	5±6	4±3	4±6	4±3	6±5	5±3
Peak RER	1.16±0.08	1.16±0.11	1.15±0.09	1.14±0.09	1.18±0.08	1.18±0.13
***f*C,peak beats·min^{-1}**	138±28	123±19**	140±26	122±20*	135±30	124±16
Peak *V*′O$_2$ mL·kg^{-1}·min^{-1}	14±5.2	11±3***	13±5.5	10±3***	14±4.6	11±3.1
***V*′O$_2$,at mL·kg^{-1}·min^{-1}**	9.7±2.9	8.2±2.5**	9.6±2.9	8±2.6*	10±2.8	8.6±2.5
***V*′E/*V*′CO$_2$,at**	49±11	58±15***	49±11	60±15***	48±13	56±14
***V*′E/*V*′CO$_2$ slope**	57±22	70±26**	58±20	70±27*	55±25	71±27
O$_2$pulse mL·beat^{-1}	6.9±2.4	6.3±2.5	7±2.6	5.9±2	6.7±2.1	7±3.2
ΔO$_2$pulse mL·beat^{-1}	3.3±2.2	2.7±2.1	3.4±2.1	2.3±1.8*	3.3±1.9	3.2±1.5
***V*′O$_2$/WR slope L·min^{-1}·Watts^{-1}**	6.7±3.6	5.5±3.7	7±3.4	6±3.7	6.2±3.8	4.8±3.7
Peak BPs mmHg	161±34	162±32	161±34	164±38	160±34	160±25
EIS	27/64	12/17	14/49	7/15	7/16	4/8

Data are presented as n or mean±SD. NYHA: New York Heart Association; *P*ra: right atrial pressure; *P*pa: pulmonary arterial pressure; PVR: pulmonary vascular resistance; *P*pcw: pulmonary capillary wedge pressure; CO: cardiac output; CI: cardiac index; S_{v,O_2}: mixed venous oxygen saturation; 6MWD: 6-min walk distance; *P*ET,CO$_2$ rest: end-tidal carbon dioxide tension at rest; *P*ET,CO$_2$,at: end-tidal carbon dioxide tension at the anaerobic threshold; Δ*P*ET,CO$_2$: increase in the end-tidal carbon dioxide tension; RER: respiratory exchange ratio, *f*C,peak: peak cardiac frequency; *V*′O$_2$: oxygen consumption; *V*′O$_2$,at: *V*′O$_2$ at anaerobic threshold; *V*′E: minute ventilation; *V*′CO$_2$: carbon dioxide production; *V*′E/*V*′CO$_2$,at: ventilatory equivalent for carbon dioxide at the anaerobic threshold; O$_2$,pulse: oxygen pulse; ΔO$_2$,pulse: change in the O$_2$,pulse between rest and peak exercise; *V*′O$_2$/WR slope: slope of *V*′O$_2$ increase with work rate; BPs: systolic blood pressure; EIS: exercise-induced shunt. Specific treatment was with antagonists to endothelin receptors, phosphodiesterase-5 inhibitors or prostacyclins. #: NYHA n=134; BPs n=107; PFO n=104; mean *P*pa, *P*ra, PVR, *P*pcw, CO, and CI n=126; S_{v,O_2} n=83. *: p<0.05; **: p<0.01; ***: p<0.001.

patients, 24 had a CW (at between 1.0 and 79.3 months), and the rate of CW at 1, 2, 3 and 4 yrs was 19.8, 38, 47.5 and 51.6%, respectively.

As shown in table 2, the PAH patients who presented with a CW were as frequently male, and of similar age and functional state. Patients with subsequent CW had higher pulmonary vascular resistance. PAH had higher *P*ra, IPAH had higher mean pulmonary artery pressure, and PAH and IPAH had lower cardiac output, cardiac index and S_{v,O_2}. Exercise capacity variables were more altered in the patients with CW, and this appeared to be driven by the IPAH subgroup. Univariate Cox analysis for prediction of CW is shown in table 5.

Peak *V*′O$_2$, *V*′O$_2$,at, *V*′E/*V*′CO$_2$ slope, *V*′E/*V*′CO$_2$,at, *P*ET,CO$_2$, O$_2$pulse, ΔO$_2$pulse and 6MWD predicted TTCW in both PAH and IPAH patients. Correcting the 6MWD for bodyweight did not affect its predictive value. No variables were associated with TTCW in the APAH patients. Peak *V*′O$_2$ predicted TTCW independently in both PAH and IPAH patients, as shown in by the ROC analysis.

Results for receiver operating characteristics analysis are shown in table 6. Of the PAH patients, optimal cut-off values to predict TTCW were: 11.6 mL·kg^{-1}·min^{-1} for peak *V*′O$_2$ (fig. 4b); 9 mL·kg^{-1}·min^{-1} for *V*′O$_2$,at; 46 for *V*′E/*V*′CO$_2$,at; 55 for *V*′E/*V*′CO$_2$ slope; 23.5 for *P*ET,CO$_2$,at;

TABLE 2 Demographic and clinical data of nonclinical worsening (non-CW) *versus* clinical worsening (CW) in the pulmonary arterial hypertension (PAH) cohort and idiopathic PAH (IPAH) and PAH with associated conditions (APAH) subgroups

	PAH#		IPAH		APAH	
	Non-CW	CW	Non-CW	CW	Non-CW	CW
Subjects	136		85		51	
Males/females	18/30	37/51	7/16	26/36	11/14	11/15
Age yrs	52±18	54±15	54±20	54±15	50±15	52±15
Weight kg	68±20	72±17	69±19	74±17	68±22	69±19*
Height cm	166±9	166±20	166±9	167±10	166±9	166±9
Specific treatment yes/no	10/38	27/61	9/14	20/42	1/24	7/19*
NYHA I/II/III/IV	2.7±0.5	2.8±0.5	2.6±0.6	2.8±0.5	2.8±0.4	2.8±0.5
P_{ra} mmHg	7±5	9±5*	7±5	9±5	7±5	9±5
Mean P_{pa} mmHg	47±13	52±14	45±11	51±9*	49±16	56±23
PVR Wood units	8.8±4.5	12±5.3**	8.6±3.8	11.8±5.5*	8.9±5.2	12.4±5.7*
P_{pcw} mmHg	10±3	10±3	10±4	10±4	9±5	10±3
CO L·min^{-1}	4.7±1.3	4±1.1**	4.5±1.3	3.9±1.1*	4.8±1.4	4.1±1.2
CI L·min^{-1}·m^{-2}	2.6±0.7	2.2±0.6***	2.5±0.6	2.2±0.5*	2.7±0.7	2.3±0.6
S_{v,O_2} %	68±7	56±10*	67±9	54±10***	69±6	64±10
6MWD m	429±133	373±126*	422±141	372±131	435±126	379±118
Work rate Watts	59±31	48±24*	61±31	48±23	57±32	49±27
$P_{ET,CO_2,rest}$ mmHg	28±4	25±4***	27±4	25±4*	28±4	25±4**
$P_{ET,CO_2,at}$ mmHg	28±5	24±5***	27±5	24±5***	27±6	24±5
$\Delta P_{ET,CO_2}$ mmHg	5±5	5±6	4±5	4±5	5±3	5±3
Peak RER	1.16±0.10	1.16±0.07	1.14±0.06	1.15±0.10	1.18±0.08	1.18±0.10
$f_{C,peak}$ beats·min^{-1}	139±29	132±24	144±28	132±25	135±31	130±24
Peak V'_{O_2} mL·kg^{-1}·min^{-1}	15±6	12±3.6***	16±7	11±3.4***	14±4.7	12±3.9
$V'_{O_2,at}$ mL·kg^{-1}·min^{-1}	10±2.8	8.8±2.7**	11±3.2	8.5±2.5***	9.9±2.4	9.4±3.2
$V'_E/V'_{CO_2,at}$	45±11	55±13***	44±10	55±13***	46±13	54±13*
V'_E/V'_{CO_2} slope	52±23	65±23**	50±16	65±23**	54±28	65±25
O_{2pulse} mL·beat^{-1}	7.3±2.6	6.4±2.3	7.8±3.1	6.3±2*	6.8±2	6.8±2.8
ΔO_{2pulse} mL·beat^{-1}	3.8±2.2	2.8±1.9**	4.2±2.7	2.7±17**	3.5±1.7	3.1±2.9
V'_{O_2}/WR slope L·min^{-1}·Watts^{-1}	7.4±3.8	5.8±3.4*	8.4±6.0	6.1±3.3***	6.4±3.7	5.1±3.7
Peak BPs mmHg	166±34	158±32	169±35	159±34	164±34	157±30
EIS	13/34	26/47	3/20	18/44	4/14	7/11

Data are presented as n or mean±SD. NYHA: New York Heart Association; P_{ra}: right atrial pressure; P_{pa}: pulmonary arterial pressure; PVR: pulmonary vascular resistance; P_{pcw}: pulmonary capillary wedge pressure; CO: cardiac output; CI: cardiac index; S_{V,O_2}: mixed venous oxygen saturation; 6MWD: 6-min walk distance; P_{ET,CO_2} rest: end-tidal carbon dioxide tension at rest; $P_{ET,CO_2,at}$: end-tidal carbon dioxide tension at the anaerobic threshold; $\Delta P_{ET,CO_2}$: increase in the end-tidal carbon dioxide tension; RER: respiratory exchange ratio, $f_{C,peak}$: peak cardiac frequency; V'_{O_2}: oxygen consumption; $V'_{O_2,at}$: V'_{O_2} at anaerobic threshold; V'_E: minute ventilation; V'_{CO_2}: carbon dioxide production; $V'_E/V'_{CO_2,at}$: ventilatory equivalent for carbon dioxide at the anaerobic threshold; O_{2pulse}: oxygen pulse; ΔO_{2pulse}: change in the $O_{2,pulse}$ between rest and peak exercise; V'_{O_2}/WR slope: slope of V'_{O_2} increase with work rate; BPs: systolic blood pressure; EIS: exercise-induced shunt. #: NYHA n=134; BPs n=107; PFO n=104; mean P_{pa}, P_{ra}, PVR, P_{pcw}, CO and CI, n=126; and S_{V,O_2}%, n=83. *: p<0.05; **: p<0.01; ***: p<0.001.

5.3 mL·beat^{-1} for O_{2pulse}; 2.6 mL·beat^{-1} for ΔO_{2pulse}; and 367 m for 6MWD.

Of the IPAH patients, optimal cut-off values to predict CW were: 11.8 mL·kg^{-1}·min^{-1} for peak V'_{O_2} (fig. 4b); 9.6 mL·kg^{-1}·min^{-1} for $V'_{O_2,at}$; 51 for $V'_E/V'_{CO_2,at}$; 59 for V'_E/V'_{CO_2} slope; 23.5 for $P_{ET,CO_2,at}$; 2.1 mL·beat^{-1} for ΔO_{2pulse}; and 367 m for 6MWD. No optimal cut-off point was determined for O_{2pulse} IPAH as the ROC curve p-value was >0.05 and the lowest 95% confidence interval of the AUC was <0.5.

DISCUSSION

The present results show that exercise capacity predicts not only survival, but also clinical stability in PAH, with a better discrimination of exercise testing variables in IPAH than in APAH. In this study, independent predictors of survival were the 6MWD and $V'_E/V'_{CO_2,at}$ for IPAH, while no exercise variable independently predicted survival in APAH. As for TTCW, this was predicted only by peak V'_{O_2} and only in IPAH.

PAH is a right heart failure syndrome [19]. Exercise capacity in heart failure is largely determined by maximal cardiac output, which, in pulmonary hypertension, is determined by right ventricular function. The afterloaded right ventricle relies on f_C more than on stroke volume to increase flow output [19], which translates into a more decreased oxygen pulse during exercise for patient with a worse prognosis [7], as is also shown

TABLE 3 Univariate Cox analysis of proportional risks for death using continues values in pulmonary arterial hypertension (PAH) cohort and idiopathic PAH (IPAH) and PAH with associated conditions (APAH) subgroups

Variables	PAH		IPAH		APAH	
	RR (95% CI)	p-value	RR (95% CI)	p-value	RR (95% CI)	p-value
Subjects n	136		70		66	
Peak V'_{O_2} mL·kg^{-1}·min^{-1}	0.837 (0.750–0.935)	0.002	0.805 (0.690–0.939)	0.006	0.882 (0.752–1.036)	0.126
$V'_{O_2,at}$ mL·kg^{-1}·min^{-1}	0.841 (0.742–0.953)	0.007	0.830 (0.704–0.979)	0.027	0.864 (0.711–1.051)	0.144
$V'_E/V'_{CO_2,at}$	1.039 (1.017–1.061)	0.001	1.054 (1.024–1.084)	<0.001	1.020 (0.987–1.055)	0.238
V'_E/V'_{CO_2} slope	1.014 (1.004–1.025)	0.009	1.025 (1.006–1.045)	0.011	1.009 (0.994–1.024)	0.264
$P_{ET,CO_2,at}$ mmHg	0.944 (0.881–1.011)	0.100	0.943 (0.855–1.039)	0.233	0.950 (0.860–1.049)	0.308
$\Delta P_{ET,CO_2}$ mmHg	0.977 (0.892–1.071)	0.622	0.968 (0.866–1.082)	0.566	0.980 (0.821–1.169)	0.819
O_{2pulse} mL·beat^{-1}	0.930 (0.803–1.078)	0.335	0.867 (0.703–1.068)	0.180	1.051 (0.845–1.308)	0.654
ΔO_{2pulse} mL·beat^{-1}	0.871 (0.732–1.037)	0.121	0.784 (0.602–1.021)	0.071	1.008 (0.782–1.299)	0.951
Peak BPs mmHg	1.000 (0.989–1.012)	0.951	1.001 (0.986–1.017)	0.891	1.001 (0.982–1.020)	0.940
EIS	1.686 (0.769–3.694)	0.192	1.451 (0.591–3.564)	0.417	1.311 (0.383–4.491)	0.666
6MWD m	0.994 (0.991–0.997)	<0.001	0.993 (0.990–0.996)	<0.001	0.996 (0.991–1.000)	0.077

RR: relative risk; V'_{O_2}: oxygen consumption; $V'_{O_2,at}$: V'_{O_2} at anaerobic threshold; V'_E: minute ventilation; V'_{CO_2}: carbon dioxide production; $V'_E/V'_{CO_2,at}$: ventilatory equivalent for carbon dioxide at the anaerobic threshold; $P_{ET,CO_2,at}$: end-tidal carbon dioxide tension at the anaerobic threshold; $\Delta P_{ET,CO_2}$: change in end-tidal carbon dioxide tension; O_{2pulse}: oxygen pulse; ΔO_{2pulse}: change in the O_{2pulse} at rest and peak exercise; BPs: systolic blood pressure; EIS: exercise-induced shunt; 6MWD: 6-min walk distance.

in the present results by univariate analysis. However, O_{2pulse} is only an indirect measure of stroke volume derived from the Fick equation with the assumption of unchanged arteriovenous oxygen content difference. Maximal cardiac output is related to maximum V'_{O_2} and also to maximal workload, which is in turn related to the maximal average running or walking speed [4]. According to this reasoning, the information content of peak V'_{O_2} and the 6MWD in PAH are equivalent. Accordingly, in the present study, both peak V'_{O_2} and the 6MWD predicted survival and TTCW in IPAH.

Previous studies in PAH have shown that the 6MWD was more sensitive than peak V'_{O_2} to targeted therapies, such as beraprost [20] or sitaxsentan [21]. Part of this greater sensitivity of the 6MWD was ascribed to relatively less expertise in the practice of CPET in the centres that participated to these studies [22]. In the present study, the predictive capability of CPET variables in IPAH was found to be similar to those previously reported, making insufficient expertise unlikely. From another point of view, while the 6MWD and not peak V'_{O_2} independently predicted survival, peak V'_{O_2}, and not the 6MWD, predicted CW. The reasons for this apparent contradiction are unclear, but this result underlines the interest of CPET when added to a 6MWT in the evaluation of PAH patients.

The correlation between a maximal average running speed and maximum V'_{O_2} or peak V'_{O_2} is generally significant, but rather loose, with correlation coefficients in the range of 0.5–0.7 in normal subjects [23], as well as in patients with IPAH [5, 22, 24]. This is explained by variable mechanical efficiency of running or walking, which is related in part to different body

TABLE 4 Receiver operating characteristics for death at 4 yrs for pulmonary arterial hypertension (PAH) cohort and idiopathic PAH (IPAH) and PAH with associated conditions (APAH) subgroups

Variables	PAH		IPAH		APAH#	
	AUC % (95% CI)	p-value	AUC % (95% CI)	p-value	AUC % (95% CI)	p-value
Subjects n	136		70		66	
Peak V'_{O_2} mL·kg^{-1}·min^{-1}	73.2 (63.8–82.6)	<0.001	71.9 (58.0–85.9)	0.007		
$V'_{O_2,at}$ mL·kg^{-1}·min^{-1}	69.0 (58.6–79.3)	0.001	71.8 (57.9–85.7)	0.007		
$V'_E/V'_{CO_2,at}$	69.8 (59.7–80.0)	0.001	69.5 (54.6–84.4)	0.017	Not calculated	
V'_E/V'_{CO_2} slope	63.9 (51.3–76.5)	0.033	65.7 (49.3–82.0)	0.054		
6MWD m	73.1 (62.2–84.0)	<0.001	78.0 (63.6–92.4)	0.001		

AUC: area under the curve; V'_{O_2}: oxygen consumption; $V'_{O_2,at}$: V'_{O_2} at anaerobic threshold; V'_E: minute ventilation; V'_{CO_2}: carbon dioxide production; $V'_E/V'_{CO_2,at}$: ventilatory equivalent for carbon dioxide at the anaerobic threshold; 6MWD: 6-min walk distance. #: no receiver operating characteristic curve was calculated in the APAH subgroup.

TABLE 5 Univariate Cox analysis of proportional risks for clinical worsening (CW) using continues values for pulmonary arterial hypertension (PAH) cohort and idiopathic PAH (IPAH) and PAH with associated conditions (APAH) subgroups

Variables	PAH		IPAH		APAH	
	RR (95% CI)	p-value	RR (95% CI)	p-value	RR (95% CI)	p-value
Subjects n	136		70		66	
Peak V'_{O_2} mL·kg^{-1}·min^{-1}	0.871 (0.817–0.929)	<0.001	0.836 (0.770–0.907)	<0.001	0.950 (0.857–1.053)	0.328
$V'_{O_2,at}$ mL·kg^{-1}·min^{-1}	0.879 (0.815–0.949)	0.001	0.861(0.787–0.941)	0.001	0.942 (0.816–1.087)	0.411
$V'_E/V'_{CO_2,at}$	1.025 (1.011–1.039)	0.001	1.032 (1.014–1.050)	0.001	1.017 (0.993–1.041)	0.710
V'_E/V'_{CO_2} slope	1.009 (1.002–1.016)	0.008	1.020 (1.009–1.030)	<0.001	1.004 (0.993–1.016)	0.474
$P_{ET,CO_2,at}$ mmHg	0.947 (0.909–0.987)	0.009	0.940 (0.891–0.991)	0.022	0.950 (0.860–1.049)	0.308
$\Delta P_{ET,CO_2}$ mmHg	1.023 (0.968–1.081)	0.422	1.045 (0.987–1.106)	0.129	0.958 (0.895–1.026)	0.218
O_{2pulse} mL·beat^{-1}	0.908 (0.825–1.000)	0.050	0.894 (0.800–1.000)	0.050	0.974 (0.863–1.100)	0.674
ΔO_{2pulse} mL·beat^{-1}	0.858 (0.768–0.957)	0.006	0.812 (0.703–0.938)	0.005	0.939 (0.776–1.137)	0.520
Peak BPs mmHg	0.994 (0.986–1.002)	0.123	0.992 (0.983–1.002)	0.111	0.995 (0.982–1.009)	0.485
EIS	1.465 (0.871–2.467)	0.150	1.275 (0.735–2.212)	0.387	1.484 (0.574–3.838)	0.416
6MWD m	0.997 (0.995–0.998)	<0.001	0.996 (0.994–0.998)	<0.001	0.997 (0.994–1.000)	0.095

RR: relative risk; peak V'_{O_2}: peak oxygen consumption; $V'_{O_2,at}$: V'_{O_2} at anaerobic threshold; V'_E: minute ventilation; V'_{CO_2}: carbon dioxide production; $V'_E/V'_{CO_2,at}$: ventilatory equivalent for carbon dioxide at the anaerobic threshold; $P_{ET,CO_2,at}$: end-tidal carbon dioxide tension measured at the anaerobic threshold; $\Delta P_{ET,CO_2}$: change in end-tidal carbon dioxide tension between rest and peak exercise; O_{2pulse}: oxygen pulse; ΔO_{2pulse}: change in the O_{2pulse} between rest and peak exercise; BPs: systolic blood pressure; 6MWD: 6-min walk distance.

dimensions or weight. Correction of the 6MWD for bodyweight has indeed been shown to improve these correlations in chronic obstructive pulmonary disease [18], as well as in PAH [22, 24]. However, in the present study, correcting the 6MWD for bodyweight did not improve its prognostic value.

In the present study, the nonsurvivors had similar pulmonary haemodynamics compared with survivors, even though S_{v,O_2} was lower and P_{ra} higher (in the APAH group only) in the nonsurvivors. Haemodynamic severity of PAH was more clearly associated with the occurrence of clinical deterioration. However, while these results are in keeping with the previously known poorer prognosis associated with more severe pulmonary hypertension and a lower cardiac output [1, 2, 5, 6], further analysis of the compared prognostic values of haemodynamic and exercise test variables was limited by the fact that the measurements were separated in time in too many of the patients.

The present results confirm the prognostic value of the ventilatory equivalents for carbon dioxide previously reported in chronic heart failure [25, 26], as well as in PAH [7, 12], but with significance only in the patients with IPAH and not those with APAH. This is probably related to the inhomogeneity of

TABLE 6 Receiver-operating characteristics at 2 yrs for clinical worsening for pulmonary arterial hypertension (PAH) cohort and idiopathic PAH (IPAH) and PAH with associated conditions (APAH) subgroups

Variables	PAH		IPAH		APAH#	
	AUC % (95% CI)	p-value	AUC % (95% CI)	p-value	AUC % (95% CI)	p-value
Subjects n	136		70		66	
Peak V'_{O_2} mL·kg^{-1}·min^{-1}	73.9 (65.6–82.2)	<0.001	77.8 (66.9–88.7)	<0.001		
$V'_{O_2,at}$ mL·kg^{-1}·min^{-1}	71.0 (62.2–79.8)	<0.001	72.0 (59.9–84.2)	0.001		
$V'_E/V'_{CO_2,at}$	70.3 (61.5–79.1)	<0.001	69.3 (56.9–81.6)	0.005		
V'_E/V'_{CO_2} slope	65.5 (55.5–75.6)	0.003	69.0 (57.5–81.5)	0.005	Not calculated	
$P_{ET,CO_2,at}$	67.4 (57.8–77.1)	0.001	69.0 (56.4–81.5)	0.007		
O_{2pulse} mL·beat^{-1}	62.8 (53.3–72.3)	0.010	59.5 (46.6–72.3)	0.168		
ΔO_{2pulse} mL·beat^{-1}	66.3 (57.1–75.4)	0.001	67.0 (54.9–79.1)	0.013		
6MWD m	69.6 (60.8–78.5)	<0.001	73.0 (61.9–84.2)	0.001		

AUC: area under the curve; peak V'_{O_2}: peak oxygen consumption; $V'_{O_2,at}$: V'_{O_2} at anaerobic threshold; V'_E: minute ventilation; V'_{CO_2}: carbon dioxide production; $V'_E/V'_{CO_2,at}$: ventilatory equivalent for carbon dioxide at the anaerobic threshold; $P_{ET,CO_2,at}$: end-tidal carbon dioxide tension measured at the anaerobic threshold; $\Delta P_{ET,CO_2}$: change in end-tidal carbon dioxide tension between rest and peak exercise; O_{2pulse}: oxygen pulse; ΔO_{2pulse}: change in the $O_{2,pulse}$ between rest and peak exercise; 6MWD: 6-min walk distance. #: no receiver operating characteristic curve was calculated in the APAH subgroup.

the APAH group, as it is known that survival is much better in CHD-APAH and worse survival in systemic sclerosis APAH [27]. Whether the V'_E/V'_{CO_2} slopes during CPET are different in APAH subcategories is not exactly known.

It has been recommended to measure V'_E/V'_{CO_2} below or at the anaerobic threshold, as the V'_E/V'_{CO_2} slope calculated on the entire CPET may be influenced by the maximal or peak level of exercise and variable associated acidosis [14]. In the present study, the predictive value of $V'_E/V'_{CO_2,at}$ was better than that of the V'_E/V'_{CO_2} slope, even though the latter was measured after the beginning of loaded exercise to the end of the isocapnic buffering period.

Another problem of the V'_E/V'_{CO_2} ratio or slope may be the sudden increase occurring with right-to-left shunting [15]. For that reason, WENSEL *et al*. [12] excluded patients with a resting patent foramen ovale from the analysis of V'_E/V'_{CO_2} slope in relation to survival. The development or the persistence of such shunting during the course of therapy has been found to be associated with an altered prognosis in PAH [28]. In the present study, however, EIS did not predict survival or TTCW.

GROEPENHOFF *et al*. [7] found that $V'_E/V'_{CO_2,at}$ or V'_E/V'_{CO_2} slope predicted survival in their mixed PAH–CTEPH population with cut-off values in the same range as ours (*i.e.* 52 for $V'_E/V'_{CO_2,at}$ and 48 for the V'_E/V'_{CO_2} slope). It is of interest that survival cut-off values for V'_E/V'_{CO_2} are higher in PAH than in heart failure, with typical values >50 and of ~35, respectively [25, 26, 29]. Both conditions are associated with increased ventilation at any given level of metabolic rate [30] in relation to increased chemosensitivity and physiological dead space [31, 32]; however, the respective contributions of both mechanisms are not exactly known.

Peak V'_{O_2} values inferior to 11.5 and 10.6 $mL \cdot kg^{-1} \cdot min^{-1}$ in our PAH and IPAH subjects, respectively, were associated with a decreased survival. The cut-off of 10.6 $mL \cdot kg^{-1} \cdot min^{-1}$ is in agreement with a report by WENSEL *et al*. [12] on similar severity IPAH patients, while GROEPENHOFF *et al*. [7] found a higher cut-off of 13.2 $mL \cdot kg^{-1} \cdot min^{-1}$ in a mixed group of PAH and CTEPH patients. The isolated impact of CTEPH on the predictive value of peak V'_{O_2} remains to be investigated. Slight differences in ''cut-off values'' and predictions are attributable to differences in severity of disease in apparently similar patient populations.

A limitation to the present study is the heterogeneous nature of the APAH group, with too small numbers to identify specific profiles of subgroups such as CTD–PAH or CHD–PAH. Another limitation is that the walking ability may be impaired in CTD patients, so that the 6MWT as a measure of exercise capacity in these patients remains insufficiently validated [33]. Finally, because of the heterogeneous nature and smaller size of the APAH group, it happened that all conclusions for IPAH patients were transposable to the PAH patient population as a whole in the present study, but this of course may be affected the nature of associated conditions and sizes of APAH subgroups.

To our knowledge, this is the first report of prediction of TTCW from exercise testing variables. Our results clearly show that clinical stability is better predicted in IPAH than in APAH and that, for this purpose, peak V'_{O_2} may be superior to the 6MWT. This is relevant to the definition of clinical deterioration and inclusion criteria for event-driven clinical trials of new therapeutic interventions in PAH. Moreover, our study documents the importance of V'_E/V'_{CO_2} as an outcome predictor independently associated with survival and also able to predict TTCW in PAH and IPAH.

SUPPORT STATEMENT

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STATEMENT OF INTEREST

None declared.

REFERENCES

1 McLaughlin VV, Archer SL, Badesch DB, *et al.* ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension. A Report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association. *Circulation* 2009; 119: 2250–2294.

2 Task Force for Diagnosis and Treatment of Pulmonary Hypertension of European Society of Cardiology (ESC), European Respiratory Society (ERS), International Society of Heart and Lung Transplantation (ISHLT), et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2009; 34: 1219–1263.

3 Sun XG, Hansen JE, Oudiz RJ, *et al.* Exercise pathophysiology in patients with pulmonary hypertension. *Circulation* 2001; 104: 429–435.

4 Naeije R. The 6-min walk distance in pulmonary arterial hypertension: "Je t'aime, moi non plus". *Chest* 2010; 137: 1258–1260.

5 Miyamoto S, Nagaya N, Satoh T, *et al.* Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2000; 161: 487–492.

6 Sitbon O, Humbert M, Nunes H, *et al.* Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol* 2002; 40: 780–788.

7 Groepenhoff H, Vonk-Noordegraaf A, Boonstra A, *et al.* Exercise testing to estimate survival in pulmonary hypertension. *Med Sci Sports Exerc* 2008; 40: 1725–1732.

8 Humbert M, Sitbon O, Chaouat A, *et al.* Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation* 2010; 122: 156–163.

9 Humbert M, Sitbon O, Yaïci A, *et al.* Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. *Eur Respir J* 2010; 36: 549–555.

10 Benza RL, Miller DP, Gomberg-Maitland M, *et al.* Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation* 2010; 122: 164–172.

11 McLaughlin VV, Badesch DB, Delcroix M, *et al.* End points and clinical trial design in pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; 54: S97–S107.

12 Wensel R, Opitz CF, Anker SD, *et al.* Assessment of survival in patients with primary pulmonary hypertension. Importance of cardiopulmonary exercise testing. *Circulation* 2002; 106: 319–324.

13 Souza R, Humbert M, Sztrymf B, *et al.* Pulmonary arterial hypertension associated with fenfluramine exposure: report of 109 cases. *Eur Respir J* 2008; 31: 343–348.

14 Wasserman K, Hansen JE, Sue DY, *et al*. Principles of Exercise Testing and Interpretation, 4th Edn. Baltimore, Lippincott Williams & Wilkins, 2005.
15 Sun XG, Hansen JE, Oudiz RJ, *et al.* Gas exchange detection of exercise-induced right-to-left shunt in patients with primary pulmonary hypertension. *Circulation* 2002; 105: 54–60.
16 Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* 1986; 60: 2020–2027.
17 American Thoracic Society. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166: 111–117.
18 Chuang ML, Lin IF, Wasserman K. The body weight-walking distance product as related to lung function, anaerobic threshold and peak V'_{O_2} in COPD patients. *Respir Med* 2001; 95: 618–626.
19 Champion HC, Michelakis ED, Hassoun PM. Comprehensive invasive and noninvasive approach to the right ventricle-pulmonary circulation unit: state of the art and clinical and research implications. *Circulation* 2009; 120: 992–1007.
20 Barst RJ, McGoon M, McLaughlin V. Beraprost therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2003; 41: 2119–2125.
21 Barst RJ, Langleben D, Frost A, *et al.* Sitaxsentran therapy for pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2004; 169: 441–447.
22 Oudiz RJ, Barst RJ, Hansen JE, *et al.* Cardiopulmonary exercise testing and six-minute walk correlations in pulmonary arterial hypertension. *Am J Cardiol* 2006; 9: 123–126.
23 Cooper KH. A means of assessing maximal oxygen intake. Correlation between field and treadmill testing. *JAMA* 1968; 203: 135–138.
24 Deboeck G, Niset G, Vachiery JL, *et al.* Physiologic response to the 6MWT in pulmonary arterial hypertension. *Eur Respir J* 2005; 26: 667–672.
25 Chua TP, Ponikowski P, Harrington D, *et al.* Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. *J Am Coll Cardiol* 1997; 29: 1585–1590.
26 Kleber FX, Vietzke G, Wernecke KD, *et al.* Impairment of ventilatory efficiency in heart failure: prognostic impact. *Circulation* 2000; 101: 2803–2809.
27 McLaughlin VV, Presberg KW, Doyle RL, *et al.* Prognosis of pulmonary arterial hypertension. ACCP Evidence-Based Clinical Practice Guidelines. *Chest* 2004; 126: 78S–92S.
28 Oudiz RJ, Midde R, Hovenesyan A, *et al.* Usefulness of right-to-left shunting and poor exercise gas exchange for predicting prognosis in patients with pulmonary arterial hypertension. *Am J Cardiol* 2010; 105: 1186–1191.
29 Arena R, Myers J, Aslam SS, *et al.* Peak V'_{O_2} and V_E/V_{CO_2} slope in patients with heart failure: a prognostic comparison. *Am Heart J* 2004; 147: 354–360.
30 Deboeck G, Niset G, Lamotte M, *et al.* Cardiopulmonary exercise testing in pulmonary arterial hypertension and in congestive heart failure. *Eur Respir J* 2004; 23: 747–751.
31 Johnson RL Jr. Gas exchange efficiency in congestive heart failure. II. *Circulation* 2001; 103: 916–918.
32 Naeije R, van de Borne P. Clinical relevance of autonomic nervous system disturbances in pulmonary arterial hypertension. *Eur Respir J* 2009; 34: 792–794.
33 Avouac J, Kowal-Bielecka O, Pittrow D, *et al.* Validation of the 6 min walk test according to the OMERACT filter: a systematic literature review by the EPOSS-OMERACT group. *Ann Rheum Dis* 2010; 69: 1360–1363.