ERJ Express. Published on March 22, 2012 as doi: 10.1183/09031936.00217911

EXERCISE TO PREDICT OUTCOME IN IDIOPATHIC VS ASSOCIATED PULMONARY ARTERIAL HYPERTENSION

Authors:

1. Gaël Deboeck,

gael.deboeck@erasme.ulb.ac.be – Erasmus University Hospital, Department of cardiology. Free University of Brussels.

2. Cristina Scoditti,

c_scod@yahoo.it - University of Bari, Department of lung disease, Bari, Italy

3. Sandrine Huez,

Sandrine.huez@erasme.ulb.ac.be – Erasmus University Hospital, Department of Cardiology, Free University of Brussels.

4. Jean Luc Vachiéry,

jeanluc.vachiery@erasme.ulb.ac.be – Erasmus University Hospital, Department of cardiology, Free University of Brussels.

6. Michel Lamotte,

michel.lamotte@erasme.ulb.ac.be – Erasmus University Hospital, Department of cardiology, Free University of Brussels.

8. Linda Sharples,

Linda.Sharples@papworth.nhs.uk – Papworth hospital, Papworth, Cambridge, UK.

7. Christian Melot,

cmelot@ulb.ac.be – Erasmus University hospital, Department of Emergency Medicine, Free University of Brussels

9. Robert Naeije,

rnaeije@ulb.ac.be - Department of Physiology, Faculty of Medicine of the Free University of Brussels.

Address for correspondence and reprints:

Pr Naeije Robert, Department of Physiology, Faculty of Medicine of the Free University of Brussels. Erasme Campus, CP 604, 808 route de Lennik, 1070 Bruxelles, Belgique FAX: 32 25554124 - Email: rnaeije@ulb.ac.be

Running Title: Exercise and outcome in pulmonary hypertension

Word count:

Abstract: 199 words

Body text: 3086 words

ABSTRACT

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

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

Thirty-two patients died and 4 had lung transplantation. At univariate analysis, PAH patients survival was associated with oxygen uptake (VO_2) at peak exercise and at anaerobic threshold, ventilatory equivalent for CO2 (V_EVCO_2) at anaerobic threshold (at), V_E/VCO_2slope and distance walked. Time to clinical worsening was associated with peakVO_2 and VO_2at, $V_EVCO_2$at, end-tidal CO_2 partial pressure measured at anaerobic threshold, peakO_2 pulse, increase in O_2pulse and distance walked. At multivariable analysis, distance walked and $V_EVCO_2$at predicted survival, and only peakVO_2 predicted time to clinical worsening. The ROC curve-derived cut-off values were 305 m for the 6-min walk distance, 54 for $V_EVCO_2$at and 11.6 mL/Kg.min for peakVO_2. In the subgroup of associated PAH, no variable independently predicted survival or clinical worsening.

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

Key-words : Pulmonary hypertension, pulmonary arterial hypertension, 6 minute walk test, cardiopulmonary exercise testing, clinical worsening, survival,

INTRODUCTION

The symptomatology of pulmonary arterial hypertension (PAH) is dominated by dyspnea 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 a distance walked in 6-minutes (6MWD) are used in clinical practice to estimate disease severity.[3,4]

The 6 minute 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 consumption (VO_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 PH patient 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 endpoint in newly designed event-driven randomised controlled trials in PAH.[11] However, no study has until now 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.

METHODS

PROTOCOL

The study included the CPET and 6MWT data of 136 PAH patients of the pulmonary hypertension clinic of University Erasmus Hospital, Brussels, 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 of mortality or lung transplantation with the remaining cases designated as event-free survival. The clinical worsening end point was defined as previously reported [11].: all cause of mortality; non elective 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 2 studies done within 2 weeks plus worsening functional class.

PATIENTS

The diagnosis of PAH rested on a right heart catheterization with demonstration of an increase in mean pulmonary artery pressure (>25mmHg), a normal pulmonary artery wedge pressure (<15mmHg), no identifiable cardiac or pulmonary cause, and possibly associated with conditions such as appetite suppressant intake, connective tissue disease (CTD), liver cirrhosis, human immunodeficiency virus (HIV) infection, and congenital left-to-right shunt (CHD).[1,2] Seventy patients had IPAH and 66 patients had PAH with associated conditions, which were previous intake of anorexigen in 15, CTD (all systemic sclerosis) without lung function impairment in 19, hepatic cirrhosis in 11, HIV infection in 4, CHD in 16 or schistosomiasis in 1. 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 indiscernable [2,13]. Thus, the study considered two subgroups of respectively 85 patients with IPAH and 51 patients with APAH

EXERCISE TESTING

CPET

Each patient underwent standard cycle ergometer incremental cardiopulmonary exercise test until the symptom-limited maximum.[14] The CPET protocol consisted in a pedalling at 0 to 20 watts during the 3 first minutes and then an increment of load of 5 to 15 watts/min aimed to obtain an exercise duration

between 8 and 12 minutes. Because of equipment renewal over the years, ventilation and gas analysis were performed using a "CPX/D" (Medical Graphics, St Paul, MN) in 16 tests and a Vmax, (sensormedics, Yorba Linda, CA) in 120. Gas analysers and pneumotachograph were calibrated prior to each test. Heart rate and blood pressure were obtained via automatic standard ECG and sphygmomanometer.

PeakVO_2, VO_2 at anaerobic threshold (VO_2at), the ventilatory equivalent for carbon dioxide (CO_2) measured at anaerobic threshold ($V_E VCO_2$at) or as a slope from 1 minute after the beginning of loaded exercise to the end of the isocapnic buffering period (V_E/VCO_2slope), the end-expiratory partial pressure of CO_2 ($PetCO_2$) measured at the anaerobic threshold, the delta (Δ, max-rest) $PetCO_2$, the oxygen pulse, calculated by the ratio VO_2/heart rate, at peak exercise (O_2pulse), the difference in O_2pulse between rest and peak exercise (ΔO_2pulse), the peak systolic blood pressure (BPs) and the occurrence of a right to left exercise induced shunt (EIS) through a patent foramen ovale (PFO) following criteria as previously described[15] were reviewed as potential prognostic markers. Peak VO_2 was defined as the highest VO_2 measured during a period of 20 seconds at the end of the CPET and anaerobic threshold was determined using the V-slope method [16]. In case of uncertainty, the anaerobic threshold was counter checked using the nadir of ventilatory equivalents.[14]

6MWT

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

6MWD and 6MW work (6MWW) evaluated by the formula: "6MWD x weight"[18] were considered as potential prognostic markers.

STATISTICS

Statistical analysis (SPSS 18.0.0, Inc., Chicago, IL) was performed including the 136 PAH patients. The 85 IPAH and 51 APAH 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 study if still alive.

Data are presented in mean ± standard deviation (SD). PAH and, IPAH and APAH sub-groups were compared by an unpaired t test. Proportion differences were tested by Chi-square or Fisher 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 value from the likelihood ratio test are given.

For the variables that were predictive of survival or TTCW, receiver operating characteristic (ROC) curve were designed at 4 years for death and at 2 years for TTCW. The area under the curve (AUC) with 95% confidence interval and P value was determined using the non parametric 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 to describe survival rates. Log Rank test was used to compare survival curves.

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 analysis a P value<0.05 was considered significant.

RESULTS

Demographic, hemodynamic and clinical data and pertinent exercise variables are given in tables 1 and 2. The diagnostic right heart catheterizations 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 a targeted treatment for PAH such as endothelin receptors antagonists, phosphodiesterase-5 inhibitors or prostacyclins.

SURVIVAL

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

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

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

As can be seen in Table 1, non-survivors compared to survivors had similar sex distribution and were of the same age, functional state and hemodynamic severity of pulmonary hypertension (with exception of a lower SvO_2 in PAH and APAH and a higher right atrial pressure (RAP) in the APAH subgroups). Exercise capacity variables were more altered in the non survivors PAH patients and this appeared entirely driven by the IPAH subgroup.

Uni and multivariable Cox analysis for prediction of survival (Table 3)

PeakVO_2, VO_2at, $V_E VCO_2$at, V_E/VCO_2slope and 6MWD were predictive of survival in PAH and IPAH patients. No variable was associated with mortality in APAH patients.

The 6MWD and $V_E VCO_2$at predicted death independently in PAH and in IPAH patients.

Correcting the 6MWD for body weight did not affect its predictive value.

Receiver Operating Characteristics Analysis (Table 4)

In the PAH patients, optimal cut-off values to predict survival were 11.5 mL/Kg.min for peakVO_2, 8.8 mL/Kg.min for VO_2at, 54 for $V_E VCO_2$at, 62 for V_E/VCO_2slope and 305 m for 6MWD.

In the IPAH patients, optimal cut-off values to predict survival were 10.6 mL/Kg.min for peakVO_2, 9.8 mL/Kg.min for VO_2at, 54 for $V_E VCO_2$at and 307 m for 6MWD. No optimal cut-off point was

determined for V_E/VCO_2slope as the ROC curve P value was > 0.05 and the lowest IC95% of the AUC was < 0.5.

CLINICAL WORSENING

Of the 136 PAH patients followed, 88 encountered a CW (between 1.0 and 101 months). The rate of CW after 1, 2, 3 and 4 years for the PAH group was 33.6, 51.6, 59.8 and 64.6 % respectively.

Of the IPAH patients 56 had a CW (between 1.0 and 101months) and rate of CW at 1, 2, 3 and 4 years was respectively of 41.9, 58.2, 67.3 and 73.1 %.

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

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 (PVR). PAH had higher RAP, IPAH higher mean pulmonary artery pressure, and, PAH and IPAH lower cardiac output, cardiac index and mixed venous O_2 saturation. Exercise capacity variables were more altered in the patients with CW and this appeared driven by the IPAH subgroup.

Uni and multivariable Cox analysis for prediction of clinical worsening (Table 5)

PeakVO_2, VO_2at, V_E/VCO_2slope, $V_EVCO_2$at, PetCO_2at, O_2pulse, ΔO_2pulse and 6MWD predicted TCW in both PAH and IPAH patients. Correcting the 6MWD for body weight did not affect its predictive value.

No variables were associated with TTCW in the APAH patients.

PeakVO_2 predicted TTCW independently in both PAH and IPAH patients.

Receiver Operating Characteristics Analysis (table 6)

Of the PAH patients, optimal cut-off values to predict TTCW were 11.6 mL/Kg.min for peakVO_2, 9 mL/Kg.min for VO_2at, 46 for $V_E VCO_2$at, 55 for V_E/VCO_2slope, 23.5 for PetCO_2at, 5.3ml/beat for O_2pulse, 2.6 ml/beat. for ΔO_2 pulse and 367 m for 6MWD.

Of the IPAH patients, optimal cut-off values to predict CW were 11.8 mL/Kg.min for peakVO_2, 9.6 mL/Kg.min for VO_2at, 51 for $V_E VCO_2$at, 59 for V_E/VCO_2slope, 23.5 for PetCO_2at, 2,1 ml/beat for ΔO_2 pulse and 367m 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 IC95% 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 however a better discrimination of exercise testing variables in IPAH than in APAH. In this study, independent predictors of survival were the 6MWD and $V_EVCO_2$at for IPAH, while no exercise variable independently predicted survival in APAH. As for TTCW, this was predicted only by peak VO_2 and only in IPAH.

Pulmonary arterial hypertension 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 heart rate more than on stroke volume to increase flow output[19] which translates in more decreased oxygen pulse during exercise for patient with worse prognosis[7] as also shown in the present data base at univariate analysis. However, O_2 pulse is only an indirect measure of stroke volume derived from the Fick equation with the assumption of unchanged arterio-venous O_2 content difference. Maximal cardiac output is related to VO_2max, 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 VO_2 and the 6MWD in PAH is equivalent. Accordingly, in the present study, both peakVO_2 and the 6MWD predicted survival and TTCW in IPAH.

Previous studies in PAH have shown that the 6MWD was more sensitive than peak VO_2 to targeted therapies, such as beraprost[20] or sitaxsentan.[21] Part of this greater sensitivity of the 6MWD was ascribed to relative less expertise in the practice of CPET in the centres which participated to these studies.[22] In the present study the predictive capability of CPET variables in IPAH was found to be similar to previously reported, making insufficient expertise unlikely. On the other hand, while the 6MWD and not peak VO_2 independently predicted survival, peak VO_2 and not the 6MWD predicted CW. The reasons for this apparent contradiction are unclear, but this result underscores the interest of CPET added to a 6MWT in the evaluation of PAH patients.

The correlation between a maximal average running speed and VO_2max or peak VO_2 is generally significant, but rather loose, with correlation coefficients in the range of 0.5 to 0.7, in normal subjects[24] as well as in patients with IPAH.[5,22,23] This is explained by variable mechanical efficiency of running or walking, related in part to different body dimensions or weight. Correction of the 6MWD for body weight has indeed been, shown to improve these correlations in COPD[18] as well as in PAH.[22,23] However, in the present study, correcting the 6MWD for body weight did not improve its prognostic value.

In the present study, the nonsurvivors had similar pulmonary hemodynamics compared to survivors, even though SvO_2 was lower and RAP higher (in the APAH group only) in the nonsurvivors. Hemodynamic 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 hemodynamic 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 CO_2 previously reported in chronic heart failure (CHF) [25,26] as well as in PAH,[7,12] with however significance only in the patients with IPAH, not APAH. This is probably related to the inhomogeneity of 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/VCO_2 slopes during CPET are different in APAH subcategories is not exactly known.

It has been recommended to measure V_EVCO_2 below or at the anaerobic threshold, as the V_E/VCO_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_EVCO_2 at the anaerobic threshold was better than that of the V_E/VCO_2 slope, even though the latter was measured after the beginning of loaded exercise to the end of the isocapnic buffering period. ~~This result agree with the notion that the optimal measure of $VEVCO_2$ is at the anaerobic threshold [14].~~

Another problem of the V_E/VCO_2 ratio or slope may be the sudden increase occurring with right-to-left shunting.[15] For that reason, Wensel et al. excluded patients with a resting patent foramen ovale from the analysis of V_E/VCO_2 slope in relation to survival.[12] 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, exercise-induced shunting did not predict survival or TTCW.

Groepenhoff et al found that $V_EVCO_2$at or V_E/VCO_2slope predicted survival in their mixed PAH-CTEPH population with cut off values in the same range as ours. (ie. 52 for $V_EVCO_2$at and 48 for V_E/VCO_2 slope). It is of interest that survival cut-off values for V_E/VCO_2 are higher in PAH than in heart failure, with typical values > 50 and of approximately 35 respectively.[25,26,29] Both conditions are associated with an increased ventilation at any given level of metabolic rate,[30] in relation to increased chemosensitivity and physiologic dead space,[31,32] however, respective contributions of both mechanisms is not exactly known.

PeakVO_2 values inferior to 11.5 and 10.6 mL/Kg.min in our PAH and IPAH respectively were associated with a decreased survival. The cut-off of 10.6 mL/Kg.min is in agreement with a report by Wensel et al on similar severity IPAH patients,[12] while Groepenhoff et al found higher cut-off of 13.2 mL/Kg.min in a mixed group of PAH and CTEPH patients.[7] The isolated impact of CTEPH on the predictive value of peak VO_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 VO_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_EVCO_2 as an outcome predictor independently associated to survival and also able to predict TTCW in PAH and IPAH.

FUNDING – DISCLOSURE

Dr Gael DEBOECK is recipient of a European Respiratory Society Fellowship (LTRF 21-2010)

No disclosure to declare

REFERENCES

1. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J. 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), Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G. Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2009; 34: 1219-1263.

3. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. 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, Kyotani S, Sakamaki F, Fujita M, Nakanishi N, Miyatake K. 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, Parent F, Garcia G, Hervé P, Rainisio M, Simonneau G. 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, Spreeuwenberg MD, Postmus PE, Bogaard HJ. Exercise testing to estimate survival in pulmonary hypertension. *Med Sci Sports Exerc* 2008;40:1725-1732.
8. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaïci A, Weitzenblum E, Cordier JF, Chabot F, Dromer C, Pison C, Reynaud-Gaubert M, Haloun A, Laurent M, Hachulla E, Cottin V, Degano B, Jaïs X, Montani D, Souza R, Simonneau G. 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, Montani D, O'Callaghan DS, Jaïs X, Parent F, Savale L, Natali D, Günther S, Chaouat A, Chabot F, Cordier JF, Habib G, Gressin V, Jing ZC, Souza R, Simonneau G; French Pulmonary Arterial Hypertension Network. 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, Frantz RP, Foreman AJ, Coffey CS, Frost A, Barst RJ, Badesch DB, Elliott CG, Liou TG, McGoon MD. 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, Fleming TR, Gaine SP, Galiè N, Gibbs JS, Kim NH, Oudiz RJ, Peacock A, Provencher S, Sitbon O, Tapson VF, Seeger W. End points and clinical trial design in pulmonary arterial hypertension. *J Am Coll Cardiol* 2009;54:S97–107.
12. Wensel R, Opitz CF, Anker SD, Winkler J, Höffken 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.
13. Souza R, Humbert M, Sztrymf B, Jaïs X, Yaïci A, Le Pavec J, Parent F, Hervé P, Soubrier F, Sitbon O, Simonneau G. 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, Stringer WW, Whipp BJ. Principles of Exercise Testing and Interpretation. 4th ed.Baltimore, Md. Lippincott Williams & Wilkins, 2005.
15. 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.
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 VO_2 in COPD patients. Respir Med 2001;95:618-26.
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, Horn EM, Oudiz R, Shapiro S, McLaughlin V, Hill N, Tapson VF, Robbins IM, Zwicke D, Duncan B, Dixon RA, Frumkin LR; STRIDE-1 Study Group. Sitaxsentran therapy for pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2004; 169: 441-447.

22. Oudiz RJ, Barst RJ, Hansen JE, Sun XG, Garofano R, Wu X, Wasserman K. Cardiopulmonary exercise testing and six-minute walk correlations in pulmonary arterial hypertension. *Am J Cardionl* 2006; 9: 123-126

23. Deboeck G, Niset G, Vachiery JL, Moraine J-J, Naeije R. Physiologic Response to the 6MWT in pulmonary arterial hypertension. *Eur Resp J* 2005,26:667-672.

24. Cooper KH. A means of assessing maximal oxygen intake. Correlation between field and treadmill testing. *JAMA* 1968;203:135–138.

25. Chua TP, Ponikowski P, Harrington D, Anker SD, Webb-Peploe K, Clark AL, Poole-Wilson PA, Coats AJ. 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, Bauer U, Opitz C, Wensel R, Sperfeld A, Gläser S. Impairment of ventilatory efficiency in heart failure: prognostic impact. *Circulation* 2000; 101: 2803–2809

27. McLaughlin VV, Presberg KW, Doyle RL, Abman SH, McCrory DC, Fortin T, Ahearn G; American College of Chest Physicians. Prognosis of pulmonary arterial hypertension. ACCP Evidence-Based Clinical Practice Guidelines. *Chest* 2004;126;78S-92S.

28. Oudiz RJ, Midde R, Hovenesyan A, Sun XG, Roveran G, Hansen JE, Wasserman K.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, Varughese EB, Peberdy MA. Peak VO2 and VE/VCO2 slope in patients with heart failure: a prognostic comparison. *Am Heart J* 2004; 147:354-60.

30. Deboeck G, Niset G, Lamotte M, Vachiéry JL, Naeije R. 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, and 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, Huscher D, Behrens F, Denton CP, Foeldvari I, Humbert M, Matucci-Cerinic M, Nash P, Opitz CF, Rubin LJ, Seibold JR, Distler O, Furst DE; EPOSS Group. 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.

LEGENDS OF THE FIGURES

Figure 1. Kaplan–Meier cumulative survival curves for the 6-min walk distance (6MWD) in 136 patients with PAH (a), 85 patients with IPAH (b). Cut off value determined by ROC curve.

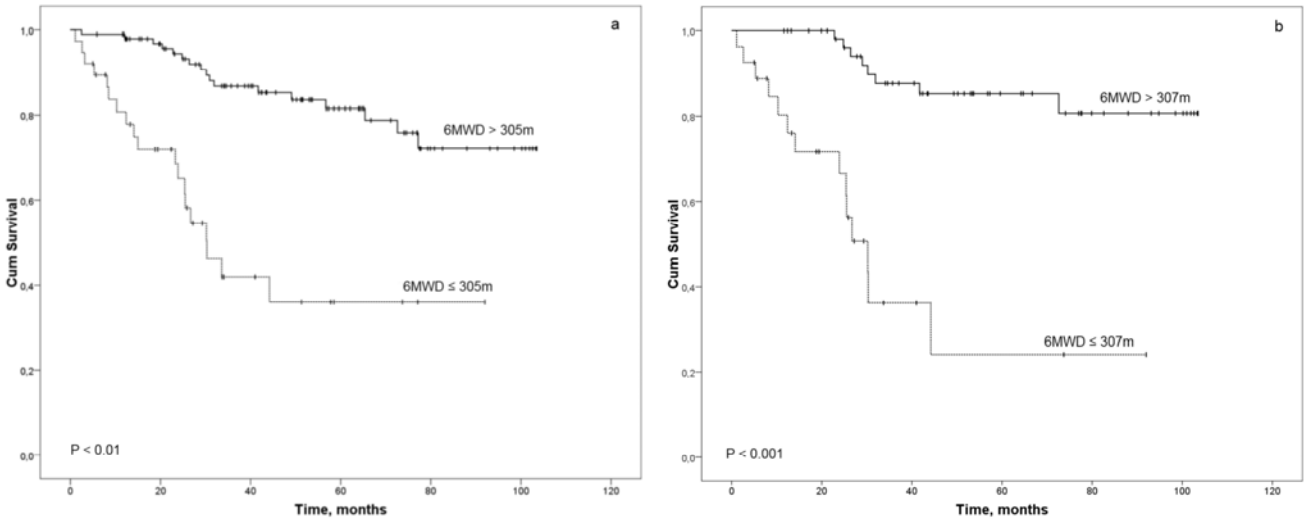

Figure 2. Kaplan–Meier cumulative survival curves for the ventilatory equivalent for carbon dioxide at the anaerobic threshold (V_EVCO_2at) in 136 patients with PAH (a) and 85 patients with IPAH (b). Cut off value determined by ROC curve

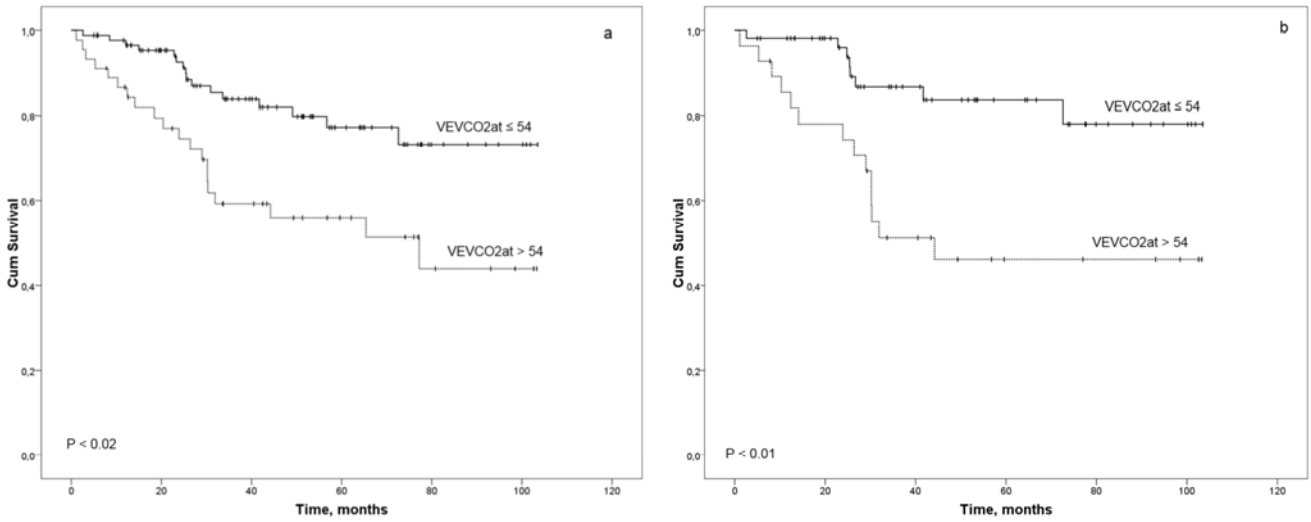

Figure 3. Kaplan–Meier cumulative survival curves for 0, 1 or 2 additional risks factors being a 6-min walk distance < 305m in PAH and 307m IPAH and a ventilatory equivalent for carbon dioxide at the anaerobic threshold > 54 in PAH and IPAH in 136 patients with PAH (a) and 85 patients with IPAH (b).

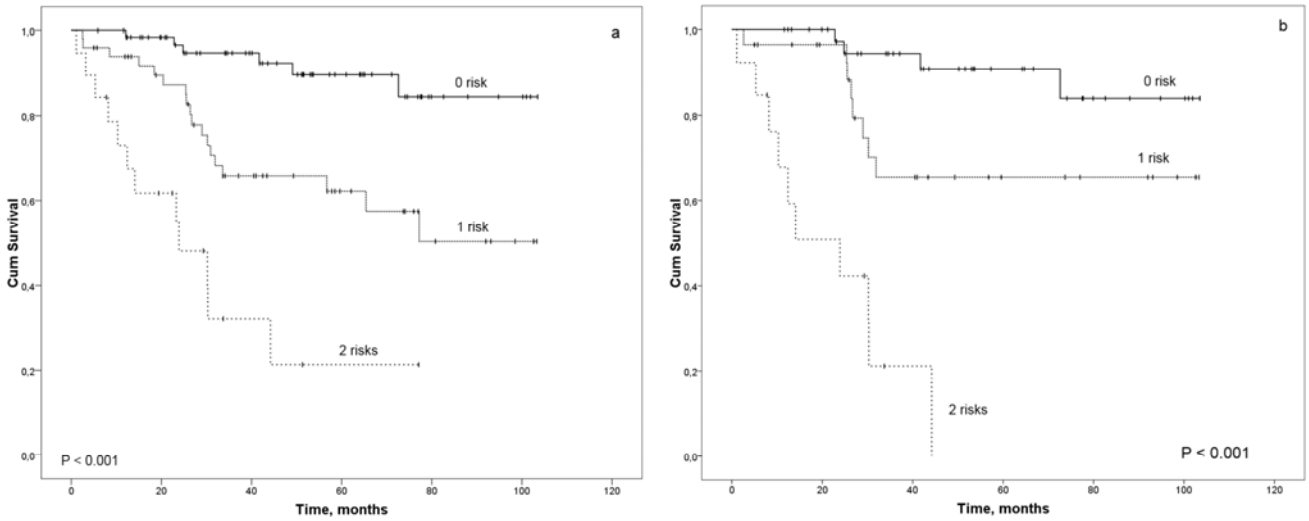

Figure 4. Kaplan–Meier cumulative curves for clinical worsening for peak oxygen uptake (peak VO_2) in 136 patients with PAH (a) and 85 patients with IPAH (b). Cut off value determined by ROC curve

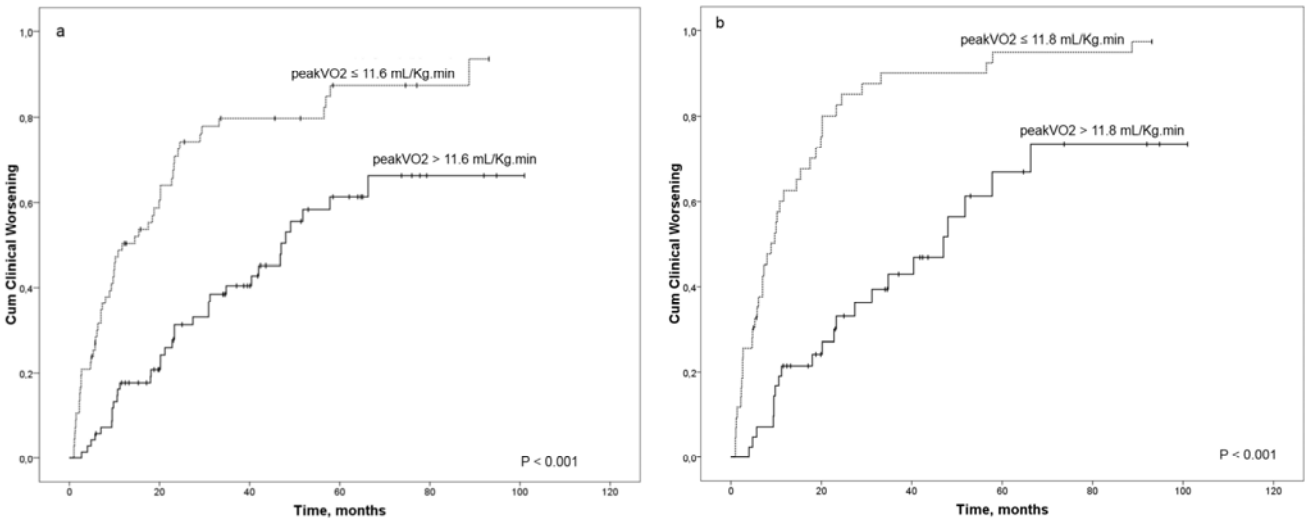

Table 1 :

Demographic and clinical data of survivors vs no-survivors in the PAH cohort and IPAH and APAH subgroups

item	PAH (n=136)		IPAH (n=85)		APAH (n=51)	
	survivors	no-survivors	survivors	no-survivors	survivors	no-survivors
Sex, male/women	36 / 64	19 / 17	21 / 42	12 / 10	15 / 22	7 / 7
Age, years	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
RAP, mmHg	8 ± 5	9 ± 5	8 ± 5	9 ± 4	7 ± 5	10 ± 6*
PAPm, mmHg	51 ± 15	50 ± 14	49 ± 11	49 ± 9	52 ± 19	53 ± 21
RVP, woods	11 ± 6	11 ± 4	11 ± 6	11 ± 4	10 ± 6	11 ± 5
PCWP, mmHg	10 ± 3	10 ± 3	9 ± 4	10 ± 4	10 ± 3	11 ± 3
CO, L/min	4,3 ± 1,3	4 ± 1	4,1 ± 1,3	4 ± 0,8	4,7 1 13	4 ± 1,3
CI, L/min.m²	2,4 ± 0,7	2,2 ± 0,5	2,3 ± 0,6	2,2 ± 0,4	2,7 ± 0,7	2,2 ± 0,6
SvO2, %	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
$PetCO_2$rest, mmHg	27 ± 4	24 ± 5**	26 ± 5	24 ± 5	27 ± 3	25 ± 4*
$PetCO_2$at, mmHg	25 ± 5	23 ± 5*	25 ± 4	23 ± 5	26 ± 6	23 ± 4
Δ PetCO2, mmHg	5 ± 6	4 ± 3	4 ± 6	4 ± 3	6 ± 5	5 ± 3
RERpeak	1,16 ± 0,08	1,16 ± 0,11	1,15 ± 0,09	1,14 ± 0,09	1,18 ± 0,08	1,18 ± 0,13
HRpeak, bpm	138 ± 28	123 ± 19**	140 ± 26	122 ± 20*	135 ± 30	124 ± 16
PeakVO_2, mL/Kg.min	14 ± 5,2	11 ± 3***	13 ± 5,5	10 ± 3***	14 ± 4,6	11 ± 3,1
VO_2at, mL/Kg.min	9,7 ± 2,9	8,2 ± 2,5**	9,6 ± 2,9	8 ± 2,6*	10 ± 2,8	8,6 ± 2,5
$V_EVCO_2$at	49 ± 11	58 ± 15***	49 ± 11	60 ± 15***	48 ± 13	56 ± 14
V_E/VCO_2 slope	57 ± 22	70 ± 26**	58 ± 20	70 ± 27*	55 ± 25	71 ± 27
O_2 pulse, mL/beat	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	3,3 ± 2,2	2,7 ± 2,1	3,4 ± 2,1	2,3 ± 1,8*	3,3 ± 1,9	3,2 ± 1,5
VO2/WRslope, L/min/Watt	6,7 ± 3,6	5,5 ± 3,7	7 ± 3,4	6 ± 3,7	6,2 ± 3,8	4,8 ± 3,7
BPs peak, 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

Specific treatment: antagonists to endothelin receptors, phosphodiesterase-5 inhibitors or prostacyclins, NYHA: functional classification of the New York heart association, RAP: right atrial pressure, PAPm: mean pulmonary artery pressure, PVR: pulmonary vascular resistance, PCWP: pulmonary capillary wedge pressure, CO: cardiac output, CI: cardiac index, SvO_2%: mixed venous oxygen saturation, 6MWD : distance walked in 6 minutes, $PetCO_2$: CO_2 partial pressure in exhaled air at rest (rest), anaerobic threshold (at) and increase (max – rest) (Δ), RERpeak : peak respiratory exchange ratio, VO_2peak : peak oxygen consumption, VO_2at: VO_2 at anaerobic threshold, $V_EVCO_2$at: ventilatory equivalent for CO_2 at the anaerobic threshold, ΔO_2 pulse: delta O_2pulse between rest and peak exercise, VO_2/WRslope: slope of VO_2

increase with work rate, EIS: exercise induced shunt. BPs : systolic blood pressure.. In PAH group for NYHA: n=134, BPs : n= 107, PFO: n = 104, PAPm, RAP, PVR, PCWP, CO, CI: n= 126 and SvO2%: n= 83.
*: Pvalue<0.05, **: <0.01, ***: <0.001

Table 2 : Demographic and clinical data of no-CW vs CW in the PAH cohort and IPAH and APAH subgroups

item	PAH (n=136)		IPAH (n=85)		APAH (n=51)	
	no-CW	CW	no-CW	CW	no-CW	CW
Sex, male/women	18 / 30	37 / 51	7 / 16	26 / 36	11 / 14	11 / 15
Age, years	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
RAP, mmHg	7 ± 5	9 ± 5*	7 ± 5	9 ± 5	7 ± 5	9 ± 5
PAPm, mmHg	47 ± 13	52 ± 14	45 ± 11	51 ± 9*	49 ± 16	56 ± 23
RVP, woods	8,8 ± 4,5	12 ± 5,3**	8,6 ± 3,8	11,8 ± 5,5*	8,9 ± 5,2	12,4 ± 5,7*
PCWP, mmHg	10 ± 3	10 ± 3	10 ± 4	10 ± 4	9 ± 5	10 ± 3
CO, L/min	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.m²	2,6 ± 0,7	2,2 ± 0,6***	2,5 ± 0,6	2,2 ± 0,5*	2,7 ± 0,7	2,3 ± 0,6
SvO2, %	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
$PetCO_2$rest, mmHg	28 ± 4	25 ± 4***	27 ± 4	25 ± 4*	28 ± 4	25 ± 4**
$PetCO_2$at, mmHg	28 ± 5	24 ± 5***	27 ± 5	24 ± 5***	27 ± 6	24 ± 5
Δ $PetCO_2$, mmHg	5 ± 5	5 ± 6	4 ± 5	4 ± 5	5 ± 3	5 ± 3
RERpeak	1,16 ± 0,10	1,16 ± 0,07	1,14 ± 0,06	1,15 ± 0,10	1,18 ± 0,08	1,18 ± 0,10
Hrpeak, bpm	139 ± 29	132 ± 24	144 ± 28	132 ± 25	135 ± 31	130 ± 24
PeakVO_2, mL/Kg.min	15 ± 6	12 ± 3,6***	16 ± 7	11 ± 3,4***	14 ± 4,7	12 ± 3,9
VO_2at, mL/Kg.min	10 ± 2,8	8,8 ± 2,7**	11 ± 3,2	8,5 ± 2,5***	9,9 ± 2,4	9,4 ± 3,2
$V_EVCO_2$at	45 ± 11	55 ± 13***	44 ± 10	55 ± 13***	46 ± 13	54 ± 13*
V_E/VCO_2 slope	52 ± 23	65 ± 23**	50 ± 16	65 ± 23**	54 ± 28	65 ± 25
O_2 pulse, mL/beat	7,3 ± 2,6	6,4 ± 2,3	7,8 ± 3,1	6,3 ± 2*	6,8 ± 2	6,8 ± 2,8
ΔO_2 pulse, mL/beat	3,8 ± 2,2	2,8 ± 1,9**	4,2 ± 2,7	2,7 ± 17**	3,5 ± 1,7	3,1 ± 2,9
VO2/WRslope,mL/min/Watt	7,4 ± 3,8	5,8 ± 3,4*	8,4 ± 6,0	6,1 ± 3,3***	6,4 ± 3,7	5,1 ± 3,7
BPs peak, 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

Table 3 :

Univariate Cox Analysis of proportional risks for death using continues values in PAH cohort and IPAH and APAH subgroups

Variables	PAH (n=136)		IPAH (n=70)		APAH (n=66)	
	RR (IC 95%)	P	RR (IC 95%)	P	RR (IC 95%)	P
ı peakVO_2 mL/Kg.min	0.837 (0.750 – 0.935)	0.002	0.805 (0.690 – 0.939)	0.006	0.882 (0.752 – 1.036)	0.126
VO_2at, mL/Kg.min	0.841 (0.742 – 0.953)	0.007	0.830 (0.704 – 0.979)	0.027	0.864 (0.711 – 1.051)	0.144
$V_E VCO_2$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/VCO_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
$PetCO_2$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
$\Delta petCO_2$, 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_2 pulse, mL/beat	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_2 pulse, mL/beat	0.871 (0.732 – 1.037)	0.121	0.784 (0.602 – 1.021)	0.071	1.008 (0.782 – 1.299)	0.951
BPs peak, 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, IC95%: 95% confidence interval. Abbreviations: see legend table 1

Table 4 :

Receiving operating characteristics (ROC) for death at 4 years for PAH cohort and IPAH and APAH subgroups

Variables	PAH (n=136)		IPAH (n=70)		APAH (n=66)	
	AUC, % (IC 95 %)	Pvalue	AUC, % (IC 95 %)	Pvalue	AUC, % (IC 95 %)	Pvalue
peakVO_2, mL/Kg.min	73.2 (63.8 – 82.6)	<0.001	71.9 (58.0 – 85.9)	0.007	-	
VO_2at, mL/Kg.min	69.0 (58.6 – 79.3)	0.001	71.8 (57.9 – 85.7)	0.007	-	
$V_E VCO_2$at	69.8 (59.7 – 80.0)	0.001	69.5 (54.6 – 84.4)	0.017	-	
V_E/VCO_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, IC95%: 95% confidence interval. Abbreviations: see legend table 1

Table 5 :

Univariate Cox Analysis of proportional risks for CW using continues values for PAH cohort and IPAH and APAH subgroups

Variables	PAH (n=136)		IPAH (n=70)		APAH (n=66)	
	RR (IC 95%)	P	RR (IC 95%)	P	RR (IC 95%)	P
peakVO_2 mL/Kg.min	0.871 (0.817 – 0.929)	<0.001	0.836 (0.770 – 0.907)	<0.001	0.950 (0.857 – 1.053)	0.328
VO_2at, mL/Kg.min	0.879 (0.815 – 0.949)	0.001	0.861(0.787 – 0.941)	0.001	0.942 (0.816 – 1.087)	0.411
$V_E VCO_2$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/VCO_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
$PetCO_2$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
$\Delta PetCO_2$, 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_2 pulse, mL/beat	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_2 pulse, mL/beat	0.858 (0.768 – 0.957)	0.006	0.812 (0.703 – 0.938)	0.005	0.939 (0.776 – 1.137)	0.520
BPs peak, 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, IC95%: 95% confidence interval. Abbreviations: see legend table 1

Table 6 :

Receiving operating characteristics (ROC) at 2 years for CW for PAH cohort and IPAH and APAH subgroups

Variables	PAH (n=136)		IPAH (n=70)		APAH (n=66)	
	AUC, % (IC 95 %)	Pvalue	AUC, % (IC 95 %)	Pvalue	AUC, % (IC 95 %)	Pvalue
peakVO_2, mL/Kg.min	73.9 (65.6 – 82.2)	<0.001	77.8 (66.9 – 88.7)	<0.001	-	
VO_2at, mL/Kg.min	71.0 (62.2 – 79.8)	<0.001	72.0 (59.9 – 84.2)	0.001	-	
$V_E VCO_2$at	70.3 (61.5 – 79.1)	<0.001	69.3 (56.9 – 81.6)	0.005	-	
V_E/VCO_2 slope	65.5 (55.5 – 75.6)	0.003	69.0 (57.5 – 81.5)	0.005	-	
PetCO_2at	67.4 (57.8 – 77.1)	0.001	69.0 (56.4 – 81.5)	0.007		
O_2 pulse, ml/beat	62.8 (53.3 – 72.3)	0.010	59.5 (46.6 – 72.3)	0.168	-	
ΔO_2 pulse, ml/beat	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, IC95%: 95% confidence interval. Abbreviations: see legend table 1