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Incremental prognostic value of cardiopulmonary exercise testing and resting haemodynamics in pulmonary arterial hypertension

Roland Wensel [a,b,*], Darrel P. Francis [a], F. Joachim Meyer [c], Christian F. Opitz [d], Leonhard Bruch [e], Michael Halank [f], Jörg Winkler [g], Hans-Jürgen Seyfarth [h], Sven Gläser [i], Friedrich Blumberg [j], Anne Obst [i], Michael Dandel [k], Roland Hetzer [k], Ralf Ewert [i]

[a] International Centre for Circulatory Health, National Heart & Lung Institute, Imperial College London, UK
[b] Department of Internal Medicine II, Universitätsklinikum Regensburg, Germany
[c] Department of Cardiology/Respiratory Medicine, Universitätsklinikum Heidelberg, Germany
[d] Department of Internal Medicine/Cardiology, DRK Kliniken Berlin Köpenick, Germany
[e] Department of Internal Medicine, Unfallkrankenhaus Berlin, Germany
[f] Department of Internal Medicine I, Universitätsklinikum Carl Gustav Carus Dresden, Germany
[g] Praxis für Pneumologie/Allergologie, Kreuzstrasse, Leipzig, Germany
[h] Department of Internal/Respiratory Medicine, Universitätsklinik Leipzig, Germany
[i] Department of Internal Medicine B, Ernst-Moritz-Arndt Universität Greifswald, Germany
[j] Department of Internal Medicine, Prosper-Hospital, Recklinghausen, Germany
[k] Department of Cardiothoracic Surgery, Deutsches Herzzentrum Berlin, Germany

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ABSTRACT

Background: Pulmonary arterial hypertension (PAH) is a fatal disease despite recent treatment advances. Individual risk stratification is important. Exercise capacity and invasive haemodynamic data are both relevant, but data on the combined prognostic power are lacking.
Methods: 226 consecutive patients with idiopathic or familial PAH were included at seven specialised tertiary centres. All patients underwent right heart catheterization and cardiopulmonary exercise testing (CPET).
Results: During follow-up (1508 ± 1070 days) 72 patients died and 30 underwent transplantation. On multivariate analysis percentage of predicted peak oxygen uptake (%predicted peak VO_2 [risk ratio 0.95]), pulmonary vascular resistance (PVR [1.105,]) and increase in heart rate during exercise (ΔHR [0.974]) were independent prognostic predictors (all $p<0.0001$). Peak VO_2 allowed for risk stratification with a survival of 100, 92.9, 87.4 and 69.6% at 1 year and 97.7, 63.2, 41 and 23% at 5 years for the 4th, 3rd, 2nd and 1st quartiles, respectively. Dichotomizing by median peak VO_2 and intra-group median PVR showed a worse 1-year survival for patients with low peak VO_2/higher PVR compared to patients with low peak VO_2/low PVR, high peak VO_2/high PVR and high peak VO_2/low PVR (65 vs. 93, 93, 100%, $p<0.001$). At 10 years survival was different for all 4 subgroups (19 vs. 25 vs. 48 vs. 75%, adjusted $p<0.05$).
Conclusions: Peak VO_2, PVR and ΔHR independently predict prognosis in patients with PAH. Low peak VO_2, high PVR and low ΔHR refer to poor prognosis. Combined use of peak VO_2 and PVR provides accurate risk stratification underlining the complementary prognostic information from cardiopulmonary exercise testing and resting invasive haemodynamic data.

1. Introduction

Pulmonary arterial hypertension (PAH) carries a poor prognosis [1]. Recent advances in medical therapy have improved survival [2–5]. Risk stratification is crucial for the development of an appropriate treatment strategy. Parameters characterizing haemodynamic derangement, neurohumoral activation, and reduced exercise capacity have been shown to be prognostically relevant [6–10]. Exercise capacity is reduced in patients with PAH and the extent of this limitation corresponds to the severity of underlying pulmonary vasculopathy and resulting right heart failure [9,11]. Measurement of the six-minute-walk distance and indirect calculation of the peak-exercise metabolic rate predict prognosis. Recently measurement of peak oxygen uptake (peak VO_2) and peak systolic blood pressure (SBP) during cardiopulmonary exercise testing (CPET) was shown to be of major prognostic value in 70 patients with idiopathic PAH [12]. It remains unclear whether addition of resting haemodynamic parameters yields more accurate risk stratification. The aim of the current study was to investigate the potential incremental prognostic value of the combined use of CPET derived parameters and

* Corresponding author at: International Centre for Circulatory Health, Imperial College London, 59 North Wharf Rd, London, W2 1LA, UK. Tel.: +44 7794524546; fax: +44 2075941706.
E-mail address: rolandwensel@gmail.com (R. Wensel).

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resting haemodynamic parameters in a large cohort of patients with idiopathic or familial PAH in a multicentre setting.

2. Methods

2.1. Participants

The study was performed at seven tertiary care centres. Between January 1996 and July 2008 all patients with diagnosed idiopathic or familial PAH who were able and agreeable to undergo CPET were prospectively included. Diagnosis was established according to the NIH and WHO criteria, respectively [13–15]. The study complies with the declaration of Helsinki and was approved by the local ethics committees. Informed consent was obtained from all patients.

2.2. Procedures

2.2.1. Cardiopulmonary exercise testing and six minute walk test

CPET was performed to exhaustion on a treadmill (n = 97) or a bicycle ergometer (n = 129). For treadmill, the modified Naughton protocol was used. For bicycle an initial load of 20 W with 16 W increment per minute was used. Ventilation and respiratory gas analyses were performed continuously (CPX/D, MedGraphics, St Paul, US; Oxycon, Jaeger, Würzburg Germany). Oxygen uptake (VO_2), carbon dioxide output (VCO_2), expiratory gas concentrations and minute ventilation (VE) were measured breath-by-breath. Peak VO_2 was defined as highest 30 s average of VO_2 in the last minute of exercise. To correct for differences in age and gender as well as for different exercise modalities, the percentages of peak predicted values were calculated using the Wasserman formula [16,17], which recently has been shown to be the best predictive power in heart failure patients [18]. The anaerobic threshold was detected by the V-slope method [19]. If this failed, the lowest VE/VO_2-ratio and lowest endtidal pO_2 were used for definition. Pulmonary gas exchange was assessed by measuring VE/VCO_2-ratio and endtidal pCO_2 ($petCO_2$) at rest and at the anaerobic threshold, the linear regression slope of the relation of VE to VCO_2 over the whole exercise period (VE/VCO_2-slope), and by percutaneous oxygen saturation. ECG was recorded continuously. Blood pressure (by sphygmomanometer) was measured at rest and during each stage of exercise.

Six minute walk test was performed only in those patients in whom outpatient assessment has been feasible.

2.2.2. Haemodynamic studies

All patients underwent right heart catheterization at baseline. This was performed via right internal jugular or subclavian veins (8F Baxter Swan-Ganz IntelliCath). An arterial line (VygonLeader cath 20G) was inserted into the radial artery. Arterial blood pressures (AP), pulmonary artery pressures (PAP), right atrial pressures (RAP), pulmonary capillary wedge pressures (PCWP) and arterial and mixed venous blood gases and oxygen saturation were measured. Cardiac output (CO) was calculated by Fick-principle with estimated oxygen consumption [20]. In patients with a PFO pulmonary blood flow was calculated assuming pulmonary-venous oxygen saturation of 98% on room air and of 100% on oxygen supplementation. Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were calculated using the standard formula, using the pulmonary blood flow for calculation of PVR in patients with a PFO.

2.2.3. Pulmonary function test

Spirometry and body plethysmography were performed with the use of a constant volume body plethysmograph (Master Laboratory, Jaeger) to rule out underlying restrictive or obstructive pulmonary disease [21].

2.3. Follow-up

All patients were followed up in the participating centres. End of follow up was on the 1st of February 2009. Patients that have been lost on follow up were censored alive on the last contact.

2.4. Statistical analysis

All data are expressed as mean ± SD. The endpoint of the study was defined as all-cause mortality or urgent lung or heart/lung transplantation, with the remaining cases designated as event-free survival. Decision for urgent lung or heart/lung transplantation was not based on the baseline measurements obtained from exercise testing in this study. Cox proportional hazards analysis was performed using baseline values to assess the association between variables and the predefined end point. Hazard ratios and 95% confidence intervals for risk factors, as well as levels for χ^2-test (likelihood-ratio test), are given, and Kaplan–Meier cumulative survival plots were constructed (SPSS version 17.0). Differences in survival were analysed by the log-rank test, with Holm–Sidak adjustment of p-value for multiple comparisons. A p-value < 0.05 was considered significant. Cut-off values for best discrimination were calculated using receiver-operating-characteristics. Co-linearity and interaction between variables were tested with standard software (SAS 9.1.3, SAS Institute Inc., Cary, NC, USA).

3. Results

226 patients out of 280 patients were recruited (demographic and haemodynamic data shown in Table 1). 54 patients have not been included because they either did not agree to undergo CPET or were unstable on clinical assessment and therefore not suitable for CPET. Few patients had been on targeted PAH therapy (inhaled Iloprost n = 4). Medication included calcium channel blockers (n = 50), anticoagulation (n = 92) and oxygen supplementation (n = 37). Subsequently, patients were started on targeted PAH therapy. First-line therapy included inhaled Iloprost (n = 80), intravenous Iloprost (n = 7), oral Beraprost (n = 24), oral Bosentan (n = 76) and oral Sildenafil (n = 6). During follow-up 10 patients were switched to inhaled Iloprost (after 394 ± 222 days), 23 to intravenous Iloprost (after 426 ± 326 days), 6 to oral Beraprost (after 315 ± 192 days), 32 to oral Bosentan (after 688 ± 514 days) and 5 to oral Sildenafil (n = 5 after 490 ± 357 days). In 59 patients therapy was subsequently escalated to various combination therapies (inhaled Iloprost/Bosentan n = 20, inhaled Iloprost/Sildenafil n = 5, inhaled Iloprost/Beraprost n = 2, Bosentan/Sildenafil n = 27, Bosentan/Beraprost n = 1, Bosentan/intravenous Iloprost n = 3, and one to Sildenafil/intravenous Iloprost).

3.1. CPET and six minute walk test

No adverse events occurred during or after the exercise test. The predominant exercise limiting symptom was intolerable shortness of breath. No significant ischaemic changes where noted on ECG. A marked reduction in peak VO_2 and poor blood pressure response were observed (Table 2). VE/VCO_2-slope was elevated. The VE/VCO_2-ratio was high both at rest and during exercise, with $petCO_2$ low both at rest and during exercise. In 70 patients the anaerobic threshold could not be identified due to an early fall in $petCO_2$ and rise in VE/VCO_2-ratio, which is commonly observed in more advanced PAH [22].

In 118 (52%) patients the 6-minute walking distance (348 ± 128 m) was measured.

3.2. Haemodynamic data

Patients had increased PVR, pulmonary artery pressures and right atrial pressures (Table 1). Cardiac output, cardiac index and mixed venous oxygen saturation (SvO_2) were reduced. Arterial blood

Table 1
Demographic and haemodynamic data.

Demographics	
Age, years	49 ± 15
Gender, female/male	157/69
Time from development of dyspnea, days	1060 ± 1582
Time from diagnosis of PAH, days	400 ± 902
NYHA functional class, II/III/IV	45/166/15
Haemodynamics	
HR, min^{-1}	82 ± 14
AP_{mean}, mm Hg	93 ± 17
PAP_{mean}, mm Hg	54 ± 15
RAP_{mean}, mm Hg	8 ± 3
SaO_2, %	93 ± 5
SvO_2, %	60.5 ± 10
Cardiac output, $L \cdot min^{-1}$	3.5 ± 1.5
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	1.9 ± 0.6
PVR, $dyn \cdot s \cdot cm^{-5}$	1250 ± 663
SVR, $dyn \cdot s \cdot cm^{-5}$	2158 ± 786

HR: heart rate, AP_{mean}: mean arterial blood pressure, PAP_{mean}: mean pulmonary artery pressure, RAP_{mean}: mean right atrial pressure, SaO_2, %: arterial oxygen saturation, SvO_2: mixed venous oxygen saturation, PVR: pulmonary vascular resistance, SVR: systemic vascular resistance.