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# Assessment of Survival in Patients With Primary Pulmonary Hypertension

## Importance of Cardiopulmonary Exercise Testing

Roland Wensel, MD\*; Christian F. Opitz, MD\*; Stefan D. Anker, MD, PhD; Jörg Winkler, MD; Gert Höffken, MD; Franz X. Kleber, MD; Rakesh Sharma, BSc, MRCP; Manfred Hummel, MD; Roland Hetzer, MD, PhD; Ralf Ewert, MD

**Background**—Primary pulmonary hypertension (PPH) is a life-threatening disease. Prognostic assessment is an important factor in determining medical treatment and lung transplantation. Whether cardiopulmonary exercise testing data predict survival has not been reported previously.

**Methods and Results**—We studied 86 patients with PPH (58 female, age  $46 \pm 2$  years, median NYHA class III) between 1996 and 2001 who were followed up in a tertiary referral center. Right heart catheterization was performed and serum uric acid levels were measured in all patients. Seventy patients were able to undergo exercise testing. At the start of the study, the average pulmonary artery pressure was  $60 \pm 2$  mm Hg, average pulmonary vascular resistance was  $1664 \pm 81$  dyne  $\cdot$  s  $\cdot$  cm<sup>-5</sup>, average serum uric acid level was  $7.5 \pm 0.35$  mg/dL, and average peak oxygen uptake during exercise (peak  $\dot{V}O_2$ ) was  $11.2 \pm 0.5$  mL  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup>. During follow-up (mean:  $567 \pm 48$  days), 28 patients died and 16 underwent lung transplantation (1-year cumulative event-free survival: 68%; 95% CI 58 to 78). The strongest predictors of impaired survival were low peak  $\dot{V}O_2$  ( $P < 0.0001$ ) and low systolic blood pressure at peak exercise (peak SBP;  $P < 0.0001$ ). In a multivariable analysis, serum uric acid levels (all  $P < 0.005$ ) and diastolic blood pressure at peak exercise independently predicted survival ( $P < 0.05$ ). Patients with peak  $\dot{V}O_2 \leq 10.4$  mL  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup> and peak SBP  $\leq 120$  mm Hg (ie, 2 risk factors) had poor survival rates at 12 months (23%), whereas patients with 1 or none of these risk factors had better survival rates (79% and 97%, respectively).

**Conclusions**—Peak  $\dot{V}O_2$  and peak SBP are independent and strong predictors of survival in PPH patients. Hemodynamic parameters, although also accurate predictors, provide no independent prognostic information. (*Circulation*. 2002;106:319-324.)

**Key Words:** exercise ■ risk factors ■ prognosis ■ pulmonary heart disease

Primary pulmonary hypertension (PPH) is a life-threatening disease with a median survival rate of 2.8 years.<sup>1,2</sup> Prognostic assessment is important, particularly in the context of evaluation for lung transplantation, and is currently based on hemodynamic and clinical data. Exercise limitation, mainly caused by dyspnea, is the major symptom in these patients. Exercise capacity, as measured by the 6-minute walk test, is an independent prognostic marker among noninvasive parameters.<sup>3</sup> Furthermore, serum uric acid levels correlate with exercise capacity and severity of PPH and independently relate to prognosis.<sup>4</sup>

The prognostic relevance of peak oxygen uptake (peak  $\dot{V}O_2$ ) and of the slope of the linear regression of the ventilation to carbon dioxide production during exercise ( $\dot{V}E/\dot{V}CO_2$  slope) as a measure of ventilatory efficiency have not been investigated so far. These

parameters, obtained from a symptom-limited exercise test, are the most powerful prognostic markers in chronic heart failure.<sup>5-7</sup> In patients with PPH, it is well established that peak  $\dot{V}O_2$  is decreased and that the  $\dot{V}E/\dot{V}CO_2$  slope is increased compared with normal controls and that both parameters improve with prostaglandin treatment.<sup>8-10</sup> In the present study, we sought to determine the prognostic value of peak  $\dot{V}O_2$ ,  $\dot{V}E/\dot{V}CO_2$  slope, and serum uric acid levels in comparison with clinical and hemodynamic parameters.

## Methods

### Patients

We prospectively recruited all consecutive patients who were referred to our center with the diagnosis of PPH (n=86; 58 female; mean age  $46 \pm 2$  years) between May 1996 and May 2001. The

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diagnosis was established according to the National Institutes of Health criteria.<sup>11</sup> A patent foramen ovale (PFO) was diagnosed in 29 patients. The median New York Heart Association (NYHA) functional class was III (20 patients class II, 56 patients class III, and 10 patients class IV). PPH was diagnosed on average  $22 \pm 4$  months before admission to our institution. At the first visit (ie, at baseline), medications included calcium channel blockers (n=29), oral anticoagulants (n=49), nasal oxygen supplementation (n=16), and iloprost inhalation (n=2) in varying combinations. During follow-up, iloprost inhalation was started in 55 patients, and 25 of these patients were later switched to intravenous iloprost treatment because of progressive right heart failure. Eleven patients were primarily started on intravenous iloprost, and 5 patients were subsequently treated with oral beraprost. The local ethics committee approved the study, and all patients gave written informed consent.

### Cardiopulmonary Exercise Testing

Of the 86 patients in the study, 16 did not undergo exercise testing (10 because of clinical instability and 6 because of patient refusal). A symptom-limited exercise test was performed, with 53 patients using a treadmill and 17 patients using a cycle ergometer. The modified Naughton protocol for treadmill exercise testing was used. Exercise testing with the use of a cycle ergometer (ER900; Jäger) was started at 20 W, with a stepwise increment of 16 W/min. Oxygen uptake ( $\dot{V}O_2$ ), carbon dioxide output ( $\dot{V}CO_2$ ), instantaneous expiratory gas concentrations throughout the respiratory cycle, and minute ventilation ( $\dot{V}E$ ) were measured continuously on a breath-by-breath basis (CPX/D, MedGraphics).

Peak  $\dot{V}O_2$  was defined as the highest 30-second average of oxygen uptake in the last minute of exercise. Pulmonary gas exchange was assessed with the  $\dot{V}E/\dot{V}CO_2$  slope,<sup>7,10</sup> the end-tidal partial pressure of carbon dioxide (PETCO<sub>2</sub>) at rest, and percutaneous oxygen saturation. Heart rate and blood pressure (by sphygmomanometer) were measured at rest, during each stage of exercise, and at peak exercise.

### Hemodynamic Studies

At baseline, all patients underwent right heart catheterization, which was performed within 24 (n=59) to 48 hours (n=11) after the exercise test. This was performed via the right internal jugular or the right subclavian veins with an 8F Swan-Ganz catheter (Baxter Swan Ganz IntelliCath). We monitored arterial blood pressure and arterial blood gases with an arterial line (Vygon leader cath 20G) inserted into the radial artery. Cardiac output (Fick method), arterial blood pressure, pulmonary artery pressure, mean right atrial pressure (RAP), and pulmonary capillary wedge pressure were measured. Systemic vascular resistance and pulmonary vascular resistance were calculated according to the standard formula. In the patients with a PFO, pulmonary blood flow was calculated by the Fick method, assuming a pulmonary venous oxygen saturation of 98% at room air and of 100% during oxygen supplementation. Accordingly, pulmonary blood flow was used for the calculation of pulmonary vascular resistance.

### Pulmonary Function Test

Spirometry and body plethysmography were performed with the use of a constant volume body plethysmograph (Master Laboratory, Jäger). Vital capacity, forced vital capacity, the ratio of forced expiratory 1-second volume to forced vital capacity, peak expiratory flow, midexpiratory flow when 25%, 50%, or 75% of forced vital capacity remains in the lung, airway resistance, total lung capacity, and the ratio of residual volume to total lung capacity were used for the final analysis. The single-breath technique using carbon monoxide (CO) was used for the measurement of diffusion capacity. For final analysis, lung transfer factor for carbon monoxide ( $T_{LCO}$ ) and the carbon monoxide transfer coefficient ( $K_{CO}$ ), as transfer factor for CO/alveolar volume [ $V_A$ ];  $T_{LCO}/V_A$ ) in  $\text{mmol} \cdot \text{min}^{-1} \cdot \text{kPa}^{-1}$  (1 kPa=7.502 mm Hg) were selected. All measurements were done according to the guidelines of the European Community for Steel and Coal and for each individual value were also expressed in percent of

**TABLE 1. Demographic and Hemodynamic Data and Serum Uric Acid Levels**

Demographics	
Age, y	46 $\pm$ 1.5
Sex, male/female	28/58
Time from development of dyspnea, mo	47 $\pm$ 6
Time from diagnosis of PPH, mo	22 $\pm$ 4
Hemodynamics	
PFO, yes/no	29/57
Heart rate, bpm	84 $\pm$ 2
Ao <sub>mean</sub> , mm Hg	88 $\pm$ 2
PCWP, mm Hg	8 $\pm$ 0.4
PAP <sub>mean</sub> , mm Hg	60 $\pm$ 2
RAP, mm Hg	9 $\pm$ 0.6
SaO <sub>2</sub> , %	91 $\pm$ 0.7
SvO <sub>2</sub> , %	56 $\pm$ 1.2
avDO <sub>2</sub> , mL/100 mL	7.2 $\pm$ 0.2
CO, L/min	3.1 $\pm$ 0.1
Cardiac index, L/min per m <sup>2</sup>	1.8 $\pm$ 0.1
SVR, dyne $\cdot$ s $\cdot$ cm <sup>-5</sup>	2216 $\pm$ 89
PVR, dyne $\cdot$ s $\cdot$ cm <sup>-5</sup>	1664 $\pm$ 81
Laboratory data	
Uric acid, mg/dL	7.6 $\pm$ 0.4

Values are presented as mean $\pm$ SEM.

Ao<sub>mean</sub> indicates mean aortic pressure; PCWP, pulmonary capillary wedge pressure; PAP<sub>mean</sub>, mean pulmonary artery pressure; SaO<sub>2</sub>, arterial oxygen saturation; SvO<sub>2</sub>, mixed venous oxygen saturation; avDO<sub>2</sub>, arteriovenous difference of oxygen content; CO, cardiac output; and SVR, systemic vascular resistance.

predicted values derived from age- and sex-matched healthy controls.<sup>12</sup>

### Uric Acid

Serum uric acid levels were measured from a standard venous blood sample taken in the morning to avoid any confounding effects of previous exercise.

### Statistical Analysis

All data are expressed as mean $\pm$ SEM. The end point of the study was defined as all-cause mortality and urgent lung or heart/lung transplantation, with the remaining cases designated as event-free survival. The 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 combined end point of all-cause mortality and urgent lung or heart/lung transplantation. Hazard ratios (HRs) and 95% CIs for risk factors, as well as levels for  $\chi^2$  test, are given, and Kaplan-Meier cumulative survival plots were constructed using StatView 5 software (Abacus Concepts). Receiver-operating characteristic curves for independent parameters were drawn and the areas under the curves calculated (MedCalc 5.0, MedCalc Inc). For a specific parameter, the cutoff level that resulted in the highest product of sensitivity and specificity was considered the optimal cutoff for prognostication.

### Results

The demographic and hemodynamic data and serum uric acid levels of the patients are summarized in Table 1. No adverse

**TABLE 2. Cardiopulmonary Exercise and Pulmonary Function Test Parameters**

Test duration, s	306±22
HR rest, bpm	90±2
HR peak, bpm	129±3
Rest SBP, mm Hg	113±2
Peak SBP, mm Hg	129±2
Rest DBP, mm Hg	76±1
Peak DBP, mm Hg	81±1
PETCO <sub>2</sub> rest, mm Hg	24±1
$\dot{V}E/\dot{V}CO_2$ slope (47/70)	54±2
Peak $\dot{V}O_2$ , mL · kg <sup>-1</sup> · min <sup>-1</sup>	11.2±0.5
VC, % predicted	88±2
TLC, % predicted	96±1
FVC, % predicted	86±2
FEV <sub>1</sub> , % predicted	83±2
PEF, % predicted	85±2
MEF <sub>75</sub> , % predicted	85±3
MEF <sub>50</sub> , % predicted	67±3
MEF <sub>25</sub> , % predicted	48±0.1
R <sub>tot</sub> , % predicted	114±5
RV, % predicted	118±3
RV/TLC, %	40±1
T <sub>LCO</sub> , % predicted	62±3
K <sub>CO</sub> , % predicted	69±3
pH	7.46±0.01
P <sub>CO2</sub> , mm Hg	30±1
P <sub>O2</sub> , mm Hg	67±2

Values are presented as mean±SEM.

HR res/peak indicates resting heart rate/heart rate at peak exercise; rest/peak-SBP, systolic blood pressure at rest/peak exercise; rest/peak-DBP, diastolic blood pressure at rest/peak exercise; PETCO<sub>2</sub> rest, endtidal partial pressure of carbon dioxide at rest;  $\dot{V}E/\dot{V}CO_2$ -slope (47/86) determined in 47 of 86 patients; RV/TLC, ratio of residual volume to total lung capacity, absolute percentage; P<sub>CO2</sub>, arterial partial pressure of carbon dioxide; and P<sub>O2</sub>, arterial partial pressure of oxygen.

events occurred during or after the exercise test. The performance-limiting symptom was intolerable shortness of breath in all patients. No patient reported retrosternal pressure, pain, or burning. No ischemic ECG changes were observed during exercise. There was a marked reduction in peak  $\dot{V}O_2$  and a pronounced increase in the resting  $\dot{V}E/\dot{V}CO_2$  ratio and the  $\dot{V}E/\dot{V}CO_2$  slope (Table 2). The lung function test (Table 2) revealed some degree of peripheral obstruction and a reduced diffusion capacity. There was a marked degree of hypocapnia with moderate hypoxemia.

### Survival

Of the 86 patients who were followed up (mean: 567±48 days), 28 died and 16 underwent double lung (n=8) or heart/lung transplantation after 5 to 1061 days (mean: 343±41). The mean follow-up period of the 42 survivors was 801±73 days (range 68 to 1943). The cumulative event-free survival rate of all patients was 84% at 6 months (95% CI: 76 to 91) and 68% at 1 year (95% CI: 58 to 78).

**TABLE 3. Parameters Predictive of Survival in Univariate Analysis**

Variable	RR	95% CI	P	$\chi^2$
Peak SBP, mm Hg	0.932	0.906–0.958	<0.0001	30.7
Peak $\dot{V}O_2$ , mL · kg <sup>-1</sup> · min <sup>-1</sup>	0.79	0.705–0.886	<0.0001	19.8
Exercise duration, s	0.996	0.994–0.999	0.001	10.8
PETCO <sub>2</sub> rest, mm Hg	0.902	0.844–0.965	0.0018	9.7
$\dot{V}E/\dot{V}CO_2$ slope	1.027	1.010–1.044	0.0037	8.4
Peak DBP, mm Hg	0.960	0.930–0.991	0.01	6.6
HR peak, bpm	0.982	0.969–0.996	0.01	6.4
SvO <sub>2</sub> , %	0.946	0.920–0.973	<0.0001	15.9
avDO <sub>2</sub> , mL/100 mL	1.322	1.156–1.511	<0.0001	15.7
RAP, mm Hg	1.118	1.060–1.179	0.0001	14.9
Cardiac index, L/min per m <sup>2</sup>	0.399	0.206–0.773	0.0027	9.0
PVR, dyne · s · cm <sup>-5</sup>	1.000	1.000–1.001	0.006	7.5
HR, bpm	1.032	1.009–1.055	0.0062	7.5
CO, L/min	0.684	0.491–0.952	0.017	5.7
Uric acid, mg/dL	1.103	1.010–1.205	0.039	4.3
P <sub>O2</sub> , mm Hg	0.977	0.954–1.000	0.048	3.9

P values and  $\chi^2$  values as calculated by the likelihood ratio test. RR indicates risk ratio. All other abbreviations as in Tables 1 and 2.

### Cox Proportional Hazards Analyses

In the 70 patients in whom exercise test data were available, systolic blood pressure at peak exercise (peak SBP), peak  $\dot{V}O_2$ , exercise duration, PETCO<sub>2</sub> at rest,  $\dot{V}E/\dot{V}CO_2$  slope, diastolic blood pressure at peak exercise (peak DBP), and heart rate at peak exercise predicted survival (Table 3). Among hemodynamic variables, mixed venous oxygen saturation (SvO<sub>2</sub>), arteriovenous difference of oxygen content (avDO<sub>2</sub>), RAP, cardiac index, pulmonary vascular resistance, heart rate, and cardiac output were predictive for survival (Table 3). In addition to these exercise-related and hemodynamic parameters, NYHA class and serum uric acid levels predicted survival. Treatment (inhaled, intravenous, or oral prostaglandin versus conventional medical therapy) did not predict survival (*P*=0.6). The presence of a PFO was not a predictor of survival (*P*=0.7). Patients with a PFO had a 64.6% (95% CI: 47.0 to 82.0) 1-year event-free survival rate (without PFO: 70.7%; 95% CI: 58.5 to 82.8%).

Multivariable forward stepwise Cox proportional hazards analysis was performed including all parameters significant at univariate analysis apart from the  $\dot{V}E/\dot{V}CO_2$  slope, arteriovenous difference of oxygen content, and cardiac index.  $\dot{V}E/\dot{V}CO_2$  slope had been removed from the analysis because it would have limited the analysis to the patients without a PFO (n=47). Arteriovenous oxygen difference and cardiac index were highly collinear with cardiac output. This multivariable model showed that peak SBP, serum uric acid levels, peak  $\dot{V}O_2$  (all *P*<0.005), and peak DBP (*P*<0.05) were independent predictors of prognosis (Table 4). Backward stepwise analysis showed the same results. Hemodynamic parameters were not independently predictive of survival.

A forward stepwise multivariable Cox proportional hazards analysis of cardiac output, SvO<sub>2</sub>, pulmonary vascular resistance, and RAP showed that only RAP (HR: 1.076,

**TABLE 4. Parameters Predictive of Survival in Forward Stepwise Multivariate Cox-proportional Hazards Analysis**

Step	Variable	RR	P	Cumulative $\chi^2$
1	Peak SBP, mm Hg	0.955	0.0046	27.6
2	Peak DBP, mm Hg	0.961	0.0495	33.7
3	Peak $\dot{V}O_2$ , mL · kg <sup>-1</sup> · min <sup>-1</sup>	0.814	0.0024	40.7
4	Uric acid, mg/dL	1.178	0.0037	44.7

P value and  $\chi^2$  values as calculated by the likelihood ratio test.

$P < 0.05$ ) and  $SvO_2$  (HR: 0.963,  $P < 0.05$ ) were independent predictors of survival.

**Receiver-Operating Characteristics**

Receiver-operating characteristic (ROC) curves for 12 months were plotted for peak SBP, peak DBP, serum uric acid levels, peak  $\dot{V}O_2$ , RAP, and  $SvO_2$  (Table 5). Peak SBP and peak  $\dot{V}O_2$  were found to be highly accurate predictors of 1-year survival.

**Kaplan-Meier Survival Analysis**

From the ROC curves, the optimal cutoffs were determined ( $\leq 120$  mm Hg and  $\leq 10.4$  mL · kg<sup>-1</sup> · min<sup>-1</sup> for peak SBP and peak  $\dot{V}O_2$ , respectively). Kaplan-Meier survival analysis showed that patients with a peak SBP  $> 120$  mm Hg had a significantly better prognosis ( $P < 0.001$ ) at 1 year (cumulative survival 93%; 95% CI: 86 to 100) than those with a peak SBP  $\leq 120$  mm Hg (cumulative survival 34%; 95% CI: 15 to 53; Figure 1). Patients with a peak  $\dot{V}O_2 > 10.4$  mL · kg<sup>-1</sup> · min<sup>-1</sup> had a significantly better 1-year survival rate than patients with a peak  $\dot{V}O_2 \leq 10.4$  mL · kg<sup>-1</sup> · min<sup>-1</sup> (91%, 95% CI: 82 to 97 versus 50%; 95% CI: 40 to 67,  $P < 0.001$ ). Peak SBP  $\leq 120$  mm Hg and peak  $\dot{V}O_2 \leq 10.4$  mL · kg<sup>-1</sup> · min<sup>-1</sup> were independent predictors of survival in bivariate Cox analysis (HR 5.9,  $P < 0.0001$ , and HR 2.6,  $P < 0.05$ , respectively). In Kaplan-Meier survival analysis (Figure 2), the absence peak SBP of  $\leq 120$  mm Hg and peak  $\dot{V}O_2 \leq 10.4$  mL · kg<sup>-1</sup> · min<sup>-1</sup> predicted excellent prognosis at 1 year (survival 97%; 95% CI: 90 to 100). The 19 patients with both of these risk factors had a 1-year survival rate of 23% (95% CI: 3 to 42). The 21 patients with only 1 of these risk factors had an intermediate 1-year survival rate (79%; 95% CI: 61 to 98).

**Discussion**

In the present study, we show for the first time that peak  $\dot{V}O_2$  and peak SBP obtained during a standardized exercise test are

**TABLE 5. Receiver-Operating Characteristics**

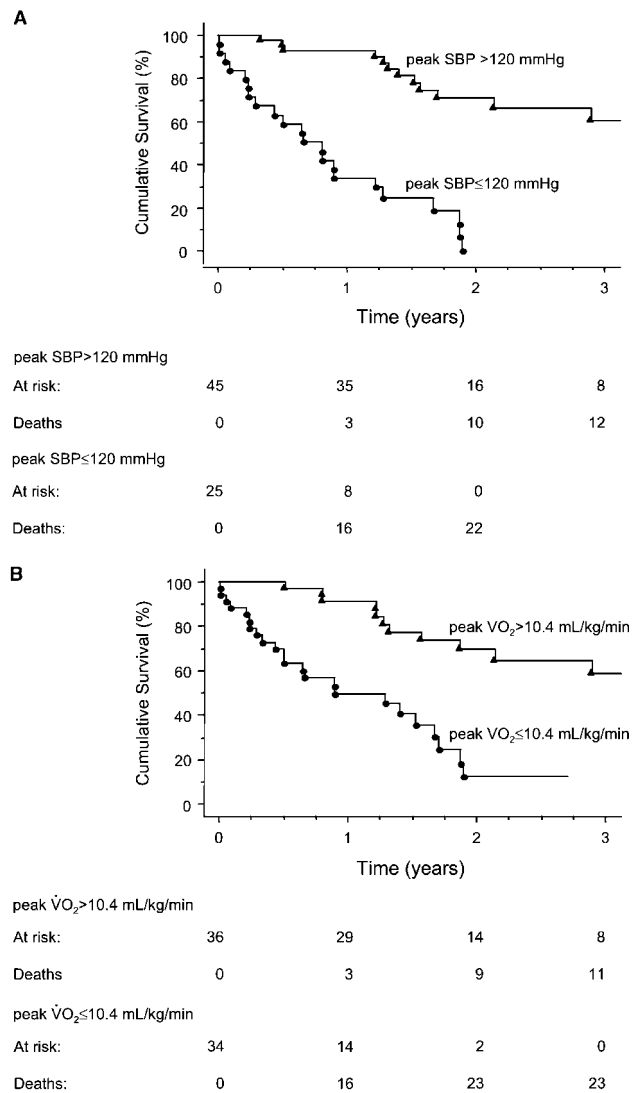
Variable	12-month	
	AUC %	95% CI
Peak SBP	87.2	77–93.9
Peak DBP	70.0	57.9–80.4
Uric acid	54.1	42.3–65.5
Peak $\dot{V}O_2$	76.9	65.3–86.1
RA	72.4	61.7–81.6
$SvO_2$	77.2	66.9–85.6

AUC indicates area under the curve.

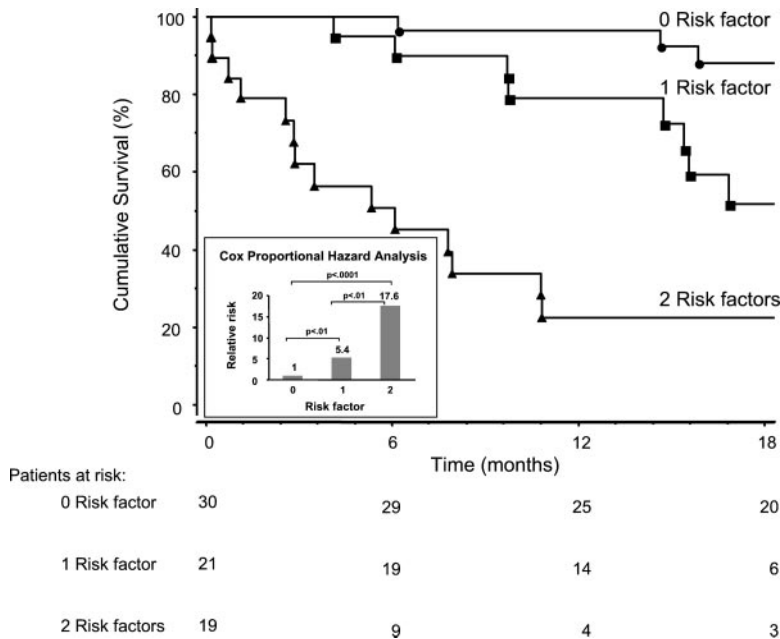
independent and highly accurate predictors of survival in patients with PPH. Furthermore, apart from serum uric acid levels and peak DBP, all other clinical and hemodynamic variables measured in this study did not provide additional independent prognostic information.

Exercise testing yields invaluable prognostic information in a variety of cardiovascular disorders.<sup>3,5</sup> Measurement of exercise capacity as duration of exercise or distance walked in finite time interval (ie, the 6-minute walk test) correlates with severity, treatment used, and prognosis in PPH.<sup>3,13</sup>

In patients with PPH, peak  $\dot{V}O_2$  is reduced compared with normal controls.<sup>8,14</sup> The integral information on the primary hemodynamic disorder and the adaptive peripheral changes renders peak  $\dot{V}O_2$  one of the most powerful prognosticators in chronic heart failure,<sup>5–7,15</sup> and our data strongly suggest that the same applies for patients with PPH. Patients with and without a PFO did not differ with regard to peak  $\dot{V}O_2$  ( $P = 0.13$ ). The prognostic information of peak  $\dot{V}O_2$  was not



**Figure 1.** Kaplan-Meier cumulative survival curves for 3-year survival of 70 patients with PPH. A, Patients with a SBP at peak exercise of  $> 120$  mm Hg versus  $\leq 120$  mm Hg. B, patients with a peak  $\dot{V}O_2 > 10.2$  mL · kg<sup>-1</sup> · min<sup>-1</sup> versus  $\leq 10.2$  mL · kg<sup>-1</sup> · min<sup>-1</sup>.



**Figure 2.** Kaplan-Meier cumulative survival curves for 18-month survival of 70 patients with PPH. Inset, Cox proportional hazard analysis.

changed when the patients with a PFO were excluded. There was no prognostic interference between PFO and peak  $\dot{V}O_2$ . Therefore, the high prevalence of a PFO in our study population (34%) compared with other populations (19% to 26%)<sup>16,17</sup> is unlikely to have affected the prognostic value of peak  $\dot{V}O_2$ . In contrast to other studies,<sup>18</sup> a PFO was not a predictor of survival in our study.

The  $\dot{V}E/\dot{V}CO_2$  slope was predictive of survival in univariate analysis. Dantzker et al<sup>19</sup> showed that in patients with PPH, an abnormal pulmonary gas exchange results from a small percentage of pulmonary blood flow distributed to units with (1) a very low  $\dot{V}/\dot{Q}$  ratio, (2) shunt, and (3) from low mixed venous oxygen saturation, whereas only mild impairments in  $\dot{V}/\dot{Q}$  matching have been found. The major determinant of a worsening gas exchange during exercise was a widening arterial-venous oxygen difference.<sup>20</sup> The  $\dot{V}E/\dot{V}CO_2$  slope could be determined only in patients without a PFO ( $n=47$ ) because the presence of a right/left shunt results in typical gas exchange abnormalities during exercise,<sup>21</sup> which lead to an exponential shape of the  $\dot{V}E/\dot{V}CO_2$  plot. Thus, the fitting of a linear slope becomes somewhat arbitrary. Therefore, the prognostic value of this variable is limited by the fact that it can only be obtained in patients without a right/left shunt during exercise.

The SBP during exercise was the most powerful predictor of survival in our patient population. Similar results have been reported for patients with chronic heart failure, where peak SBP was the most powerful prognostic marker in patients with a peak  $\dot{V}O_2 < 14 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ .<sup>22</sup>

In PPH, the presence of a high right ventricular pressure renders coronary perfusion more vulnerable to a low SBP, which can lead to right ventricular ischemia. Recently, Gomez et al<sup>23</sup> showed a direct correlation between right ventricular ischemia and right ventricular dysfunction in patients with PPH. The prognostic consequence of a low SBP could therefore be explained by more severe right ventricular dysfunction as a result of ischemia. No patient reported

retrosternal pressure, pain, or burning. No ischemic ECG changes were observed during exercise. Some patients, however, did describe their shortness of breath as chest or throat tightness, which may have reflected ischemia. The prognostic value of serum uric acid levels in PPH has been reported previously,<sup>4</sup> and it is speculated that this association reflects the effects of impaired oxidative metabolism on prognosis of these patients. Our data show that serum uric acid level was an independent predictor of survival. The ROC analysis, however, showed little prognostic power.

Excellent risk stratification could be obtained using the cutoff values of peak SBP and peak  $\dot{V}O_2$  as calculated by ROC curves (Figure 1). A peak SBP  $\leq 120$  mm Hg and a peak  $\dot{V}O_2 \leq 10.4 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  were both found to be independent risk factors. Risk stratification according to these parameters allowed clearer subgrouping of high-risk versus medium- and low-risk patients.

Several studies have shown a prognostic relevance of hemodynamic variables in patients with PPH.<sup>24,25,26</sup> Our data confirm this observation insofar as hemodynamic parameters were predictive of survival in univariate analysis with good prognostic accuracy. None of these variables, however, was an independent predictor of prognosis in multivariable analysis. This implies that even though resting hemodynamic data do have prognostic value, they do not add further prognostic information to the data obtained from peak  $\dot{V}O_2$  and SBP during exercise. In the subgroup of patients who are too sick to exercise, they can serve as prognostic markers.

Treatment did not predict survival in our population, which most likely reflects the fact that prostaglandins have been given to the sicker patients and the proven (for intravenous)<sup>13</sup> or potential (for oral and inhaled) beneficial effect of this treatment compensated for that.

A limitation of our study is that some patients (18.6%) did not undergo cardiopulmonary exercise testing. This was in part because of the poor clinical status of those patients, which ruled out exercise testing. We feel, however, that it is

important to evaluate the data on those patients who did not undergo exercise testing because this group includes patients with more severe disease.

### Conclusions

Low peak  $\dot{V}O_2$  and peak SBP are strong predictors of impaired survival in patients with primary pulmonary hypertension, eclipsing all hemodynamic parameters. The combined use of these 2 parameters allows for accurate risk stratification in these patients, which in the future may help to determine the therapeutic strategy.

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### References

1. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension: results from a national prospective registry. *Ann Intern Med.* 1991;115:343–349.
2. Ewert R, Opitz C, Wensel R, et al. Iloprost as inhalational and intravenous long-term treatment of patients with primary pulmonary hypertension: register of the Berlin Study Group for Pulmonary Hypertension [in German]. *Z Kardiol.* 2000;89:987–999.
3. 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.
4. Nagaya N, Uematsu M, Satoh T, et al. Serum uric acid levels correlate with the severity and the mortality of primary pulmonary hypertension. *Am J Respir Crit Care Med.* 1999;160:487–492.
5. Mancini DM, Eisen H, Kussmaul W, et al. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation.* 1991;83:778–786.
6. 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.
7. Kleber FX, Vietzke G, Wernecke KD, et al. Impairment of ventilatory efficiency in heart failure: prognostic impact. *Circulation.* 2000;101:2803–2809.
8. Sun XG, Hansen JE, Oudiz RJ, et al. Exercise pathophysiology in patients with primary pulmonary hypertension. *Circulation.* 2001;104:429–435.
9. Jones DK, Higenbottam TW, Wallwork J. Treatment of primary pulmonary hypertension intravenous epoprostenol (prostacyclin). *Br Heart J.* 1987;57:270–278.
10. Wensel R, Opitz CF, Ewert R, et al. Effects of iloprost inhalation on exercise capacity and ventilatory efficiency in patients with primary pulmonary hypertension. *Circulation.* 2000;101:2388–2392.
11. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension: a national prospective study. *Ann Intern Med.* 1987;107:216–223.
12. European Community for Steel and Coal Standardized lung function testing. *Eur Respir J.* 1993;6(suppl 16):1–100.
13. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med.* 1996;334:296–302.
14. D'Alonzo GE, Gianotti LA, Pohil RL, et al. Comparison of progressive exercise performance of normal subjects and patients with primary pulmonary hypertension. *Chest.* 1987;92:57–62.
15. Osman AF, Mehra MR, Lavie CJ, et al. The incremental prognostic importance of body fat adjusted peak oxygen consumption in chronic heart failure. *J Am Coll Cardiol.* 2000;36:2126–2131.
16. Nootens MT, Berarducci LA, Kaufmann E, et al. The prevalence and significance of a patent foramen ovale in pulmonary hypertension. *Chest.* 1993;104:1673–1675.
17. Glanville AR, Burke CM, Theodore J, et al. Primary pulmonary hypertension: length of survival in patients referred for heart-lung transplantation. *Chest.* 1987;91:675–681.
18. Rozkovec A, Montanes P, Oakley CM. Factors that influence the outcome of primary pulmonary hypertension. *Br Heart J.* 1986;55:449–458.
19. Dantzker DR, Bower JS. Mechanisms of gas exchange abnormality in patients with chronic obstructive pulmonary vascular disease. *J Clin Invest.* 1979;64:1050–1055.
20. Dantzker DR, D'Alonzo GE, Bower JS, et al. Pulmonary gas exchange during exercise in patients with chronic obstructive pulmonary hypertension. *Am Rev Respir Dis.* 1984;130:412–416.
21. 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.
22. Osada N, Chaitman BR, Miller LW, et al. Cardiopulmonary exercise testing identifies low risk patients with heart failure and severely impaired exercise capacity considered for heart transplantation. *J Am Coll Cardiol.* 1998;31:577–582.
23. Gomez A, Bialostozky D, Zajarias A, et al. Right ventricular ischemia in patients with primary pulmonary hypertension. *J Am Coll Cardiol.* 2001;38:1137–1142.
24. Sandoval J, Bauerle O, Palomar A, et al. Survival in primary pulmonary hypertension: validation of a prognostic equation. *Circulation.* 1994;89:1733–1744.
25. Okada O, Tanabe N, Yasuda J, et al. Prediction of life expectancy in patients with primary pulmonary hypertension: a retrospective nationwide survey from 1980–1990. *Intern Med.* 1999;38:12–16.
26. Chapman PJ, Bateman ED, Benatar SR. Prognostic and therapeutic considerations in clinical primary pulmonary hypertension. *Respir Med.* 1990;84:489–494.