Prognostic value of blood gas analyses in patients with idiopathic pulmonary arterial hypertension

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ABSTRACT: **Blood gas abnormalities in patients with idiopathic pulmonary arterial hypertension (IPAH) may be related to disease severity and prognosis.**

The present authors performed a 12-yr retrospective analysis assessing arterialised capillary blood gases, haemodynamics, exercise variables and survival in 101 patients with IPAH.

At baseline, arterial oxygen tension (Pa,O$_2$) and carbon dioxide arterial tension (Pa,CO$_2$) were 9.17$\pm$1.86 and 4.25$\pm$0.532 kPa, respectively. While Pa,O$_2$ was not associated with survival, a low Pa,CO$_2$ was a strong and independent prognostic marker. When patients were divided according to a baseline Pa,CO$_2$ value above or below 4.25 kPa, a cut-off value determined by receiver operating characteristics analysis, survival rates were 98 and 86% at 1 yr, 82 and 69% at 2 years, 80 and 51% at 3 yrs, 77 and 41% at 5 yrs, and 65 and 12% at 8 yrs, respectively. Pa,CO$_2$ after 3 months of medical therapy was strongly associated with survival. Hypocapnia at rest and during exercise correlated with low cardiac output, low peak oxygen uptake and reduced ventilatory efficacy. Multiple regression analysis revealed that 6-min walking distance, right atrial pressure and Pa,CO$_2$ were independently associated with survival.

In patients with idiopathic pulmonary arterial hypertension, hypocapnia (carbon dioxide arterial tension <4.25 kPa) is an independent marker of mortality.

KEYWORDS: Blood gases, carbon dioxide, hyperventilation, hypoxia, pulmonary hypertension

Idiopathic pulmonary arterial hypertension (IPAH) is a disease of the pulmonary vasculature that may lead to right heart failure and death if left untreated [1]. Since the initial comprehensive characterisation by the National Institutes of Health (NIH) registry of this disease, formerly referred to as primary pulmonary hypertension, it has been known that IPAH is commonly associated with abnormal blood gases [2]. The typical constellation is mild-to-moderate hypoxaemia and mild-to-moderate hypocapnia. In the NIH registry the mean arterial oxygen tension (Pa,O$_2$) was 9.31$\pm$1.72 and 9.57$\pm$1.72 kPa in male and female patients, respectively; while the mean carbon dioxide arterial tension (Pa,CO$_2$) was 3.99$\pm$0.79 and 4.12$\pm$0.66 kPa in males and females, respectively [2]. However, the pathogenesis of both hypoxaemia and hypocapnia in patients with IPAH is incompletely understood, and it has never been investigated as to whether changes in blood gases reflect the severity of the disease, whether they contribute to exercise limitation and whether they are of prognostic significance.

For these reasons, a 12-yr retrospective study was conducted in patients with IPAH in order to assess relationships between blood gases at rest and during exercise, haemodynamic parameters, variables obtained during cardiopulmonary exercise testing (CPET) and survival.

METHODS

Hospital charts from all patients with IPAH who were seen for the first time at the Hannover Medical School (Hannover, Germany) between January 1995 and December 2005 were reviewed. The follow-up period for survival analysis ended on April 30, 2006. Eligibility criteria for analysis were: 1) a diagnosis of IPAH according to current classification; 2) aged 18–75 yrs; and 3) normal or near normal results of pulmonary function testing, as defined by a vital capacity (VC) >70% predicted and a forced expiratory volume in one second/VC ratio >50%. Patients with a persistent foramen ovale, as evident from echo studies or from characteristic findings during cardiopulmonary exercise testing [3], were

excluded, as were patients with profound anaemia (haemo-globin level <10 g·dL^{-1}).

Patients were regularly seen 3 months after their baseline evaluations and then in 1–6 month intervals, or whenever clinically indicated. Right heart catheterisations were performed at the initial diagnostic work-up in all patients and at irregular follow-up intervals based on clinical situation. Cardiac output was assessed by the thermo-dilution technique. Mixed venous blood gases were obtained from the distal (pulmonary arterial) opening of the Swan–Ganz catheter.

Pulmonary function testing was performed using standard technology. During each visit, arterialised capillary blood gases were obtained by experienced technicians from hyper-aemisised earlobes after a resting period $\geqslant$10 min while patients were breathing room air. The alveolar–arterial oxygen tension difference (PA–a,O$_2$) was estimated using the following equation:

$$P_{A–a,O_2} = 150 - (P_{a,O_2} + P_{a,CO_2}/0.8) \qquad (1)$$

In 2001, CPET was introduced at the Hannover Medical School as a standard follow-up procedure for patients with IPAH. CPET was performed on a cycle ergometer, as described elsewhere [4]. Briefly, after a resting period of 3 min, patients were asked to cycle at 60–70 rpm while the work rate was increased by 5–15 W·min^{-1} until maximum tolerance. Gas exchange measurements were performed continuously (Oxycon Champion; Jaeger, Wuerzburg, Germany). Cardiac frequency, pulse oxymetry, 12-lead ECG and blood pressure were monitored and recorded. Arterialised capillary blood gases were obtained at rest and at the anaerobic threshold (AT) using the same technique as described previously.

Minute ventilation (V'E), oxygen uptake (V'O$_2$), carbon dioxide output (V'CO$_2$), end-tidal carbon dioxide tension (ET-PCO$_2$) and dead space/tidal volume (VD/VT) ratio were measured breath by breath, interpolated second by second and averaged over 10-s intervals. AT was defined as the V'O$_2$ at the point when the respiratory exchange ratio reached 1.0. Ventilatory efficacy was expressed as the ratio between V'E and V'CO$_2$ at rest (V'E/V'CO$_2$,rest) and at AT (V'E/V'CO$_2$,AT).

Since the present study comprised a 12-yr period, medical therapies differed substantially among patients depending on their clinical needs and the time when they were treated. Only four patients were successfully treated solely with calcium channel blockers. The other patients received treatments that were available in the respective periods, including inhaled iloprost, beraprost, s.c. treprostinil, bosentan, sildenafil, or i.v. iloprost, either as monotherapy or in various combinations. The criteria for therapeutic decision making in recent years have been described in detail elsewhere [5].

The study protocol was approved by the local institutional review board. In accordance with German regulations, informed consent was waived due to the retrospective nature of the present study.

Statistical analysis
All data are shown as mean±SD. The end-point of the study was all-cause mortality or lung or heart–lung transplantation. Survival rates at different time-points were estimated using the

Kaplan–Meier method and any differences between groups were evaluated with a stratified log-rank test. Changes in individual variables from rest to exercise were compared using Wilcoxon's signed rank test. Pearson's correlation analysis was used to assess relationships between blood gases, haemody-namics, 6-min walking distance (6MWD) and variables obtained during cardiopulmonary exercise testing.

In order to identify the Pa,CO$_2$ value with the best predictive value for survival, receiver operating characteristic (ROC) curves for survival at 2 yrs were drawn and the areas under the curves (AUC) calculated. The cut-off level that resulted in the highest product of sensitivity and specificity was considered the optimal Pa,CO$_2$ value for predicting survival. ROC curves were also drawn for other markers of potential prognostic importance, such as 6MWD and certain haemody-namic variables.

Multiple logistic regression analysis was performed to assess the association between variables and the combined end-point of all-cause mortality and lung or heart–lung transplantation. Odds ratios (ORs) and 95% confidence intervals (CIs) for risk factors are given. CPET variables were not included in the survival analyses since this tool was introduced relatively late in the course of the present study. A p-value <0.05 was considered statistically significant.

RESULTS
The present authors identified 101 consecutive patients with IPAH fulfilling the inclusion and exclusion criteria of the current study. In general, these patients suffered from severe pulmonary hypertension at baseline with a mean 6MWD of 305 m and a mean pulmonary vascular resistance (PVR) of 1,157 dyn·s·cm^{-5}, and the vast majority presented in functional class III or IV. A summary of the patients' baseline character-istics is shown in table 1.

During the observation period, 38 patients died and three underwent lung or heart–lung transplantation, resulting in a total number of 41 events. The rates for survival without transplantation were 93% at 1 yr, 77% at 2 yrs, 67% at 3 yrs, 60% at 5 yrs and 41% at 8 yrs.

Correlations between blood gases at rest, haemodynamics and 6MWD at baseline
Blood gas analysis at baseline showed a mean Pa,O$_2$ of 9.17±1.86 kPa and a mean Pa,CO$_2$ of 4.25±0.53 kPa. The mean arterial oxygen saturation was 93±4%. Further variables are shown in table 1.

Neither Pa,O$_2$ nor Pa,CO$_2$ correlated with mean pulmonary arterial pressure (mPAP) or PVR. As shown in table 2, there was a weak but statistically significant correlation between Pa,O$_2$ and 6MWD (r=0.298, p=0.001) and between Pa,O$_2$ and the mixed venous oxygen saturation (Sv,O$_2$; r=0.277, p=0.026). A significant inverse correlation was also observed between Pa,O$_2$ and the right atrial pressure (RAP; r=-0.269, p=0.007). The change in Sv,O$_2$ during the course of the disease did not correlate with the change in Pa,O$_2$ (r=0.136, p=0.158).

Pa,CO$_2$ was not correlated with 6MWD or RAP and showed weak but significant correlations with the cardiac index (r=0.235, p=0.019) and Sv,O$_2$ (r=0.226, p=0.026), suggesting

TABLE 1	Summary of baseline demographics, haemodynamics, pulmonary function results, blood gases at rest and variables obtained during cardiopulmonary function testing	
	Study population	CPET subgroup
Subjects n	101	53
Female/male	76/25	43/10
NYHA		
II	3	2
III	78	44
IV	20	7
Age yrs	48 ± 15	47 ± 14
6MWD m	305 ± 118	334 ± 100
RAP mmHg	9 ± 6	9 ± 6
mPAP mmHg	56 ± 13	55 ± 14
Cardiac output $L \cdot min^{-1}$	3.7 ± 1.1	3.7 ± 1.1
Cardiac index $L \cdot min^{-1} \cdot m^{-2}$	2.0 ± 0.5	2.0 ± 0.5
PVR $dyn \cdot s \cdot cm^{-5}$	1157 ± 492	1142 ± 465
S_{V,O_2} %	61 ± 9	60 ± 10
FVC % pred	89 ± 13	93 ± 14
FEV_1/VC %	75 ± 11	75 ± 11
$D_{L,CO}$ % pred	64 ± 23	65 ± 25
Peak V'_{O_2} $mL \cdot kg^{-1} \cdot min^{-1}$	NA	13.4 ± 3.6
O_2/f_C mL	NA	7.1 ± 2.1
$V'_E/V'_{CO_2,AT}$	NA	48 ± 15
ET-P_{CO_2}		
At rest	NA	27 ± 5
At AT	NA	25 ± 7
V_D/V_T		
At rest	NA	16 ± 6
At AT	NA	18 ± 4
P_{a,O_2} mmHg		
At rest	69 ± 14	69 ± 12
At AT	NA	65 ± 14
P_{a,CO_2} mmHg		
At rest	32 ± 4	33 ± 4
At AT	NA	32 ± 5
pH		
At rest	7.46 ± 0.03	7.46 ± 0.03
At AT	NA	7.44 ± 0.04
HCO_3^-		
At rest	22.6 ± 2.7	22.8 ± 2.8
At AT	NA	20.8 ± 2.9

Data are presented as mean$\pm$SD, unless otherwise stated. CPET: cardiopulmonary exercise testing; NYHA: New York Heart Association; 6MWD: 6-min walking distance; RAP: right atrial pressure; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; S_{V,O_2}: mixed venous oxygen saturation; FVC: forced vital capacity; % pred: % predicted; FEV_1: forced expiratory volume in one second; VC: vital capacity; $D_{L,CO}$: diffusing capacity of the lungs for carbon monoxide; V'_{O_2}: oxygen uptake; O_2/f_C: oxygen pulse, where f_C is the cardiac frequency; $V'_E/V'_{CO_2,AT}$: ventilatory efficacy expressed as the ratio between minute ventilation and carbon dioxide output at the anaerobic threshold (AT); ET-P_{CO_2}: end-tidal carbon dioxide tension; V_D/V_T: dead space/tidal volume ratio; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: carbon dioxide arterial tension; NA: not assessed. 1 mmHg = 0.133 kPa.

TABLE 2	Correlations between blood gases at rest, haemodynamics and 6-min walking distance (6MWD)					
	6MWD	RAP	mPAP	Cardiac index	PVR	S_{V,O_2}
P_{a,O_2}						
r	0.298	-0.269	0.108	0.008	0.161	0.227
p-value	0.001	0.007	NS	NS	NS	0.026
P_{a,CO_2}						
r	0.104	-0.054	-0.049	0.235	-0.185	0.226
p-value	NS	NS	NS	0.019	NS	0.026

RAP: right atrial pressure; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; S_{V,O_2}: mixed venous oxygen saturation; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: carbon dioxide arterial tension; NS: nonsignificant.

that the degree of hyperventilation was partly related to reduced cardiac output. In accordance, the change in P_{a,CO_2} during the course of the disease correlated significantly with the change in cardiac index (r=0.362, p<0.001).

Correlations between blood gases at rest and during exercise and CPET

As CPET was introduced in the present programme in 2001, only 53 patients had exercise tests performed at baseline. In this subpopulation, exercise caused a mild drop in P_{a,O_2} from 9.17 ± 1.59 kPa at rest to 8.64 ± 1.86 kPa at AT (p=0.004), while P_{a,CO_2} remained virtually unchanged (table 1). HCO_3^- decreased from 22.8 ± 2.8 $mmol \cdot L^{-1}$ at rest to 20.8 ± 2.9 $mmol \cdot L^{-1}$ at AT (p<0.001) and the pH decreased from 7.46 ± 0.03 to 7.44 ± 0.04 (p<0.001). ET-P_{CO_2} fell from 3.59 ± 0.66 kPa at rest to 3.32 ± 0.66 kPa at AT (p=0.017) and the V_D/V_T ratio increased from 16 ± 6 to 18 ± 4 (p=0.004). There were no significant correlations at rest or during exercise between either P_{a,CO_2} or ET-P_{CO_2} and the V_D/V_T ratio. In addition, there was no correlation between P_{a,O_2} and P_{a,CO_2} at rest and during exercise but a significant correlation was observed between P_{a,O_2} at rest and ET-P_{CO_2} at rest (r=0.439, p<0.001), as well as between P_{a,O_2} at AT and ET-P_{CO_2} at AT (r=0,632, p<0.001), probably reflecting, at least partly, effects of ventilation/perfusion abnormalities.

As shown in table 3, P_{a,O_2} at rest, but not P_{a,CO_2} at rest, showed a weak but significant correlation with the peak V'_{O_2} (r=0.303, p=0.03). In contrast, there were stronger correlations between the peak V'_{O_2} and both P_{a,O_2} and P_{a,CO_2} at AT (r=0.404, p=0.005 and r=0.479, p<0.001, respectively). There were also significant inverse correlations between peak V'_{O_2} and ventilatory efficacy at rest as well as during exercise (table 3), supporting the hypothesis that ventilatory efficacy is inversely related to cardiac output, i.e. pulmonary perfusion.

$V'_E/V'_{CO_2,AT}$ showed significant inverse correlations with P_{a,O_2} and P_{a,CO_2} at rest (table 3) and an even stronger inverse correlation with the P_{a,O_2} at AT (r=-0.729, p<0.001).

Relationship between blood gases at baseline and survival
The baseline P_{a,O_2} at rest had no significant impact on survival. When patients were divided according to a baseline P_{a,O_2} value

TABLE 3	Correlations between blood gases and variables obtained during cardiopulmonary exercise testing				
	Peak $V'O_2$	$V'E/V'CO_2$,rest	$V'E/V'CO_2$,AT	Pa,O_2,AT	Pa,CO_2,AT
Pa,O_2 at rest					
r	0.303	-0.367	-0.431	0.682	0.132
p-value	0.03	0.008	0.002	<0.001	NS
Pa,CO_2 at rest					
r	0.191	-0.250	-0.389	0.137	0.659
p-value	NS	NS	0.006	NS	≤0.001
Peak $V'O_2$					
r	NA	-0.343	-0.541	0.404	0.479
p-value		0.015	<0.001	0.005	<0.001

$V'O_2$: oxygen uptake; $V'E/V'CO_2$: ventilatory efficacy expressed as the ratio between minute ventilation and carbon dioxide output; AT: anaerobic threshold; Pa,O_2: arterial oxygen tension; Pa,CO_2: carbon dioxide arterial tension; NS: nonsignificant; NA: not assessed.

above or below the median of 67.5 mmHg, survival rates were 98 and 84% at 1 yr, 79 and 73% at 2 yrs, 70 and 63% at 3 yrs, 58 and 57% at 5 yrs, and 58 and 16% at 8 yrs, a difference that did not reach statistical significance (p=0.18 by log-rank analysis; fig. 1). Similar results were obtained when $PA–a,O_2$, rather than Pa,O_2, was examined. The median was 5.58 kPa and no significant survival differences were observed between patients who had a $PA–a,O_2$ above or below that value (p=0.115).

In contrast, baseline Pa,CO_2 at rest had a much stronger impact on survival. ROC analysis did identify a Pa,CO_2 of 4.25 kPa as the optimal cut-off level with a sensitivity of 0.73 and a specificity of 0.66 to predict survival at 2 yrs (AUC (95% CI) 0.70 (0.59–0.81); p<0.001). This cut-off point was identical to the median value of Pa,CO_2 in the present patient population. When patients were divided according to a baseline Pa,CO_2 value above or below 4.25 kPa, survival rates were 98 and 86% at 1 yr, 82 and 69% at 2 yrs, 80 and 51% at 3 yrs, 77 and 41% at 5 yrs, and 65 and 12% at 8 yrs, a difference that was of high statistical significance (p<0.001 by log-rank analysis; fig. 2).

Blood gases obtained after 3 months of medical treatment gave similar results. Pa,O_2 after 3 months was not significantly associated with survival (table 4). Pa,CO_2 after 3 months of therapy, however, appeared to be even more strongly associated with survival than baseline values. In this case the cut-off value was 4.32 kPa. Patients with Pa,CO_2 values >4.32 kPa had survival rates at 1, 2, 3, 5 and 8 yrs of 95, 86, 83, 83 and 78%, respectively, whereas patients with Pa,CO_2 values <4.32 kPa had survival rates at 1, 2, 3, 5 and 8 yrs of 88, 70, 57, 46 and 15%, respectively (p<0.001 by log-rank analysis; fig. 3).

Univariate logistic regression analysis revealed that 6MWD, RAP, cardiac output, PVR, Sv,O_2 and Pa,CO_2 at baseline, as well as after 3 months of therapy, were associated with survival (table 4). This was not the case for mPAP and Pa,O_2. Multiple logistic regression analysis revealed that only 6MWD, RAP and Pa,CO_2 both at baseline and after 3 months were independently associated with mortality (table 5).

Comparison of several variables as predictors of mortality
As shown in figure 4, ROC analysis demonstrated that the prognostic value of a low Pa,CO_2 at baseline (AUC (95% CI) 0.70
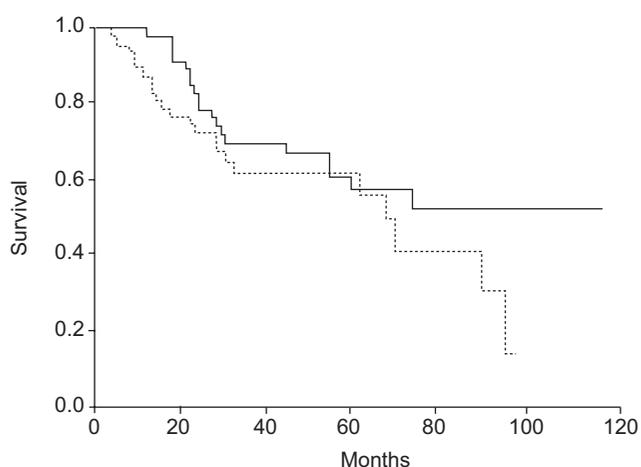

FIGURE 1. Impact of baseline arterial oxygen tension (Pa,O_2) on survival in patients with idiopathic pulmonary arterial hypertension (IPAH). Kaplan–Meier survival estimates of 101 patients with IPAH according to their baseline Pa,O_2. ——: Pa,O_2 ≥8.97 kPa; ·······: Pa,O_2 <8.97 kPa. For a Pa,O_2 ≥8.97 kPa, the number of subjects at risk was 51, 47, 31, 18, 14, 12 and 5 for the baseline, 20, 40, 60, 80, 100 and 120 months, respectively. For a Pa,O_2 <8.97 kPa, the number of subjects at risk was 50, 38, 25, 18, 6, 2 and 0 for the baseline, 20, 40, 60, 80, 100 and 120 months, respectively. p=0.18.
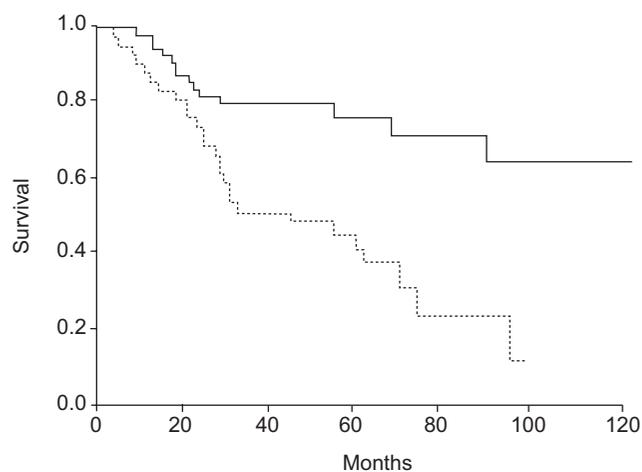

FIGURE 2. Impact of baseline carbon dioxide arterial tension (Pa,CO_2) on survival in patients with idiopathic pulmonary arterial hypertension (IPAH). Kaplan–Meier survival estimates of 101 patients with IPAH according to their baseline Pa,CO_2. ——: Pa,CO_2 ≥4.25 kPa; ·······: Pa,CO_2 <4.25 kPa. For a Pa,CO_2 ≥4.25 kPa, the number of subjects at risk was 57, 51, 35, 16, 13, 12 and 5 for the baseline, 20, 40, 60, 80, 100 and 120 months, respectively. For a Pa,CO_2 <4.25 kPa, the number of subjects at risk was 44, 34, 21, 12, 4, 2 and 0 for the baseline, 20, 40, 60, 80, 100 and 120 months, respectively. p<0.001.

TABLE 4	Parameters predictive of survival in univariate analysis	
Independent variable	OR (95% CI)	p-value
6MWD	1.007 (1.003–1.011)	<0.001
RAP	0.873 (0.805–0.947)	0.001
mPAP	0.984 (0.954–1.014)	0.292
Cardiac index	2.591 (1.075–6.241)	0.034
PVR	0.999 (0.998–1.000)	0.040
Sv,O_2	1.057 (1.007–1.109)	0.025
Pa,O_2		
At baseline	1.025 (0.996–1.056)	0.097
At 3 months	1.020 (0.991–1.049)	0.176
Pa,CO_2		
At baseline	1.191 (1.058–1.341)	0.004
At 3 months	1.449 (1.242–1.690)	<0.001

OR: odds ratio; CI: confidence interval; 6MWD: 6-min walking distance; RAP: right atrial pressure; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; Sv,O_2: mixed venous oxygen saturation; Pa,O_2: arterial oxygen tension; Pa,CO_2: carbon dioxide arterial tension.

FIGURE 3. Impact of carbon dioxide arterial tension (Pa,CO_2) obtained after 3 months of therapy on survival in patients with idiopathic pulmonary arterial hypertension (IPAH). Kaplan–Meier survival estimates of 101 patients with IPAH according to their Pa,CO_2 after 3 months of therapy. ——: $Pa,CO_2 \geqslant 4.32$ kPa; ·······: $Pa,CO_2 < 4.32$ kPa. For a $Pa,CO_2 \geqslant 4.32$ kPa, the number of subjects at risk was 57, 51, 35, 16, 13, 12 and 5 for the baseline, 20, 40, 60, 80, 100 and 120 months, respectively. For a $Pa,CO_2 < 4.32$ kPa, the number of subjects at risk was 44, 34, 21, 12, 4, 2 and 0 for the baseline, 20, 40, 60, 80, 100 and 120 months, respectively. p<0.001.

(0.59–0.81); p<0.001) was similar to that of 6MWD (0.79 (0.69–0.87); p<0.001) and RAP (0.29 (0.18–0.40); p<0.001), and better than mPAP (0.41 (0.29–0.53); p=0.138) or the cardiac index (0.64 (0.53–0.76); p=0.021).

DISCUSSION

The present study confirmed that mild hypoxaemia and mild-to-moderate hypocapnia at rest and during exercise are common findings in patients with IPAH. Neither hypoxaemia nor hypocapnia were related to the magnitude of the pulmonary artery pressure. There were significant but weak correlations between Pa,O_2 at rest and 6MWD, and RAP and Sv,O_2, respectively. Pa,CO_2 at rest correlated with cardiac index and Sv,O_2. The most important finding of the present study, however, was the prognostic importance of a low Pa,CO_2 both at baseline and after 3 months of medical therapy in patients with IPAH. In contrast, Pa,O_2 had no significant prognostic value.

Several questions arise from the present findings. What is the relationship between blood gases and exercise limitation in patients with IPAH? What is the pathophysiological explanation for chronic hypocapnia, or, in other words, why do patients with IPAH hyperventilate? And finally, why is hypocapnia a marker of a poor prognosis, even if the Pa,CO_2 levels were not closely related to other variables of prognostic importance?

What is the relationship between blood gases and exercise limitation in patients with IPAH?

The 6MWD correlated with both Pa,O_2 at rest (r=0.3, p=0.001) and during exercise (r=0.68, p<0.001). This was to be expected since the main exercise limiting factor in patients with IPAH is oxygen delivery, which is the product of cardiac output and arterial oxygen content.
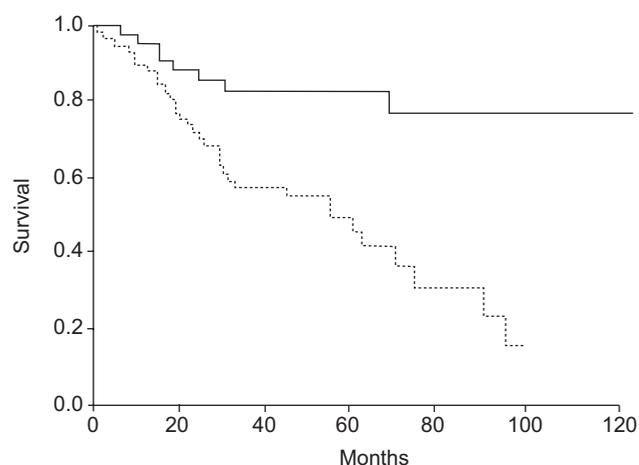
The peak $V'O_2$ also correlated with the Pa,O_2 at rest but not with Pa,CO_2 at rest, in accordance with what has been shown in patients with left heart failure [6]. However, when blood gases were obtained during exercise, both Pa,O_2 at AT (r=0.404, p=0.005) and Pa,CO_2 at AT (r=0.479, p<0.001) did correlate significantly with peak $V'O_2$. It is likely that both a higher Pa,O_2 and a higher Pa,CO_2 during exercise are indicators of a more effective pulmonary perfusion [7, 8].

This concept is further supported by the rather strong inverse correlation between peak $V'O_2$ and $V'E/V'CO_2,AT$ (r=-0.541, p<0.001). A very similar correlation between these variables has been reported previously in patients with IPAH [9] but also in patients with congestive left heart failure, where the $V'E/V'CO_2$ ratio is usually regarded as an indicator of pulmonary perfusion [6, 10].

Thus, exercise limitation was weakly related to Pa,O_2 at rest but more closely so to blood gases obtained during exercise, i.e. both Pa,O_2 and Pa,CO_2 at AT. Since the patients under study had no relevant ventilatory impairment, there is reason to believe that better blood gases during exercise reflect better pulmonary blood flow, e.g. a higher cardiac output.

Why do patients with IPAH hyperventilate?

An elevated $V'E/V'CO_2$ ratio is not sufficient to explain a low Pa,CO_2. The $V'E/V'CO_2$ ratio, or ventilatory efficacy, describes the amount of ventilation needed to remove a given amount of CO_2. Elevated $V'E/V'CO_2$ ratios and low ET-PCO_2 values have been reported in patients with pulmonary hypertension [11, 12] and heart failure [13], and are explained by insufficient perfusion of the lungs, including its extreme variant, dead space ventilation. While this concept is well suited to explain why patients with pulmonary vascular disease need to breathe

TABLE 5 Multiple logistic regression analysis with survival as dependent variable

Independent variable	OR (95% CI)	p-value
6MWD	1.006 (1.001–1.010)	0.022
RAP	0.874 (0.788–0.968)	0.010
Cardiac index	1.041 (0.340–3.185)	0.944
P_{a,CO_2}		
At baseline	1.166 (1.020–1.333)	0.025
At 3 months	1.512 (1.224–1.867)	< 0.001

OR: odds ratio; CI: confidence interval; 6MWD: 6-min walking distance; RAP: right atrial pressure; P_{a,CO_2}: carbon dioxide arterial tension.

FIGURE 4. Ability of several variables to predict survival in patients with idiopathic pulmonary arterial hypertension. ——: Right atrial pressure; — - —: cardiac index; – – –: carbon dioxide arterial tension; ⋯⋯: 6-min walking distance; — - - —: mean pulmonary arterial pressure; -----: no discrimination line.

more to maintain a physiological P_{a,CO_2}, it does not explain why they hyperventilate, *i.e.* why their P_{a,CO_2} is reduced to sub-physiological levels, sometimes <3.99 kPa.

Many lines of evidence suggest that hyperventilation is partly linked to a low cardiac output, *i.e.* low pulmonary perfusion. The correlation between cardiac output and P_{a,CO_2} at rest was weak but significant (r=0.235, p=0.019), and strikingly similar to what has been reported in patients with left heart failure [14]. It is noteworthy that there was a stronger correlation between P_{a,CO_2} at AT and peak V'_{O_2} (r=0.479, p=0.005), the latter partly reflecting cardiac output during exercise. In addition, there was a highly significant inverse correlation between P_{a,CO_2} at AT and $V'_E/V'_{CO_2,AT}$ (r=-0.649, p<0.001), a finding that has also been reported with similar numbers (r=-0.651) in patients with left heart failure [10, 15–17]. This indicates that ventilatory efficacy declines with hyperventilation. Finally, changes in P_{a,CO_2} during the course of the disease were significantly correlated with changes in cardiac output. Thus, there is strong reason to assume that cardiac output (or oxygen delivery) is an important regulator of the ventilatory drive and an inadequately low cardiac output at rest or during exercise seems to be a potent ventilatory stimulus, regardless of the underlying condition.

Why is hypocapnia an independent marker of a poor prognosis in patients with pulmonary arterial hypertension?
The available evidence suggests that hypocapnia reflects an increased ventilatory drive caused by several mechanisms, including low cardiac output, impaired V'_E/V'_{CO_2} and oxygen delivery at rest as well as during exercise. It is tempting to speculate that regulatory mechanisms are active which stimulate ventilation in order to optimise systemic oxygen delivery. Therefore, the extent of hyperventilation appears to reflect the extent of pulmonary vascular disease, cardiac dysfunction and impairment in oxygen delivery, which would directly explain the prognostic significance of hypocapnia in patients with pulmonary arterial hypertension.

Study limitations
The present study has several limitations, including its retrospective design and the fact that all data came from a single centre. Treatment strategies varied over the long study period and thus it was difficult to assess the effect of medical therapies on blood gases. Regular follow-up catheterisations
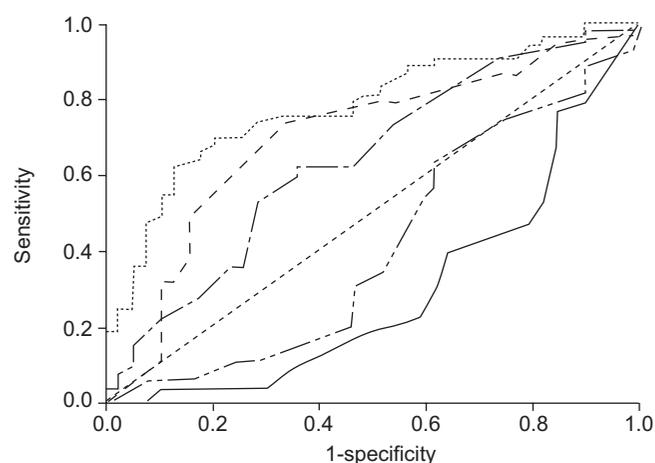
were not part of the present clinical programme and exercise haemodynamics were not available. In addition, the present study relied on arterialised capillary blood gases rather than directly measuring arterial blood gases and, therefore, the present results formally apply only to blood gases obtained using this technique. However, before adopting the technique of measuring arterialised capillary blood gases, the present authors' centre performed extensive studies comparing these with arterial blood gases and excellent agreements were found (unpublished data). Thus, it is unlikely that the present findings would have been different with arterial blood gases. Finally, since only patients with IPAH were included, the present findings may not be transferable to other forms of pulmonary hypertension or to patients with confounding factors, such as restrictive or obstructive lung disease or anaemia. Despite these limitations, the relatively large sample size, the long follow-up and the fact that blood gases were routinely obtained from all patients allow the current authors to draw some meaningful and clinically important conclusions.

Conclusion
A low carbon dioxide arterial tension (<4.25 kPa) is an independent prognostic marker in patients with idiopathic pulmonary arterial hypertension with similar predictive value for mortality than established variables, such as the 6-min walking distance or the right atrial pressure. Carbon dioxide arterial tension is easily assessable and well suited for repeated measurements, possibly making it a useful addition to the growing list of biomarkers that reflect the severity of the disease.

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