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Revision 2

# Prognostic Value of Blood Gas Analyses in Patients with Idiopathic Pulmonary Arterial Hypertension

Running title: Blood gases in IPAH

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**Abstract**

Blood gas abnormalities in patients with idiopathic pulmonary arterial hypertension (IPAH) may be related to disease severity and prognosis.
We performed a 12-year, retrospective analysis assessing arterialized capillary blood gases, hemodynamics, exercise variables and survival in 101 patients with IPAH.
At baseline $Pa,O_2$ was 69 ± 14 mmHg and $Pa,CO_2$ was 32 ± 4 mmHg. 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 their baseline $Pa,CO_2$ above or below 32 mmHg, a cut-off value determined by receiver-operating characteristics analysis, survival rates were 98% and 86% at 1 year, 82% and 69% at 2 years, 80% and 51% at 3 years, 77% and 41% at 5 years and 65% and 12% at 8 years ($p < 0.001$ by log rank analysis). $Pa,CO_2$ 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 walk distance, right atrial pressure, and $Pa,CO_2$ were independently associated with survival.
In patients with IPAH, hypocapnia ($Pa,CO_2 < 32$ mmHg) is an independent marker of mortality.

Word count, abstract: 200

**Key words**: Hypertension, pulmonary; blood gases, hypoxia, carbon dioxide, hyperventilation

## Introduction

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 characterization of this disease (which was formerly called primary pulmonary hypertension, PPH) by the National Institutes of Health (NIH) Registry it has been known that IPAH is commonly associated with abnormal blood gases [2]. The typical constellation is mild-to-moderate hypoxemia and mild-to-moderate hypocapnia. In the NIH registry the mean $Pa,O_2$ was 70 ± 13 mmHg in male patients and 72 ± 13 mmHg in female patients, respectively, and the mean $Pa,CO_2$ was 30 ± 6 mmHg in males and 31 ± 5 mmHg in females, respectively [2]. However, the pathogenesis of both hypoxemia and hypocapnia in patients with IPAH is incompletely understood, and it has never been investigated 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 we conducted a 12-year retrospective study in patients with IPAH to assess relationships between blood gases at rest and during exercise, hemodynamic parameters, variables obtained during cardiopulmonary exercise testing, and survival.

## Methods

We reviewed hospital charts from all patients with IPAH who were seen for the first time at Hannover Medical School between January 1995 and December 2005. The follow-up period for survival analysis ended April 30, 2006. Patients were eligible for this analysis when they had a diagnosis of IPAH according to the current classification, were between 18 and 75 years old, and had normal or near normal results of pulmonary function testing as defined by a vital capacity (VC) > 70% predicted and an $FEV_1$/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 (haemoglobin level < 10 g/dl).

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

Pulmonary function testing was performed with standard technology. During each visit, arterialized capillary blood gases were obtained by experienced technicians from hyperaemisized earlobes after a resting period of at least 10 min while the patients were

breathing room air. The alveolo-arterial oxygen gradient was estimated as $PAa,O_2 = 150 - (Pa,O_2 + Pa,CO_2/0.8)$.

In 2001, cardiopulmonary exercise testing (CPET) was introduced as a standard follow-up procedure for patients with IPAH in our center. CPET was performed on a cycle ergometer as described elsewhere [4]. Briefly, after a resting period of 3 min, the patients were asked to cycle at 60-70 rpm while the work rate was increased by 5-15 $W \cdot min^{-1}$ until maximum tolerance. Gas exchange measurements were made continuously (Oxycon Champion, Jaeger, Germany). Heart rate, pulse oxymetrie, 12-lead ECG and blood pressure were monitored and recorded. Arterialized capillary blood gases were obtained at rest and at the anaerobic threshold using the same technique as described above.

Minute ventilation ($V_E$), oxygen uptake ($VO_2$), carbon dioxide output ($VCO_2$), end-tidal $PCO_2$ ($P_{ET}CO_2$) and dead space/tidal volume ($V_D/V_T$) ratio were measured breath by breath, interpolated second by second and averaged over 10-second intervals. The anaerobic threshold (AT) was defined as the oxygen uptake at the point when the respiratory exchange ratio reached 1.0. Ventilatory efficacy was expressed as the ratio between ventilation and $CO_2$ output at rest ($V_E/VCO_2$@rest) and at the AT ($V_E/VCO_2$@AT).

Since this study comprised a 12-year period, medical therapies differed substantially among patients depending on their clinical needs and the time when they were treated. Only 4 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, subcutaneous treprostinil, bosentan, sildenafil, or intravenous 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 because of the retrospective nature of this study.

*Statistical analysis*

All data are shown as mean ± standard deviation (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 with Wilcoxon's signed rank test.

Pearson's correlation analysis was used to assess relationships between blood gases, hemodynamics, 6 min walk distances and variables obtained during cardiopulmonary exercise testing.

To identify the $Pa,CO_2$ value with the best predictive value for survival, receiver-operating characteristic (ROC) curves for survival at 2 years were drawn and the areas under the curves were 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 the 6 min walk distance and certain hemodynamic 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 this study (see above).
P-values < 0.05 were considered statistically significant.

**Results**

We identified 101 consecutive patients with IPAH fulfilling the inclusion and exclusion criteria of this study. In general these patients suffered from severe pulmonary hypertension at baseline with a mean 6 min walk distance of 305 m and a mean pulmonary vascular resistance of 1,157 $dyn \cdot s \cdot cm^{-5}$, and the vast majority presented in functional class III or IV. A summary of the patients' baseline characteristics is shown in table 1.
During the observation period, 38 patients died and 3 underwent lung or heart-lung transplantation, resulting in a total number of 41 events. The rates for survival without transplantation were 93% at 1 year, 77% at 2 years, 67% at 3 years, 60% at 5 years and 41% at 8 years.

*Correlations between blood gases at rest, hemodynamics and 6 min walk distance at baseline*

Blood gas analysis at baseline showed a mean $Pa,O_2$ of 69 ± 14 mmHg and a mean $Pa,CO_2$ of 32 ± 4 mmHg. The mean $Sa,O_2$ was 93 ± 4%. Further variables are shown in table 1.
Neither $Pa,O_2$ nor $Pa,CO_2$ correlated with mean pulmonary artery pressure or pulmonary vascular resistance, respectively. As shown in Table 2, there was a weak but statistically significant correlation between $Pa,O_2$ and the 6 min walk distance ($r = 0.298$; $p = 0.001$) as well as the mixed venous oxygen saturation ($r = 0.277$; $p = 0.026$), and a significant inverse correlation between $Pa,O_2$ and the right atrial pressure ($r = -0.269$; $p = 0.007$). The change in the mixed venous oxygen saturation 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 the 6 min walk distance or the right atrial pressure but showed weak but significant correlations with the cardiac index ($r = 0.235$; $p = 0.019$) and the mixed

venous oxygen saturation ($r = 0.226$; $p = 0.026$), suggesting that the degree of hyperventilation was partly related to reduced cardiac output. In accordance, the change in $Pa,CO_2$ 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 cardiopulmonary exercise testing*

Since cardiopulmonary exercise testing was introduced in our clinical PH program in 2001, only 53 patients had exercise tests performed at baseline.
In this subpopulation, exercise caused a mild drop in $Pa,O_2$ from 69 ± 12 mmHg at rest to 65 ± 14 mmHg at the anaerobic threshold ($p = 0.004$), while $Pa,CO_2$ remained nearly unchanged (Table 1). $HCO_3^-$ decreased from 22.8 ± 2.8 mmol/l at rest to 20.8 ± 2.9 mmol/l at the anaerobic threshold ($p < 0.001$), and the pH decreased from 7.46 ± 0.03 to 7.44 ± 0.04 ($p < 0.001$). The end-tidal $PCO_2$ ($P_{ET}CO_2$) fell from 27 ± 5 mmHg at to 25 ± 5 mmHg at the anaerobic threshold ($p = 0.017$), 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 $Pa,CO_2$ or $P_{ET}CO_2$, respectively, and the $V_D/V_T$ ratio. In addition, there was no correlation between $Pa,O_2$ and $Pa,CO_2$ at rest and during exercise but a significant correlation between $Pa,O_2$ at rest and $P_{ET}CO_2$ at rest ($r = 0.439$, $p < 0.001$) as well as between $Pa,O_2$ at the anaerobic threshold and $P_{ET}CO_2$ at the anaerobic threshold ($r = 0,632$; $p < 0.001$), probably reflecting, at least partly, effects of ventilation/perfusion abnormalities.
As shown in Table 3, $Pa,O_2$ at rest but not $Pa,CO_2$ at rest showed a weak but significant correlation with the peak oxygen uptake ($r = 0.303$, $p = 0.03$). In contrast, there were stronger correlations between the peak oxygen uptake and both $Pa,O_2$ and $Pa,CO_2$ at the anaerobic threshold ($r = 0.404$; $p = 0.005$, and $r = 0.479$; $p < 0.001$, respectively). There were also significant inverse correlations between peak oxygen uptake 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.
Ventilatory efficacy during exercise ($VE/VCO_2$@AT) showed significant inverse correlations with $Pa,O_2$ and $Pa,CO_2$ at rest (Table 3) and an even stronger inverse correlation with the $Pa,O_2$ at the anaerobic threshold ($r = -0.729$; $p < 0.001$).

*Relationship between blood gases at baseline and survival*

The baseline $Pa,O_2$ at rest had no significant impact on survival. When patients were divided according to their baseline $Pa,O_2$ above or below the median of 67.5 mmHg, survival rates

were 98% and 84% at 1 year, 79% and 73% at 2 years, 70% and 63% at 3 years, 58% and 57% at 5 years, and 58% and 16% at 8 years, a difference that did not reach statistical significance ($p = 0.18$ by log rank analysis; Fig. 1). Similar results were obtained when the alveolar-arterial oxygen gradient ($PAa,O_2$) rather than the $Pa,O_2$ was examined (median 42 mmHg, no significant survival difference between patients who had a $PAa,O_2$ 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 32 mmHg as the optimal cut-off level with a sensitivity of 0.73 and a specificity of 0.66 to predict survival at 2 years (area under curve 0.70, 95% confidence interval 0.59-0.81, $p < 0.001$). This cut-off point was identical to the median value of $Pa,CO_2$ in this patient population, which also was 32 mmHg. When patients were divided according to their baseline $Pa,CO_2$ above or below 32 mmHg, survival rates were 98% and 86% at 1 year, 82% and 69% at 2 years, 80% and 51% at 3 years, 77% and 41% at 5 years and 65% and 12% at 8 years, 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 stronger associated with survival than baseline values. Here the cut-off value was 32.5 mmHg. Patients with $Pa,CO_2$ values above 32.5 mmHg had survival rates at 1, 2, 3, 5 and 8 years of 95%, 86%, 83%, 83%, and 78%, respectively, whereas patients with $Pa,CO_2$ values below 32.5 mmHg had survival rates at 1, 2, 3, 5 and 8 years of 88%, 70%, 57%, 46%, and 15% respectively, ($p < 0.001$ by log rank analysis, Fig. 3).

Univariate logistic regression analysis revealed that 6 min walk distance, right atrial pressure, cardiac output, pulmonary vascular resistance, mixed venous oxygen saturation and $Pa,CO_2$ at baseline as well as after 3 months of therapy, but not mean pulmonary artery pressure and $Pa,O_2$, were associated with survival (Table 4). Multiple logistic regression analysis revealed that only 6 min walk distance, right atrial pressure, 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,CO2 at baseline (AUC 0.70, 95% confidence interval 0.59-0.81, $p < 0.001$) was similar to that of the 6 min walk distance (AUC 0.79, 95% confidence interval 0.69-0.87, $p < 0.001$) and the right atrial pressure (AUC 0.29, 95% confidence interval 0.18-0.40, $p < 0.001$), and better than the mean pulmonary artery pressure (AUC 0.41, 95% confidence interval 0.29-0.53, $p = 0.138$) or the cardiac index (AUC 0.64, 95% confidence interval 0.53-0.76, $p = 0.021$).

**Discussion**

The present study confirmed that mild hypoxemia and mild-to-moderate hypocapnia at rest and during exercise are common findings in patients with IPAH. Neither hypoxemia 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 the 6 min walk distance, right atrial pressure and mixed venous oxygen saturation, respectively. $Pa,CO_2$ at rest correlated with cardiac index and mixed venous oxygen saturation. The most important finding of this study, however, was the prognostic importance of a low $Pa,CO_2$ both at baseline as well as 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 relation 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 relation between blood gases and exercise limitation in patients with IPAH?*

The 6 min walk distance 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 $VO_2$ also correlated with the $Pa,O_2$ at rest but not with $Pa,CO_2$ at rest, in accordance to what has been shown in patients with left heart failure [6]. However, when blood gases were obtained during exercise, both $Pa,O_2$ at the anaerobic threshold ($r = 0.404$, $p = 0.005$) and $Pa,CO_2$ at the anaerobic threshold ($r = 0.479$, $p < 0.001$) did correlate significantly with peak $VO_2$. 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 $VO_2$ and $VE/VCO_2$@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 $VE/VCO_2$ 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 (both $Pa,O_2$ and $Pa,CO_2$ at the anaerobic threshold). 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 $VE/VCO_2$ ratio is not sufficient to explain a low $Pa,CO_2$. The $VE/VCO_2$ ratio, or ventilatory efficacy, describes the amount of ventilation needed to remove a given amount of $CO_2$. Elevated $VE/VCO_2$ ratios and low end-tidal $PCO_2$ values have been reported in patients with pulmonary hypertension [11, 12] as well as left 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 more to maintain a physiological $PaCO_2$, it does not explain why they hyperventilate, i.e. why they reduce their $Pa,CO_2$ to subphysiological levels, sometimes way below 30 mmHg.

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 $Pa,CO_2$ 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]. Of note, there was a stronger correlation between $Pa,CO_2$ at the anaerobic threshold and peak $VO_2$ ($r = 0.479$, $p = 0.005$), the latter partly reflecting cardiac output during exercise. In addition, there was a highly significant inverse correlation between $Pa,CO_2$ at the anaerobic threshold and $VE/VCO_2$@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], indicating that ventilatory efficacy declines with hyperventilation. Finally, changes in $Pa,CO_2$ during the course of 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 PAH?*

The available evidence suggests that hypocapnia reflects an increased ventilatory drive caused by several mechanisms including low cardiac output, impaired ventilatory efficacy, 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 optimize 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 PAH.

*Study limitations*

The present study has several limitations including its retrospective design and the fact that all data came from a single center. 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 catheterizations were not part of our clinical program and exercise hemodynamics were not available. In addition, our study relied on arterialized capillary blood gases rather than directly measuring arterial blood gases, and thus, or results formally apply only to blood gases obtained by this technique. However, before adopting the technique of measuring arterialized capillary blood gases our center performed extensive studies comparing these with arterial blood gases, and we found excellent agreements (unpublished data), so that it is unlikely that the present findings would have been different with arterial blood gases. Finally, since we included only patients with IPAH, our findings may not be tranferable 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 and the long follow-up as well as the fact that blood gases were routinely obtained from all patients allow us to draw some meaningful and clinically important conclusions.

*Conclusion*

A low $Pa,CO_2$ (< 32 mmHg) is an independent prognostic marker in patients with IPAH with similar predictive value for mortality than established variables such as the 6 min walking distance or the right atrial pressure. $Pa,CO_2$ 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.

**Table 1. Summary of baseline demographics, hemodynamics, pulmonary function results, blood gases at rest, and variables obtained during cardiopulmonary function testing**

| | Whole study population | CPET subgroup |
|---|---|---|
| n | 101 | 53 |
| Female/male | 76/25 | 43/10 |
| NYHA II | n = 3 | n = 2 |
| NYHA III | n = 78 | n = 44 |
| NYHA IV | n = 20 | n = 7 |
| Age (years) | 48 ± 15 | 47 ± 14 |
| 6 min walk distance (m) | 305 ± 118 | 334 ± 100 |
| RAP (mmHg) | 9 ± 6 | 9 ± 6 |
| PAPmean (mmHg) | 56 ± 13 | 55 ± 14 |
| CO (l/min) | 3.7 ± 1.1 | 3.7 ± 1.1 |
| CI (l/min/$m^2$) | 2.0 ± 0.5 | 2.0 ± 0.5 |
| PVR ($dyn \cdot s \cdot cm^{-5}$) | 1,157 ± 492 | 1,142 ± 465 |
| $Sv,O_2$ (%) | 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 $VO_2$ (ml/kg/min) | n/a | 13.4 ± 3.6 |
| $O_2$/HR (ml) | n/a | 7.1 ± 2.1 |
| $VE/VCO_2$@AT | n/a | 48 ± 15 |
| $P_{ET}CO_2$ at rest | n/a | 27 ± 5 |
| $P_{ET}CO_2$@AT | n/a | 25 ± 7 |
| $V_D/V_T$ at rest | n/a | 16 ± 6 |
| $V_D/V_T$@AT | n/a | 18 ± 4 |
| $Pa,O_2$ (mmHg) at rest | 69 ±14 | 69 ± 12 |
| $Pa,O_2$ (mmHg)@AT | n/a | 65 ± 14 |
| $Pa,CO_2$ (mmHg) at rest | 32 ± 4 | 33 ± 4 |
| $Pa,CO_2$ (mmHg)@AT | n/a | 32 ± 5 |
| pH at rest | 7.46 ± 0.03 | 7.46 ± 0.03 |
| pH@AT | n/a | 7.44 ± 0.04 |
| $HCO_3^-$ at rest | 22,6 ± 2,7 | 22,8 ± 2,8 |
| $HCO_3^-$ @AT | n/a | 20.8 ± 2,9 |

Abbreviations: CPET, cardiopulmonary exercise testing; NYHA, New York Heart Association; RAP, right atrial pressure; PAPm, mean pulmonary artery pressure; CO, cardiac

output; CI, cardiac index; PVR, pulmonary vascular resistance; $Sv,O_2$, mixed venous oxygen saturation; Peak $VO_2$, peak oxygen uptake; $O_2$/HR, oxygen pulse; $VE/VCO_2$@AT, ventilatory efficacy at the anaerobic threshold; $P_{ET}CO_2$, end-tidal $PCO_2$; $V_D/V_T$, dead space/tidal volume ratio; FVC, forced vital capacity; $FEV_1$, forced expiratory volume at 1 second; $D_L$,CO, diffusion capacity of the lungs for carbon monoxide; n/a, not assessed

**Table 2 Correlations between blood gases at rest, hemodynamics and 6 min walk distance**

| | 6 mwt | RAP | PAPm | CI | PVR | $Sv,O_2$ |
|---|---|---|---|---|---|---|
| $Pa,O_2$ | r = 0.298<br>p = 0.001 | r = -0.269<br>p = 0.007 | r = 0.108<br>p = n.s. | r = 0.008<br>p = n.s. | r = 0.161<br>p = n.s. | r = 0.227<br>p = 0.026 |
| $Pa,CO_2$ | r = 0.104<br>p = n.s. | r = -0.054<br>p = n.s. | r = -0.049<br>p = n.s. | r = 0.235<br>p = 0.019 | r = -0.185<br>p = n.s. | r = 0.226<br>p = 0.026 |

Abbreviations: 6 mwt, 6 min walk test; RAP, right atrial pressure; PAPm, mean pulmonary artery pressure; CI, cardiac index; PVR, pulmonary vascular resistance; $Sv,O_2$, mixed venous oxygen saturation

**Table 3 Correlations between blood gases and variables obtained during cardiopulmonary exercise testing**

| | Peak $VO_2$ | $VE/VCO_2$@rest | $VE/VCO_2$@AT | $Pa,O_2$@AT | $Pa,CO_2$@AT |
|---|---|---|---|---|---|
| $Pa,O_2$ at rest | r = 0.303<br>p = 0.03 | r = -0.367<br>p = 0.008 | r = -0.431<br>p = 0.002 | r = 0.682<br>p < 0.001 | r = 0.132<br>p = n.s. |
| $Pa,CO_2$ at rest | r = 0.191<br>p = n.s. | r = -0.250<br>p = n.s. | r = -0.389<br>p = 0.006 | r = 0.137<br>p = n.s. | r = 0.659<br>p = < 0.001 |
| Peak $VO_2$ | n/a | r = -0.343<br>p = 0.015 | r = -0.541<br>p < 0.001 | r = 0.404<br>p = 0.005 | r = 0.479<br>p < 0.001 |

**Table 4 Parameters predictive of survival in univariate analysis**

| Ind. Variable | Odds Ratio | 5% Conf. Lower | 95% Conf. Upper | P value |
|---|---|---|---|---|
| | | | | |
| 6 mwt | 1.007 | 1.003 | 1.011 | < 0.001 |
| RAP | 0.873 | 0.805 | 0.947 | 0.001 |
| PAPm | 0.984 | 0.954 | 1.014 | 0.292 |
| CI | 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 |
| $Pa,O_2$ (baseline) | 1.025 | 0.996 | 1.056 | 0.097 |
| $Pa,CO_2$ (baseline) | 1.191 | 1.058 | 1.341 | 0.004 |
| $Pa,O_2$ (3 months) | 1.020 | 0.991 | 1.049 | 0.176 |
| $Pa,CO_2$ (3 months) | 1.449 | 1.242 | 1.690 | < 0.001 |

Abbreviations: 6 mwt, 6 min walk test; RAP, right atrial pressure; PAPm, mean pulmonary artery pressure; CI, cardiac index; PVR, pulmonary vascular resistance; $Sv,O_2$, mixed venous oxygen saturation

**Table 5 Multiple logistic regression analysis with survival as the dependent variable**

| Ind. Variable | Odds Ratio | 5% Conf. Lower | 95% Conf. Upper | P value |
|---|---|---|---|---|
| | | | | |
| 6 mwt | 1.006 | 1.001 | 1.010 | 0.022 |
| RAP | 0.874 | 0.788 | 0.968 | 0.010 |
| CI | 1.041 | 0.340 | 3.185 | 0.944 |
| $Pa,CO_2$ (baseline) | 1.166 | 1.020 | 1.333 | 0.025 |
| Pa,CO2 (3 months) | 1.512 | 1.224 | 1.867 | < 0.001 |

Abbreviations: 6 mwt, 6 min walk test; RAP, right atrial pressure; CI, cardiac index

**Figure legends**

Fig 1 Impact of baseline $Pa,O_2$ on survival in patients with IPAH. Kaplan-Meier survival estimates of 101 patients with idiopathic pulmonary arterial hypertension according to their baseline $Pa,O_2$.

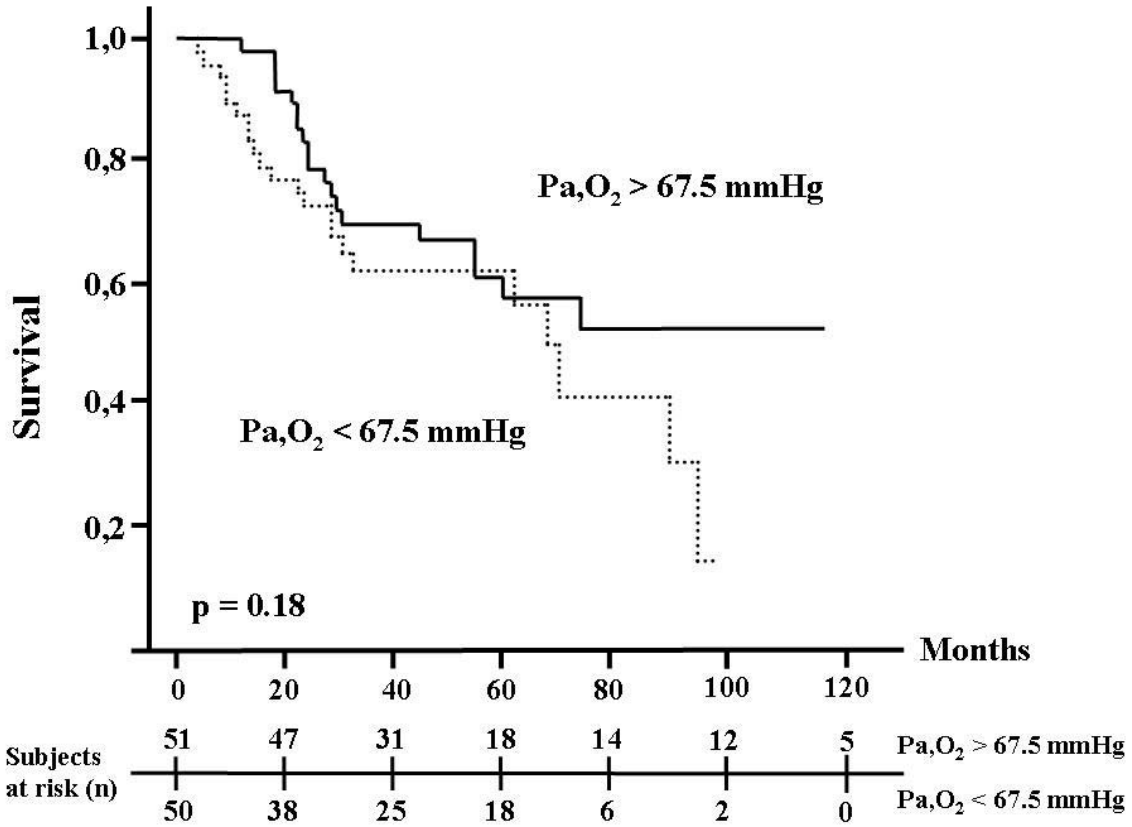



Fig 2 Impact of baseline $Pa,CO_2$ on survival in patients with IPAH. Kaplan-Meier survival estimates of 101 patients with idiopathic pulmonary arterial hypertension according to their baseline $Pa,CO_2$.

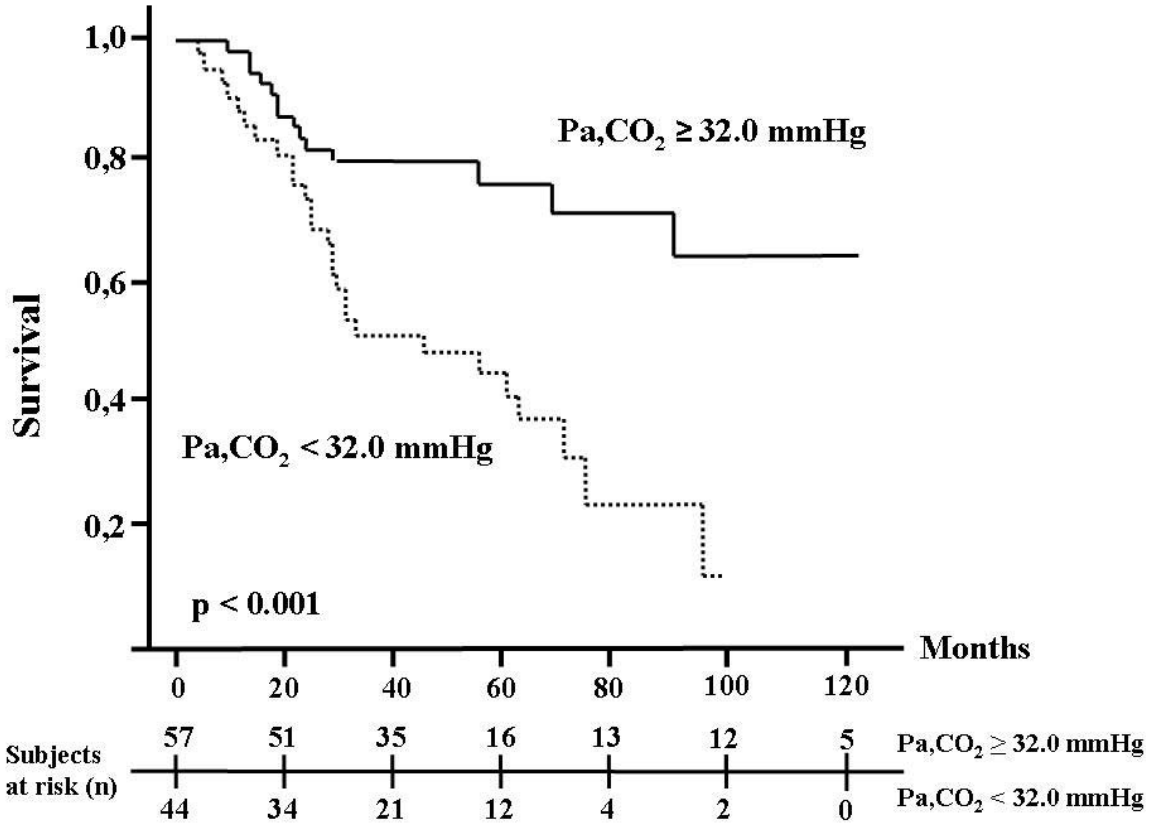



Fig 3 Impact of Pa,CO2 obtained after 3 months of therapy on survival in patients with IPAH. Kaplan-Meier survival estimates of 101 patients with idiopathic pulmonary arterial hypertension according to their $Pa,CO_2$ after 3 months of therapy.

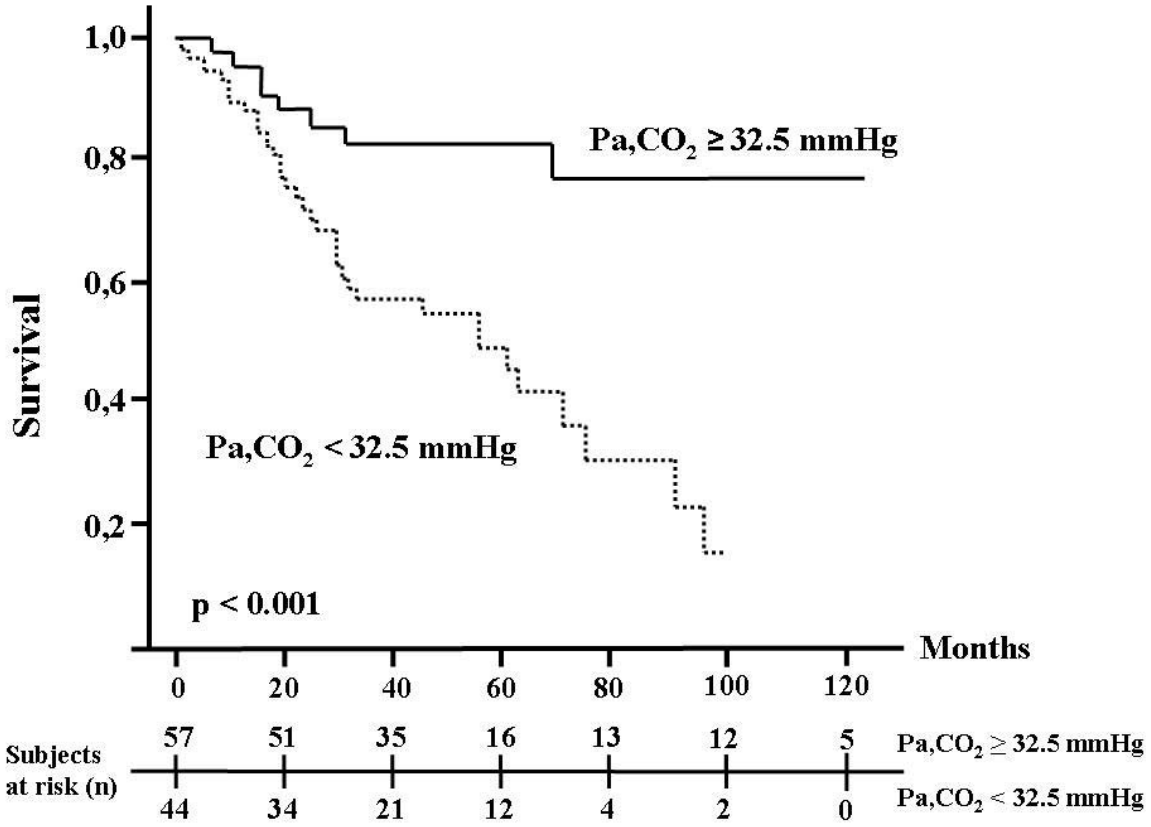
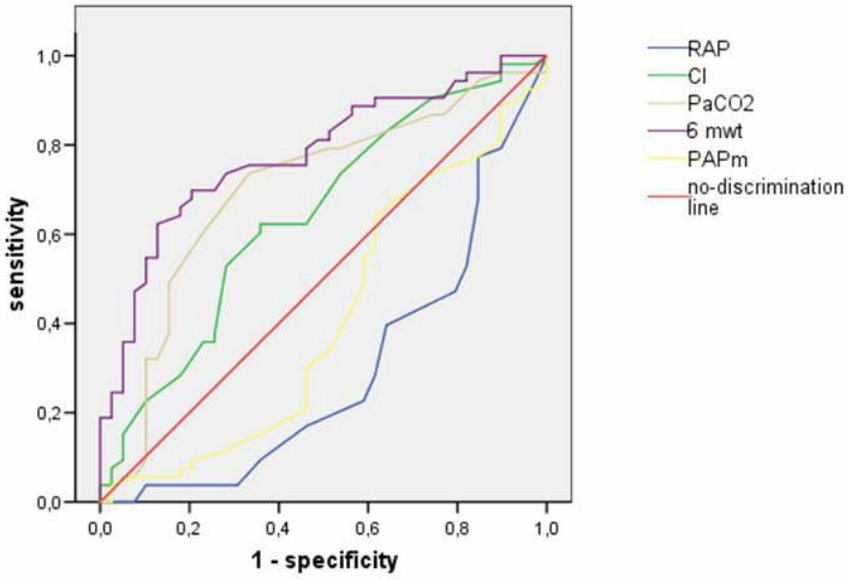



Fig 4 Ability of several variables to predict survival in patients with IPAH. RAP denotes right atrial pressure; CI, cardiac index; 6 mwt, 6 min walk test and PAPm, mean pulmonary arterial pressure.


sensitivity
1 - specificity
0,0
0,2
0,4
0,6
0,8
1,0
RAP
CI
PaCO2
6 mwt
PAPm
no-discrimination line

## References


1. Galie N, Torbicki A, Barst R, Dartevelle P, Haworth S, Higenbottam T, Olschewski H, Peacock A, Pietra G, Rubin LJ, Simonneau G, Priori SG, Garcia MA, Blanc JJ, Budaj A, Cowie M, Dean V, Deckers J, Burgos EF, Lekakis J, Lindahl B, Mazzotta G, McGregor K, Morais J, Oto A, Smiseth OA, Barbera JA, Gibbs S, Hoeper M, Humbert M, Naeije R, Pepke-Zaba J. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J* 2004; 25: 2243-78.
2. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Koerner SK. Primary pulmonary hypertension. A national prospective study. *Ann Intern Med* 1987; 107: 216-23.
3. 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.
4. Hoeper MM, Taha N, Bekjarova A, Gatzke R, Spiekerkoetter E. Bosentan treatment in patients with primary pulmonary hypertension receiving nonparenteral prostanoids. *Eur Respir J* 2003; 22: 330-4.
5. Hoeper MM, Markevych I, Spiekerkoetter E, Welte T, Niedermeyer J. Goal-oriented treatment and combination therapy for pulmonary arterial hypertension. *Eur Respir J* 2005; 26: 858-63.
6. Wensel R, Georgiadou P, Francis DP, Bayne S, Scott AC, Genth-Zotz S, Anker SD, Coats AJ, Piepoli MF. Differential contribution of dead space ventilation and low arterial pCO2 to exercise hyperpnea in patients with chronic heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 2004; 93: 318-23.
7. Metra M, Dei Cas L, Panina G, Visioli O. Exercise hyperventilation chronic congestive heart failure, and its relation to functional capacity and hemodynamics. *Am J Cardiol* 1992; 70: 622-8.
8. Reindl I, Wernecke KD, Opitz C, Wensel R, Konig D, Dengler T, Schimke I, Kleber FX. Impaired ventilatory efficiency in chronic heart failure: possible role of pulmonary vasoconstriction. *Am Heart J* 1998; 136: 778-85.
9. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. *Circulation* 2001; 104: 429-35.
10. Johnson RL, Jr. Gas exchange efficiency in congestive heart failure II. *Circulation* 2001; 103: 916-8.
11. Wensel R, Opitz CF, Anker SD, Winkler J, Hoffken 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: 319-24.
12. Yasunobu Y, Oudiz RJ, Sun XG, Hansen JE, Wasserman K. End-tidal PCO2 Abnormality and Exercise Limitation in Patients With Primary Pulmonary Hypertension. *Chest* 2005; 127: 1637-46.
13. Ponikowski P, Francis DP, Piepoli MF, Davies LC, Chua TP, Davos CH, Florea V, Banasiak W, Poole-Wilson PA, Coats AJ, Anker SD. Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. *Circulation* 2001; 103: 967-72.

14. Fanfulla F, Mortara A, Maestri R, Pinna GD, Bruschi C, Cobelli F, Rampulla C. The development of hyperventilation in patients with chronic heart failure and Cheyne-Strokes respiration: a possible role of chronic hypoxia. *Chest* 1998; 114: 1083-90.
15. Gitt AK, Wasserman K, Kilkowski C, Kleemann T, Kilkowski A, Bangert M, Schneider S, Schwarz A, Senges J. Exercise anaerobic threshold and ventilatory efficiency identify heart failure patients for high risk of early death. *Circulation* 2002; 106: 3079-84.
16. Buller NP, Poole-Wilson PA. Mechanism of the increased ventilatory response to exercise in patients with chronic heart failure. *Br Heart J* 1990; 63: 281-3.
17. 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: 1585-90.