Eur Respir J 2002; 20: 300–305
DOI: 10.1183/09031936.02.00222302
Printed in UK – all rights reserved

Copyright ©ERS Journals Ltd 2002
European Respiratory Journal
ISSN 0903-1936

Effect of hypobaric hypoxia on blood gases in patients with restrictive lung disease

C.C. Christensen*,#,¶, M.S. Ryg#,¶, O. Kåre Refvem¶, O. Henning Skjønsberg*

Effect of hypobaric hypoxia on blood gases in patients with restrictive lung disease. C.C. Christensen, M.S. Ryg, O. Kåre Refvem, O. Henning Skjønsberg. ©ERS Journals Ltd 2002.

ABSTRACT: Several publications have reported effects of hypobaric conditions in patients with chronic obstructive pulmonary disease. To the current authors' knowledge, similar studies concerning patients with restrictive lung disease have not been published.

The effect of simulated air travel in a hypobaric chamber on arterial blood gases, blood pressure, and cardiac frequency during rest and 20 W exercise, and the response to supplementary oxygen in 17 patients with chronic restrictive ventilatory impairment has been investigated.

Resting oxygen tension in arterial blood (P_{a,O_2}) decreased from 10.4±1.6 kPa at sea level to 6.5±1.1 kPa at 2,438 m simulated altitude, and decreased further during light exercise in all patients (5.1±0.9 kPa). P_{a,O_2} at this altitude correlated positively with sea-level P_{a,O_2} and transfer factor of the lung for carbon monoxide ($T_{L,CO}$), and negatively with carbon dioxide tension in arterial blood (P_{a,CO_2}). P_{a,O_2} increased to acceptable levels with an O_2 supply of 2 L·min^{-1} at rest and 4 L·min^{-1} during 20 W exercise.

In conclusion, most of the patients with restrictive ventilatory impairment developed hypoxaemia below the recommended levels of in-flight oxygen tension in arterial blood during simulated air travel. Light exercise aggravated the hypoxaemia. Acceptable levels of oxygen tension in arterial blood, with only a minor increase in carbon dioxide tension in arterial blood, were obtained by supplementary oxygen.
Eur Respir J 2002; 20: 300–305.

*Dept of Pulmonary Medicine, Ullevål Hospital, Oslo, #Institute of Aviation Medicine, Blindern, Oslo and ¶Glittreklinikken, Hakadal, Norway.

Correspondence: C.C. Christensen
Glittreklinikken
1488 Hakadal
Norway
Fax: 47 67075344
E-mail: carl.christian.christensen@nih.no

Keywords: Air travel
cabin pressure altitude
commercial aircraft
hypoxia
oxygen
restrictive lung disease

Received: March 7 2001
Accepted after revision: December 12 2001

Federal aviation regulations specify rules for commercial aircraft of a maximal cabin altitude of 2,438 m (8,000 feet) in order to avoid hypoxaemia in crew and passengers [1, 2]. The oxygen saturation (S_{a,O_2}) in healthy subjects will exceed 90% at this cabin altitude and only a slight reduction in mental performance will be observed [3–5].

Passengers with chronic obstructive pulmonary disease (COPD) may experience a severe decrease in arterial blood oxygen content at a cabin altitude of 2,438 m [6, 7]. Three medical guidelines for COPD patients conclude that in-flight O_2 supplementation should be considered if the O_2 tension in arterial blood (P_{a,O_2}) at 2,438 m altitude is <6.7 kPa (50 mmHg) [8, 9] or 7.3 kPa (55 mmHg) [10], respectively, since hypoxaemia below these levels is considered to be associated with increased risk of medical complications [11, 12]. Several studies concerning preflight evaluation of COPD patients have suggested screening criteria based on sea-level blood gases, spirometry, and exercise capacity [8–10, 13–16]. However, to the current authors' knowledge, similar studies concerning hypobaric conditions on patients with restrictive ventilatory impairment have not previously been performed.

The present investigation was carried out to study the influence of low atmospheric pressure on arterial blood gases in patients with chronic restrictive ventilatory impairment. In addition, the authors wanted to evaluate the effect of supplementary O_2 on arterial blood gases and cardiovascular function under these conditions, both at rest and during light exercise. The exercise tests were performed because it is recommended that passengers take brief walks during long distance flights to avoid thromboembolic complications. Seventeen patients with chronic restrictive ventilatory impairment were studied at rest and during bicycle exercise (at a rate equivalent to slow walking along the aisle of an airplane) at sea level and at 2,438 m simulated altitude in a hypobaric chamber.

Methods

Seventeen patients, 10 females and seven males, attending a rehabilitation programme were recruited for the study (group 1, table 1). They all suffered from chronic restrictive ventilatory impairment (total lung capacity (TLC) <95% confidence interval) [17], caused by either sequelae from tuberculosis (five patients), kyphoscoliosis (two patients), or lung fibrosis (sarcoidosis: three patients; fibrosing alveolitis: two patients;

Table 1. – Lung function and arterial blood gases in 17 patients with chronic restrictive ventilatory impairment (group 1)

	Mean±1SD	Range	% pred
Age yrs	56.8±14.9	26–74	
Height cm	170.5±11.7	144–190	
Weight kg	72.2±14.0	50–102	
Hgb g %	14.0±4.1	12.8–17.1	
BP_{sys} mmHg	149.6±36.5	105–266	
BP_{dia} mmHg	81.7±18.3	50–118	
fC min^{-1}	87.2±10.7	68–105	
VC L	2.0±0.7	1.0–3.6	54±16
FEV1 L	1.4±0.6	0.7–2.8	49±18
TLC L	3.2±1.0	1.7–4.7	52±11
$T_{L,CO}$ mmol·min^{-1}·kPa^{-1}	4.8±1.4	2.6–7.4	54±18
P_{a,O_2} kPa	10.4±1.6	6.6–13.0	
S_{a,O_2} %	95.0±2.2	87.9–97.7	
P_{a,CO_2} kPa	5.2±0.7	4.1–6.4	
Aerobic capacity mL·min^{-1}·kg^{-1}	13.8±3.7	8.6–22.8	44±11

Hgb: haemoglobin concentration; BP_{sys}: systolic blood pressure at rest, sea level; BP_{dia}: diastolic blood pressure at rest, sea level; fC: cardiac frequency; VC: vital capacity; FEV1: forced expiratory volume in one second; TLC: total lung capacity; $T_{L,CO}$: single-breath transfer factor of the lung for carbon monoxide; P_{a,O_2}: oxygen tension in arterial blood; S_{a,O_2}: arterial oxygen saturation; P_{a,CO_2}: carbon dioxide tension in arterial blood; aerobic capacity: oxygen consumption divided by body weight.

unspecified lung fibrosis: five patients). At the time of testing, all were in a stable phase of their disease. Two patients with mild hypertension received amlodipine (2.5 mg·day^{-1}) or spironolactone (50 mg·day^{-1}), and seven used oral or inhaled corticosteroids. Two had a history of myocardial infarction, without ventricular dysfunction. Patients with coexisting medical problems that might influence their physical capacity were excluded from the study. However, because analysis of blood pressures was performed after completion of the experiments, the authors failed to observe that one of the patients had a resting diastolic pressure of 118 mmHg on the day of the experiment. To test an equation for the prediction of in-flight P_{a,O_2} from preflight variables in these 17 patients, a separate group, consisting of 11 patients with chronic restrictive ventilatory impairment, was studied (group 2, table 2). The Regional Medical Ethics Committee approved the study, and written informed consent was obtained from all participants.

Vital capacity (VC), forced expiratory volume in one second (FEV1), TLC, single-breath transfer factor of the lung for carbon monoxide ($T_{L,CO}$) [18], and aerobic capacity were measured before the altitude experiment, as previously reported [7].

The experiments were performed with one patient and three technicians present in an air-conditioned (3 m^3·min^{-1}, 25°C) hypobaric altitude chamber (20 m^3) with stable concentrations of O_2 and carbon dioxide. In group 1, the subjects sat in a chair to use a cycle ergometer. After $\geqslant$10 min rest, they started cycling at 20 W, increasing by 10 W every 4 min, but here only responses during rest and 20 W exercise are

Table 2. – Lung function and arterial blood gases at rest at sea level in 11 patients with chronic restrictive ventilatory impairment (group 2)

	Mean±1SD	Range	% pred
Age yrs	57.5±9.0	42–71	
Height cm	167.6±11.7	153–187	
Weight kg	76.2±20.4	47–111	
VC L	2.4±0.9	1.1–4.3	69±21
FEV1 L	1.8±0.7	0.9–3.44	63±26
TLC L	3.9±0.9	3.0–5.7	68±14
$T_{L,CO}$ mmol·min^{-1}·kPa^{-1}	4.7±2.5	1.3–9.7	53±20
P_{a,O_2} kPa	10.3±2.0	6.2–12.6	
S_{a,O_2} %	95.3±4.6	82.3–98.3	
P_{a,CO_2} kPa	5.1±0.8	4.1–7.0	
Aerobic capacity mL·min^{-1}·kg^{-1}	19.9±5.8	13.4–30.1	66±15

VC: vital capacity; FEV1: forced expiratory volume in one second; TLC: total lung capacity; $T_{L,CO}$: single-breath transfer factor of the lung for carbon monoxide; P_{a,O_2}: oxygen tension in arterial blood; S_{a,O_2}: arterial oxygen saturation; P_{a,CO_2}: carbon dioxide in arterial blood; aerobic capacity: oxygen consumption divided by body weight.

reported. The procedure was performed in a random order at sea level and a simulated altitude of 2,438 m (8,000 ft), with 60 min rest between each exercise test. In group 2, the subjects were only exposed to hypobaric hypoxia (2,438 m) without exercise. Arterial blood samples were drawn every 4 min from a catheter in the radial artery. The samples were stored on melting ice in sealed syringes for 10–15 min before being sluiced out of the chamber and analysed for blood gases [7]. The heart rhythm was continuously monitored, and arterial blood pressure was recorded through the catheter in the radial artery using a Mingograf 7 (Siemens-Elema, Solna, Sweden) and a Baxter TruWave disposable pressure transducer (Glendale, CA, USA).

After terminating the measurements at sea level and 2,438 m, the patients in group 1 were tested at 2,438 m at rest and during 20 W exercise with and without a supply of 100% O_2 through a double nasal cannula. The O_2 flow rates of 1, 2 and 4 L·min^{-1} were blinded for the patients. Arterial blood gases, intra-arterial blood pressure and cardiac frequency were measured at 4 min intervals. Two of the subjects did not participate in the study of supplementary O_2, because they feared increased dyspnoea during a repeated exercise test.

Results are expressed as mean±SD. All variables, except S_{a,O_2}, were normally distributed, and as a result, paired t-tests were used to evaluate differences between sea level and altitude. A Mann-Whitney test was used for S_{a,O_2}. To test for combined effects, linear regression analysis of P_{a,O_2} (2,438 m) *versus* P_{a,O_2} (sea level), $T_{L,CO}$ (% of predicted [8]), and P_{a,CO_2} (sea level) was performed, because of the significant bivariate correlations between the first and the latter three variables. The effect of O_2 supply was tested using a two factor (rest *versus* exercise, and level of O_2 supply) repeated measures analysis of variance (ANOVA), followed by contrasts

between different flow rates. Two-tailed p-values <0.05 were considered statistically significant.

Results

All subjects had a TLC <80% pred, as shown in table 1. Values for VC, FEV1 and $T_{L,CO}$ were also reduced to ~50% pred. All except one of the subjects were nonsmokers.

Individual values for arterial blood gases are presented in figure 1 (a–c). There was a considerable decrease in P_{a,O_2} and S_{a,O_2} as the patients were taken from sea level to 2,438 m altitude (table 3). During 20 W exercise, P_{a,O_2} and S_{a,O_2} decreased markedly as compared to resting values, both at sea level and at 2,438 m (table 3). All subjects managed the work load (20 W) at sea level for $\geq$4 min, but at 2,438 m three subjects terminated after 2 min because of dyspnoea. In the figures showing 20 W exercise, blood values from these subjects are also included.

There was a statistically significant decrease in resting P_{a,CO_2} from sea level to 2,438 m (table 3). During 20 W exercise, P_{a,CO_2} increased significantly at sea level, but not at altitude. Resting ventilation was not significantly different at sea level and at 2,438 m. During 20 W exercise, however, the ventilation at 2,438 m was significantly higher than at sea level (table 3).

The resting P_{a,O_2} at 2,438 m was correlated to both the sea-level P_{a,O_2} (r=0.73, p<0.001), $T_{L,CO}$ (r=0.59, p<0.02) and $T_{L,CO}$ in per cent of predicted values (r=0.69, p<0.01), and negatively correlated to P_{a,CO_2} (r=-0.55, p<0.05). There was no significant correlation between in-flight P_{a,O_2} and sea-level values of VC, FEV1, TLC, or aerobic capacity.

A multiple linear regression analysis of P_{a,O_2} (in kPa) at 2,438 m *versus* $T_{L,CO}$ and P_{a,O_2} at sea level gave the following equation:

$$P_{a,O_2}\,(2{,}438\text{ m}) = 0.74 + 0.39 \times P_{a,O_2}(\text{sea level}) + 0.033 \times T_{L,CO}(\%\text{ pred}) \quad (1)$$

with multiple r=0.88. The deviations from predicted P_{a,O_2} ranged from an overestimate of 1.0 kPa to an underestimate of 0.7 kPa and were normally distributed. Sea-level P_{a,CO_2} had no significant relation to P_{a,O_2} at altitude in the multiple regression. In group 2, no significant difference between measured in-flight P_{a,O_2} and P_{a,O_2} pred from the equation above (0.25±0.46 kPa, range -0.43–0.81 kPa) was observed.

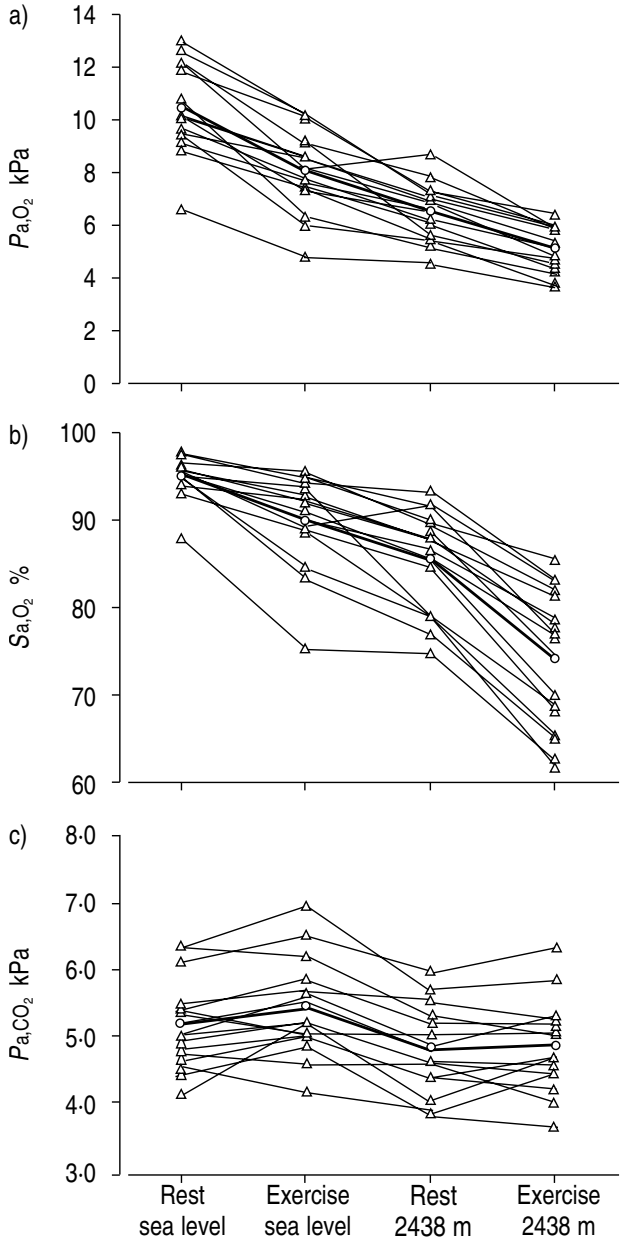

Fig. 1.–Arterial blood gas values from 17 patients with chronic restrictive ventilatory impairment during rest and 20 W ergometer cycle exercise at sea level and at 2,438 m (8,000 feet) altitude. Individual (△) and mean values (○) of a) oxygen tension in arterial blood (P_{a,O_2}), b) arterial oxygen saturation (S_{a,O_2}) and c) carbon dioxide tension in arterial blood (P_{a,CO_2}).

Table 3.–Blood gases and ventilation at rest and during 20 W exercise at sea level and 2,438 m simulated altitude (group 1)

	Sea level		2,438 m	
	Rest	Exercise	Rest	Exercise
P_{a,O_2} kPa	10.4±1.6	8.1±1.5***	6.5±1.1###	5.1±0.9***
S_{a,O_2} %	95.0±2.2	90.1±5.1***	85.4±5.6###	74.2±7.8****
P_{a,CO_2} kPa	5.2±0.7	5.4±0.7**	4.8±0.6###	4.9±0.7
Ventilation L·min^{-1}	11.3±3.4	23.7±7.5	12.1±4.5	27.2±8.1###

P_{a,O_2}: oxygen tension in arterial blood; S_{a,O_2}: arterial oxygen saturation; P_{a,CO_2}: carbon dioxide tension in arterial blood. **: p<0.01; ***: p<0.001; ****: p<0.0001, rest *versus* exercise; ###: p<0.001, sea level *versus* 2,438 m.

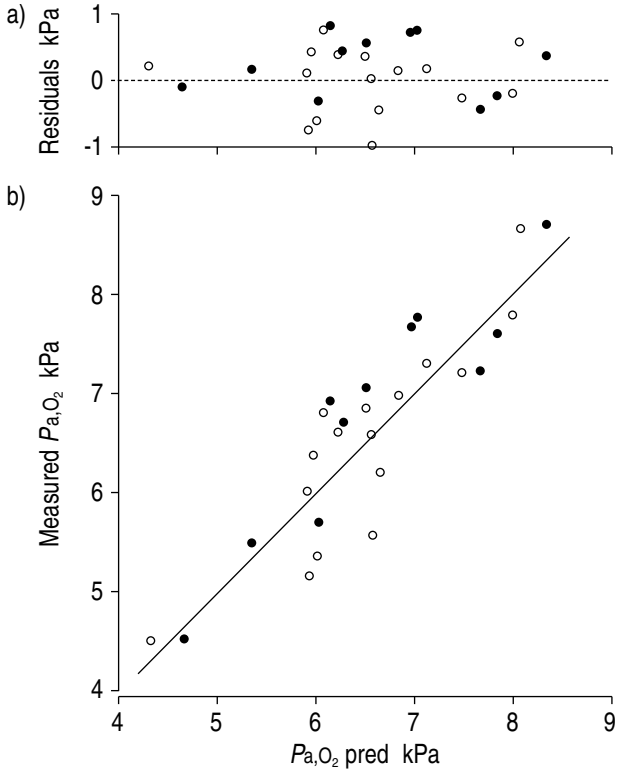

Fig. 2. – Comparison of measured in-flight oxygen pressure in arterial blood (P_{a,O_2}) and P_{a,O_2} pred from the equation P_{a,O_2} (2,438 m)=0.74+0.39×P_{a,O_2} (sea level)+0.033×transfer factor of the lung for carbon monoxide (% pred). ○: group 1; ●: group 2.

A comparison of measured and predicted P_{a,O_2} values at 2,438 m is shown in figure 2.

By giving resting patients supplementary O_2 (1 L·min^{-1}) at 2,438 m, there was a statistically significant increase in P_{a,O_2} at rest and during exercise (fig. 3a). Further increases were observed at flow rates of 2 and 4 L·min^{-1}. Likewise, S_{a,O_2} increased with increasing rates of O_2 supply (fig. 3b). At rest and during exercise, S_{a,O_2} increased markedly when the O_2 supply increased from 0 to 1 L·min^{-1}, and increased further with 2 L·min^{-1}. At a flow rate of 4 L·min^{-1}, S_{a,O_2} increased relative to 2 L·min^{-1} during exercise, but not at rest. At rest, supplementary O_2 resulted in a small but significant increase in P_{a,CO_2} at flow rates of 1 and 2 L·min^{-1}, but no further increase at 4 L·min^{-1} (fig. 3c). During 20 W exercise, there was no increase in P_{a,CO_2} from 0 to 1 L·min^{-1}, but a minor increase with 4 L·min^{-1} (fig. 3c).

O_2 supply at 2,438 m caused a decrease of ~9% in systolic blood pressure during 20 W exercise, but did not cause significant changes in blood pressure at rest (fig. 3d). Diastolic blood pressure was not affected by O_2 supply. Resting cardiac frequency was reduced with an O_2 supply of 2 L·min^{-1}. During 20 W exercise the heart rate decreased ~8% with an O_2 supply of 4 L·min^{-1} (fig. 3e).

Discussion

Patients with various diseases leading to chronic restrictive ventilatory impairment developed pronounced

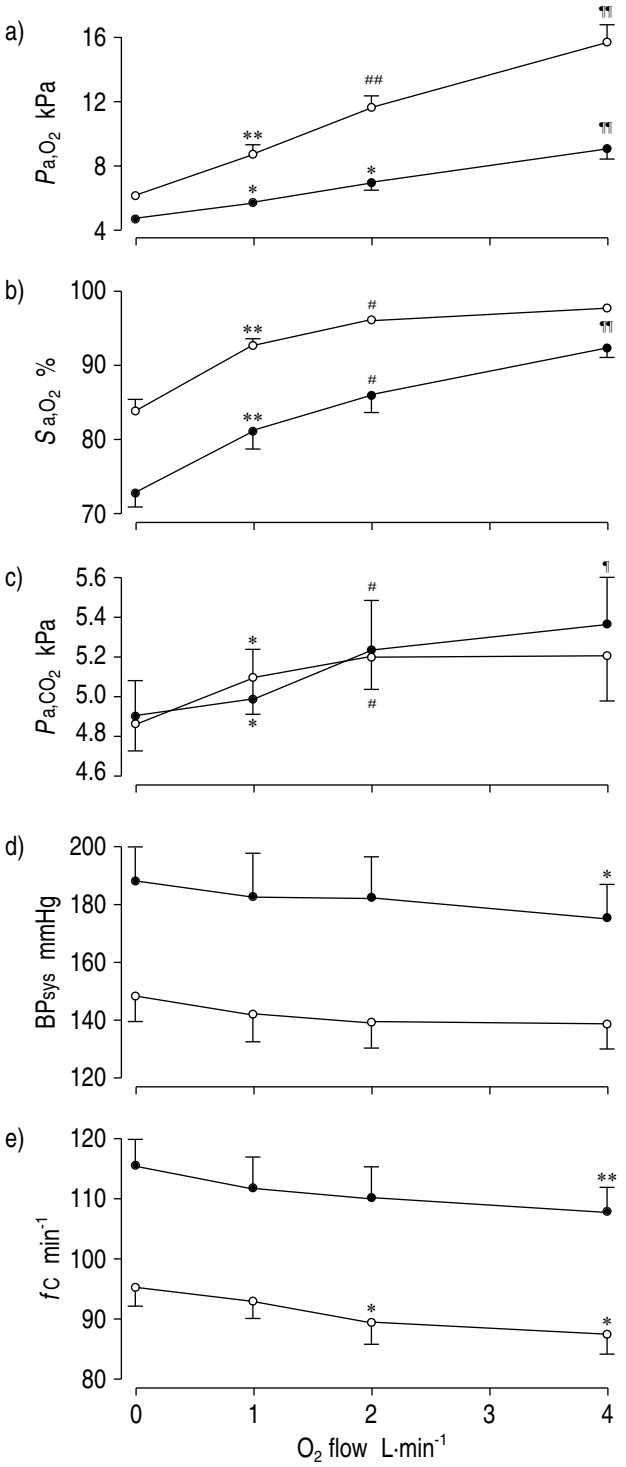

Fig. 3. – Effect of supplementary oxygen (O_2) (mean±SEM) in 15 patients with chronic restrictive impairment at 2,438 m (8,000 feet) simulated cabin altitude at rest (○) and during 20 W ergometer cycle exercise (●). a) Oxygen tension in arterial blood (P_{a,O_2}), b) arterial oxygen saturation (S_{a,O_2}), c) carbon dioxide tension in arterial blood (P_{a,CO_2}), d) systolic blood pressure (BP_{sys}) and e) cardiac frequency (f_C). *: $p<0.05$; **: $p<0.01$ compared to values without supplementary oxygen; #: $p<0.05$; ##: $p<0.01$ compared to values with supplementary oxygen at flow rate 1 L·min^{-1}; ¶: $p<0.05$; ¶¶: $p<0.01$ compared to values with supplementary oxygen at flow rate 2 L·min^{-1}.

hypoxaemia during simulated air travel at a cabin altitude of 2,438 m. The hypoxaemia was aggravated by light exercise, equivalent to slow walking along the aisle. The number of subjects was too small to evaluate each group of patients separately, but taken as a whole they seemed to respond to hypoxia in a similar manner. The spirometry and blood gas values showed an equal distribution among the different diagnoses, with a mean reduction in lung function parameters of ~50% pred. All patients included in the study were physically capable of travelling, and were thus potential aircraft passengers.

Guidelines for preflight medical evaluation are available for COPD patients [8–10], but not for other categories of lung patients. The intention of preflight medical evaluation is to avoid severe hypoxaemia provoked by the lowered cabin pressure in the aircraft. The lower limits for in-flight P_{a,O_2} (2,438 m), recommended in medical guidelines for COPD patients, are 7.3 kPa [10] and 6.7 kPa [8, 9], respectively, but it is not evident how these values have been established [11, 12]. To the present authors' knowledge, studies on patients with restrictive ventilatory impairment at high altitude have not been published. According to the results presented here, these patients run a high risk of developing in-flight hypoxaemia, below the recommended levels. It was found that 82% expressed in-flight P_{a,O_2} values <7.3 kPa and 53% <6.7 kPa at rest. Even patients with P_{a,O_2} values close to normal at sea level, experienced a pronounced drop in P_{a,O_2} in the altitude chamber.

Effects of exercise at altitude have received little attention in the medical guidelines. However, passengers are recommended to take light exercise during longer flights to avoid thromboembolic complications [19]. In this study, light exercise at sea level resulted in a reduced P_{a,O_2} compared to the resting situation, but none of the patients became severely hypoxaemic. However, the same level of exercise at 2,438 m resulted in a P_{a,O_2} level <6.7 kPa in all subjects, with a mean value of 5.1 kPa. In one patient with P_{a,O_2} 9.4 kPa (sea level) at rest, the exercise P_{a,O_2} (2,438 m) was as low as 3.7 kPa.

Medical guidelines for COPD patients [8–10] recommend sea-level P_{a,O_2} as a reliable predictor of P_{a,O_2} at 2,438 m. Based on a study performed by the current authors on COPD patients in an altitude chamber, this recommendation could not be supported [7]. In the present study, there was a significant correlation between P_{a,O_2} at sea level and P_{a,O_2} at 2,438 m, but only 53% of the variance of in-flight P_{a,O_2} could be accounted for by differences in sea-level P_{a,O_2}. The prediction of P_{a,O_2} at 2,438 m could be improved by including $T_{L,CO}$ (% pred) in the regression, but in this study, sea-level P_{a,O_2} and $T_{L,CO}$ accounted for only 77% of the variance in P_{a,O_2} at 2,438 m. Even though the patients in group 2 showed no significant difference between measured in-flight P_{a,O_2} and P_{a,O_2} predicted from this regression, there is still a possibility of overestimating the in-flight P_{a,O_2} by using pre-flight parameters for prediction. Therefore, patients who might be particularly vulnerable to hypoxaemia should have priority to the limited resources of pre-flight evaluation under hypoxic conditions, either in a hypobaric chamber or testing by breathing a hypoxic gas mixture, as in the hypoxic altitude simulation test (HAST) [6]. The current authors used a hypobaric chamber in the present investigation because it was easily accessibly. However, breathing a hypoxic gas at sea-level pressure gives similar results [20]. Preflight evaluation might be offered to patients with accompanying heart disease and probably patients with hypercapnia, considering the observed negative correlation between pre-flight P_{a,CO_2} and in-flight P_{a,O_2}. Hypercapnic patients might be less capable of increasing their ventilation in response to hypoxaemia. Conversely, preflight evaluation is controversial, and NAEIJE [21] recently pointed out that the benefit of such testing had never been documented.

At a cabin altitude of 2,438 m, an O_2 supply of 2 $L \cdot min^{-1}$ on a nasal cannula increased the P_{a,O_2} (>8 kPa) and S_{a,O_2} (>92%) to acceptable levels in all subjects at rest, without causing alarmingly high levels of P_{a,CO_2} (range 4.2–6.8 kPa). There was a minor decrease in resting cardiac frequency and systolic blood pressure. During 20 W exercise at 2,438 m, equivalent to slow walking along the aisle, an O_2 supply at 4 $L \cdot min^{-1}$ was sufficient to maintain P_{a,O_2} >7.3 kPa and S_{a,O_2} >88% in all but two patients. There was a significant decrease in both cardiac frequency and systolic blood pressure at 20 W exercise, reflecting the improved oxygenation. There was only a minor increase in P_{a,CO_2} with this O_2 flow (range 4.1–7.4 kPa).

The pronounced decrease in oxygen tension in arterial blood at altitude seems to contrast with the low level of medical emergencies among patients with pulmonary disease [21–23]. This low incidence cannot be explained by a liberal prescription of supplementary oxygen. In a study among consultant respiratory physicians in England [24], approximately half of those measuring blood gas levels did not recommend in-flight supplementary oxygen unless the preflight oxygen tension in arterial blood was <8.0 kPa, and an additional 25% recommended that it should not be used unless the oxygen tension in arterial blood was <7.3 kPa. According to the results presented in this study, both chronic obstructive pulmonary disease [7] and restrictive lung patients with such preflight oxygen tension in arterial blood values will experience a decrease in oxygen tension in arterial blood to levels far below what is recommended in present guidelines [8–10]. One reason could be that the cabin altitude during most flights is lower than at 2,438 m [25]. However, the low frequency of medical emergencies indicate that these levels of hypoxaemia are generally well tolerated, and raises the question of whether the limit of acceptable in-flight oxygen tension in arterial blood should be reconsidered in future guidelines.

Acknowledgements. The authors would like to the staff at the Institute of Aviation Medicine, Oslo, Norway, for helping with laboratory work and with controlling the hypobaric chamber during experiments.

References

1. US Government Printing Office. Code of Federal Regulations. Title 14, Vol. 1, Part 25. 1527. Washington, DC, US Government Printing Office, 1999.
2. Harding RM, Mills JF. Problems of altitude I: Hypoxia and hyperventilation. *BMJ* 1983; 286: 1408–1410.
3. Kelman GR, Crow TJ. Impairment of mental performance at a simulated altitude of 8,000 feet. *Aerospace Med* 1969; 40: 981–982.
4. McFarland RA. Human factors in relation to the development of pressurized cabins. *Aerospace Med* 1971; 42: 1303–1318.
5. DeHart RL. Fundamentals of aerospace medicine. 2nd Edn. Washington Square, Lea Fabinger 600, 1996; pp. 96–97.
6. Gong H Jr, Tashkin DP, Simmons MS. Hypoxia-altitude simulation test. *Am Rev Respir Dis* 1984; 135: 980–986.
7. Christensen CC, Ryg M, Refvem OK, Skjønsberg OH. Development of severe hypoxaemia in COPD patients at 2,438 m (8,000 ft) altitude. *Eur Respir J* 2000; 15: 635–639.
8. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995; 152: S112–S113.
9. Siafakas NM, Vermeire P, Pride NB, *et al.* Optimal assessment and management of chronic obstructive pulmonary disease (COPD): a consensus statement of the European Respiratory Society. *Eur Respir J* 1995; 8: 1398–1420.
10. Aerospace Medical Association, Air Transport Medicine Committee. Medical guidelines for air travel. *Aviat Space Environ Med* 1996; 67: B1–B16.
11. Mills JF, Harding RM. Fitness to travel by air. *BMJ* 1983; 286: 1269–1271.
12. AMA Commision on Emergency Medical Services. Medical aspects of transportation aboard commercial aircraft. *JAMA* 1982; 247: 1007–1011.
13. Gong H Jr. Advising pulmonary patients about commercial air travel. *J Resp Dis* 1990; 11: 484–499.
14. Gong H, Lee Mark JA, Cowan MN. Pre-flight medical screenings of patients. Analysis of health and flight characteristics. *Chest* 1993; 104: 788–794.
15. Schwartz JS, Bencowitz HZ, Moser KM. Air travel hypoxaemia with chronic obstructive pulmonary disease. *Ann Intern Med* 1984; 100: 473–477.
16. Vohra KP, Klocke RA. Detection and correction of hypoxaemia associated with air travel. *Am Rev Respir Dis* 1993; 148: 1215–1219.
17. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis* 1991; 144: 1202–1218.
18. Quanjer PH. Standardized lung function testing. *Bull Eur Physiopathol Respir* 1983; 19: 39–44.
19. Mercer A, Brown JD. Venous thromboembolism associated with air travel: a report of 33 patients. *Aviat Space Environ Med* 1998; 69: 154–157.
20. Dillard TA, Moores LK, Bilello KL, Phillips YY. The preflight evaluation. A comparison of the hypoxia inhalation test with hypobaric exposure. *Chest* 1995; 107: 352–357.
21. Naeije R. Preflight medical screening of patients. *Eur Respir J* 2000; 16: 197–199.
22. Rayman RB. Passenger safety, health and comfort: a review. *Aviat Space Environ Med* 1997; 68: 432–440.
23. Speizer C, Rennie C, Breton H. Prevalence of in-flight medical emergencies on commercial airlines. *Ann Emerg Med* 1989; 18: 26–29.
24. Coker RK, Patridge MR. Assessing the risk of hypoxia in flight: the need for more rational guidelines. *Eur Respir J* 2000; 15: 128–130.
25. Cottrell JJ. Altitude exposures during aircraft flight. Flying higher. *Chest* 1988; 93: 81–84.