

## Development of severe hypoxaemia in chronic obstructive pulmonary disease patients at 2,438 m (8,000 ft) altitude

C.C. Christensen<sup>\*\*\*+</sup>, M. Ryg<sup>\*\*\*+</sup>, O.K. Refvem<sup>+</sup>, O.H. Skjønsberg<sup>\*</sup>

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**ABSTRACT:** The arterial oxygen tensions ( $P_{a,O_2}$ ) in chronic obstructive pulmonary disease (COPD) patients travelling by air, should, according to two different guidelines, not be lower than 7.3 kPa (55 mmHg) and 6.7 kPa (50 mmHg), respectively, at a cabin pressure altitude of 2,438 m (8,000 ft). These minimum in-flight  $P_{a,O_2}$  values are claimed to correspond to a minimum  $P_{a,O_2}$  of 9.3 kPa (70 mmHg) at sea-level. The authors have tested whether this limit is a safe criterion for predicting severe in-flight hypoxaemia.

The authors measured arterial blood gases at sea-level, at 2,438 m and at 3,048 m (10,000 ft) in an altitude chamber at rest and during light exercise in 15 COPD patients with forced expiratory volume in one second (FEV<sub>1</sub>) <50% of predicted, and with sea-level  $P_{a,O_2}$  >9.3 kPa.

Resting  $P_{a,O_2}$  decreased below 7.3 kPa and 6.7 kPa in 53% and 33% of the patients, respectively, at 2,438 m, and in 86% and 66% of the patients at 3,048 m. During light exercise,  $P_{a,O_2}$  dropped below 6.7 kPa in 86% of the patients at 2,438 m, and in 100% of the patients at 3,048 m. There was no correlation between  $P_{a,O_2}$  at 2,438 m and pre-flight values of  $P_{a,O_2}$ , FEV<sub>1</sub> or transfer factor of the lung for carbon monoxide.

In contrast to current medical guidelines, it has been found that resting arterial oxygen tension >9.3 kPa at sea-level does not exclude development of severe hypoxaemia in chronic obstructive pulmonary disease patients travelling by air. Light exercise, equivalent to slow walking along the aisle, may provoke a pronounced aggravation of the hypoxaemia.

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At high altitudes, the partial pressure of oxygen decreases as a function of decreasing total barometric pressure. Reduced supply of oxygen results in both mental and physical changes, which is well-known from mountaineering, air travel, and, during the last few decades, experimental simulated hypoxia [1]. With this background, the maximal cabin pressure altitude in passenger aircraft is designed to be lower than the barometric pressure corresponding to 2,438 m (8,000 ft) [2], which is sufficient to keep a normal, healthy person physically and mentally fit without the aid of special protective equipment [3]. Regulations for actual flight operations allow for temporarily higher cabin altitudes [4, 5]. Cabin altitudes above 3,048 m (10,000 ft) are regulated by international rules of flight crew and passengers' use of supplemental oxygen [4–6]. In aircraft without pressurized cabins, the flying altitude is not supposed to exceed 3,048 m [2, 4]. Supplemental oxygen is required above this altitude.

Patients with lung disease are more vulnerable to low atmospheric pressure than healthy individuals. Therefore, the Aerospace Medical Association [7] and the American Thoracic Society [8] have presented guidelines for air transport of patients with chronic obstructive pulmonary disease (COPD). It is recommended that pre-flight evaluation of patients should be carried out at a simulated alt-

itude of 2,438 m [7, 8]. According to the two guidelines, the arterial oxygen tension ( $P_{a,O_2}$ ) during flight should be maintained above 7.3 kPa (55 mmHg) [7] or 6.7 kPa (50 mmHg) [8] to prevent negative effects of hypoxaemia. It is recommended that an extra supply of oxygen should be prescribed for patients in whom one can anticipate a drop in  $P_{a,O_2}$  below these levels [7–9].

Moreover, in patients with severely reduced lung function (vital capacity (VC), forced expiratory volume in one second (FEV<sub>1</sub>) or transfer factor of the lung for carbon monoxide ( $T_{L,CO}$ ) of <50% of predicted, hypercapnic patients or patients suffering from severe dyspnoea when walking 50 yards or climbing 10–12 stairs), it is recommended that  $P_{a,O_2}$  is measured in order to better evaluate their risk of becoming severely hypoxaemic during air travel [8, 9, 10–12]. A pre-flight  $P_{a,O_2}$  level exceeding 9.3 kPa (70 mmHg) is considered sufficient to fly without supplemental oxygen [7, 13].

The authors wanted to study whether a  $P_{a,O_2}$  >9.3 kPa at sea-level is in fact adequate to avoid severe hypoxaemia at altitude [7]. Therefore, the authors have examined COPD patients with FEV<sub>1</sub> <50% pred and a  $P_{a,O_2}$  exceeding 9.3 kPa at sea-level [7], and evaluated their response to low atmospheric pressure with regard to development of severe hypoxaemia. In addition, the authors have examined the influence of light exercise under these conditions, since

<sup>\*</sup>Dept of Pulmonary Medicine, Ullevål Hospital, 0407 Oslo, Norway. <sup>\*\*</sup>Institute of Aviation Medicine, Blindern, 0313 Oslo, Norway, <sup>+</sup>Glittrelinikken AS, 1488 Hakadal, Norway.

Correspondence: C.C. Christensen, Glittrelinikken, 1488 Hakadal, Norway, Fax: 47 67075344

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passengers are recommended to walk along the aisle during long distance air travel to avoid thromboembolic complications [14]. All subjects were tested at three different atmospheric pressures in an altitude chamber, at sea-level, at 2,438 m and at 3,048 m simulated altitude.

### Material and methods

#### Study subjects

Fifteen male patients suffering from COPD, according to the criteria of the American Thoracic Society [15], who were in a stable phase, with an FEV1 of <50 % pred and a resting  $P_{a,O_2}$  exceeding 9.3 kPa, were recruited for the study. None had clinical signs of left ventricular dysfunction. Their mean age was 62.2 yrs (range 48–73 yrs). At the time of the examination all but one of the subjects used daily bronchodilating medication, and 12 of the patients were also taking low doses of prednisolone.

The Regional Ethical Committee approved the study, and written informed consent was obtained from all participants.

#### Lung function tests

Measurements of VC and FEV1 were repeated on the day of the altitude experiment with a portable Vitalograph (Vitalograph, UK), and together with the bellow function, the single-breath  $T_{L,CO}$  was measured using Jaeger MasterLab equipment (Erich Jaeger, Würzburg, Germany).

#### Experimental procedure

The experiments were performed in an air-conditioned altitude chamber at the Royal Institute of Aviation Medicine in Oslo, Norway. The subjects were sitting in a chair to use a cycle ergometer (Ergoline 800; Erich Jaeger GmbH, Würzburg, Germany). After at least 10 min rest, they started cycling at 20 W, increasing 5 W·min<sup>-1</sup> until exhaustion, in order to determine the aerobic capacity. Arterial blood samples were drawn from a catheter in the radial artery at rest and every 3 min during exercise, and after completing the exercise test. The samples were placed on melting ice before being analysed for arterial blood gases outside the chamber using an ABL300 or ABL500 and an OSM3 co-oxymeter (Radiometer, Copenhagen, Denmark). A 12 channel electrocardiogram (ECG) was taken prior to the experiment, and thereafter the heart rhythm was continuously monitored. Ventilation, oxygen consumption ( $\dot{V}O_2$ ) and expired carbon dioxide ( $\dot{V}CO_2$ ) were continuously measured with an Oxycon Champion (Mijnhardt, Bunnich, the Netherlands). The Oxycon Champion was calibrated at each altitude. The maximal  $\dot{V}O_2$  (mL·min<sup>-1</sup>) was defined as the highest  $\dot{V}O_2$  measured during 30 s. At sea-level, the exercise time was shorter than 3 min in four of the subjects, with maximal work loads of 20–30 W, while at 2,438 m and 3,048 m, six subjects had maximal work load of 20–30 W. In the figure of 30 W exercise (fig. 1), the end-exercise blood gas values from these patients are also included. The procedure was performed in a random order at sea-level, and at simulated altitudes of 2,438 m and 3,048 m. A 60 min rest was allowed between exercise tests.

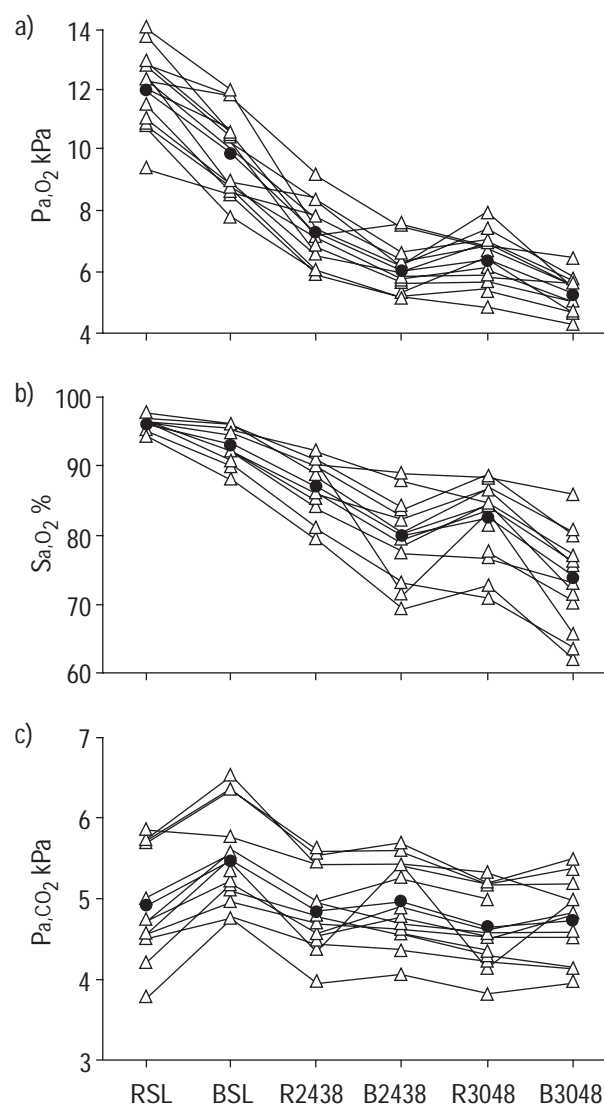


Fig. 1. – Arterial blood gas values from 15 chronic obstructive pulmonary disease patients during rest and light bicycle exercise (20–30 W) at sea level and 2,438 m and 3,048 m simulated altitude. Individual ( $\Delta$ ) and mean ( $\bullet$ ) values on the ordinate; various parameters on the abscissa. RSL: rest at sea level; BSL: exercise at sea level; R2438: rest at 2,438 m; B2438: exercise at 2,438 m; R3048: rest at 3,048 m; B3048: exercise at 3,048 m;  $P_{a,O_2}$ : arterial oxygen tension;  $S_{a,O_2}$ : arterial oxygen saturation;  $P_{a,CO_2}$ : arterial carbon dioxide tension.

#### Statistical analysis

Results are expressed as the mean $\pm$ 1SD. Paired t-tests were used to evaluate differences in variables between sea-level and 2,438 m and 3,048 m. Relationships between  $P_{a,O_2}$  at altitude and lung function tests were assessed from Pearson correlation coefficients. Two-tailed p-values of <0.05 were considered to have statistical significance.

### Results

The results of the lung function tests are presented in table 1. In accordance with the inclusion criteria, the FEV1 was <50 % of predicted and the resting  $P_{a,O_2}$  at sea-level >9.3 kPa in all participants. The mean VC and  $T_{L,CO}$  values were 80% and 55 % pred, respectively.

Table 1. – Lung function and arterial blood gases in 15 chronic obstructive pulmonary disease

	Mean±1SD	Range	% of predicted
Age yrs	62.2±7.5	48–73	
Height cm	174.5±4.7	168–183	
Weight kg	75.4±19.0	59–134	
VC L	3.30±0.59	2.55–4.15	80.2±14.7
FEV <sub>1</sub> L	0.98±0.38	0.50–1.55	30.3±11.6
<i>T<sub>L,CO</sub></i>			
mmol·min <sup>-1</sup> ·kPa <sup>-1</sup>	5.2±2.0	1.49–8.39	55.1±20.0
<i>S<sub>a,O<sub>2</sub></sub></i>	96.0±1.1	94.2–97.8	
<i>P<sub>a,O<sub>2</sub></sub></i>	11.97±1.25	9.39–14.06	
<i>P<sub>a,CO<sub>2</sub></sub></i>	4.93±0.60	3.78–5.86	
<i>V</i> O <sub>2max</sub> L·min <sup>-1</sup>	0.95±0.23	0.55–1.21	
Aerobic capacity mL·min <sup>-1</sup> ·kg <sup>-1</sup>	13.4±2.8	9.1–18.2	37.5±13.8

Values are presented as mean±sd. VC: vital capacity; FEV<sub>1</sub>: forced expiratory volume in one second; *T<sub>L,CO</sub>*: single-breath transfer factor of the lung for carbon monoxide; *S<sub>a,O<sub>2</sub></sub>*: arterial oxygen saturation; *P<sub>a,O<sub>2</sub></sub>*

Figure 1a shows the *P<sub>a,O<sub>2</sub></sub>*

The mean pre-flight aerobic capacity was 13.4±2.8 mL·min<sup>-1</sup>·kg<sup>-1</sup>, which is 37.5 % pred (table 1). All subjects with aerobic capacity exceeding 12.1 mL·min<sup>-1</sup>·kg<sup>-1</sup> expressed *P<sub>a,O<sub>2</sub></sub>*

During exercise (20–30W) at sea-level, *P<sub>a,O<sub>2</sub></sub>*

At sea-level, arterial oxygen saturation (*S<sub>a,O<sub>2</sub></sub>*) exceeded 94% in all subjects (96±1%) (fig. 1b), and was reduced to 87±4% at 2,438 m (p<0.001), and 82±6% at 3,048 m (p<0.001). During exercise, the *S<sub>a,O<sub>2</sub></sub>*

The resting carbon dioxide tension in arterial blood (*P<sub>a,CO<sub>2</sub></sub>*) at sea-level was <6.0 kPa in all subjects (table 1). At rest, the *P<sub>a,CO<sub>2</sub></sub>*

20–30 W exercise at the different altitudes, a significant reduction in the *P<sub>a,CO<sub>2</sub></sub>*

The *P<sub>a,O<sub>2</sub></sub>*

## Discussion

The medical guidelines for air travel recommend further assessment of patients with pulmonary disease if spirometry reveals a lung function of <50 % pred [7, 9]. It is pointed out that pre-flight measurement of arterial blood gases is the single most helpful test because the *P<sub>a,O<sub>2</sub></sub>*

The present study shows that a considerable number of patients with moderate to severe COPD, but with no or mild pre-flight hypoxaemia (9.4–11.0 kPa) and normal *P<sub>a,CO<sub>2</sub></sub>*

proposed a regression equation for estimating the  $P_{a,O_2}$  between 1,524 m (5,000 ft) and 2,438 m, based on the pre-flight  $P_{a,O_2}$ . By using this equation, the current authors found a higher calculated than measured value of  $P_{a,O_2}$  (2,438 m) in all but one patient, the mean difference being  $1.01 \pm 0.87$  kPa. The discrepancy between the calculated and measured values were most pronounced in the patients with the lowest pre-flight  $P_{a,O_2}$ . Consequently, the authors cannot support the use of this equation for calculating the in-flight  $P_{a,O_2}$  at 2,438 m.

Because of the increased risk of thromboembolism during flight, passengers are advised to take a short walk inside the aircraft when the duration of the flight exceeds 1 h [14]. Also, most passengers need to visit the lavatory during a long flight. The bicycle exercise employed in the present study (20–30W) is equivalent to slow walking ( $2.4$ – $3.0$  km·h<sup>-1</sup>) with an oxygen consumption of  $0.75$  L·min<sup>-1</sup> [17], an effort which may simulate the physical challenge of walking down the aisle of an aeroplane. This light exercise provoked a pronounced reduction in  $P_{a,O_2}$  and  $S_{a,O_2}$  from the resting situation, and may thus promote serious hypoxaemia during air travel, even in patients with  $P_{a,O_2} > 9.3$  kPa at sea-level [18]. Neither resting nor exercise  $P_{a,O_2}$  at sea-level or resting  $P_{a,O_2}$  values at 2,438 m and 3,048 m could predict which patients would experience in-flight hypoxaemia during light exercise. Therefore, pre-flight hypobaric exercise tests in patients who would be especially vulnerable to hypoxaemia, e.g. COPD patients with co-existing heart disease should probably be considered. This influence of physical effort has not been an explicit issue in the published guidelines [7–10, 13].

Although the sea-level  $P_{a,CO_2}$  values in the patients were within the normal range, the authors found a weak, but significant, negative relationship between sea-level  $P_{a,CO_2}$  and  $P_{a,O_2}$  at 2,438 m. It is likely, therefore, that COPD patients with elevated  $P_{a,CO_2}$  levels may experience severe hypoxaemia during air travel, as suggested in the medical guidelines [7]. However, this assumption seems to be poorly documented. The lack of an increase in  $P_{a,CO_2}$  during exercise at high altitude, compared to the increase in  $P_{a,CO_2}$  at sea-level, may be explained by increased ventilation due to severe hypoxaemia.

The pre-flight aerobic capacity of the COPD patients was positively correlated with the  $P_{a,O_2}$  at 2,438 m. This finding is in line with the statement of the medical guidelines recommending 50 yards of walking as a simple clinical test of the fitness to fly [3, 7]. The authors tested the work capacity on an ergometer cycle, and, according to the results, all the subject with a pre-flight aerobic capacity above  $12.1$  mL·min<sup>-1</sup>·kg<sup>-1</sup> maintained an in-flight  $P_{a,O_2}$  of  $>6.7$  kPa at 2,438 m. The number of patients in the present study is too small to state a definite limit of aerobic capacity in order to secure an acceptable in-flight  $P_{a,O_2}$ . However, determination of aerobic capacity might give valuable information about which COPD patients should be evaluated further under hypoxic conditions.

According to the results of the present study, it could be anticipated that a frequent occurrence of symptoms related to reduced blood oxygen content in chronic obstructive pulmonary disease patients travelling by air. However, medical emergencies among passengers during flight seem to be rare [19–21]. This disparity may depend on several factors [22]. Hypoxaemia-related symptoms may be rare because the cabin pressure during most flights corres-

ponds to an altitude lower than 2,438 m, as described by COTTRELL *et al.* [5]. They found a mean cabin altitude in commercial aircraft of 1,894 m, with 2,717 m as the highest recorded value. In addition, there may be under-reporting of symptoms caused by hypoxaemia. Giving a patient supplemental oxygen during a flight may not be reported by the staff as a medical emergency, if only vague symptoms of hypoxaemia are present. Also, reduced mental performance as a consequence of hypoxaemia may be difficult to observe during a regular flight. In spite of a possible underreporting of events caused by hypoxaemia, most chronic obstructive pulmonary disease patients do not seem to experience major problems during air travel [18]. This is in accordance with the lack of symptoms reported by the patients during the performance of the present study, even though many of them became severely hypoxaemic. This may imply that chronic obstructive pulmonary disease patients in fact tolerate short time hypoxaemia well, without developing serious complications, and that one ought to reconsider the limit of the lowest acceptable in-flight oxygen tension in arterial blood stated in the medical guidelines for air travel, at least for chronic obstructive pulmonary disease patients without accompanying heart disease.

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