



# Impact of hypobaric flight simulation on walking distance and oxygenation in COPD patients



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## ABSTRACT

**Background:** Chronic obstructive pulmonary disease (COPD) is a disease that compromises fitness to fly.

**Objective:** To investigate, whether hypobaric mid-distance flight simulation limits exercise endurance in COPD patients.

**Methods:** Patients with COPD GOLD stages 2–4 were challenged by hypobaric flight simulation. Patients completed 6-minute walking distances before and after the simulation test. Pulse oximetry and Borg dyspnea scale were measured every 30 min during the test.

**Results:** Thirty-five patients were included in the study. The distance of the 6-min walking exercise decreased from  $343 \pm 93$  m to  $308 \pm 101$  m ( $p < 0.0001$ ). The oxygen saturation nadir for the whole group was  $72.2\% \pm 9.1\%$ . The Borg-dypnea-score did not correlate with oxygen desaturation (R-square 0.009,  $p > 0.05$ ).

**Conclusions:** A 3-h hypobaric flight simulation compromises exercise endurance by 35 m or 10%. Hypoxia was well tolerated and more liberal recommendations might be justifiable since hypoxemia appears to be unrelated to dyspnea perception.

## 1. Background

The passenger volume of worldwide yearly air travel in 2016 was estimated to be 3.81 billion. Chronic obstructive pulmonary disease (COPD), a disease of high prevalence, is known to affect the capability for air travel (Edvardson et al., 2012; Schwartz et al., 1984) and respiratory symptoms are among the top three findings in medical emergencies on commercial airline flights (Chandra and Conry, 2013; Peterson et al., 2013). The pathophysiology of COPD is characterized by airflow obstruction and diffusion impairment. The cabin pressure of commercial aircrafts is usually set to 2438 m above sea level (NN), and some newer planes (Boing B787 and Airbus A350) are calibrated to 1828 m above NN (Wikipedia, 2018). The cabin pressure reduces the amount of oxygen within the cabin, resulting in decreased blood oxygenation and increased work of breathing due to an increase in minute ventilation (Furian et al., 2018; Grazzini et al., 2005). In general, there is great uncertainty among physicians regarding preflight evaluations (Coker and Partridge, 2000). The hypoxia altitude simulation test (HAST) which was first described in 1984 (Gong et al., 1984) is recommended to evaluate the fitness to fly (Edvardson et al., 2012). The test consists of a 20-min challenge to 15.1% of inspired oxygen, which

is equivalent to the amount of oxygen of usual air oxygen at 2438 m above NN (Kelly et al., 2008). If oxygen saturation decreases to less than 85%, patients are advised to use in-flight (Dillard et al., 1998) oxygen delivery systems (Johnson, 2003). The HAST does not evaluate the subjective tolerance of the patient, nor does it cover longer observation periods, which is a clear limitation, since the majority of flights will exceed a duration of 20 min.

Airports are spacious buildings and passengers have to cover large distances before and after air travel. Exercise endurance is frequently limited in COPD patients and undergoes further reduction if respiration is challenged (O'Donnell and Laveneziana, 2007).

The primary objective of this study is to measure the impact of a mid-distance flight simulation on exercise endurance in COPD patients. Secondly, we wanted to evaluate the degree and tolerability of hypoxia during mid-distance flight simulation in light of the current recommendations for the use of in-flight oxygen.

## 2. Method

Thirty-five patients with COPD of different severity were challenged to hypoxia by means of a hypobaric pressure chamber (Fig. 1) adjusted

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Fig. 1. Hypobaric chamber.

to 2440 m above sea level for a duration of 3 h including decompression and recompression times.

Exercise endurance was measured 1 h before and immediately after flight simulation. The study was approved by the medical association Westfalen-Lippe (2011-320-f-S), and the trial was registered at ClinicalTrials.gov (NCT02848391).

Patients had to be 18 years or older with a spirometric-confirmed diagnosis of COPD GOLD stage 2 or higher. They had to be ambulatory. Patients with a history of heart failure, coronary artery disease peripheral artery disease, and renal failure were excluded. All patients had to have used civil aviation within the past year or intended to do so in the near future.

### 2.1. Lung function test

Spirometry, body plethysmography, and measurement of the diffusion capacity were performed using a Jaeger Masterscreen (Jaeger/CareFusion, Hoechberg, Germany). Predicted values for static and dynamic lung function parameters were calculated according to the European Community for Coal and Steel (ECCS) (Quanjer et al., 1993). The diffusing capacity of the lung for carbon monoxide (DLCO) was measured according to the American Thoracic Society (ATS) recommendations (American Thoracic Society, 1995a). Measurements were corrected for alveolar ventilation (DLCO/VA [KCO]). Arterial blood gas samples were taken from the arterialized earlobe (Finalgon Extra Strong®; Boehringer Ingelheim Austria GmbH, Vienna, Austria) for immediate analysis (MD 300D; Oxigeno Healthcare, D-85098 Grossmehring, Germany). Lung function tests were performed at least 1 day prior to hypobaric simulation.

### 2.2. The 6-min walking test

We decided to use the 6-min walking test because it is easy to administer, better tolerated, and more reflective of activities of daily living than other walking tests (Solway et al., 2001). All of the patients performed two practice tests on the day before study measurements were taken (Butland et al., 1982). The tests were conducted according to current guidelines (Laboratories ATSCoPSfCPF, 2002; Holland et al., 2014) under supervision of a respiratory therapist. Pre-flight walking distance was performed 1 h prior to hypobaric simulation, and post-flight measurements were performed immediately after flight simulation. We thought that this design is most suitable to simulate exercise challenges within an airport. Despite the history of previous oxygen use of the patients, the 6-min walking test was conducted without supplementary oxygen in every patient.

### 2.3. Hypobaric flight simulation

The hypobaric chamber has an internal volume of 10.4 m<sup>3</sup> (Fig. 1). Negative pressure was generated by means of a vacuum pump (SV 1040 B, Busch, Chevèze, Switzerland). Cabin pressure was measured with a barometer with a built-in altimeter function (Casio PG 240 –ER, Tokio, Japan), which was calibrated before every flight simulation.

The chamber has four seating accommodations. The study subjects were accompanied by a ACLS trained nurse who monitored symptoms and pulse oximetry and was able to provide oxygen from a compressed 2-L cylinder if medically indicated or requested by a patient. A phone inside the chamber enabled communication at any time with a technician and physician outside the chamber. Decompression was initiated after sealing the chamber and was targeted to reach 2440 m after 10 min. Compression at the end of the study was also accomplished over a 10-min period. Oxygen saturation, heart rate, and Borg dyspnea score were measured before decompression, every 30 min during the flight, and after compression was completed. Since the decompression target of 2440 m was achieved after 10 min, a 20-min exposure to in-flight conditions was achieved at 30 min into the experiment. Measurements taken at 30 min therefore appear comparable to the results that would have been achieved by a regular hypoxia-altitude simulation test (Dillard et al., 1995). The hypobaric challenge was conducted without supplementary oxygen in all patients.

### 2.4. Statistics

The minimal clinically important difference for the 6-min walking distance in terms of prognosis was determined to be 30 m (Polkey et al., 2013). A change that appears to be meaningful for the patient's activities of daily living was determined to be 54–80 m (Wise and Brown, 2005). For our research question, we thought that a 20% reduction in walking distance after a mid-distance flight would represent a meaningful limitation for COPD patients in terms of mobility requirements after leaving a plane. With an estimated average 6-min walking distance of 300 ± 90 m, a meaningful reduction of 20%, an alpha error of 0.5 and a power of 0.95, the effect size was calculated to be 0.67. This translates into a required sample size of N = 31. The comparison of two groups was performed using a two-sided t test; analysis of variance (ANOVA) was used for multiple comparisons; and post-hoc analysis was performed with the Scheffé procedure and the Games-Howell test in cases of equal and unequal variance, respectively. Repeated measurements during the simulation test were evaluated by ANOVA with repeated measures. Regression analysis was done by means of a linear model. We used the Pearson correlation to test for linear relationships of normally distributed data. A p value ≤ 0.05 was considered significant. All calculations were done with the SPSS software version 22.

## 3. Results

Basic demographic and lung function data are shown in Table 1.

Eighteen patients with chronic hypercapnea were treated with home mechanical ventilation according to national guidelines (pCO<sub>2</sub> > 55 mm Hg or an increase in nighttime pCO<sub>2</sub> of ≥ 10 mm Hg) (Windisch et al., 2017). Their noninvasive ventilators were set to a spontaneous timed (ST) mode with an inspiratory pressure of 23 ± 4 cm H<sub>2</sub>O, an expiratory pressure of 6 ± 2 H<sub>2</sub>O, and a backup rate of 17 ± 3 breaths per minute. Patients were on noninvasive ventilation (NIV) for the last 18 ± 8 months with a mean nighttime use of 7 ± 1 h. Among the 18 patients treated with NIV, 12 patients were additionally treated with long-term oxygen therapy (LTOT) according to current guidelines (Qaseem et al., 2011); their baseline PO<sub>2</sub> pre-flight was 48.6 ± 5 mm Hg, whereas the six patients in this group without LTOT had a baseline PO<sub>2</sub> of 60.6 ± 2.3 mm Hg. Among the 17 patients without NIV, nine patients were treated with LTOT; their baseline PO<sub>2</sub> was 50.1 ± 3.4 mm Hg, whereas the eight patients in this group

**Table 1**

Basic demographic, laboratory, lung function, and arterial blood gas data of the participants (FeV1 = forced expiratory volume in one second, SaO<sub>2</sub> = oxygen saturation, PO<sub>2</sub> = partial pressure of oxygen, PCO<sub>2</sub> = partial pressure of carbon dioxide).

Number of participants	35
Male (N)	19 (56%)
Height (cm)	169 ± 8
Weight (kg)	80 ± 21
Age (years)	61 ± 8
Hemoglobin (mg/dL)	14 ± 1.5
Vital capacity (L)	2.3 ± 0.8
Vital capacity (% predicted)	64 ± 16
FeV1 (L)	1.1 ± 0.5
FeV1 (% predicted)	41 ± 17
Residual volume (L)	4.5 ± 1.8
Residual volume (% predicted)	216 ± 94
FeV1 / vital capacity	51 ± 14
FeV1 / vital capacity (% predicted)	66.5 ± 18.4
Diffusion capacity (% predicted)	56 ± 19
SaO <sub>2</sub> (%) baseline	90 ± 6
pO <sub>2</sub> (mm Hg)	54 ± 8
pCO <sub>2</sub> (mm Hg)	40 ± 6
pH	7.42 ± 0.02
Bicarbonate (mmol/L)	25 ± 2.7

without LTOT had a baseline PO<sub>2</sub> of 62.9 ± 5.8 mm Hg.

Pre-flight patients were able to walk 343 ± 93 m within 6 min. The post-flight walking distance decreased to 308 ± 101 m (Fig. 2).

The preflight walking distance of non-NIV patients was 356 ± 89 m, whereas patients using NIV walked 331 ± 97 m pre-flight. The post-flight distances were 324 ± 95 m for non-NIV patients and 292 ± 108 m for patients using NIV. The differences between the four groups, however, failed to reach statistical significance (Fig. 3).

The measured oxygen saturations during hypobaric simulation differ significantly from pre- and post-flight saturations (Fig. 4).

Thirty of the 35 patients (86%) had decreased oxygen saturation to less than 85% after 20 min of exposure to the hypobaric environment corresponding to an altitude of 2440 m above NN. According to current recommendations, these patients would have been advised to use in-flight oxygen. Two patients requested to terminate the experiment due to the sensation of dyspnea after 60 and 90 min, respectively. The first patient was using NIV and LTOT, and had a pre-flight oxygenation of 88% and a saturation of 70% after 20 min of hypobaric exposure

(corresponding to a positive HAST test). The second patient was not using NIV or LTOT, and had a pre-flight oxygen saturation of 97% and a saturation of 85% after 20 min of hypobaric exposure (corresponding to a negative HAST test). Both patients were given oxygen by nasal cannula, and altitude simulation was aborted. These two patients were excluded from analysis of pre- and post-flight waking distance.

The participants' heart rates and Borg dyspnea scores are shown in Figs. 5 and 6. Neither parameter showed a significant change at any time during the simulation test. The lowest measured oxygen saturation during simulation was determined for every patient (oxygen saturation nadir). For the whole group, the measured nadir was 72.2% ± 9.1%.

We performed a linear stepwise regression analysis to predict this value including the following pre-flight variables: baseline oxygen saturation, heart rate, hemoglobin level, FeV1 in % predicted, residual volume in % predicted, vital capacity in % predicted, diffusion capacity in % predicted, and 6-minute walking distance. The diffusion capacity was the only predictive parameter (R-square 0.759, p < 0.0001).

The correlation of the oxygen saturation nadir and the diffusion capacity is shown in Fig. 7.

The correlation of dyspnea perception as measured by the Borg score to in-flight oxygen saturation is shown in Fig. 8.

#### 4. Discussion

We found a significant reduction in the 6-min walking distance after a 3-hour hypobaric flight simulation in patients with COPD GOLD stages 2–4. The absolute reduction of the walking distance was determined to be 35 m, which equals approximately 10% of the preflight walking distance. The reduction in walking distance, however, failed to reach the predefined minimal clinical significance, and we doubt that the measured reduction represents a meaningful compromise to our patients. To our knowledge, there are no systematical data about average pre-flight and post-flight walking distances that have to be covered by passengers who enter and leave the airport during their travel. Assuming equal pre- and post-flight walking requirements, it is unlikely that disembarking becomes a problem if entering the plane was hassle-free. Although there are missing data, that NIV increases walking endurance in hypercapnic COPD patients (Struik et al., 2013), it is notable that patients treated with NIV experienced a similar effect of the hypobaric challenge on their walking endurance when compared with patients without NIV. The differences in walking distances between NIV and non-NIV patients were not significant (ANOVA); the

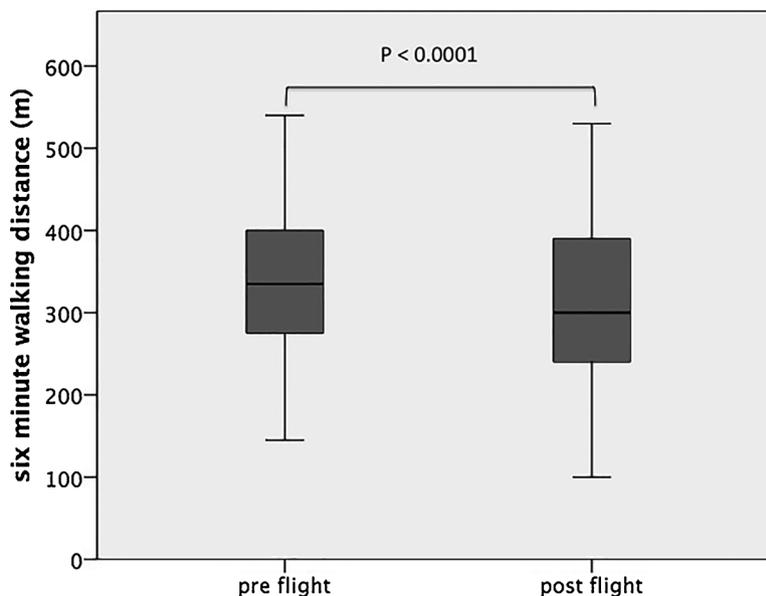


Fig. 2. The 6-min walking distance before and after flight simulation.

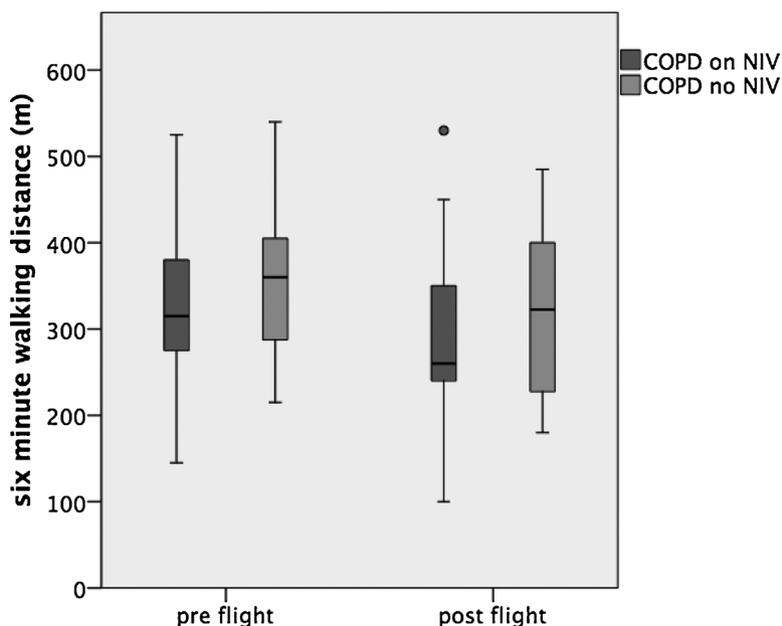


Fig. 3. The 6-min walking distance before and after flight simulation for patients with and without NIV treatment. By analysis of variance, there were no significant differences between groups ( $p > 0.05$ ).

study, however, was not powered to analyze differences between these subgroups.

Preflight evaluations are aimed to avoid in-flight medical problems. Twelve percent of in-flight emergencies are of a respiratory nature (Peterson et al., 2013; Nicholson and Sznajder, 2014). The HAST is the usually recommended gold standard in patients with respiratory disease (Edvardsen et al., 2012; Johnson, 2003; Nicholson and Sznajder, 2014; Ahmedzai et al., 2011; Siafakas et al., 1995; Wedzicha, 1999; American Thoracic Society, 1995b; Lien and Turner, 1998; Foundation, 2017), HAST testing, however, does not consider the impact of the hypobaric environment on lung mechanics. Experimental data suggest that hypobaric conditions are associated with a decreased forced expiratory volume (FEV1), a decreased forced vital capacity (FVC), and increased residual volume (RV), functional residual capacity (FRC), and total lung capacity (TLC) (Dillard et al., 1998; Coates et al., 1979). The inspired

oxygen fraction (15.1%) of the HAST was selected to predict in-flight oxygen desaturation, and comparative studies contain comparable results (Kelly et al., 2008). HAST, however, does not detect symptoms that derive from lung function parameter changes due to the hypobaric environment. In our cohort, 30 of 35 patients had decreased SaO2 level less than 85% and, according to guidelines, should have used in-flight oxygen. Twenty-nine of these patients, however, tolerated the 3-hour hypobaric challenge without symptoms, whereas one of the five patients who would not have required oxygen developed dyspnea and requested stopping the experiment. From a medical perspective, pre-flight evaluation aims to prevent medical emergencies; from an economic perspective, it should avoid flight deviations. In light of our results, one has to notice that hypoxemia at 20 min of hypobaric flight simulation does not adequately predict critical in-flight situations. Edvardsen et al. evaluated the relation of HAST results to respiratory

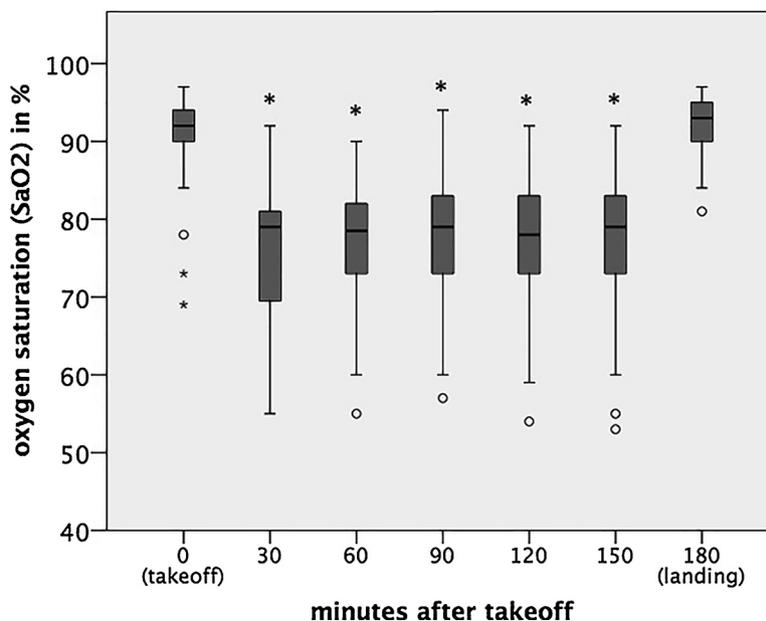


Fig. 4. Oxygen saturation during the experiment. Take-off and landing values were significantly different from in-flight (\*) values ( $p < 0.0001$ ).

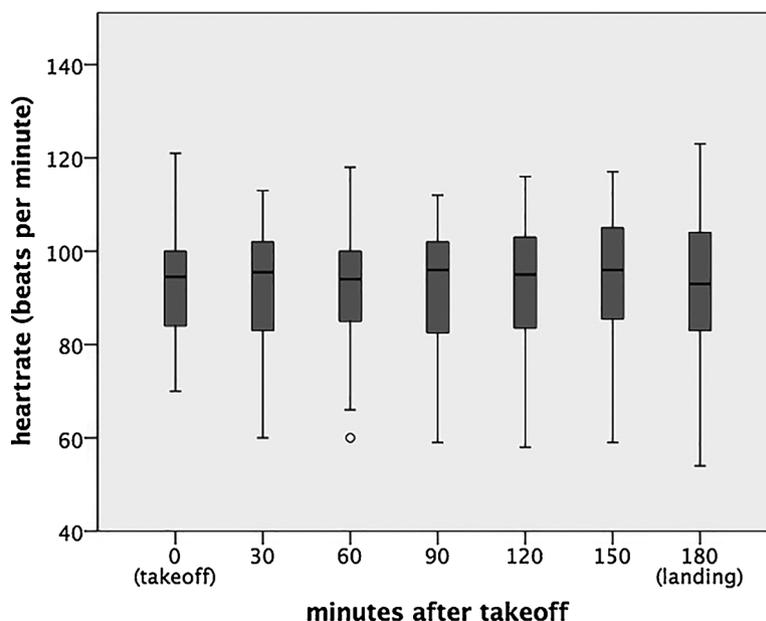


Fig. 5. Heart rate during the experiment showed no significant changes ( $p > 0.05$ ).

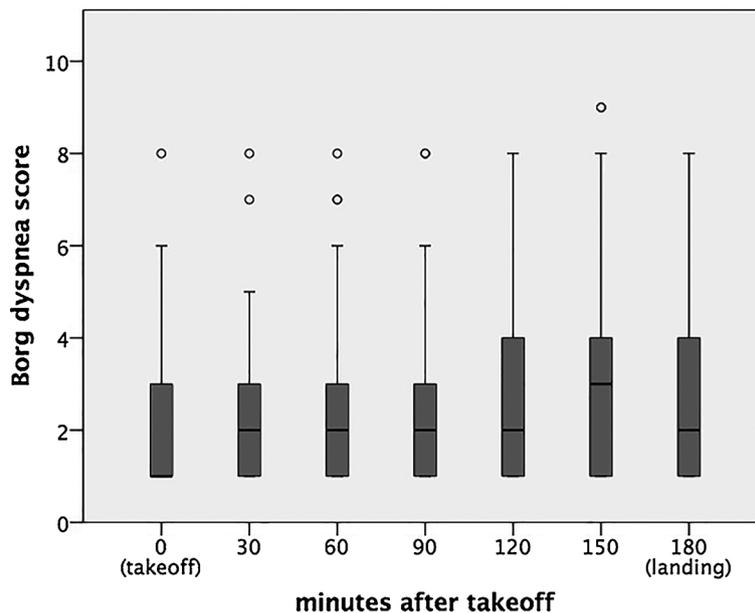


Fig. 6. Borg dyspnea score during the experiment showed no significant changes ( $p > 0.05$ ).

symptoms during air travel. They found no different HAST results in patients with and without respiratory symptoms (Edvardsen et al., 2013). Nakano et al. classified hypoxia as a non dyspnogenic factor during altitude simulation tests in a hypobaric chamber at 4500 m (Nakano et al., 2015). Our experiment confirms, that hypoxemia appears to be unrelated to dyspnea symptoms during hypobaric challenge (Fig. 8). As mentioned earlier, HAST is well suited to predict in-flight desaturation, and patients who passed this test are considered safe to fly (Coker et al., 2007). The threshold level of the HAST however was selected arbitrary without any prospective validation (Johnson, 2003). Prediction of on-board respiratory emergencies might better be detected by experimental settings, such as used in our investigation. Hypobaric testing, however, is not widely available (Ahmedzai et al., 2011); therefore, it would be of interest if the timely extension of HAST would improve the prediction of respiratory emergencies. This strategy could potentially detect more patients that could safely fly without oxygen since procedures to receive in-flight oxygen are perceived

cumbersome by patients (Campbell et al., 2018).

In order to simplify screening, equations based on lung function parameters have been developed, to predict in flight hypoxemia and HAST results respectively. These equations however appeared to have clear limitations (Nicholson and Sznajder, 2014; Akero et al., 2008; Christensen et al., 2000). Edvardsen et al. developed an algorithm based on oxygen saturation at sea level and desaturation during a 6-minute walking challenge to predict relevant desaturations during HAST. Their approach aimed to simplify preflight evaluations, and their algorithm had a sensitivity of 100% and a specificity of 80%.

In our experiment, diffusion capacity was the only significant parameter to predict in-flight hypoxemia, and diffusion capacity was well correlated to in-flight hypoxemia (Fig. 7). This is of no surprise, since diffusion capacity measures the capability of the lungs to transfer diffusible gases such as oxygen into the blood. These results are in line with previous investigations (Kelly et al., 2008). One should therefore consider incorporating the diffusion capacity into models (Nicholson

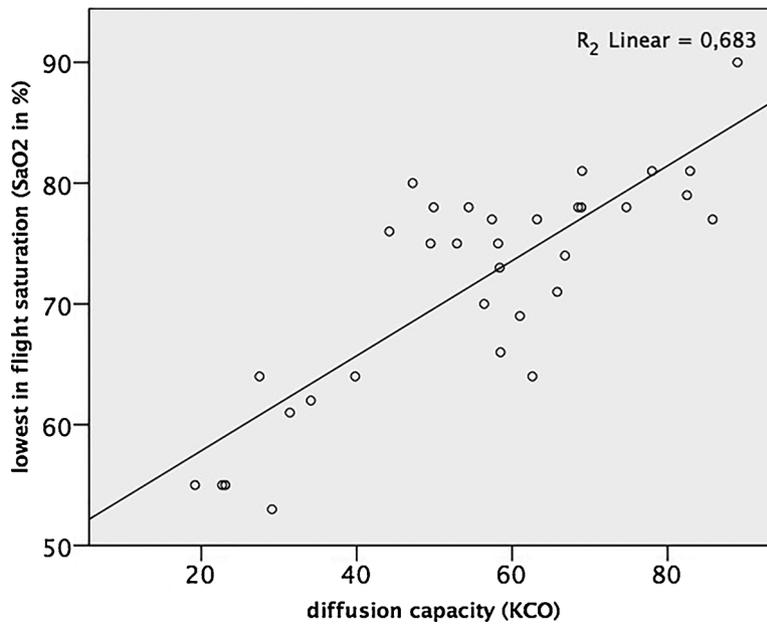


Fig. 7. Diffusion capacity/SaO2 nadir correlation ( $p < 0.0001$ ).

and Sznajder, 2014) for in-flight hypoxemia prediction.

#### 4.1. Safety considerations

The question has to be raised, whether it was ethically acceptable to expose patients to such low oxygen saturations during the experiment. Sixteen of the 35 patients, that participated on our investigation had flown on commercial aircrafts within the previous year and twelve of them did not use oxygen during the flight. The latter group included the patient with the lowest saturation (53% SaO<sub>2</sub>) during the experiment. In flight medical emergencies occur at an incidence of 13–33 per day and 13% of these emergencies result in carrier diversion (Gendreau and DeJohn, 2002). Our investigation therefore reflects daily reality under controlled circumstances within a safe medical environment as described in the method section. For safety reasons we excluded patients with a history of heart failure and coronary artery disease. Given the

safety measures as described in the method section, we, as well as the competent ethics committee felt, that the investigation was safe and justified to answer the research question.

#### 4.2. Limitations

We excluded patients with a history of heart failure or coronary artery disease. We cannot rule out that hypoxemia levels achieved in our experiments would have caused symptoms in this group of patients.

#### 5. Conclusion

Walking endurance reduction evoked by a 3-h hypobaric flight simulation was measured to be 35 m or 10%. Although statistically significant, the measured endurance decrease is unlikely to be clinically relevant. Current recommendations for the use of in-flight oxygen aim

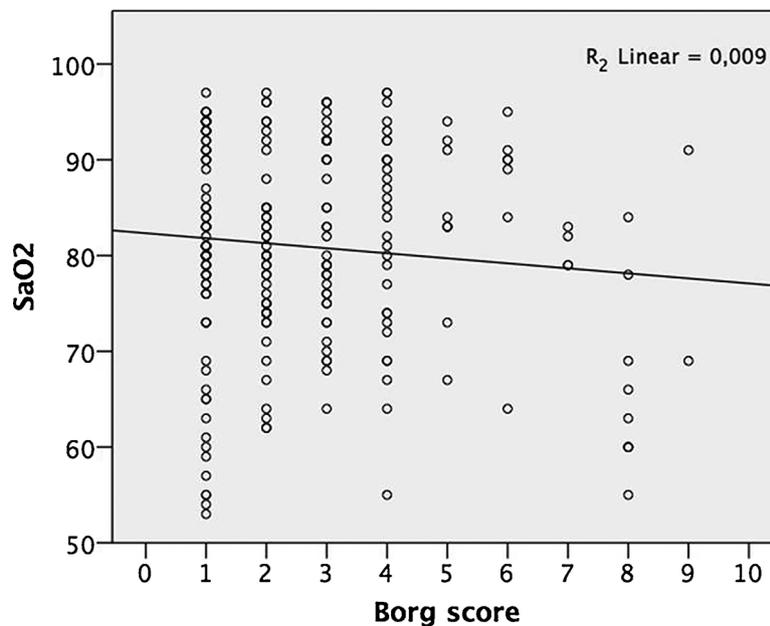


Fig. 8. Correlation of the Borg dyspnea score and the measured oxygen saturation during the experiment ( $p > 0.05$ ).

to prevent hypoxemia. The latter, however, appears to be well tolerated by patients and is not mandatorily related to in-flight symptoms. Diffusion capacity was the only significant parameter to predict in-flight hypoxemia and could be a useful parameter to predict hypobaric hypoxemia.

### Conflicts of interest

The authors have no conflicts of interest to declare.

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