Hypoxia Altitude Simulation and Reduction of Cerebral Oxygenation in COPD Patients

Lukas Dehe; Felix Hohendanner; Emin Gültekin; Gordon Werth; Alexander Wutzler; Thorsten Onno Bender

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is highly prevalent and often associated with chronic hypoxia. Previous studies have shown alterations of cerebral oxygenation and cardiac repolarization in COPD patients (GOLD stage II–IV). Airplane travel is common in patients with COPD; however, the clinical effects of a diminished oxygen partial pressure in aircraft cabin environments at cruising altitude remain elusive. The aim of this study was to assess changes of cerebral oxygenation as well as parameters of cardiac repolarization during a hypoxia altitude simulation combined with mild physical activity in these patients.

METHODS: Patients with COPD and healthy subjects (10 per group) randomly selected from the Charité outpatient clinic conducted a hypoxia altitude simulation test which consisted of three phases. The regional cerebral oxygen saturation (rSO_2) of the frontal cortex was measured at rest using near-infrared spectroscopy (NIRS). Furthermore, oxygen saturation (S_pO_2), blood pressure, and heart rate values, as well as a 12-lead-ECG, were recorded. Subsequently, a mild treadmill exercise program (25 W) was divided into 10 min of normoxia (pre-hypoxia), 30 min of mild hypoxia ($F_iO_2 = 0.15$), followed by a second 10-min period of normoxia (post-hypoxia). Meanwhile, mentioned parameters were recorded in 2-min intervals. P, PQ, QRS, QT, QTc, QTd, T-peak-T-end interval (TpTe), and corrected TpTe (TpTec) were measured on three ECG complexes, each at baseline, at the end of the normoxic phase, and at the end of the hypoxic phase.

RESULTS: A total of 10 patients with COPD and 10 control subjects were included in this study. S_pO_2 was significantly lower in COPD patients throughout the whole test. Frontal cerebral rSO_2 was significantly lower in the left hemisphere during hypoxia altitude simulation in COPD patients (59.5 ± 8.5 vs. 67.5 ± 5.7).

CONCLUSIONS: We show reduced left frontal cerebral oxygenation during hypoxia and mild exercise in patients with COPD, suggesting diminished altitude resilience and altitude capabilities. Preflight hypoxia assessment might be recommended to patients with severe COPD.

KEYWORDS: airplane travel, hypoxia, COPD, NIRS.

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Chronic obstructive pulmonary disease (COPD) is a chronic disease of middle and older age[2] and is marked by chronic inflammation, progressive obstruction of the airways, and destruction of lung tissue.[14] COPD is known to be a common disease with a prevalence of 13.1% worldwide[5] and is associated with significant morbidity and mortality. It is among the leading causes of death worldwide, with up to 3.23 million deaths in 2019.[18]

Since the number of passengers traveling by commercial airlines worldwide is increasing every year, with more than 4.5 billion passengers in 2020, the number of passengers with pre-existing condition like COPD is rapidly increasing.[13] The rising number of passengers aboard larger aircraft and long-distance

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flights make emergencies more likely, especially for patients with chronic conditions like COPD.[11]

Due to a reduced oxygen partial pressure at cruising altitude, cabin pressure is adjusted to the ambient pressure of a maximum of 8000 ft (244 m) above sea level to maintain oxygen supply for the passengers and crew. According to Dalton's law, this is equivalent to a fraction of inspired oxygen (F_IO_2) of 15.1% at sea level.[3]

Cabin pressure and reduced oxygen partial pressure at cruising altitude are usually well tolerated by healthy passengers but might pose a risk for passengers suffering from COPD.[3,7] As compared to sea level, at 8000 ft, oxygen saturation decreases by 4.4% points in healthy passengers. However, this reduction is markedly more pronounced in patients with COPD and often accompanied by dyspnea.[15]

Cerebral oxygen desaturation is associated with decreased muscular strength, impaired coordination, and unconsciousness and, therefore, of particular interest. In healthy subjects cerebral oxygen saturation is known to be reduced under hypoxic conditions and further reduced during physical exercise.[16] In COPD patients with chronic hypoxemia, cerebral oxygen saturation was significantly reduced under normoxic conditions and further reduced during physical exercise.[10] The prevention of commercial in-flight passenger emergency situations is paramount for the current high volume and low threshold international travel using airplanes. Yet alterations of the regional cerebral oxygen saturation (rSO_2) of the frontal cortex and thus safe travel of airplane passengers with COPD still remain elusive. The aim of the present proof of concept study was to reveal whether mild hypoxia is associated with a reduction of cerebral oxygen saturation in these patients. In addition, parameters of cardiac de- and repolarization were assessed to elucidate the role of hypoxia on cardiac electrophysiological properties.

METHODS

Subjects

Following approval by the local ethics committee (EA 2/031/14) of the Charité-Universitätsmedizin Berlin and by the Federal Data Protection Agency, volunteer patients from the local COPD outpatient clinic at Charité-Universitätsmedizin Berlin were recruited between April 2015 and September 2017. The subjects of this proof-of-concept study were 17 adult patients who presented with COPD (GOLD stage II–IV; biometric characteristics of the study cohort can be found in **Table I**). Due to premature termination of the exercise protocol, six subjects met exclusion criteria and one subject's ECG was invalid [see the CONSORT diagram in supplemental **Fig. A**, found online at https://doi.org/10.3357/AMHP.6102sd.2023). Spirometry results were recorded (FEV_1, FVC, Tiffeneau-index) or spirometry was conducted before the standardized treadmill protocol. The control group consisted of 10 adult, healthy volunteers without history of previous lung disease. In addition, control patients had to produce a valid air worthiness certificate. Exclusion criteria included patients with long-term home oxygen therapy. Patient age, gender, body mass index, COPD GOLD stage, spirometry results, and pre-existing medical conditions, i.e., arterial hypertension, diabetes mellitus, peripheral artery disease, atrial fibrillation, asthma, obstructive sleep apnea syndrome, and chronic kidney failure, were used to characterize the study population and to identify possible confounders. Furthermore, chronic medication was assessed.

Table I. Biometrical Characteristics.

PARAMETER	COPD (*N* = 10)	CONTROL (*N* = 10)	*P*-VALUE
Age (yr)	66.0 ± 6.7	60.2 ± 7.9	0.089
Sex (Male)	6 (60%)	6 (60%)	1
BMI (kg · m−2)	26.6 ± 5.4	24.1 ± 2.3	0.315
COPD GOLD Stage			
II (%)	8 (80%)		
III (%)	1 (10%)		
IV (%)	1 (10%)		
Spirometry			
FEV1 (% vom Soll)	55.6 ± 17.1		
FEV1 (L)	1.6 ± 0.4		
FVC (L)	2.9 ± 0.6		
FEV1/FVC (%)	55.6 ± 9.4		
Pre-existing medical conditions			
Arterial hypertension	7 (70%)	1 (10%)	0.023
Peripheral artery disease	0	0	
Atrial fibrillation	0	0	
Diabetes mellitus	1 (10%)	0	0.739
Chronic kidney disease	0	0	
Sleep apnea	0	0	0.739

BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, FEV: Forced Expiratory Volume, FVC: Forced vital capacity.

Regional cerebral oxygenation was chosen as primary outcome parameter. Secondary outcome parameters were S_pO_2 (%), heart rate (bpm), mean arterial pressure (mmHg), and ECG parameters: P (ms), PQ (ms), QRS (ms), QT (ms), QTc (ms), QTd (ms), T-peak-T-end interval (TpTe; ms), and TpTed (ms).

Procedure

Patients with COPD and control subjects without lung disease underwent a modified hypoxia-altitude simulation test (HAST) which consisted of three phases. First, rSO_2 of the frontal cortex was measured at rest using near-infrared spectroscopy (NIRS; Equanox, Nonin Medical Inc., Plymouth, MN, USA) at a wave length of 730–880 nm. Results were measured using a NIRS X-100 Monitor (Nonin Medical Inc.). Furthermore, oxygen saturation (S_pO_2), blood pressure, and heart rate values were recorded every 2 min as well as a 12-lead continuous ECG (Propaq CS, Welch Allyn, Skaneateles Falls, NY, USA). As for ECG parameters, P, PQ, QRS, QT, QTc, QTd, and TpTe were measured on three ECG complexes each at baseline, at the end of 10 min of mild exercise, and at the end of HAST. Severity of dyspnea was documented using the Borg CR10 scale at all phases.

Subsequently, a mild treadmill exercise program (GE Healthcare eBike Ergometer, Chalfont St. Giles, United

Table II. Comparison Between COPD Patients and Control During All Phases of HAST.

	BASELINE			PREHYPOXIA			HYPOXIA		
PARAMETER	**COPD**	**CONTROL**	***P*-VALUE**	**COPD**	**CONTROL**	***P*-VALUE**	**COPD**	**CONTROL**	***P*-VALUE**
S_pO_2 (%)	96.0 ± 1.4	97.5 ± 1.1	0.023	95.7 ± 1.6	97.4 ± 1.1	0.019	84.6 ± 7.6	91.6 ± 1.3	0.004
rSO_2 left (%)	66.9 ± 5.8	70.1 ± 5.1	0.247	67.6 ± 5.5	70.8 ± 5.6	0.165	59.5 ± 8.5	67.5 ± 5.7	0.035
rSO_2 right (%)	69.0 ± 6.1	69.5 ± 5.0	0.971	69.8 ± 6.4	70.2 ± 5.0	0.971	62.1 ± 8.5	66.0 ± 4.1	0.190
HR (bpm)	88 ± 5	76 ± 14	0.043	98 ± 13	81 ± 12	0.003	110 ± 16	85 ± 10	<0.001
MAP (mmHg)	88 ± 12	87 ± 14	0.853	89 ± 12	88 ± 13	0.853	96 ± 13	84 ± 17	0.143
ECG									
RR (ms)	687 ± 98	813 ± 128	0.029	612 ± 71	761 ± 105	<0.001	553 ± 73	720 ± 89	<0.001
P (ms)	101 ± 11	109 ± 10	0.143	86 ± 13	106 ± 12	0.002	91 ± 8	101 ± 9	0.029
PQ (ms)	155 ± 20	164 ± 16	0.247	138 ± 10	160 ± 16	0.003	139 ± 11	157 ± 15	0.009
QRS (ms)	86 ± 9	90 ± 14	0.912	81 ± 10	89 ± 15	0.165	78 ± 9	89 ± 15	0.075
QT (ms)	356 ± 18	377 ± 25	0.043	337 ± 23	365 ± 20	0.009	321 ± 25	361 ± 21	0.002
QTc (ms)	431 ± 19	421 ± 26	0.579	431 ± 19	420 ± 23	0.353	432 ± 14	426 ± 20	0.353
QTd (ms)	31 ± 2	27 ± 6	0.393	32 ± 11	27 ± 10	0.393	24 ± 6	29 ± 9	0.105
TpTe (ms)	81 ± 13	76 ± 14	0.393	81 ± 0.8	76 ± 10	0.353	78 ± 15	74 ± 17	0.529
TpTec (ms)	98 ± 16	85 ± 16	0.075	104 ± 10	88 ± 14	0.004	104 ± 17	88 ± 20	0.075

HAST: Hypoxia-altitude simulation test, S_pO_2: oxygen saturation, rSO_2: regional oxygen saturation, HR: Heart rate (bpm), MAP: Mean arterial pressure, ECG: Electrocardiogram.

Kingdom) at 25 W was divided into 10 min of normoxia (F_IO_2 = 0.21, pre-hypoxia) and 30 min of mild hypoxia (F_IO_2 = 0.15), simulating a normal walk on an airplane. The hypoxic gas mixture (compressed liquid gas, Linde, Munich, Germany) consisted of 15% oxygen and 85% nitrogen. The fraction of inspired oxygen of 15% at sea level was used to simulate conditions as they are observed at 8000 ft (2438 m) above sea level. Gas flow was reduced to 25 L · min^{-1} (pressure regulator, FDR-200F-40-PG, Linde) and guided to a ventilation bag. It was then inhaled through an airtight CPAP mask (Fisher&Paykel Healthcare Ltd, Auckland, New Zealand). A one-way valve between the ventilation bag and the CPAP mask ensured the inspiration of the hypoxic gas mixture. Absolute and relative termination conditions according to the American Heart Association[8] are shown in supplemental **Table A** (found online at https://doi.org/10.3357/AMHP.6102sd.2023).

Statistical Analysis

Descriptive analyses and statistical testing were performed using SPSS Version 24 (SPSS, Chicago, IL, USA). For variables failing the normality test, a Mann-Whitney U-Test was used to assess differences between groups (COPD vs. control). The Wilcoxon signed-rank test was used to assess significant alterations within the group during HAST. For supplemental **Fig. B** (online at https://doi.org/10.3357/AMHP.6102sd.2023) 2-sided *t*-tests were used to investigate between group differences. Tukey's multiple comparisons post hoc test was used to determine statistical differences between mean values determined during normoxia and hypoxia in both groups. $P < 0.05$ was considered statistically significant.

RESULTS

Biometric characteristics are shown in Table I. Age, sex, and body mass index did not differ between groups. Patients of the COPD group were more likely to suffer from arterial hypertension ($P = 0.023$) as compared to the control group.

Hypoxia significantly reduced oxygen saturation in both the control and COPD groups ($P < 0.01$). COPD patients showed a lower oxygen saturation during all phases of HAST (**Table II**), especially under hypoxic conditions, i.e., the reduction of oxygen saturation was more pronounced in COPD as compared to controls ($P < 0.01$; **Fig. 1**). Interestingly this was mirrored in cerebral oxygen saturation. As indicated in **Fig. 2**, regional cerebral oxygen saturation was significantly reduced in the COPD patients during modified HAST ($P < 0.05$; Fig. 2).

Mean arterial pressure during exercise did not differ between the groups, even though COPD was associated with a higher heart rate during HAST ($P < 0.01$; Table II, **Fig. 3**). Mean Borg-score between controls and COPD patients was not significantly different: one patient in each group reported slight dyspnea (Borg score 2) during the study. Moreover, we could not detect any gender related differences in oxygen

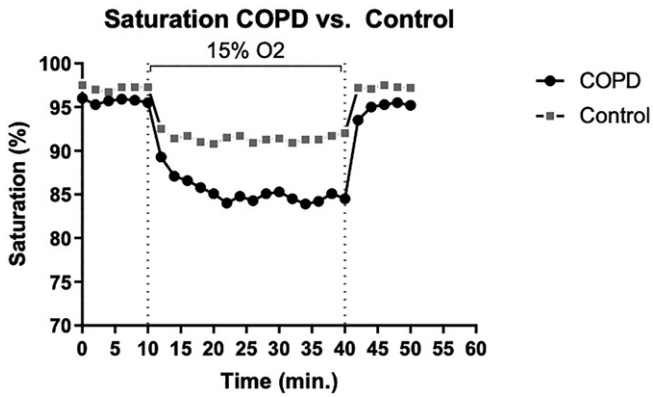

Fig. 1. Oxygen saturation during HAST. During the hypoxia-altitude simulation test (HAST), general oxygen saturation was significantly reduced under hypoxic conditions (F_IO_2 = 0.15; N = 10 control and N = 10 COPD patients).

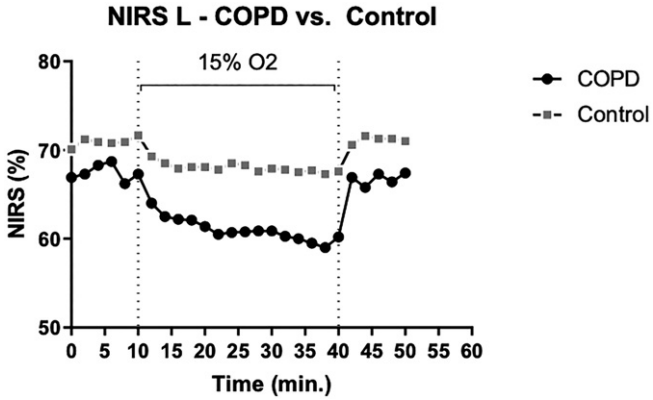

Fig. 2. Cerebral regional oxygen saturation during HAST. During the hypoxia-altitude simulation test (HAST), cerebral oxygen saturation was significantly reduced under hypoxic conditions ($F_IO_2 = 0.15$; $N = 10$ control and $N = 10$ COPD patients).

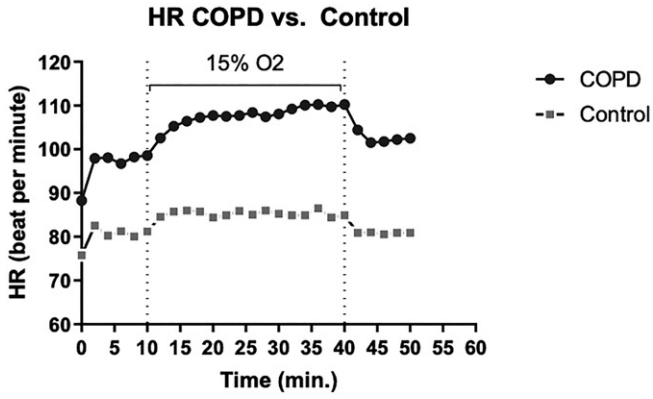

Fig. 3. Heart rate during HAST. During the hypoxia-altitude simulation test (HAST), heart rate was significantly increased, especially under hypoxic conditions ($F_IO_2 = 0.15$; $N = 10$ control and $N = 10$ COPD patients).

saturation, NIRS, mean arterial pressure, heart rate, or respiratory rate upon introducing hypoxic conditions within the COPD group.

Analysis of ECG features during mild exercise unveiled an increased heart rate (Fig. 3) and prolonged P waves and PQ times, findings that consistently translated into differences observed during hypoxia and mild exercise. However, in the present patient study, none of the relevant additional ECG properties analyzed, such as QTc intervals or TpTe, showed significant differences during hypoxia (Table II).

DISCUSSION

This proof-of-concept study of COPD patients (II–IV) undergoing a modified HAST suggests that COPD is associated with a decreased cerebral oxygenation in comparison to healthy volunteers. These results may raise concerns about a diminished altitude resilience and adequate oxygen therapy for COPD patients during flights since COPD patients are known to suffer from dyspnea during air travel.[7]

In accordance with previous studies, we were able to show a significant decrease in oxygen saturation in COPD patients. Due to a reduced pulmonary gas exchange, COPD can result in hypoxia and hypercapnia.[19] Gong et al. were able to show a significant reduction of oxygen saturation in normocapnic COPD patients undergoing a hypoxia-altitude simulation test.[9] In addition, there was a significant decrease in oxygen saturation in COPD patients during exercise in a diving chamber adjusted to 8000 ft (2438 m).[6] During a 5-h flight with a cabin pressure adjusted to 6000 ft (1829 m), oxygen saturation significantly decreased in COPD patients and further decreased during a 50-m walk test.[4]

Little is known about the impact of hypoxia on brain function during air travel. Since decreased cerebral oxygen saturation comes along with impaired coordination and unconsciousness, air travel may be a risk for these passengers. There is evidence that a lowered oxygen saturation by approximately 4 percentage points at 7000 to 8000 ft (2134 to 2438 m) played an important role in the development of discomfort. The cumulative prevalence of altitude-related malaise, muscular discomfort, and fatigue were directly related to altitude and inversely related to oxygen saturation.[12] Potential follow-up studies including the assessment of broader measures of neurological function are needed to address a potential impact of hypoxia on brain function in the setting of higher altitudes beyond the mere development of discomfort. Additional follow-up studies might also allow assessing gender related differences upon introduction of hypoxic conditions.

In healthy subjects cerebral oxygen saturation is known to be reduced under hypoxic conditions and further reduced while performing physical exercise.[16] In COPD patients with chronic hypoxemia, cerebral oxygen saturation was significantly reduced under normoxic conditions and further reduced while performing physical exercise.[10] Interestingly, our study suggests that hypoxia altitude simulation is associated with a decreased cerebral oxygen saturation in COPD patients.

Mild hypoxia has been associated with cardioprotective effects due to altered ATP-sensitive potassium channel activity related to proteins like SUR2A.[1] This has also been shown to translate into changes of the QT interval in a hypoxia animal model.[17] However, in the present patient study, none of the relevant additional ECG properties analyzed, like QTc intervals or TpTe, showed significant differences. Interestingly though, P wave duration differed between control and COPD upon exercise. This might potentially be related to a more pronounced increase of pulmonary pressures during exercise and could be associated with an increased (right) atrial volume in COPD as compared to control patients and underscores the fragility of these patients.

In conclusion, our study is the first to show reduced cerebral oxygenation during HAST and mild exercise in patients with COPD. These results suggest that alterations in cerebral oxygenation may limit the ability to fly in terms of altitude resilience in COPD patients.

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