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RESEARCH ARTICLE

Judicious elevation of ambient carbon dioxide during hypobaric hypoxia to improve oxygenation in airline passengers: a randomized feasibility study

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Abstract

Despite pressurization of airliner cabins, some passengers experience in-flight hypobaric hypoxia with blood oxygen saturation dropping below 90%, potentially causing discomfort and increasing the risk of medical events. Enrichment of the cabin air with carbon dioxide (CO_2) may augment passengers' blood and tissue oxygenation by stimulating respiratory drive, thereby increasing health and safety during air travel. In a randomized double-blind crossover study, we exposed 17 healthy adults (8 women; age range: 18–40 yr) on separate days to two ambient CO_2 levels (0.1% vs. 1.0% indoor sea-level equivalents; 0.76 vs. 7.60 mmHg partial pressure) during 6 h of hypobaric hypoxia (~565 mmHg total barometric pressure; corresponding to 2,438 m altitude) in an altitude chamber simulating long-haul flight conditions. We measured oxygen saturation of the blood (Sp_{O_2}), brain, and muscle (tissue saturation index derived from near-infrared spectroscopy), respiration, and cognitive function (sustained attention, working memory, and hand-eye coordination) hourly. In addition, we conducted capillary blood gas analyses at baseline, 15 min, and 6 h after hypoxia onset. During hypobaric hypoxia, ambient CO_2 enrichment on average increased P_{CO_2} from 36.3 to 38.3 mmHg, P_{O_2} from 60.9 to 68.3 mmHg, and minute ventilation from 9.7 to 10.4 L/min, whereas reducing the time fraction of $Sp_{O_2} < 90\%$ from 18.8% to 2.5%. Tissue oxygenation increased in the brain from 62.8% to 63.9%, whereas no change was found in the muscle. High ambient CO_2 had no effect on cognitive performance. Taken together, enrichment of cabin air with CO_2 during hypobaric hypoxia may improve blood and brain oxygenation.

NEW & NOTEWORTHY Elevating ambient CO_2 can improve blood and brain oxygenation in healthy individuals during moderate hypoxia as experienced in an airliner cabin. The findings offer a new approach potentially benefiting the health and safety of airline passengers and support investigating CO_2 enrichment in broader passenger populations, especially in those at risk of hypoxemia. Exploration of CO_2-based interventions to enhance passenger oxygenation may also prompt regulatory reassessment of cabin CO_2 limits and technological innovations in ventilation systems.

aircraft cabin pressure; ambient CO_2; blood oxygen saturation; hypobaric hypoxia; respiratory rate

INTRODUCTION

Commercial jet aircraft often fly at altitudes of 30,000–43,000 ft. At such altitudes, oxygen partial pressure outside the airliner cabin is profoundly reduced and incompatible with human life. Therefore, aircraft cabins are pressurized with the corresponding maximum cabin altitude during normal operations, not to exceed 8,000 ft (~2,438 m) (1, 2). Cabin pressurization ensures adequate oxygenation for most passengers, with oxygen saturation (Sp_{O_2}) under these conditions typically ranging between 91% and 95%, which is considered safe. Most guidelines define hypoxemia as an oxygen saturation level below 90% that should be avoided (3). However, existing atmospheric conditions in the cabin fail to prevent hypoxemia in all passengers effectively. In some individuals, especially in those with respiratory or cardiopulmonary conditions, oxygen saturation can decrease below 90% (4–7). Moreover, during sleep under flight conditions, blood oxygenation can drop below 90% for a sizable fraction of time, even in healthy individuals (4, 7, 8). Hypoxemia can exacerbate medical conditions or incite medical events (9, 10). Increased mortality risk has been observed in emergency

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admissions with Sp_{O_2} levels between 86% and 89% compared with 90% or higher (10), and postoperative outcomes worsen when desaturation occurs below 90% (11). Moreover, cardiac and respiratory complaints are among the most serious in-flight medical events (9).

One potential solution for reducing the occurrence of in-flight hypoxemia is to increase cabin pressure. Indeed, most airliners nowadays operate at a lower cabin altitude than is maximally allowed (12). However, a further increase in cabin pressure is limited, as this measure would increase aircraft weight and fuel consumption due to the need for a reinforced cabin structure, subsequently worsening its environmental impact (12). Given the continuously increasing air travel volume, alternative strategies to improve oxygenation in passengers are currently being explored.

We assessed the potential of enriching the cabin atmosphere with carbon dioxide (CO_2) as a countermeasure to in-flight hypoxia. Our objective was to assess whether an increase in ambient CO_2 improves blood Sp_{O_2} in healthy individuals during hypobaric hypoxia, as typically experienced during air travel (1). Exposure to reduced oxygen partial pressure (P_{O_2}) elicits an increase in ventilation, the so-called "hypoxic ventilatory response." The ventilatory response increases CO_2 elimination, leading to hypocapnia, which in turn opposes respiratory drive. Consequently, in most people exposed to modest hypoxia, ventilation stabilizes slightly above baseline levels (13). Although these counteracting regulatory circuits maintain overall homeostasis, they can limit the ability to cope with hypoxia. Conversely, increased inspired CO_2 prevents hypocapnia and augments ventilation under hypoxia for prolonged periods of time (14). Moreover, because CO_2 is a potent cerebral vasodilator, maintaining adequate levels of arterial CO_2 can help ensure proper brain perfusion and prevent light-headedness, thereby supporting overall brain function and alertness (15).

Our primary hypothesis was that during a realistic simulation of a 6-h flight, a sea-level equivalent of 1% CO_2 inside the airliner cabin increases our primary outcome, i.e., blood Sp_{O_2}, in healthy individuals compared with a flight condition without CO_2 enrichment (control). To gain insight into the underlying mechanisms, we measured secondary endpoints, including capillary blood gases and respiration. In addition, we estimated brain and skeletal muscle oxygen saturation using near-infrared spectroscopy (NIRS). Finally, we evaluated cognitive performance as reflected in sustained attention, working memory, and hand-eye coordination.

MATERIALS AND METHODS

We obtained informed written consent from study participants before the start of the study. The protocol was approved by the ethics committee of the North Rhine Medical Association (Ärztekammer Nordrhein; Protocol No.: 2018253) and prospectively registered at the German Clinical Trials Register (DRKS, Registration No.: DRKS00015820). We conducted all procedures according to the Declaration of Helsinki (2013). Study participants were compensated for their participation. We performed the study as well as the medical screening at the Institute of Aerospace Medicine, German Aerospace Center (DLR) in Cologne, Germany.

Participants

Men and women aged 18–40 yr with a body mass index (BMI) between 18 and 30 kg/m^2 were eligible for the study. Participants were enrolled according to a predefined set of inclusion and exclusion criteria. In brief, participants were in good health, as established by a physical examination, medical history, stress-electrocardiogram, and routine blood and urine testing. Participants reported no recent exposure to altitudes above 1,500 m within 6 wk before the study, no regular practice of high-performance sports, and did not play wind instruments. Participants abstained from alcohol, nicotine, drugs, and caffeine for 1 wk before each visit to the laboratory, which was verified by urine testing upon admission. Here we report on one of the two study arms (~8,000 ft condition, see Study Design), which included 17 participants (8 women, mean age ± SD: 27.8 ± 4.2 yr, mean BMI ± SD: 24.6 ± 3.2).

Study Design

Participants were randomized to one of two study arms—one simulating a cabin pressure equivalent to the air pressure at an altitude of ~8,000 ft and the second arm simulating a pressure equivalent to ~14,000 ft (Fig. 1). In each study arm, participants underwent two ambient CO_2 conditions (0.76 and 7.60 mmHg) on separate days with a 7-day washout period, according to a randomized, double-blind, crossover design. Due to the occurrence of adverse events, the second study arm (~14,000 ft) was discontinued after 7 participants (see RESULTS). During both conditions of the first study arm, participants spent 6 h in an altitude chamber, which was depressurized to simulate an altitude of ~8,000 ft (565 mmHg), corresponding to the maximum cabin altitude of an airliner as allowed during normal operation. The two conditions differed by the ambient CO_2 concentration in the altitude chamber, consisting of either a low or high CO_2 condition with normalized indoor sea-level (760 mmHg) equivalents of 0.1% (0.76 mmHg) or 1.0% (7.60 mmHg) CO_2. We randomly assigned participants to the two sequences in which the high and low CO_2 conditions occurred. Participants were initially grouped (groups of 2) based on their availability. Subsequently, the order of treatment conditions was randomized across these groups using an R script that simulates a coin toss. Both the physician taking the measurements and the participants inside the chamber were blinded to the treatment conditions. In contrast, the study staff operating the chamber from outside were unblinded.

We collected baseline data every morning on each study day under normobaric and normoxic conditions. The experiment in the pressure chamber was divided into six test blocks, each lasting 60 min. A test block comprised the Environmental Symptoms Questionnaire (ESQ) and the 0–10 Borg CR10 Scale (3 min), a cognitive test battery (22 min), physiological measurements (20 min), and a break (15 min). Physiological measurements included spirometry, pulse oximetry, and near-infrared spectroscopy (NIRS) that were recorded simultaneously. During each break, participants received hourly isocaloric snacks and had the opportunity to use the restroom within the altitude chamber. In addition, we performed capillary blood gas analysis (cBGA) 15 min and 6 h after the start of hypoxia exposure.

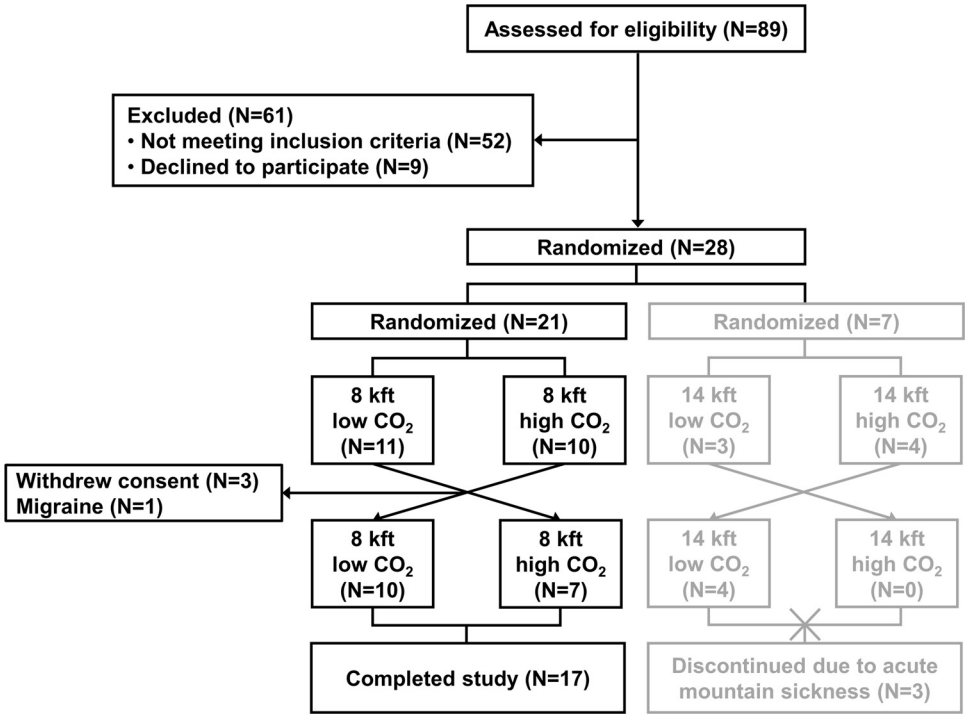

Figure 1. Flow diagram of the study.

Capillary Blood Gas Analyses

We preferably collected capillary blood from the earlobe 5 min after application of a blood flow-stimulating ointment (Finalgon, Sanofi-Aventis, Frankfurt, Germany). In rare cases, we used the finger tip as an alternative sampling site. We analyzed samples using the epoc Blood Analysis System (Siemens Healthineers, Erlangen, Germany), which involves electrodes to assess the concentration of gases in the blood.

Spirometry and Pulse Oximetry

We measured ventilation and gas-exchange parameters (O_2 and CO_2) through an oral-nasal mask using a breath-by-breath spirometer (Inn00400, Innovision, Glamsbjerg, Denmark). In between hourly spirometry recordings, the participants did not wear the mask. After conducting our analysis, we discovered that the spirometer encountered problems when exposed to high ambient CO_2 levels (7.60 mmHg) under hypobaric conditions. After consulting with the manufacturer, we chose to exclude all data that depended on CO_2 measurements of the Innovision device. In the absence of end-expiratory CO_2 measurements, we were unable to calculate alveolar ventilation. Therefore, we focused on minute ventilation as a key mediator in optimizing oxygen saturation. We assessed blood oxygen saturation (Sp_{O_2}) with a finger pulse oximeter (Nonin, Plymouth, MN).

Near-Infrared Spectroscopy

We placed sensors (Portalite and PortaMon, Artinis Medical Systems, Elst, the Netherlands) over the right frontal eminence of the skull and the belly of the right vastus lateralis muscle. We securely fixed both sensors with dark elastic tape to minimize artifacts from external light. The devices measured the tissue concentration of oxygenated (HbO_2, μmol/L tissue) and deoxygenated hemoglobin (Hb, μmol/L tissue) at a sampling rate of 10 Hz. From these values, total hemoglobin ($tHb = HbO_2 + Hb$, μmol/L tissue) and tissue oxygen saturation index (TSI; $100 \times HbO_2/tHb$) were determined.

Cognitive Performance

The cognitive test battery used in this study comprised three components: a 10-min version of the psychomotor vigilance task (PVT; 16, 17) to measure sustained attention, the N-back task with varying difficulty levels (1-, 2-, and 3-back load) to evaluate working memory (18, 19), and the adaptive tracking task to assess hand-eye coordination (20, 21). The selected measures of interest included PVT speed (s^{-1}), PVT number of lapses (response time $>$ 500 ms), 2-back number of omissions, and the mean score obtained from the adaptive tracking task. To mitigate the potential impact of training effects, each task was performed three times before the study.

Statistical Analysis

A statistical power analysis for the first arm was performed assuming a moderate effect of $f = 0.18$ for the effect of ambient CO_2 on blood oxygen saturation during hypoxia exposure (high vs. low ambient CO_2). The analysis was based on a repeated measures analysis of variance (ANOVA) with $\alpha = 0.05$ and power = 0.80. The projected sample size needed was approximately $n = 17$ for the crossover design in each arm. We analyzed the data using R, version 4.0.1 (R Foundation, Vienna, Austria). Numerical data are presented as means ± standard errors of the means unless indicated otherwise. Repeatedly measured data were analyzed with linear mixed-effects models with treatment, time, and treatment-by-time as fixed effects, and participant-specific intercepts. Measurements immediately preceding the hypoxia exposure served as baseline and

were used as covariates in the models. In cases where the interaction term was not significant, a simplified model excluding the interaction term is reported. Post hoc comparisons were done on estimated marginal means. Data shown in the figures represent descriptive means. Normality was assessed using residual plots. An alpha value of 0.05 was considered significant, with correction for multiplicity performed using the Bonferroni–Holm method. The first 5 min of physiological recordings in each test block were excluded from the analysis to minimize artifacts due to the application of the measurement equipment. The number of PVT lapses and 2-back omissions resulted in a considerable number of zeros. To account for the excess of zeros in the count variable PVT lapses, we used the zero-inflated negative binomial (ZINB) model. For the 2-back omissions, the ZINB model returned no overdispersion, and therefore a zero-inflated Poisson model was applied.

Missing Data

Two participants had missing Sp_{O_2} data in a total of five test blocks and one baseline measurement due to a sensor connection failure with the spirometry device. As the average intra-individual baseline differences were negligible (0.1% Sp_{O_2}), we imputed the missing baseline value using the available baseline data from the same individual on the other experimental day. In addition, for a third participant, all spirometry and Sp_{O_2} data from one test block were missing due to device failure. Overall, the missing data accounted for 3% of our dataset, and their occurrence could reasonably be considered random.

RESULTS

Between December 2018 and July 2019, 89 interested volunteers entered a multistep screening procedure, resulting in the selection of 28 healthy adults. The study was initially designed with two arms—one simulating a cabin pressure equivalent to the air pressure at an altitude of ~8,000 ft and the second arm simulating a pressure equivalent to ~14,000 ft (Fig. 1). However, due to signs of acute mountain sickness in three participants, we discontinued exposure to 14,000 ft after testing seven persons. Consequently, data collected from this arm were excluded from subsequent analyses. As a result, twenty-one participants were assigned to the 8,000 ft arm. Within this group, four participants did not continue the study after the first visit (low CO_2 condition in each case). Of those, three participants withdrew their consent, whereas one experienced migraine and was excluded. Consequently, the final dataset for the 8,000 ft arm included 17 complete datasets (8 women, mean age ± SD: 27.8 ± 4.2 yr, mean BMI ± SD: 24.6 ± 3.2).

In hypoxia, Sp_{O_2} values were higher in high compared with low ambient CO_2 (Fig. 2*A*, mixed model, $P < 0.001$). Time fraction of $Sp_{O_2} < 90\%$ was lower in high compared with low ambient CO_2 (Fig. 2*B*, paired *t* test, $P = 0.005$). High ambient CO_2 resulted in increased capillary blood levels of P_{CO_2} and P_{O_2} compared with low ambient CO_2 (Fig. 2, *C* and *D*, mixed model, factor treatment $P < 0.001$ in both cases), accompanied by a decrease in pH levels (Fig. 2*E*, mixed model, $P = 0.006$), and a tendency toward increased bicarbonate levels (Fig. 2*F*, mixed model, $P = 0.077$). There were no significant interactions between treatment and time for any variable.

Although the present study was not designed and powered to detect potential sex differences, we carried out explorative analyses by including sex as a covariate in the mixed-model analyses of Sp_{O_2}, P_{O_2}, and P_{CO_2}. No sex differences were observed except for a tendency toward lower P_{CO_2} in females than in males (34.1 vs. 38.6 mmHg, $P = 0.051$). There were no significant interactions between treatment and sex.

Changes from baseline in minute ventilation, respiratory rate, and tidal volume are shown in Fig. 3. High ambient CO_2 levels resulted in increased minute ventilation and respiratory rate (factor treatment $P < 0.001$ in both cases), along with a tendency toward decreased tidal volume (factor treatment $P = 0.061$). There were no significant interactions between treatment and time for any variable.

Individual trajectories between ambient CO_2 conditions are shown for Sp_{O_2} and P_{CO_2} (Fig. 4*A*) and for Sp_{O_2} and minute ventilation (Fig. 4*B*). Fifteen out of 17 participants (88%) showed an increase in Sp_{O_2} with increasing P_{CO_2}, and 13 participants (76%) showed an increase in Sp_{O_2} with increasing minute ventilation. Corresponding trajectories for P_{O_2} were somewhat less tight: 12 participants (71%) showed an increase in P_{O_2} with increasing P_{CO_2}, and 11 participants (65%) showed an increase in P_{O_2} with increasing minute ventilation (data not shown).

High ambient CO_2 resulted in higher brain tissue saturation index (TSI; Fig. 5*A*, factor treatment $P = 0.003$), with the largest difference occurring 2 h after hypoxia onset. Muscle TSI showed no difference between treatments (Fig. 5*B*). In both brain and muscle, TSI varied over time (factor time $P < 0.001$ in both cases). There were no significant interactions between treatment and time in either tissue. We observed no significant differences for tHb and HbO_2.

Cognitive performance measurements did not differ significantly between low and high ambient CO_2 (Supplemental Fig. S1). The time fraction of $Sp_{O_2} < 90\%$ did not significantly correlate with cognitive performance measures.

No significant differences in the acute mountain sickness-cerebral score derived from the ESQ were observed between treatments (Supplemental Fig. S2). In high CO_2, two participants reported slight breathlessness (Borg score = 2), whereas none did so in the low CO_2 conditions. No participant reported symptoms above slight breathlessness in any condition.

DISCUSSION

CO_2 enrichment of the ambient air during moderate hypobaric hypoxia, resembling conditions in an airliner cabin, improved blood oxygenation. The intervention was well tolerated in healthy young individuals. High CO_2 elevated minute ventilation and respiratory rate. Consequently, CO_2 enrichment increased blood gas levels of P_{CO_2} and P_{O_2}, as well as Sp_{O_2}, while reducing the time fraction of $Sp_{O_2} < 90\%$. Furthermore, CO_2 increased tissue oxygenation in the brain but not in skeletal muscle. There was no cognitive impairment in both conditions compared with normoxia.

Previous work has shown a rise in tidal volume with moderate increases in ambient CO_2, whereas in the current study, changes in ventilation were attributed to an increase in

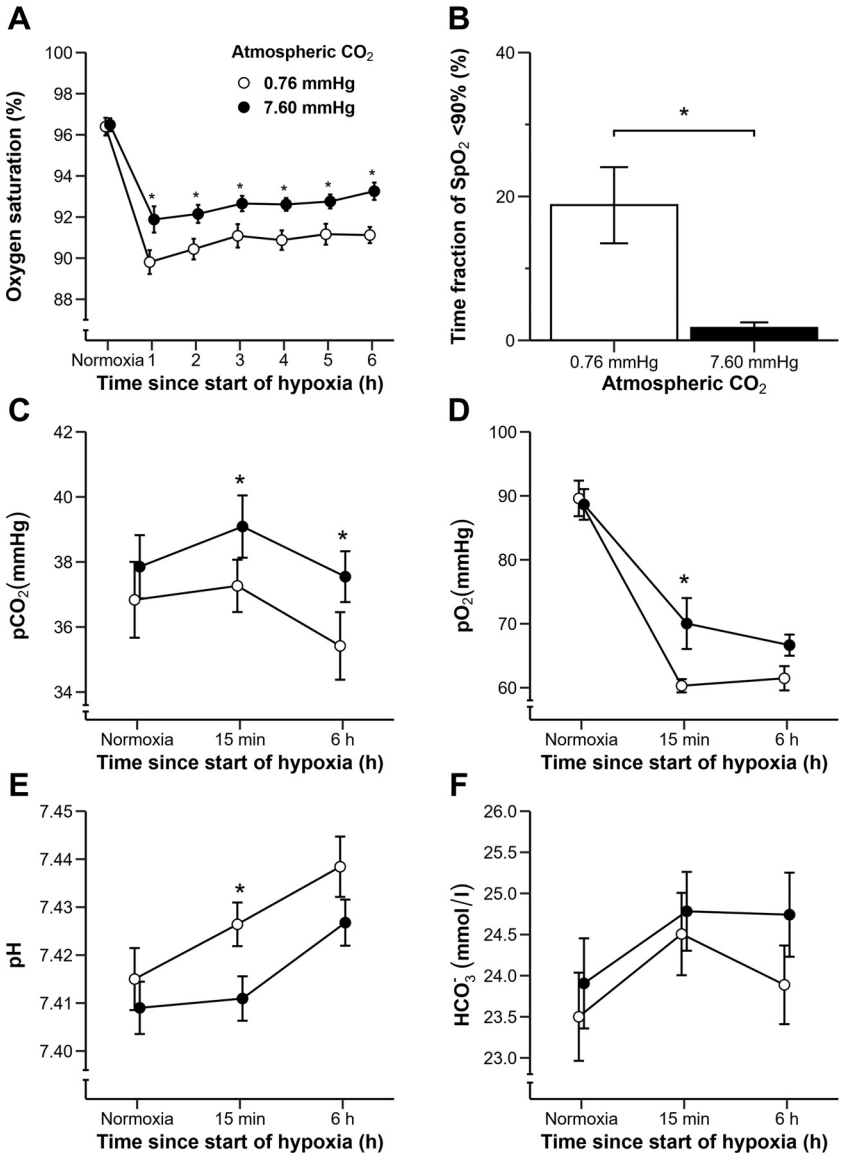

Figure 2. Blood oxygenation and blood gases during 6 h of hypobaric hypoxia with low and high ambient CO_2. *A*: mean (±SE, $n = 17$ participants) blood oxygen saturation (Sp_{O_2}) at hourly intervals during exposures. *B*: time fraction of $Sp_{O_2} < 90\%$ during exposures calculated as % of the total time of Sp_{O_2} measurements. Carbon dioxide partial pressure (*C*), oxygen partial pressure (*D*), pH (*E*), and bicarbonate (*F*) levels in capillary blood at baseline, after 15 min, and 6 h of exposure. *Significant differences between conditions ($P < 0.05$, marginal means contrasts with Bonferroni-Holm correction except for *B* where a paired *t* test was used) between conditions post Bonferroni–Holm correction. For results of mixed-model analysis, see RESULTS.

respiratory rate only. It is possible that hypobaric hypoxia, conceivably due to the reduced airway resistance to less dense air, contributed to a shift in the balance between depth and frequency of breathing with higher CO_2. Moreover, subliminal discomfort/anxiety associated with the instrumentation and the unusual and confined environment of the altitude chamber may have reinforced a bias toward faster and shallower breathing with increased CO_2.

In addition to stimulating ventilation, inspired CO_2 may have improved pulmonary gas exchange by enhancing ventilation-perfusion ($\dot{V}_A/\dot{Q}$) matching. By influencing pulmonary vascular tone and augmenting hypoxic pulmonary vasoconstriction, CO_2 may have redistributed blood flow toward better-ventilated alveoli, reducing $\dot{V}_A/\dot{Q}$ mismatch and enhancing overall oxygenation. Furthermore, CO_2-induced bronchodilation may also contribute to improving $\dot{V}_A/\dot{Q}$ matching (22).

Exposure of unacclimatized persons to simulated moderate altitude has been associated with reduced Sp_{O_2} and increased frequency of symptoms, including altitude-related malaise, muscular discomfort, and fatigue, which became manifest after 3–9 h of exposure (6). The slight increase in blood and brain oxygenation during CO_2 enrichment observed in our study may contribute to mitigating some of these effects. Although the study by Muhm et al. (6) as well as the current study used Sp_{O_2} as the primary oxygen marker, it should be noted that Sp_{O_2} is not always reliable when determining whether an individual is hypoxic or not (23). Pa_{O_2}, which is important for the delivery through diffusion of oxygen from blood to the cells, can deviate considerably from the levels of Sp_{O_2} during hypoxic events.

It is tempting to speculate that, beyond its role in improving oxygenation under hypobaric hypoxia, controlled enrichment of emergency breathing air with CO_2 could have practical applications during in-flight decompression events. By sustaining respiratory drive, CO_2 may improve the effectiveness of emergency oxygen delivery, particularly during depressurization at very high altitudes. This intervention could extend the safe duration for passengers and crew to tolerate hypobaric conditions in situations where emergency

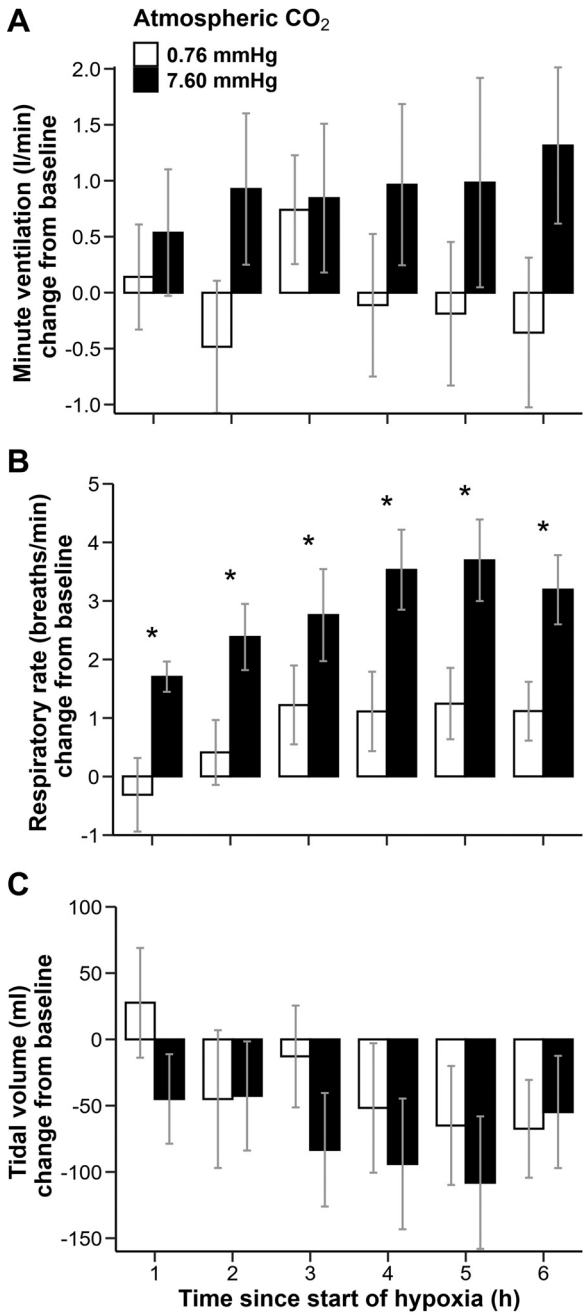

Figure 3. Changes in ventilation during 6 h of hypobaric hypoxia with low and high ambient CO_2. Data show mean (±SE, $n = 17$ participants) changes from baseline (normoxia). Minute ventilation (calculated as the product of tidal volume and respiratory rate) in L/min (*A*), respiratory rate in breaths per minute (*B*), and tidal volume in mL (*C*). *Significant differences between conditions ($P < 0.05$, marginal means contrasts with Bonferroni-Holm correction) between conditions post Bonferroni–Holm correction. For results of mixed-model analysis, see RESULTS.

descent is constrained by high terrain, potentially enabling aircraft to operate over high-terrain regions—such as the Himalayas—that are otherwise restricted due to altitude-related safety concerns.

The present study indicates that the physiological impact of ambient CO_2 could be leveraged to maintain oxygen saturation levels of airline passengers above 90%. Although acknowledging potential adverse effects of ambient CO_2, we recognize the need for a nuanced discussion. Increased inhaled ambient CO_2 can lead to adverse effects (24, 25). Aviation authorities currently mandate a cabin CO_2 limit of 0.5% (26). Under hypoxic conditions and with a controlled ambient CO_2 concentration of 1%, we did not observe impairments in cognitive function or acute well-being. By providing a comprehensive perspective, our data align with the proposal to use 1% ambient CO_2 to maintain passenger well-being during flights. Nonetheless, it is important to recognize that the current investigations need to be extended to individuals with medical conditions and those of older age.

A practical implementation of the approach outlined in this paper could be increasing cabin air recirculation to leverage the CO_2 generated by passengers. On the one hand, increasing cabin air recirculation lessens the need for air sourced from the aircraft's engines (so-called bleed air) for ventilation purposes, as proposed by the European Union's Clean Sky initiative (27). Positive effects would include lower fuel consumption, increased engine thrust, and reduced risk of toxic-fume events (12, 28). On the other hand, it might lead to concerns about increased odors and the heightened risk of spreading infectious diseases due to lower air exchange rates (29). However, these challenges can be overcome with straightforward technological adaptations to the aircraft's air conditioning systems, such as the integration of CO_2 sensors and specialized air filters (30, 31).

Harvey et al. (32) proposed the inhalation of 3% CO_2 as a potential therapy for mountain sickness, reporting symptom relief and increases in Pa_{CO_2} of 4.5 mmHg and Pa_{O_2} of 17.2 mmHg. A follow-up study confirmed these findings, although changes were smaller with increases in Pa_{CO_2} of 1.0 mmHg and Pa_{O_2} of 5.7 mmHg (33). Our research aligns with these previous studies that used a similar approach of increasing ambient CO_2, further supporting the validity and effectiveness of this method. It should be kept in mind, however, that these previous studies were carried out in climbers at considerably higher altitudes.

Previous studies have reported a favorable impact of ambient CO_2 on cerebral oxygen saturation in the presence of hypoxia and normoxia (34, 35). Our NIRS measurements on brain tissue support these findings, suggesting a temporary vasodilation and/or the effect of increased respiration due to high CO_2.

During the 6-h exposure at ~8,000 ft, there were no significant impairments observed in cognitive performance when compared with baseline under normobaric normoxia. A recent review revealed only minor impairments in some cognitive domains at oxygen levels of 80%–89% Sp_{O_2} (36). Moreover, the addition of 7.60 mmHg ambient CO_2 did not cause cognitive impairments, indicating no apparent risk to cognition in healthy individuals.

Although the current work is physiologically grounded, it draws particular strength from its application to aeronautics. Nonetheless, a limitation of our study is that we only included younger and healthy participants who abstained from alcohol, caffeine, and nicotine, which limits the generalizability of our study. Our findings cannot simply be extrapolated to older individuals and those with medical conditions. However, it is these older and diseased individuals who are at a higher risk of experiencing in-flight hypoxemia and who may benefit the most from in-flight measures

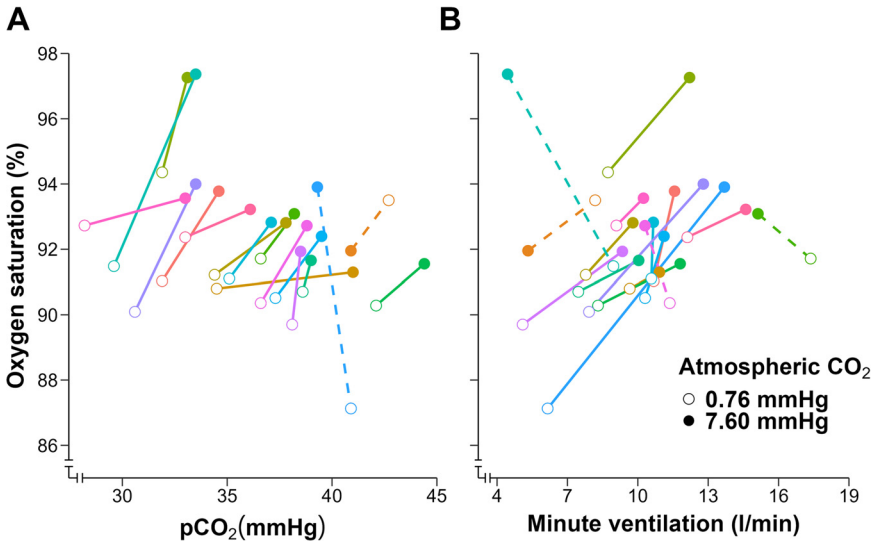

Figure 4. Individual trajectories of oxygen saturation during hypobaric hypoxia between low and high ambient CO_2. Data were obtained 6 h after hypoxia onset. Oxygen saturation plotted as a function of P_{CO_2} (*A*), and as a function of minute ventilation (*B*). Dashed lines highlight participants deviating from the predominant direction observed in the majority of participants (solid lines). In one participant, the final 6 min of Sp_{O_2} recordings were removed before averaging due to artifacts/implausible data. Sp_{O_2}, oxygen saturation.

to improve oxygenation. Passengers with respiratory diseases (e.g., chronic obstructive pulmonary disease, sleep apnea) and cardiovascular diseases (e.g., cardiomyopathy), in particular, are more vulnerable to the dangers of in-flight hypoxemia, which could prevent them from flying at all (37–39). Such increased vulnerability underscores the importance of studying their capacity to tolerate elevated ambient CO_2 levels. In clinical settings, inhalation of CO_2 at concentrations of up to 3% has shown successful therapeutic outcomes for conditions such as Cheyne–Stokes respiration and central sleep apnea (40). For passengers with respiratory diseases, the effects of increased ambient CO_2 are likely to vary depending on the underlying pathophysiology of their specific condition. Thus, it is crucial to not only evaluate the potential benefits of 1% inspiratory CO_2 in increasing oxygen saturation but also consider its potential to exacerbate the condition of these passengers. Another limitation is the absence of end-expiratory CO_2 measurements, which

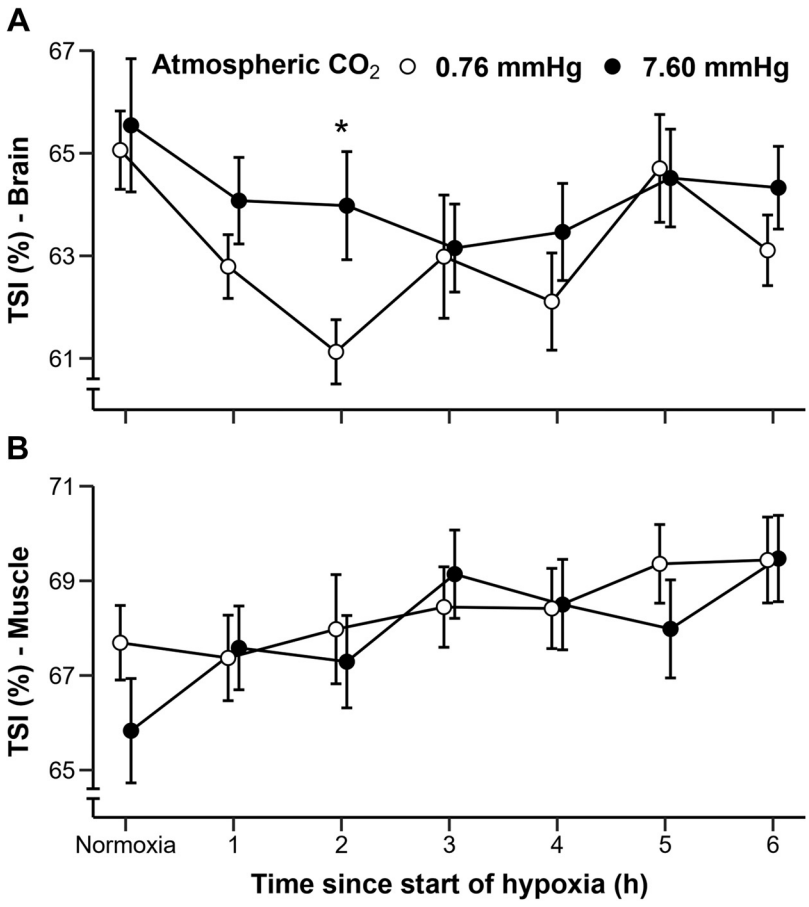

Figure 5. Tissue saturation index (TSI) derived from near-infrared spectroscopy during hypobaric hypoxia with low and high ambient CO_2. Data show means (±SE, $n = 17$ participants) for brain (*A*) and muscle (*B*). *Significant differences between conditions ($P < 0.05$, marginal means contrasts with Bonferroni-Holm correction) between conditions post Bonferroni–Holm correction. For results of mixed-model analysis, see RESULTS.

prevented us from accurately calculating alveolar ventilation in addition to minute ventilation.

Conclusions

With the popularity of air travel as a major transportation mode, atmospheric conditions within aircraft cabins should be optimized to ensure the well-being of all passengers. Our study challenges existing aviation regulations by showing that an increase of CO_2 concentration to a normalized sea-level equivalent of 1% improved mean blood oxygenation in the majority of the healthy individuals studied here. Notably, our findings demonstrate that a higher cabin CO_2 concentration effectively prevents mean blood oxygen saturation from dropping below the clinical threshold of 90%. However, considering the diverse and changing demographics of airline passengers, including more individuals who are older and/or have medical conditions, the safety implications of a 1% CO_2 concentration should be thoroughly investigated across different groups of passengers.

DATA AVAILABILITY

Source data for this study are openly available in the Open Science Framework at https://doi.org/10.17605/OSF.IO/M8GQ9.

SUPPLEMENTAL MATERIAL

Supplemental Figs. S1 and S2: https://doi.org/10.17605/OSF.IO/M8GQ9.

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GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

T.E.P., R.D.G., D.R., M.W., P.L., L.L., J.J., J.Z., J.R., and D.A. conceived and designed research; T.E.P., R.D.G., D.R., M.W., P.L., and L.L. performed experiments; T.E.P., R.D.G., D.R., M.W., L.L., J.Z., and D.A. analyzed data; T.E.P., R.D.G., D.R., M.W., L.L., J.Z., and D.A. interpreted results of experiments; T.E.P. and D.A. prepared figures; T.E.P., R.D.G., D.R., and D.A. drafted manuscript; T.E.P., R.D.G., D.R., M.W., P.L., J.J., J.Z., J.R., and D.A. edited and revised manuscript; T.E.P., R.D.G., D.R., M.W., P.L., J.J., J.Z., J.R., and D.A. approved final version of manuscript.

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