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Mild hypoxia adversely impacts human vestibular function

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Hypoxia has been found to adversely affect sensory function at altitudes above 3000 m, but sensory decrements have not been reported in peer-reviewed literature at or below 2400 m nor has research focused on the impact of hypoxia on human vestibular thresholds. These knowledge gaps are problematic, because the vestibular system has high metabolic needs and makes fundamental behavioral contributions. We hypothesized that mild hypoxia would impact vestibular function, which we tested by having participants breathe air with 15.4% O_2 to simulate an altitude of 2400 m (8000 ft)—mimicking the oxygen available on commercial aircraft. We measured earth-vertical translation thresholds and arterial oxygen saturation (SpO_2) and found that the average threshold increased by over 20% relative to thresholds measured while breathing air with 20.9% O_2, and that these threshold changes negatively correlated with changes in SpO_2. These findings suggest that vestibular changes provide a harbinger of hypoxia.

The vestibular organs—three semicircular canals and two otolith organs—are the sensory organs in our inner ear that measure head rotation, tilt relative to gravity, and linear acceleration[1]. Past work has revealed that the vestibular system plays a pivotal role in a variety of functions that support our day-to-day behavior including (a) visual stabilization when moving via vestibulo-ocular reflexes, (b) maintaining balance via vestibulo-spinal reflexes, (c) regulation of autonomic responses (e.g., helping maintain blood flow to the brain) and (d) spatial orientation (i.e., perceiving where our body is relative to the external environment)[1]. Vestibular loss can yield spatial disorientation (i.e., impaired ability to perceive head motion or orientation) and/or severe impairment to bipedal balance when standing, walking, and/or running[2,3].

Mild hypoxia (i.e., insufficient oxygenation) is routinely experienced in mountaineering and aviation (both commercial and military aviation) as well as by patients suffering from disorders like sleep apnea and chronic obstructive pulmonary disease. Furthermore, moderate to severe hypoxia is known to have a plethora of adverse effects on sensory systems, cognition, and motor control[4,5]; these adverse effects are reported to begin occurring at altitudes ranging from about 3000 m (10,000 ft) to 4500 m (15,000 ft)[6,7].

Despite evidence that hypoxia can adversely affect sensory function, only a few studies are available that report the effect of hypoxia on vestibular function. Rodent studies showed that the vestibulo-ocular reflex of mice was reduced[8] when breathing 11.3% O_2, which simulates an altitude of 5000 m (16,000 ft; roughly the height of Mt. Blanc), and that rat vestibular neuron responses were altered when breathing 5% O_2[9], which simulates an altitude greater than 9000 m (>30,000 ft; higher than Mt. Everest). A human[10] study reported that perception of rotation might be impacted when breathing 9% O_2, which simulates an altitude of 6700 m (22,000 ft; substantially higher than Mt. Denali). There is also evidence that 11% and 12% O2, which simulate 4000 m (13,100 ft) and 5000 m (16,400 ft) respectively, results in blunted postural reaction forces[11] and postural muscle responses[12] to electrical vestibular stimulation (EVS). We have been unable to find any peer-reviewed studies reporting the impacts of mild hypoxia—like that experienced on commercial aircraft—on human vestibular function. The absence of research studying the impacts of mild hypoxia on vestibular function raises concerns because mild hypoxia is commonly experienced by humans in a variety of contexts including skiing, mountaineering, and aviation (e.g., piloting or even flying commercially) where being unable to precisely sense the position of ones' body relative to the environment can have severe adverse consequences. Even athletes show small reductions in blood oxygenation during strenuous exertion[13–16] that could impact vestibular function, and hence, performance while moving.

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Despite the importance of the vestibular system—defined to include both the peripheral organs and their neural connections—there is a dearth of work examining the impact of hypoxia on human vestibular function. Despite the limited amount of research on this topic, five lines of evidence suggest that the vestibular system may be particularly sensitive to hypoxia: (a) Common early symptoms of hypoxia include dizziness and vertigo—both of which can be associated with vestibular dysfunction[17] (b) Rodent research suggests that severe hypoxia can adversely impact the function of neuroanatomical regions involved in processing vestibular information while sparing the function of other non-vestibular regions[9] (c) Recent EVS studies provide evidence of blunted vestibular reflexes in acute normobaric hypoxia, in the absence of changes in the center of pressure[11,12] (d) Data suggest the vestibular organs are more dependent on oxidative phosphorylation, which requires oxygen, than other sensory systems such as the auditory system[18]. (e) The vestibular system's neurons demonstrate a much higher resting discharge rate than other sensory systems[19], which places a high metabolic load on the vestibular system's neuronal energy delivery systems. The above lines of evidence suggest not only that vestibular function might be impacted by mild hypoxia, but that the vestibular system may be especially sensitive to hypoxia relative to other sensory systems.

Based upon the evidence reviewed above, it seems that hypoxia could adversely affect vestibular function in humans at lower altitudes than other sensory systems, but there is a paucity of research examining the impact of hypoxia on human vestibular function—with a total absence of research studying the impact of mild hypoxia on human vestibular thresholds. To address this knowledge gap, we conducted a study examining the impact of breathing air with an oxygen content of 15.4% O_2, which simulates an altitude of 2400 m (~ 8000 ft; referred to as the *15% O_2* condition) on vestibular perceptual thresholds.

We chose to measure perceptual thresholds, because thresholds (i.e., the smallest upward or downward translation one can reliably sense) have been shown to be sensitive measures of vestibular function[3,20–27]. We specifically chose earth-vertical "Z-Translation" thresholds as our primary metric because total bilateral loss of the vestibular system increases Z-Translation thresholds by over 5000%[26]. This indicates that the vestibular system predominantly determines these Z-Translation thresholds—with other cues (e.g., tactile, somatosensation) only contributing for motions that are much greater than those that are typically sensed reliably by humans with a healthy vestibular system. We hypothesized that when mildly hypoxic, participants would have higher Z-Translation thresholds, indicating less precise sensation relative to when they were breathing a gas mixture with 20.9% O_2 chosen to simulate local baseline conditions (20.9% O_2 at about 250 m [820 ft]). We also sought to characterize the time course of this effect and determine whether decreases in peripheral oxygen saturation (i.e., SpO_2) was predictive of this effect.

Method

Procedure

All participants included in the analyses reported below completed multiple separate sessions of threshold tests. All testing was performed at a real-world altitude of about 250 m (820 ft) at an associated average normobaric atmospheric pressure of about 102 kPascals or 1.01 atmospheres. Upon arrival at the facility for Day 1 testing, participants provided informed consent in accordance with the Declaration of Helsinki. Upon providing informed consent, participants were seated in a racing seat mounted to a 26″ MOOG 6-Degrees of Motion Platform in a completely darkened room (Fig. 1A). To further remove visual cues, a shroud was attached to the helmet and enclosed the participant's head. To help ensure that the participants' did not have undiagnosed

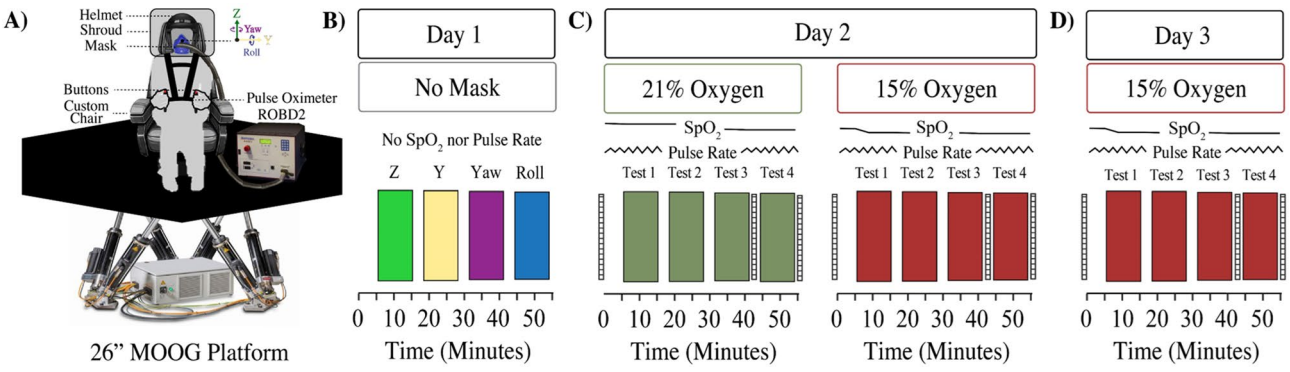

Fig. 1. Experimental Procedure. Schematic depiction of the experimental procedure. (**A**) Participants were seated upright in a custom chair on a 26″ MOOG platform and were equipped with a helmet, shroud, buttons, fingertip pulse oximeter, and breathing mask attached to a reduced oxygen breathing device (ROBD-2). (**B**) On Day 1, participants did not wear the mask nor pulse oximeter and completed 4 baseline threshold tests (Z-Translation (bright green), Y -Translation (yellow), Yaw Rotation (purple) and Roll Tilt (blue))—each consisting of 100 trials. (**C**) On Day 2, participants wore the breathing mask and pulse oximeter and then completed 4 Z-Translation tests at *21% Oxygen* (green) and then again at *15% Oxygen* (red). (**D**) On Day 3, 8 participants returned to the lab to complete 4 more Z-Translation tests at *15% Oxygen*. On Day 2 and Day 3, an attention test—shown as a small black and white block above—was performed immediately before the beginning of breathing through the mask as well as before and after the 4th test.

vestibular dysfunction, they then completed 4 baseline threshold tests (Z-Translation, Y-Translation, Yaw Rotation, and Roll Tilt)—each consisting of 100 trials (Fig. 1B). The Z-Translation, Y-Translation, and Yaw Rotation conditions all used 1 Hz single cycles of sinusoidal acceleration having a 1 s duration; the Roll Tilt condition used a slightly lower frequency (0.5 Hz stimuli lasting 2 s) to better reflect canal-otolith integration[28]. Consistent with previous work (Lim et al.[28]) the rotation axis was located between the ears near the center of the head (i.e., "head-centered").

Upon completion of these tests, participants were fitted with a silicone oronasal breathing mask (Hans Rudolph, Inc.; Shawnee, KS) and tried breathing through it while it was connected to a Reduced Oxygen Breathing Device 2 (ROBD-2) providing 20.9% O_2; this was done so each participant could experience breathing via the mask prior to their second day of testing.

Each participants' Day 2 test session was separated from the Day 1 testing by a minimum of 48 h. Upon entering the lab, participants were seated on the motion platform and completed one attention task without an oronasal mask. Each attention task consisted of 10 large suprathreshold earth-vertical translations having a magnitude of 32 cm/s. The participant pressed handheld buttons to indicate the direction of motion (i.e., much like the threshold task but for much larger motions). This task was included for three reasons: (a) to help make sure that the participants understood the task, (b) to make sure that the participants were responsive, and (c) to serve as a control to quantify any changes in self-motion cognition. Upon completion of the attention task, the experimenter affixed the breathing mask to the participant's face and ensured that there was a tight seal. Next, the ROBD-2 was activated and began releasing the desired gas mixture (i.e., 20.9% O_2, 78.1% N_2, with trace gases making up the remainder), which we will refer to as the *21% O_2* condition and a shroud was attached to the helmet to enclose the participant's head. The participant then completed four Z-translation threshold tests and two more attention tests (before and after threshold test four) over the course of an hour; see Fig. 1C for a timeline.

Upon completion of those four *21% O_2* tests, the participants were given a minimum of a 10-min break where they were encouraged to walk around to help maintain alertness. After the break, participants were seated on the motion platform again, and the procedure described above was repeated with the noteworthy exception of the gas mixture, which was reduced to 15.4% O_2 (remainder N_2), which we will refer to as the *15% O_2* condition. 15.4% O_2 was chosen to simulate the oxygen content of air at 2440 m (~8000 ft) which is set as the pressurization limit for US commercial flights by the Federal Aviation Administration (FAA). Furthermore, this test condition kept us below the altitude range between 2440 and 3050 m (~8000 ft and ~10,000 ft) at which increased respiratory ventilation typically begins to develop at rest[6]. This seems important because increased ventilation causes hypocapnia (i.e., decreased arterial CO_2 which can reduce cerebral blood flow) and respiratory alkalosis (i.e., elevated blood pH due to increased respiration rate), each of which might act to alter the impact of hypoxia. The order of conditions (i.e., *21% O_2* before *15% O_2*) was selected so that the tests in the *15% O_2* condition could not impact the tests utilizing *21% O_2*. While our consent process required that we inform subjects of the O_2 content they would experience during the study, participants were blinded to the condition.

After completing the first two test days, eight of the participants agreed to come back and complete a third day of testing where they completed four tests in the *15% O_2* condition a second time (see Fig. 1D for a timeline). This third session was separated by at least 48 h from the second session. The purpose of this 3rd day of testing was to control for any potential fatigue effect in Day 2. More specifically, the third day was added to help confirm that any threshold increases observed in the second day's *15% O_2* condition were due to breathed gases and not attention/fatigue effects. Eight participants agreed to complete Day 3, however, one participant discontinued before the end of the session leaving seven participants with complete Day 3 data sets.

During the 2nd and 3rd test days, we also recorded pulse rate and blood oxygenation—specifically peripheral oxygen saturation (SpO_2)—using a finger mounted pulse oximeter built into the reduced oxygen breathing device-2 (ROBD-2 by Environics, Inc.) that controlled O_2 content. See Fig. 1 for a schematic depicting the apparatus and order of events in each session.

Equipment

26″ MOOG six degree of freedom motion platform

Motion stimuli were delivered using a 26″ MOOG six degree of freedom motion platform (Fig. 1A; model MB-E-6DOF/26/1800 KG; MOOG, Inc.; Elma, NY). This platform was controlled by custom software, which exchanged data packets with the platform at a rate of 400 Hz. Participants were seated in a custom-built chair affixed to the motion platform. The chair was padded to distribute tactile cues as evenly as possible thus minimizing their impact on performance, as has been done in past studies (e.g. Valko et al.[26]). The participant's head was restrained in a motorcycle helmet, which was mounted to the chair, which allowed for the motions of the head and body to be coupled to the platform. The distance between the seat and helmet was adjusted dependent on height to minimize discomfort. To eliminate visual motion cues, all testing took place in a dark room with a light-tight shroud affixed to the helmet to eliminate any light leaks. Additionally, headphones were used to provide sound attenuation (~20 dB sound pressure level (SPL)), and binaural white noise (at ~60 dB SPL) was provided during each test motion to ensure motion-related auditory cues could not be utilized.

Reduced oxygen breathing device-2

A 2nd generation Reduced Oxygen Breathing Device (ROBD-2, Environics, Inc.; Tolland, CT) was used to mix breathing gases (Fig. 1A). The ROBD-2 is a breathing gas mixer capable of controlling the partial pressure of oxygen for simulated altitudes between 0 and 12,192 m (0 to 40,000 ft) by combining nitrogen, and compressed air and has a built-in pulse oximeter which was affixed to the participant's left middle finger. The ROBD-2 sent pulse oximetry data to an external computer, which recorded it at the rate of 1 Hz, via a custom program written

with LabView. Participants were exposed to the gas mixture via an oronasal breathing mask (Hans Rudolph, Inc.; Shawnee, KS) which was connected to the ROBD-2.

Perceptual thresholds

Vestibular thresholds were measured using a widely utilized direction recognition task[3,29,30] that provided earth-vertical translation stimuli. Each threshold test consisted of 100 earth-vertical (i.e., upward or downward) translation trials over a period of about 8 min; each trial consisted of a single cycle of sinusoidal acceleration that lasted 1 s (i.e., 1 Hz)[23,31]. The magnitude of the first motion was always 16 cm/s. Initially, the size of the motion decreased by half if the participant accurately identified the direction of the motion two times in a row, whereas the size of the motion doubled if they answered incorrectly. Following the first reversal, the motion magnitude was adjusted using an adaptive 4-Down, 1-Up staircase procedure, with the step sizes determined using PEST rules[32].

As in previous studies[33–35], the thresholds for each test were estimated by fitting a psychometric curve, specifically a cumulative Gaussian distribution with two parameters—a bias parameter (μ) and a threshold parameter (σ)—to the forced-choice data. This fitting procedure utilized a maximum likelihood approach. To address a known fitting error believed to result from the stair-case stimuli-selection methodology[32,36] for the threshold parameter, we fit our data using a bias-reduced general linear model with a probit link function[37]. Since participants can occasionally lose focus, individual trials were detected as lapses and removed from the analysis using a lapse identification algorithm[38]. The aforementioned procedure models a Gaussian distribution which is defined by error (μ) and the one-sigma vestibular threshold (σ). Stimuli provided having a magnitude equal to the threshold would be expected to yield 84.1% accuracy on average. The σ can be thought of as the precision with which the individual is able to sense the movement stimuli, with higher threshold values indicating lower precision. All translation thresholds are reported in centimeters per second (cm/s); all rotation thresholds are reported in degrees per second (°/s).

Participants

Twenty-one participants (nine females) participated in this study. The participants' ages ranged from 21 to 36 years (mean = 26.76, SD = 5.24). All participants denied a history of neurological, vestibular, respiratory, and cardiovascular disease. Furthermore, all reported not living at an altitude of 5000 ft (1524 m) or higher for 10 days in the year prior to their testing. All participants provided informed consent in accordance with the Declaration of Helsinki. The study protocol was approved by the Ohio State University Institutional Review Board (protocol # 2018H0249) and the Naval Medical Research Unit Dayton Institutional Review Board. The study described in this paper was performed in accordance with all relevant guidelines and regulations.

Data analysis

Four participants withdrew from the study after Day 1, leaving 17 participants who participated in Days 1 and 2. Of the seventeen participants available for analyses, two were missing data from at least 1 test leaving threshold data for fifteen participants for repeated measures ANOVAs. Of the fifteen participants with complete threshold data, three were missing ROBD-2 data for at least one test leaving twelve participants available for repeated measures ANOVAs comparing SpO_2 and pulse rate. Similar to previous studies, perceptual translation thresholds in this study were $\log_{10}$ normally distributed and thus transformed using a base 10 logarithm prior to analyses[3]. Thresholds during 3 of 60 tests (2 tests in the *21% O_2* condition and 1 test in the *15% O_2* condition) across two participants were greater than 5 standard deviations above the mean of their respective conditions and were therefore imputed using the mean of the remaining tests from the participants in each condition.

All statistical tests were conducted using R and R Studio (Version 4.4.1). To establish whether the oxygen manipulations had an effect and whether it changed over time 2 × 4 repeated measures factorial ANOVAs were performed on three dependent variables (i.e., thresholds, blood oxygenation and pulse rate). We also performed 2 × 3 repeated measures ANOVAs on the attention test data. All ANOVAs and relevant post-hoc tests were performed using the 'rstatix' package. To correct for sphericity violations when they occurred, p values were modified based on Greenhouse–Geisser corrected degrees of freedom. To analyze whether changes in SpO_2 predicted changes in Z-Translation thresholds, a linear mixed effect model with a fixed-effect factor for SpO_2 and random slopes and intercepts for participants was used. P-values were calculated using Type II analysis of variance with Satterthwaite's approximation method and the lmerTest package[39]. Given reviewer concerns about statistical power we ran a post hoc power analysis using G*Power (version 3.1.9.7)[40] on our the primary focus of the paper, the difference between the *15%* and *21% O_2* conditions.

Results

Baseline threshold tests suggest no participants exhibited vestibular dysfunction

Figure 2A shows thresholds recorded when breathing room air for four different motions—Z-Translation (the focus of the rest of this paper, geometric mean = 2.81 cm/s), Y-Translation (geometric mean = 1.28 cm/s), Yaw Rotation (geometric mean = 1.41°/s) and Roll Tilt (geometric mean = 3.30°/s). Log_{10}-normal distributions mimic published distributions for different populations of individuals with healthy vestibular systems using similar methods[23,26,39–41] After taking the $\log_{10}$-normal distribution into account, no outliers beyond 3 standard deviations above the mean were identified, which suggests this is a uniform population with no participant showing any overt indications of vestibular dysfunction.

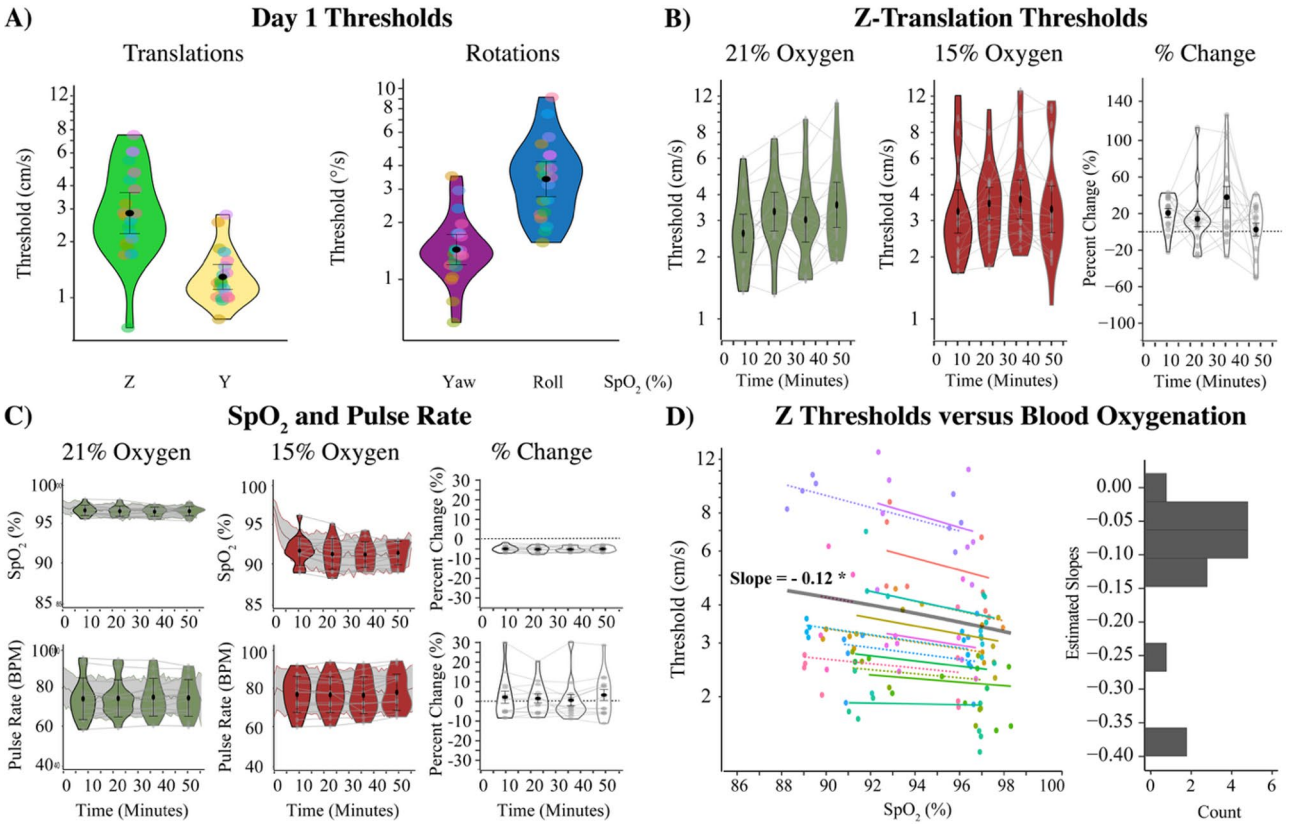

Fig. 2. Threshold, Blood Oxygenation, and Pulse Rate Results. (**A**) Violin plots which represent the means and 95% confidence intervals for Z-Translation (light green) and Y-Translation (yellow) thresholds as well as Yaw Rotation (purple) and Roll Tilt (blue) rotation thresholds. Colored dots represent individuals. (**B**) Means and 95% confidence intervals of Z-Translation thresholds when breathing *21% O_2* (green), *15% O_2* (red), as well as the mean percent change of $\log_{10}$-transformed thresholds from *21* to *15% O_2* for each test (gray). Dots and the lines connecting them represent individuals. (**C**) Violin plots represent the means and 95% confidence intervals for each test and the continuous traces show the mean values for the *21% O_2* and *15% O_2* conditions across time with the standard error shaded on either side. Dots and the lines connecting them represent individuals. (**D**) A scatter plot depicting the relationship between SpO_2 and $\log_{10}$-transformed vertical translation thresholds determined from the linear mixed effect model. Colored dots represent individuals with linear fit shown via colored lines. The solid gray line represents the mean effect across subjects. The average slope was −0.12; the * indicates that this slope was significantly different from zero ($p < .05$). The histogram shows the estimated slope for each subject.

There was no difference in thresholds, blood oxygenation, or pulse rate between the *15% O_2* condition on Day 2 and Day 3

Table 1 shows the condition means for Days 2 and 3 of threshold tests in the *15% O_2* condition. Differences between days and tests were negligible. To confirm that there were not any differences in Z-Translation thresholds across Days 2 and 3, a 2 X 4 (2 Days X 4 Threshold Tests) Repeated Measures Factorial ANOVA was performed. No statistically significant main effects or interactions were found. Similarly, two additional 2 X 4 Repeated Measures Factorial ANOVA analyses revealed no differences for either SpO_2 or pulse rate between the *15% O_2* condition tested on Day 2 *versus* Day 3. If participants completed both Day 2 and Day 3 testing, the average threshold, SpO_2, and pulse rate across days 2 and 3 were utilized in the analyses below. See Table 2 for information about analyses on the SpO_2 and pulse rate data.

Thresholds increased in the *15%* O_2 condition

Figure 2B shows the Z-translation thresholds for both the *21% O_2* condition and the *15% O_2* condition as well as the percent change in the *15% O_2* condition relative to the *21% O_2* condition. For tests 1 through 3, the average Z-Translation threshold was 22.52%, 4.23%, 22.13% higher in the *15% O_2* condition than the 21% O_2 condition. During test 4, the average threshold in the *15% O_2* condition was 1.45% lower than the *21% O_2* condition, suggesting potential acclimation to the mild hypoxia experienced. In order to determine whether the observed increases were significant, a 2 × 4 (2 O_2 Conditions X 4 Threshold Tests) Repeated Measures Factorial ANOVA was performed (Table 1). It was found that there was a main effect of condition and test, as well as an interaction between them. More specifically, as a primary finding, thresholds in the *15% O_2* condition were higher than

Dependent variable	Comparison	F(df), p, n^2_G	Condition	Geometric Mean [cm/s]	Log_{10} Mean (SD)
Threshold	Day (for 15%O_2)	$F(1,6) = 0.674$, p = .443, n^2_G = .012	Day 2 Day 3	3.574 3.417	0.553 (0.228) 0.534 (0.231)
	Test	$F(1.31,7.85) = 0.799$, p = .432, n^2_G = .016	Test 1 Test 2 Test 3 Test 4	3.307 3.609 3.784 3.391	0.519 (0.248) 0.557 (0.185) 0.578 (0.223) 0.530 (0.260)
	Day * Test	$F(3,18) = 1.766$, p = .190, n^2_G = .016	Day 2 Test 1 Day 2 Test 2 Day 2 Test 3 Day 2 Test 4 Day 3 Test 1 Day 3 Test 2 Day 3 Test 3 Day 3 Test 4	3.518 3.487 3.822 3.472 2.982 3.864 3.710 3.242	0.546 (0.287) 0.542 (0.183) 0.582 (0.225) 0.541 (0.228) 0.475 (0.169) 0.587 (0.197) 0.569 (0.234) 0.511 (0.329)
Threshold	**O_2 Condition**	**$F(1,14) = 8.440$, p = .012, n^2_G = .015**	21% Oxygen 15% Oxygen	3.095 3.502	0.491 (0.199) 0.544 (0.217)
	Test	**$F(3,42) = 3.722$, p = .017, n^2_G = .028**	Test 1 Test 2 Test 3 Test 4	2.865 3.385 3.391 3.525	0.457 (0.206) 0.530 (0.175) 0.530 (0.221) 0.547 (0.227)
	O_2 Condition * Test	**$F(3,42) = 3.829$, p = .016, n^2_G = .015**	21% Test 1 21% Test 2 21% Test 3 21% Test 4 15% Test 1 15% Test 2 15% Test 3 15% Test 4	2.593 3.300 3.015 3.559 3.207 3.477 3.843 3.489	0.414 (0.180) 0.519 (0.182) 0.479 (0.211) 0.551 (0.211) 0.506 (0.228) 0.541 (0.172) 0.585 (0.225) 0.543 (0.249)

Table 1. The pertinent information for the repeated measures Factorial ANOVAs performed on thresholds. Due to the fact that thresholds are log_{10}-normally distributed across individuals, both the geometric mean in physical units and the arithmetic mean after taking the log_{10} are shown. As justification, the geometric mean is identical to calculating the inverse log_{10} of the mean of the log_{10} of the data values (e.g., inverse log_{10}(mean[log_{10}Threshold])). Conditional mean and SD are shown after taking the base 10 log (i.e., log_{10}) of the velocity threshold. Statistically significant main effects and interactions are in bold text. Note n^2_G is the symbol for generalized eta squared.

the *21% O_2* condition ($p = .012$). A post hoc power analysis conducted using G*Power found that the observed power was 0.99, indicating that the study was sufficiently powered to detect an effect.

Follow up t-tests indicated that in the *21% O_2* condition thresholds increased from test 1 to test 2 ($T(14) = -3.01$, $p = .009$), test 1 to test 4 ($T(14) = -4.68$, $p < .001$), and from test 3 to test 4 ($T(14) = -2.50$, $p = .025$). Conversely, thresholds only increased between test 1 and test 3 ($T(14) = -2.18$, $p = .047$) in the *15% O_2* condition. Furthermore, it was also found that thresholds were higher in the *15% O_2* condition than the *21% O_2* during test 1 ($T(14) = -3.16$, $p < .01$) and test 3 ($T(14) = -3.25$, $p < .01$) but not test 2 ($T(14) = -1.43$, $p = .175$) or test 4 ($T(14) = 0.50$, $p = .623$). It is important to note that the average value for test 2 was higher in the *15% O_2* condition than the *21% O_2* condition.

Blood oxygenation decreased but pulse rate was not significantly changed in the *15% O_2* condition

Blood oxygenation substantially decreased in the *15% O_2* condition relative to the *21% O_2* condition ($p < .001$). However, no significant changes in pulse rate were observed. (See Fig. 2C and Table 2).

Lower blood oxygenation was associated with higher thresholds

The analyses above provided evidence that exposure to the *15% O_2* condition resulted in increased Z-Translation thresholds and decreased blood oxygenation. This, alongside accepted pulmonary physiology knowledge, suggests that reduced blood oxygenation might cause the Z-Translation thresholds to increase. While correlation cannot prove causation, this hypothesis is consistent with the plot in Fig. 2D which shows that Z-Translation thresholds were negatively associated with blood oxygenation. To quantify the relationship between Z-Translation thresholds and blood oxygenation, we utilized a linear mixed effects model with SpO_2 as a fixed effect and participant as a random effect. The resulting model was found to explain most of the data variability (Scaled residual median was −0.1037, 1st Quartile was −0.4049 and 3rd Quartile was 0.2692).

Lower blood oxygenation strongly and significantly predicted Z-Translation threshold increases (i.e., worse vestibular precision), (Intercept: Estimate = 15.218, Std. Error = 5.017, T = 3.034, $p < .01$; Slope: Estimate = −0.122, Std. Error = 0.050, T = −2.419, $p < .05$). The 95% confidence interval for the slope was [−0.221 to −0.0231], which does not include 0. There was moderate between-subject variability (Intercept: Variance = 159.72, SD = 12.63; Slope: Variance = 0.0132, SD = 0.115). The correlation of fixed effects (−0.997) indicated subjects with higher intercepts have more negative slopes—meaning individuals with higher thresholds exhibited larger threshold changes associated with SpO_2 changes.

Dependent variable	Comparison	F(df), p, n^2_G	Condition	Mean (SD)
SpO2 [%]	Day (for 15%O_2)	$F(1,5) = 0.491$, $p = 0.515$, $n^2_G = .038$	Day 2 Day 3	91.587 (1.881) 90.471 (1.428)
	Test	**$F(3,15) = 3.976$, $p = 0.029$, $n^2_G = .055$**	Test 1 Test 2 Test 3 Test 4	91.625 (1.963) 91.097 (2.001) 90.997 (1.716) 91.108 (1.582)
	Day* Test	$F(3,15) = 3.147$, $p = 0.056$, $n^2_G = .015$	Day 2 Test 1 Day 2 Test 2 Day 2 Test 3 Day 2 Test 4 Day 3 Test 1 Day 3 Test 2 Day 3 Test 3 Day 3 Test 4	91.935 (2.162) 91.508 (2.127) 91.456 (1.668) 91.456 (1.693) 91.081 (1.532) 90.378 (1.637) 90.081 (1.521) 90.239 (0.847)
Pulse Rate [beats/min]	Day (for 15%O_2)	$F(1,5) = 1.11$, $p = 0.348$, $n^2_G = .002$	Day 2 Day 3	75.540 (8.892) 80.612 (12.97)
	Test	$F(3,15) = 1.04$, $p = 0.403$, $n^2_G = .062$	Test 1 Test 2 Test 3 Test 4	77.269 (10.812) 77.190 (10.863) 77.117 (10.905) 77.427 (10.766)
	Day * Test	$F(3,15) = 2.63$, $p = 0.088$, $n^2_G = .003$	Day 2 Test 1 Day 2 Test 2 Day 2 Test 3 Day 2 Test 4 Day 3 Test 1 Day 3 Test 2 Day 3 Test 3 Day 3 Test 4	74.722 (9.302) 74.898 (9.127) 75.288 (8.773) 77.138 (9.123) 81.726 (12.422) 81.201 (13.053) 80.774 (14.362) 78.149 (15.155)
SpO2 [%]	**O_2 Condition**	**$F(1,11) = 190.4$, $p < .001$, $n^2_G = .811$**	21% Oxygen 15% Oxygen	96.748 (0.615) 91.425 (1.699)
	Test	$F(1.2,13.5) = 2.68$, $p = .120$, $n^2_G = .017$	Test 1 Test 2 Test 3 Test 4	94.282 (2.943) 94.020 (3.113) 93.955 (3.015) 94.174 (2.914)
	O_2 Condition * Test	$F(3,33) = 1.650$, $p = .197$, $n^2_G = .007$	21% Test 1 21% Test 2 21% Test 3 21% Test 4 15% Test 1 15% Test 2 15% Test 3 15% Test 4	96.844 (0.667) 96.739 (0.662) 96.669 (0.590) 96.740 (0.598) 91.720 (1.848) 91.301 (1.941) 91.240 (1.631) 91.437 (1.506)
Pulse rate [beats/min]	O_2 Condition	$F(1.5,16.6) = 0.786$, $p = 0.218$, $n^2_G = .008$	21% Oxygen 15% Oxygen	75.131 (9.757) 77.154 (9.248)
	Test	$F(3,33) = 1.675$, $p = 0.191$, $n^2_G = .003$	Test 1 Test 2 Test 3 Test 4	75.898 (10.073) 75.916 (9.394) 76.074 (9.595) 76.597 (9.516)
	O_2 Condition * Test	$F(1.5,16.7) = 0.603$, $p = 0.515$, $n^2_G = .0007$	21% Test 1 21% Test 2 21% Test 3 21% Test 4 15% Test 1 15% Test 2 15% Test 3 15% Test 4	74.770 (10.868) 74.993 (9.705) 75.566 (9.891) 75.187 (9.628) 77.025 (9.481) 76.839 (9.341) 76.582 (9.635) 78.101 (9.488)

Table 2. The pertinent information for the repeated measures Factorial ANOVAs performed on the SpO2 and Pulse Rate Data. Statistically Significant values are in bold.

Attention test performance did not change

The attention test data showed that all participants responded in an accurate manner—indicating that the participants both understood the threshold task and remained responsive even when mildly hypoxic. Across all subjects, the direction of these attention trials was correctly identified during 98.8% of the trials for the *21% O_2* condition and 98.5% of the trials for the *15% O_2* condition. (See Table 3 for details.) Since the rate of incorrect trials is between 1 and 2%, which is within the 0 to 5% range identified as lapses by earlier studies[42,43], the rare incorrect trials seem likely to be lapses caused by inattention, which did not change with the O_2 condition.

We conducted 2 separate 2 × 3 (2 Conditions × 3 Attention Tests) Repeated Measures Factorial ANOVAs to compare attention test scores in (1) the Day 2 and Day 3 15% O_2 conditions as well as the day 2 *21% O_2* condition and the *15% O_2* condition average. No statistically significant differences were found between conditions or across tests within conditions—further suggesting that mild hypoxia did not affect participants' attention or cognitive ability to respond in an accurate manner when movements were well above threshold (Table 3), which is consistent with earlier literature[44].

Dependent variable	Comparison	F(df), p, n^2_G	Mean % Correct (SD)
21% O_2 and 15% O_2 on Day 2	O_2 Condition	$F(1,15) = 0.06$, $p = .817$, $n^2_G = .001$	21% O_2: 98.8 (0.61) 15% O_2: 98.5 (0.46)
	Test	$F(1,15) = 1.90$, $p = .118$, $n^2_G = .064$	Test 1: 99.7 (0.18) Test 2: 98.4. (0.52) Test 3: 97.8 (0.75)
	O_2 Condition * Test	$F(1,15) = 1.00$, $p = .333$, $n^2_G = .007$	21% O_2, Test 1:100 (0.00) 21% O_2, Test 2: 96.9 (0.34) 21% O_2, Test 3: 98.8 (0.34) 15% O_2, Test 1: 99.4 (0.25) 15% O_2, Test 2: 100 (0.00) 15% O_2, Test 3: 96.8 (1.01)
15% O_2 on Day 2 and 15% O_2 on Day 3	O_2 Condition	$F(1,7) = 1.00$, $p = .351$, $n^2_G = .034$	Day 2: 98.3 (0.82) Day 3: 100 (0.00)
	Test	$F(1,7) = 1.00$, $p = .351$, $n^2_G = .051$	Test 1: 100 (0.00) Test 2: 100 (0.00) Test 3: 97.5 (0.25)
	O_2 Condition * Test	$F(1,7) = 1.00$, $p = .351$, $n^2_G = .051$	Day 2, Test 1: 100 (0.00) Day 2, Test 2: 100 (0.00) Day 2, Test 3: 95.0 (1.41) Day 3, Test 1: 100 (0.00) Day 3, Test 2: 100 (0.00) Day 3, Test 3: 100 (0.00)

Table 3. The mean percent correct and SD of participant's accuracy in the attention tests. A perfect score would be 100%.

Discussion

The aim of the present study was to establish whether mild hypoxia induced by breathing air with 15.4% O_2 adversely impacted human vestibular function. To this end participants completed multiple sessions measuring Z-Translation thresholds, which were found to exhibit statistically significant increases when exposed to simulated altitudes of 2440 m (~8000 ft), as we have earlier reported in abstract form[45]. This means that larger motions were needed to be able to reliably sense the motion direction in the *15% O_2* condition than the *21% O_2* condition. It is important to note that this is roughly 600 m below the altitude at which changes in sensory and cognitive functioning have previously been reported[6,44] and suggests that changes in vestibular function may be an early indicator of hypoxia. This is especially noteworthy because 2440 m is the altitude limit commercial airlines must pressurize to in the United States, meaning passengers and pilots may routinely experience temporary decrements in vestibular function.

We attribute these changes to changes in vestibular function because:

1. An earlier study showed the predominant impact of vestibular function on Z-Translation thresholds quantified using nearly identical methods as patients with no inner ear function (i.e., total bilateral vestibular loss) had Z-Translation thresholds that were more than 5000% higher than for healthy controls with normal vestibular function[26]. This paper concluded that other sensory systems (e.g., somatosensation) are likely making negligible contributions to Z-Translation perception at the threshold levels tested therein, which are mimicked herein, and
2. Our participants' high accuracy on attention tests suggests that the change reported above is not the result of an attentional (or other cognitive) impairment. If attentional/cognitive factors were the cause, one would expect to see a substantive difference between attention test 1 (done prior to oxygen manipulation) and one or more of the tests performed in the *15% O_2* conditions, which, as reported above, did not occur.

Additional evidence suggesting that hypoxia may impact vestibular function comes from studies of the effects of hypoxia on balance. It is established that vestibular sensation contributes to postural control[2,46], which is a complex multi-sensory sensorimotor response. A recent systematic review[47] concluded that hypoxia impacts balance and this impact is likely the result of altered processing and/or integration of sensorimotor signals within the central nervous system and motor commands produced by it. Two follow-up studies have reported that reaction forces[11] and EMG responses[12] evoked by electrical stimulation of the vestibular system are altered by hypoxia. These findings are consistent with the review's suggestion that processing of sensory cues in cortical or subcortical structures is altered by hypoxia.

However, in light of our findings that vestibular Z-Translation thresholds are impacted by mild hypoxia and that vestibular cognition is not impacted (i.e., that the perception of the direction of large motions was unchanged), these recent balance findings can also be interpreted as suggesting that hypoxia might impact vestibular function per se. Given this viable interpretation, it is important to note that the available oxygen used in the above studies that focused on vestibular contributions to balance provided a much greater cardiopulmonary challenge than we used herein. The study focused on reaction forces[11] provided 12% O_2, which simulates an altitude of 4000 m (13,100 ft; about the height of Pike's Peak), and the study focused on EMG responses[12] provided 11% O_2, which simulates an altitude of 5000 m (16,400 ft; about the height of the Mount Everest base camp). For comparison, our study showed substantial effects on earth-vertical translation thresholds at 15.4% O_2, which simulated an altitude of 2400 m (8000 ft; about the altitude of Aspen, Colorado).

The difference between findings reported herein and the aforementioned balance studies could reflect task related differences. Specifically, in our study participants were restrained in a padded chair which minimized movement and thus tactile, proprioceptive, and kinesthetic cues that could result from movement. Whereas in balance studies participants are able to move more freely thus allowing them to more easily utilize other sensory cues (e.g., kinesthetic cues) to sense the movement of their body and compensate for temporary degradation of vestibular function.

Additionally, we also found a statistically significant decrease in oxygen saturation in the *15% O_2* condition which is similar to decreases reported during commercial air travel[48] This decrease in blood oxygenation was found to be negatively correlated with increases in vestibular thresholds (Fig. 2D). Given this correlation found between thresholds and blood oxygenation, we posit that: (i) decreased blood oxygenation reduced local oxygen delivery to vestibular neurons (and other vestibular cells/tissues), this (ii) reduced ATP produced via oxidative phosphorylation, which (iii) altered the neuronal firing rates to (iv) negatively impact the precision of self-motion sensation.

As mentioned earlier, the vestibular system may be especially sensitive to this causative chain because of the high metabolic load imposed by each vestibular neuron to support their relatively high resting firing rate, which is on the order of 100 action potentials per second for vestibular afferent neurons[19]. Now that a substantial and significant effect of mild hypoxia on human vestibular function has been quantified for the first time by testing at the equivalent of 2400 m (8000 ft), the metabolic impacts of mild hypoxia on other neural and behavioral vestibular metrics should be quantified at conditions that create similar mild hypoxia—alongside other possible hypoxia moderators such as respiration rate and blood CO_2.

For context, we compare our blood oxygenation findings with data obtained during strenuous exercise. Athletes often experience small reductions in blood oxygenation during strenuous exercise[49,50] similar to those we measured herein during our *15% O_2* mild hypoxia test condition. If reduced blood oxygenation causes the threshold increase that we measured, this suggests that the vestibular function of athletes could analogously be impacted by mild hypoxia (and these impacts might be larger than in our study). For sports that require both high vestibular precision and extreme exertion (e.g., motocross, soccer, basketball, and ice hockey) such an impact, while hypothetical, could yield performance differences.

The present paper provides evidence that mild hypoxia can adversely affect the function of the vestibular system in humans. The vestibular system plays a pivotal role in our ability to sense where our body is relative to the external environment, thus vestibular function failure can result in injury and potentially death. In our study, participants exhibited statistically significant decreases in vestibular precision at a simulated altitude of 2440 m (8000 ft), which is the maximal equivalent altitude to which commercial airlines pressurize to in the United States. These decreases in precision resulted in participants needing larger earth-vertical translations to reliably sense them. The decreases in precision (i.e., higher Z-Translation thresholds) were correlated with decreased blood oxygen saturation. It is important to note that thresholds in the *15% O_2* condition dropped below thresholds in the *21% O_2* condition in the fourth test suggesting that acclimation may occur after approximately 45 min of exposure to the *15% O_2*. More work is needed to confirm this possibility.

The present study has several limitations which should be noted. One is the moderate sample size. This limitation is mitigated by a post-hoc power analysis that yields 99% power for our primary analysis of the impacts of mild hypoxia on Z-translation thresholds. Additionally, on Day 2 of threshold testing all participants completed the *21% O_2* condition prior to the *15% O_2* condition meaning fatigue/boredom could impact the results. However, it is important to note that attention test scores did not differ between the *21% O_2* and *15% O_2* conditions. Furthermore, no differences were found when comparing the *15% O_2* thresholds of the participants who completed a 3rd Day of threshold testing where thresholds were measured in the *15% O_2* condition early in that day's testing. It is also possible that tactile cues may have influenced performance of the threshold tests, however given the foam padding which reduced them and the small magnitude of the motions, this seems unlikely. Furthermore, an earlier study using similar padding showed that patients without any vestibular function (i.e., total surgical bilateral loss) showed thresholds that were over 5000% greater than for healthy controls—suggesting that motions would need to be much greater than the threshold-level motions used herein for tactile/somatosensation to contribute Z-Translation thresholds.

In sum, the present study provides evidence that the precision of the vestibular system is reduced by mild hypoxia (i.e., 15.4% O_2) and that greater reduction in peripheral oxygen saturation strongly and significantly predicts larger reductions in vestibular precision. However, much additional work is needed to better characterize the impact of hypoxia on the vestibular system in humans including vestibular impacts on human behavior. Open directions include: (a) examining lower and higher simulated altitudes, (b) examining the impact of hypoxia on individuals with vestibular dysfunction (e.g., bi-lateral vestibulopathy or vestibular migraines), and (c) determining if other types of motion (e.g., rotations, tilts, or earth-horizontal translations) show similar threshold increases during mild hypoxia.

Data availability

The data from the study described in this manuscript can be obtained from the corresponding author upon reasonable request.

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Declarations

Competing interests

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