Cardiorespiratory Responses to Voluntary Hyperventilation During Normobaric Hypoxia

Alexander Haddon; Joel Kanhai; Onalenna Nako; Thomas G. Smith; Peter D. Hodkinson; Ross D. Pollock

BACKGROUND: Unexplained physiological events (PE), possibly related to hypoxia and hyperventilation, are a concern for some air forces. Physiological monitoring could aid research into PEs, with measurement of arterial oxygen saturation (S_pO_2) often suggested despite potential limitations in its use. Given similar physiological responses to hypoxia and hyperventilation, the present study characterized the cardiovascular and respiratory responses to each.

METHODS: Ten healthy subjects were exposed to 55 mins of normobaric hypoxia simulating altitudes of 0, 8000, and 12,000 ft (0, 2438, and 3658 m) while breathing normally and voluntarily hyperventilating (doubling minute ventilation). Respiratory gas analysis and spirometry measured end-tidal gases ($P_{ET}O_2$ and $P_{ET}CO_2$) and minute ventilation. S_pO_2 was assessed using finger pulse oximetry. Mean arterial, systolic, and diastolic blood pressure were measured noninvasively. Cognitive impairment was assessed using the Stroop test.

RESULTS: Voluntary hyperventilation resulted in a doubling of minute ventilation and lowered $P_{ET}CO_2$, while altitude had no effect on these. $P_{ET}O_2$ and S_pO_2 declined with increasing altitude. However, despite a significant drop in $P_{ET}O_2$ of 15.2 mmHg from 8000 to 12,000 ft, S_pO_2 was similar when hyperventilating (94.7 ± 2.3% vs. 93.4 ± 4.3%, respectively). The only cardiovascular response was an increase in heart rate while hyperventilating. Altitude had no effect on cognitive impairment, but hyperventilation did.

DISCUSSION: For many cardiovascular and respiratory variables, there is minimal difference in responses to hypoxia and hyperventilation, making these challenging to differentiate. S_pO_2 is not a reliable marker of environmental hypoxia in the presence of hyperventilation and should not be used as such without additional monitoring of minute ventilation and end-tidal gases.

KEYWORDS: physiological episodes, arterial oxygen saturation, aircrew physiological monitoring.

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In recent years, unexplained physiological events (PE) during fast jet flight have been a concern for some military air forces. The symptoms which occur during flight are often described as 'hypoxic-like' and are often transient in nature. Numerous reports of PEs have been made,[7] but identifying their cause is challenging due to their complex and multifactorial nature, occurrence in almost all phases of flight with symptoms being self-reported by aircrew, and identification having to be inferred from this and engineering/equipment investigation.[6] Initially PEs were attributed to hypoxia; however, there are a number of factors such as acceleration atelectasis,[23,24] spatial disorientation, motion sickness, pressure changes, and decompression sickness[9] that can play a role. One factor that has been implicated in PEs, and in the United Kingdom suggested to account for two-thirds of hypoxic-like events in the Typhoon aircraft over a 10-yr period,[5] is hyperventilation.

Hyperventilation, defined as an increase in pulmonary ventilation that is out of proportion to the metabolic production

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of carbon dioxide (CO_2), causes a drop in arterial partial pressure of carbon dioxide (P_ACO_2) that can in turn oppose the increase in ventilation. The associated changes in P_ACO_2 and arterial pH will cause, among other things, heart rate to increase[11] and cerebral vasoconstriction.[12] This vasoconstriction can lead to reduced cerebral oxygenation and the ensuing cerebral hypoxia can result in symptoms such as personality changes, lack of judgment, short term memory loss, and mental incoordination, all of which can impair performance and are similar to those caused by hypoxia.[15] Hypoxia is defined as inadequate oxygen (O_2) in body tissues with hypoxic hypoxia being the most relevant in aviation.[22] The lowering of the arterial partial pressure of oxygen (P_AO_2) can lead to changes in heart rate and cerebral blood flow.[1,13,14] Ventilation is also increased through the acute hypoxic ventilatory response,[2] which is typically evident at altitudes >10,000 ft (>3048 m), although factors such as physical activity may lower this threshold.[28,29] There are also a number of additional causes of hyperventilation in flight such as whole body vibration, environmental stressors, and elevated temperatures.[15] The most common cause of hyperventilation is likely to be anxiety or stress, with it occurring more regularly in aircrew during training.[3] The deterioration in psychomotor performance associated with hyperventilation and hypoxia can be similar, and while aircrew are trained to assume any such symptom is due to hypoxia (and to take corrective action for this), it is important to emphasize that hyperventilation is an alternative potential causative factor.

There are a number of physiological variables and measurement devices that could be used to assess PEs or for routine monitoring of aircrew. One of the most often suggested is the measurement of arterial oxygen saturation (S_pO_2) through pulse oximetry.[27] Pulse oximetry is widely used in clinical settings to monitor oxygen saturation and can be used to detect hypoxia; however, there are a number of factors that can influence its readings (e.g., movement, hypotension, vasoconstriction, carboxyhemoglobinemia).[19] Hyperventilation is also known to influence the relationship between the partial pressure of inspired oxygen (P_IO_2) and saturation of oxygen in the arterial blood such that an S_pO_2 reading could be within acceptable limits despite a marked reduction in P_IO_2 and impaired oxygen delivery to the brain,[8] which could have implications for its use in an aerospace environment.

There are few studies comparing the effects of both hypoxia and hyperventilation on physiological function. Given the growing interest in the use of physiological monitoring in aircrew and its potential role in understanding PEs, it is important to understand the physiological interaction between hypoxia and hyperventilation. This is particularly relevant given the potential limitations of monitoring some physiological variables in an aviation setting. Therefore, the primary aim of the present study is to characterize the cardiovascular and respiratory responses to hypoxic hypoxia of moderate simulated altitudes and to superimposed hypocapnia induced by hyperventilation.

METHODS

Subjects

This study was approved by the King's College London Research Ethics Committee (HR-19/19-10,435). The study was conducted in accordance with the principles of the Declaration of Helsinki and participants provided written informed consent prior to taking part. A total of 10 healthy subjects (5 men and 5 women) with a mean (SD) age of 24.8 (5.47) yr, height of 1.73 (0.12) m, and mass of 71.5 (8.8) kg completed the study. All participants were nonsmokers with no history of cardiovascular, respiratory, or musculoskeletal disease.

Equipment

All physiological data were recorded and stored using LabChart (v8, ADInstruments, Sydney, Australia) following analog-to-digital conversion (Powerlab 16SP, ADInstruments). Throughout testing, heart rate (HR) was continually recorded using 3-lead ECG (LP10, HME, Bolton, UK). Beat-to-beat blood pressure was recorded noninvasively (Finapres 2300, Ohmeda, Englewood, CO, USA) using the volume-clamp method.[21] The Finapres finger cuff was placed on the third digit of the left hand at the middle phalanx with the hand supported at heart level using a sling. From the recorded blood pressure waveform systolic (SBP), diastolic (DBP), and mean arterial (MAP) blood pressure were determined. S_pO_2 was measured by pulse oximetry (7840, Kontron Instruments, Ismaning, Germany) with the probe placed on the right index finger.

During testing participants wore a low dead-space oro-nasal mask (7450 Series, Hans Rudolph Inc., Shawnee, KS, USA) to which a spirometer was attached (MLT1000L, ADInstruments), allowing respiratory flow rate to be recorded. The recorded flow signal was integrated on a breath-by-breath basis to determine tidal volume ($\dot{V}_T$) while respiratory rate (RR) was determined from the flow signal. Minute ventilation was calculated as the product of $\dot{V}_T$ and RR and displayed in real time to the participant on a screen directly in front of them. Respired O_2 and CO_2 concentrations were recorded using a rapid response analyzer (ML206-1008, ADInstruments) with the sampling tube connected to a port in the spirometer close to the mouth. Breath-by-breath end tidal partial pressures of oxygen ($P_{ET}O_2$) and carbon dioxide ($P_{ET}CO_2$) were determined from the fractional respired O_2 and CO_2 using peak/trough detection algorithms; barometric pressure was measured on each day of testing and used for the conversion.

To determine the effects of hypoxia and hyperventilation on cognitive function each participant completed the Stroop Test.[31] The time taken to complete the test and the number of errors were recorded by a member of the experimental team and an overall Stroop score was calculated using the formula:[10]

$$Stroop\ Score = Stroop\ time + \left(\frac{Stroop\ time}{100} \times number\ of\ errors \right)$$

Thus, a higher Stroop score indicates greater cognitive impairment. Following the completion of the Stroop test participants were asked whether they had developed any signs and symptoms related to hypoxia or hyperventilation (hypocapnia). To do this, participants indicated whether they had experienced any of the symptoms identified on a modified version of the hypoxia symptom questionnaire used by Self et al.[25]

Procedure

Each participant attended three sessions, separated by at least 24 h, with the same procedures followed on each day, except at a different simulated altitude. Three simulated altitudes, 0 ft (0 m), 8000 ft (2438 m), and 12,000 ft (3658 m), were investigated using a normobaric hypoxia chamber with the oxygen concentration controlled by a Sporting Edge (Sporting Edge Solutions Ltd., Market Harborough, UK) hypoxia generator. A carbon dioxide scrubber was used to prevent CO_2 build up inside the chamber. On each day of testing participants sat in the hypoxic chamber for 55 min. This began with a 15-min period of breathing normally (NB) followed by cycling at 30 W and 120 W (conducted as part of a larger study and not reported here) for a period of 10 mins. After this there was a period of 15 min rest (while remaining in the hypoxic chamber), which was followed by a 15-min period where the subjects were asked to voluntarily hyperventilate (HV) to a level which doubled their minute ventilation from that recorded during the previous period of NB. To control the level of ventilation participants watched real-time measurements of their minute ventilation on a computer screen placed directly in front of them and were asked to maintain this at the desired level. The Stroop test was administered in the final minute of the NB and HV periods.

Statistical Analysis

For each altitude and breathing condition the average value of each physiological variable was calculated over a 1-min period immediately prior to the Stroop test being administered. $\dot{V}_T$ and $\dot{V}_E$ are reported as BTPS. The normality of the data was confirmed using the Kolmogorov-Smirnov test. A 2-way (voluntary hyperventilation × altitude) repeated measure analysis of variance was conducted. If a significant main effect or interaction was found, post hoc analysis with Bonferroni correction was performed. Significance was determined with an alpha level of 0.05. The number of participants reporting symptoms was recorded but, due to the limited number of symptoms reported, no statistical analysis was performed on these data. Unless otherwise stated data are presented as mean ± SD. All statistical analysis was performed using IBM Statistics v.22 (IBM Corp, Armonk, NY, USA).

RESULTS

By design, there was a main effect of voluntary hyperventilation on $\dot{V}_E$ [$F(1,9) = 287.87$; $P < 0.001$]. The magnitude of increase in $\dot{V}_E$ when hyperventilating at simulated altitudes of 0, 8000, and 12,000 ft (0, 2438, and 3658 m) were ×1.9, ×1.9, and ×2.2, respectively, indicating that subjects were able to achieve the doubling of $\dot{V}_E$, as requested (**Fig. 1**). As would be expected in the presence of hyperventilation, there was a significant reduction in $P_{ET}CO_2$ compared to normal breathing [$F(1,9) = 201.76$; $P < 0.001$]. There was no effect of altitude [$F(2,18) = 1.69$; $P = 0.213$] or interaction between altitude and hyperventilation [$F(2,18) = 1.26$; $P = 0.777$] on $P_{ET}CO_2$ (Fig. 1).

As expected there was a main effect of altitude on $P_{ET}O_2$ [$F(2,18) = 549.75$; $P < 0.001$] such that it decreased with an increase in simulated altitude (Fig. 1). The reduction in $P_{ET}O_2$ with altitude was accompanied by a decrease in S_pO_2 [$F(2,18) = 37.26$; $P < 0.001$]. A main effect of hyperventilation was found on S_pO_2 and $P_{ET}O_2$, with both increasing when voluntarily hyperventilating [$F(1,9) = 42.31$; $P < 0.001$ and $F(1,9) = 151.71$; $P < 0.001$, respectively; Fig. 1]. For $P_{ET}O_2$ there was no interaction effect between altitude and hyperventilation [$F(2,18) = 1.90$; $P = 0.860$]; however, there was an interaction found with S_pO_2 [$F(2,18) = 10.74$; $P = 0.001$]. Post hoc analysis revealed that during both NB and HV, S_pO_2 was significantly lower at 8000 ft than 0 ft ($P < 0.001$ and $P = 0.006$, respectively). During NB S_pO_2 was lower at 12,000 ft than 8000 ft ($P = 0.011$), although this was not the case when hyperventilating. In the presence of voluntary hyperventilation, the S_pO_2 of 93.4 ± 4.3% recorded at 12,000 ft was similar to the 94.7 ± 2.3% recorded at 8000 ft ($P = 0.946$) despite a 15.2-mmHg reduction in $P_{ET}O_2$. Interestingly the S_pO_2 at 12,000 ft while hyperventilating was greater than that recorded when breathing normally at 8000 ft (90.6 ± 2.1%; $P = 0.04$) despite the $P_{ET}O_2$ being the same (75.0 ± 6.24 mmHg during HV at 12,000 ft vs. 75.9 ± 4.05 mmHg during NB at 8000 ft; $P = 0.33$).

Respiratory data is shown in **Fig. 2**. The increased $\dot{V}_E$ observed during HV was primarily driven by an increased RR [$F(1,9) = 49.70$; $P < 0.001$] with no effect of hyperventilation on $\dot{V}_T$ noted [$F(1,9) = 0.097$; $P = 0.763$]. Altitude had no effect on RR [$F(1,9) = 0.94$; $P = 0.409$], $\dot{V}_T$ [$F(2,18) = 0.20$; $P = 0.822$], or $\dot{V}_E$ [$F(2,18) = 1.03$; $P = 0.376$]. Similarly, there was no interaction effect of altitude or hyperventilation on RR [$F(1,9) = 0.16$; $P = 0.851$], $\dot{V}_T$ [$F(2,18) = 0.69$; $P = 0.934$], or $\dot{V}_E$ [$F(2,18) = 1.51$; $P = 0.247$].

A significant main effect of hyperventilation on HR was found [$F(1,9) = 18.991$; $P = 0.002$] such that HV resulted in a greater HR than NB. No effect of altitude [$F(2,18) = 0.561$; $P = 0.58$] or interaction effect [$F(2,18) = 0.361$; $P = 0.702$] was observed on HR (**Table I**). The results relating to MAP, SBP, and DBP are displayed in Table I. There was no effect of altitude, voluntary hyperventilation, or interaction effect on MAP [$F(2,18) = 0.98$; $P = 0.393$, $F(1,9) = 0.19$; $P = 0.671$, $F(2,18) = 1.45$; $P = 0.264$, respectively], SBP [$F(2,18) = 1.53$; $P = 0.243$, $F(1,9) = 3.36$; $P = 0.825$, $F(2,18) = 2.11$; $P = 0.151$, respectively], and DBP [$F(2,18) = 0.63$; $P = 0.542$, $F(1,9) = 0.70$; $P = 0.426$, $F(2,18) = 1.30$; $P = 0.296$, respectively].

Stroop score was significantly worse (greater) with HV (6.8 ± 1.9 au) compared to NB [4.2 ± 1.2 au: $F(1,9) = 42.07$; $P < 0.001$]. There was no effect of altitude [$F(2,18) = 0.406$; $P = 0.672$] or interaction of altitude and hyperventilation on Stroop score [$F(2,18) = 1.20$; $P = 0.324$; **Fig. 3**].

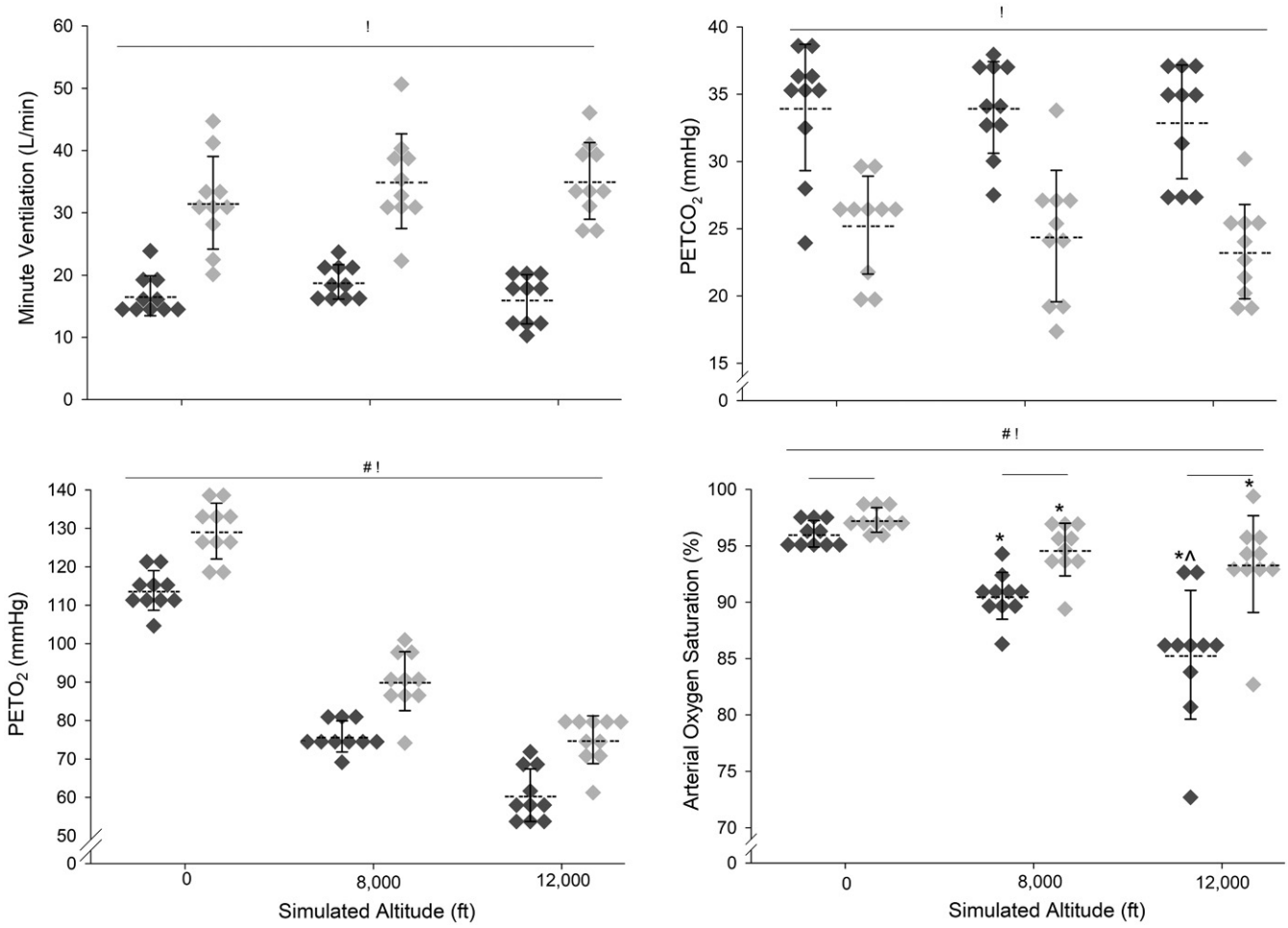

Fig. 1. Changes in minute ventilation, partial pressure of end tidal oxygen ($P_{ET}O_2$), carbon dioxide ($P_{ET}CO_2$), and oxygen saturation when breathing normally (dark) and voluntarily hyperventilating (light) while breathing gas mixtures simulating altitudes of 0 ft, 8000 ft, and 12,000 ft (0, 2438, and 3658 m). *Indicates significantly different ($P < 0.05$) from 20.9% for a given breathing pattern; ^ indicates significantly different ($P < 0.05$) from 13.2% for a given breathing pattern; # indicates main effect of altitude and ! a main effect of voluntary hyperventilation ($P < 0.05$). Short bars indicate a significant difference between breathing patterns at a given altitude ($P < 0.05$).

The number of participants reporting symptoms associated with hypoxia and hyperventilation (hypocapnia) is shown in **Table II**. Overall, very few participants reported any symptoms, with shortness of breath being the most commonly reported, primarily during HV ($N = 3$). In addition, during HV while at 8000 ft, four participants reported dizziness, but this was not the case when breathing normally or at altitudes of 0 or 12,000 ft.

DISCUSSION

This study presents a number of main findings. Firstly, as expected, both S_pO_2 and $P_{ET}O_2$ declined with increasing simulated altitude. However, when hyperventilating, despite a 15.2-mmHg reduction in $P_{ET}O_2$ with increasing simulated altitude (i.e., a greater degree of environmental hypoxia was present), the S_pO_2 response was blunted such that the recorded values were the same at 8000 and 12,000 ft. The decoupling of the S_pO_2 and $P_{ET}O_2$ response during hyperventilation was further highlighted by a greater S_pO_2 occurring when hyperventilating at 12,000 ft compared to when breathing normally at 8000 ft despite the $P_{ET}O_2$ being similar. As such, S_pO_2 cannot accurately detect environmental hypoxia in the presence of hyperventilation. Secondly, for the simulated altitudes studied, there was no effect of hypoxia on heart rate, although hyperventilation resulted in an elevated heart rate compared to hypoxia. Thirdly, cognitive function, as assessed by the Stroop test, was unaffected by hypoxia but was impaired following hyperventilating. Finally, few symptoms of hypoxia and hyperventilation were noted.

One of the main findings of this study was the discrepancy noted between measures of $P_{ET}O_2$ and S_pO_2 during a hypoxic state when hyperventilating. End tidal oxygen measures have been shown to be an accurate predictor of alveolar gases[18,20] and are routinely used as a surrogate of arterial gases. In the present study, S_pO_2 and $P_{ET}O_2$ decreased in response to increasing altitude. However, in the presence of hyperventilation there was no difference in the S_pO_2 recorded at 8000 and 12,000 ft simulated altitudes despite a significant decline in $P_{ET}O_2$, indicating a greater degree of hypoxia was present. The significance of this is highlighted in the

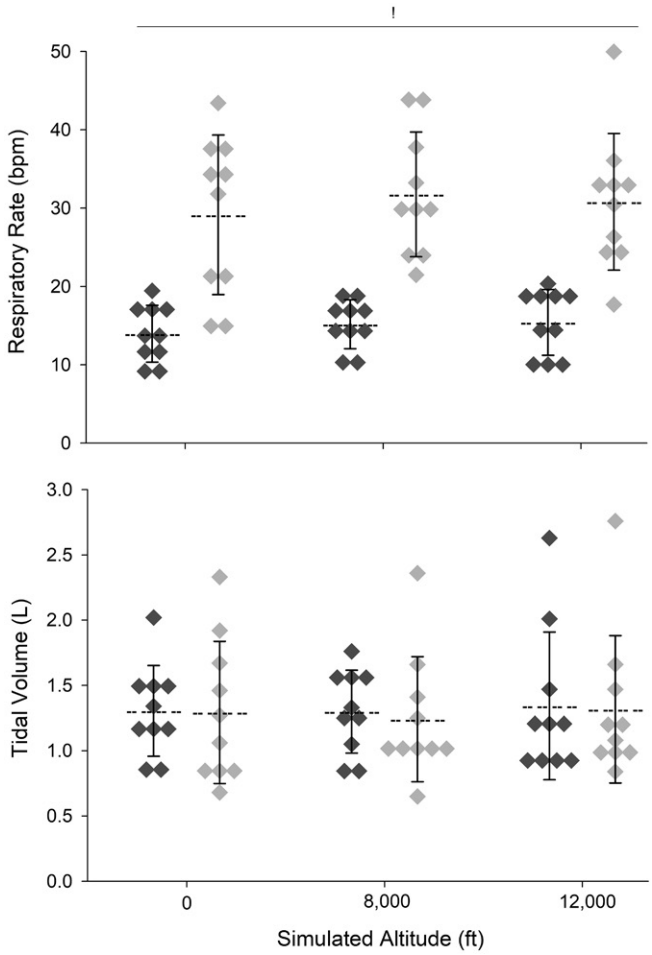

Fig. 2. Changes in respiratory rate and tidal volume when breathing normally (dark) and voluntarily hyperventilating (light) while breathing gas mixtures simulating altitudes of 0 ft, 8000 ft, and 12,000 ft (0, 2438, and 3658 m).The ! indicates a main effect of breathing pattern ($P < 0.05$).

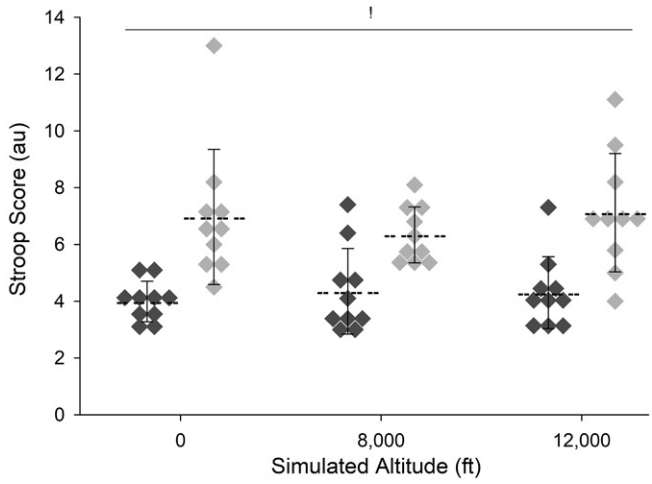

Fig. 3. Change in Stroop score in response to breathing normally (dark) and voluntarily hyperventilating (light) when breathing gas mixtures simulating altitudes of 0 ft, 8000 ft, and 12,000 ft (0, 2438, and 3658 m).The ! indicates a main effect of breathing pattern ($P < 0.05$). A higher Stroop score indicates greater cognitive impairment.

study by the S_pO_2 recorded at 12,000 ft while hyperventilating (93.4 ± 4.3%) being greater than the S_pO_2 recorded at the lower altitude of 8000 ft (90.6 ± 2.1%) despite similar $P_{ET}O_2$, i.e., hyperventilation raised the S_pO_2 above that seen at a lower altitude. This has serious implications for the use of S_pO_2 measurements when assessing environmental hypoxia as there is a relative decoupling of the relationship between S_pO_2 and P_IO_2 when hyperventilating. This can be explained by the alveolar gas equation with a further contributing factor being a leftward shift in the oxyhemoglobin-dissociation curve associated with the respiratory alkalosis caused by hyperventilation. A consequence of the decoupling could be that an individual may be experiencing a significant degree of environmental hypoxia (low P_IO_2) which is not reflected in measures of S_pO_2.

S_pO_2 is routinely suggested as a key variable for potential aircrew monitoring. The present study shows that without adequate knowledge of the ventilation state of aircrew, this may not be a reliable indicator of environmental hypoxia. Furthermore, S_pO_2 measures are routinely used for acceptance testing of oxygen delivery systems. If hyperventilation was present during testing (e.g., due to mask usage or increased breathing resistance associated with the experimental setup), it could result in approval of oxygen delivery systems which are not necessarily providing adequate protection against hypoxia. Currently if S_pO_2 is being considered for physiological monitoring or acceptance testing of oxygen delivery systems, it is essential to ensure that as a minimum minute ventilation is recorded and preferably also $P_{ET}O_2$ and $P_{ET}CO_2$ to account for the confounding effects that hyperventilation may have.

Hypoxia would be expected to stimulate peripheral chemoreceptors and sympathetic nerve activity (SNA), resulting in an increase in HR. In the present study there was no effect of hypoxia on HR, indicating that the levels studied were below the threshold required to increase SNA.[30] Hypocapnia has been suggested to have a modulatory effect on the SNA response to hypoxia.[30] This was not the case in the present study, with HV

Table I. Cardiovascular Responses to Hypoxia and Voluntary Hyperventilation.

	0 ft		8000 ft		12,000 ft	
	NB	HV	NB	HV	NB	HV
HR (BPM)[#]	78.9 (10.1)	86.3 (12.5)	83.4 (11.8)	90.3 (16.3)	81.4 (16.4)	90.2 (18.8)
SBP (mmHg)	132.2 (8.6)	136.8 (16.5)	125.9 (19.8)	124.3 (17.9)	132.6 (21.9)	128.3 (18.1)
MAP (mmHg)	101.4 (9.2)	105.4 (11.8)	97.4 (12.5)	95.7 (11.5)	99.9 (12.6)	100.2 (11.0)
DBP (mmHg)	84.1 (10.2)	88.0 (12.8)	81.4 (13.2)	79.9 (11.5)	81.8 (14.3)	84.5 (12.0)

NB: normal breathing, HV: voluntary hyperventilation, HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure. [#]Indicates a main effect of voluntary hyperventilation ($P = 0.002$).

Table II. Number of Participants Reporting Symptoms Associated with Hypoxia/Hyperventilation (Hypocapnia).

	0 ft		8000 ft		12,000 ft	
	NB	HV	NB	HV	NB	HV
S.O.B.	1	3	0	3	2	3
Fatigue	0	0	0	2	1	1
Dizziness	0	0	0	4	1	1
Light dimming	0	1	0	0	0	0
Trouble concentrating	0	0	1	2	1	2
Blurred vision	0	0	0	0	0	1
Lack of coordination	0	0	0	1	0	0
Tunnel vision	0	0	0	0	0	1
Hot flashes	0	0	0	0	1	0
Cold flashes	0	0	0	0	1	0
Euphoria	0	0	0	0	0	1
Headache	0	0	0	0	0	1
Tingling	0	2	0	2	0	1
Apprehension	1	0	0	0	1	2
Pressure in eyes	0	1	0	0	0	0
Nausea	0	0	0	0	0	1

S.O.B.: shortness of breath. All data are presented as the number (*N*) of participants displaying the symptom.

resulting in a greater HR at all altitudes, but with no interaction effect between altitude and hyperventilation. This likely reflects the lesser degree of hypoxia studied as the modulatory effect of HV may only be present when the severity of hypoxia is sufficient to cause hyperventilatory responses that also affect SNA.[17]

The present study simulated altitudes of 8000 and 12,000 ft while also having subjects double their $\dot{V}_E$ to induce hypocapnia. The increases in $\dot{V}_E$ under each hypoxia condition ranged from 1.9–2.2, indicating the subjects were able to achieve the desired level of HV. Similarly, the reduction in $P_{ET}O_2$ shows that the appropriate levels of hypoxia were achieved. Despite this there were no meaningful symptoms of hypoxia or hyperventilation noted other than a small number of participants reporting dizziness during HV. This, combined with similarities in many of the cardiovascular variables when hypoxic and/or hyperventilating, along with the minimal response noted in respiratory variables, highlights the potential challenges associated with physiological monitoring of aircrew. With the growing number of wearable sensors and technological advances in monitoring an individual's physiological response to the environment/exercise, in-flight physiological monitoring has been suggested as a means of monitoring aircrew in real time to identify adverse physiological states associated with the flight environment. However, the flight environment is extremely dynamic, as are the responses of aircrew, with the current findings highlighting the difficulties in distinguishing the physiological response to different stressors; in this case, hypoxia and hyperventilation (and associated hypocapnia). Given similar difficulties have been noted with other potential variables (e.g., transcutaneous PcO_2[26]) and monitoring devices (wrist mounted S_pO_2[16]) that could be used for physiological monitoring, before in-flight physiological monitoring is considered it is important that further research is conducted to ensure the output of such monitoring can be used to accurately predict the cause of the physiological response so that appropriate corrective action can be taken. This requires careful consideration of which physiological (and environmental) variables are monitored, with validated algorithms applied to identify the cause of the response reliably and accurately.

Cognitive impairment has been a feature noted in many PEs. Hypoxia is known to cause cognitive impairment, the severity of which is largely determined by the degree of hypoxia experienced.[22] In the present study there was no effect of hypoxia on cognitive function as assessed by the Stroop test, which is a used as an indicator of selective attention capacity and central processing speed. The lack of hypoxia-related cognitive deficit could potentially be due to the relatively low altitudes investigated (8000 and 12,000 ft equivalents) or the inability of the test used to distinguish the aspects of cognitive function that were affected by the levels of hypoxia studied. In contrast, compared to normal breathing, hyperventilation resulted in significant cognitive impairment. This finding is unsurprising given that hyperventilation and the resultant hypocapnia are associated with elevated blood pH levels, which ultimately cause cerebral vasoconstriction. The consequent alterations in cerebral blood flow and oxygenation can impair cognitive function, which was likely the case in the present study. These findings highlight the importance of considering the role of hyperventilation in the occurrence of PEs with investigation of factors such as increased work of breathing due to the aircrew equipment assembly bulk, inflation of chest counterpressure garments, ejection seat (or torso) harness tightness, or aircrew workload/anxiety required.[6]

Some limitations of the present study should be considered. Firstly, only two altitude equivalents were investigated, 8000 and 12,000 ft. As there is a relationship between altitude and severity of symptoms, it is likely that had higher altitudes been investigated, a greater physiological and possibly cognitive response would have been observed. In addition, the physiological response to normobaric hypoxia may differ from hypobaric hypoxia;[4,25] therefore, it is possible the present findings may not be equivalent to those that would occur during the hypobaric hypoxia which would occur during flight. Finally, a voluntary hyperventilation model was used where subjects were asked to double their minute ventilation. This is a marked level of hyperventilation; had lower levels of hyperventilation been assessed and consequently less severe hypocapnia developed, the effects of hyperventilation may have been partially ameliorated.

In summary, the present study highlights the similarities and differences in basic physiological responses from exposure to low to moderate levels of hypoxia and hyperventilation/hypocapnia. A main finding of the study is that, in the presence of hyperventilation, measures of S_pO_2 alone cannot accurately predict the level of environmental hypoxia experienced. This highlights the potential difficulties in the use of physiological monitoring to provide reliable information to assess the condition of aircrew and whether, and what, corrective action should be taken. In particular, the current data draw into question the use of pulse oximetry for physiological monitoring without the concurrent measurement of end-tidal gases and minute ventilation. Further research is required to identify specifically how an

individual will respond to the different environmental challenges faced by aircrew and how to interpret this data to make informed decisions as to the cause of the physiological response.

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