Title: The threshold for the stimulation of breathing at altitude: physiological support for the aviation industry standard for aircraft pressurization.

by

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Abstract (163 words)

As aircraft ascend, cabin pressure is always maintained below an equivalent altitude of 8,000ft (~120mmHg O_2, ~15.4% O_2). The choice of 8,000ft is a compromise between engineering, fuel efficiency, cost, human comfort and human physiology (Aerospace Medical Association, 2008). The brain's response to hypoxia is to stimulate breathing to counteract its effects. Currently, the threshold at which breathing is stimulated by hypoxia is inconsistent with cabin pressure regulations, being reported in 1947 by Dripps and Comroe, to be at a far higher altitude, at ~85mmHg O_2 (~10% O_2) (~17,500ft). This research team is unaware of any study, since 1947, that has tried to identify the ventilatory threshold to hypoxia. Using modern experimental methodology and statistical design this study reassesses the breathing threshold to hypoxia in 20 participants. This research indicates that breathing is more sensitive than previously demonstrated, with significant stimulation of breathing (by 1 $L.min^{-1}$), combined with a significant lower $PetCO_2$ (by 1 mmHg), being detectable at 15.2% oxygen (~121mmHg O_2, ~7900ft).

Introduction:

“The most important single hazard of flight at high altitude is hypoxia” (Ernsting et al. 1988). With this in mind, an assumption may be made that hypoxic exposures and the human response would have been thoroughly researched. However, even recently hypoxia related accidents occur in aviation. The National Transportation Safety Board recorded 24 accidents relating to hypoxia in the last decade, 22 of them included fatalities. Taneja and Wiegmann (2002) state that hypoxia was reported to be the cause of impairment or incapacitation, in more than 4% of flight related incidents. Within this study, an attempt will be made to provide a stepping stone to modernise the aviation medicine field and place into context the previous research conducted. This research focuses on primarily the ventilatory responses to hypoxic exposures in humans. In order to justify this approach, the research conducted systematically reviewed the key cognitive and psychomotor studies in hypoxic exposures.

The foundation for the advancement of the aviation medicine field has already been established in a study by Dripps and Comroe (1947). If every independent laboratory contributed to a dose response curve, such as that of Figure 1, one could build a more detailed response on not only the cognitive but the physiological human response to hypoxia. The research conducted outlines why this is of key importance to understanding hypoxia and data is combined to see how the response curve changes with modernised methods and scientific equipment.

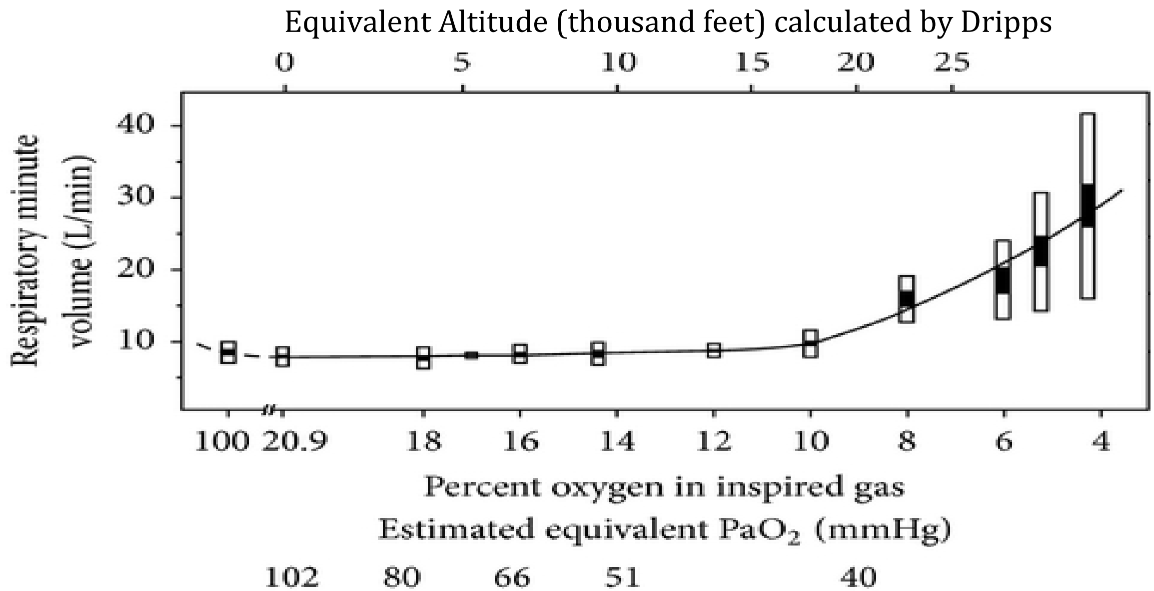


Figure 1). Ventilatory Response for a given inspired oxygen percentage (FiO_2). The effect of inhalation of various low oxygen mixtures upon respiratory minute volume. The data of Shock and Soley for 17 and 12 per cent O_2 and of Horvath et al. for 6, 5.2 and 4.2 per cent O_2 are included. Dripps and Comroe (1947).

Figure 1 illustrates what is currently known about the human ventilatory response to hypoxia. At a glance, the ventilatory response appears relatively insensitive to hypoxia and decreasing PaO_2 levels. Parkes (2013) indicates that even in extreme hypoxia, an increase in breathing to that of maximal exercise does not occur (>100L.min^{-1}). Previous research indicates that a large hypoxic stimulus, approximately 6% inspired oxygen, can cause humans to lose consciousness (Horvath 1943, Gibbs 1943, Cohen 1967, Shimojyo 1968). As Figure 1 suggests, with agreement from Parkes (2013), the ventilatory threshold resides between 10% and 8% inspired oxygen, approximately between 18,000 and 23,000 feet as respiration increases. What is more, Dripps and Comroe (1947) do not state themselves what or where the threshold resides. When comparing this ventilatory threshold with the current cabin pressurization regulations (Aerospace Medical Association, 2008, FAR 25 section 25.841a) at a maximum altitude of 8,000 feet it would appear to be an overly safe compromise. MacMillan (1988) supports that there is no evidence to suggest at an equivalent altitude of 8,000 feet that prolonged exposure will induce hypoxia. Within this study, an attempt was made to identify if a threshold can be detected and measured. With a view to providing physiological evidence for or against cabin pressure regulations set at a maximum equivalent altitude of 8,000 feet.

Defining Hypoxia – A Dangerous Generalisation?

This may appear seemingly straight forward, however, not all scientific fields agree when a human is classed as "hypoxic." This research replicated the type of hypoxia that a passenger would experience on a flight or climb to altitude known as Hypoxic Hypoxia. Ernsting's Aviation and Space Medicine (5th Edition, 2016) defines hypoxic hypoxia as "the result of a reduction in the oxygen tension of arterial blood and, hence, in the capillary blood. The aetiology includes the low oxygen tension of inspired gas associated with exposure to altitude, i.e. hypobaric hypoxia."

Hypoxia is detailed by the Oxford Handbook of Clinical Medicine as a PaO_2 of <8kPa. Converting this into mmHg the P_aO_2 must fall below 60mmHg for a person to be classed as medically hypoxic. This is in agreement with Weil et al. (1970), however, 60mmHg PaO_2 equates to approximately 90% SpO_2 which appears to be less sensitive than the acute hypoxic ventilatory threshold found in this research.

In relation to this study, an attempt was made to identify how sensitive humans are to hypoxic hypoxia and at which point PaO_2 has decreased enough to stimulate ventilation. As David Gradwell in Ernstings Aviation and Space Medicine (5th Edition, 2016) describes, acute hypobaric hypoxia is "a combination of the cardiorespiratory responses and neurological effects, consequently, the symptoms and signs are extremely variable." In addition, as Ernsting et al. (1963) showed in six resting participants breathing air at 18,000 feet, oxygen saturations of arterial blood varied between 65 and 78%. Therefore, it can be difficult to generalise what specific altitude/inspired oxygen percentage (FiO_2) causes humans to be classed as hypoxic. This may have caused an oversimplification and generalisation in detailing the human responses to hypoxia and perhaps a subsequent dangerous naivety to the potential consequences.

In particular, it is important to define the time frame of acute hypoxia. "Acute hypoxia comprises a biphasic ventilatory response with an initial (3-5min) gross increase in minute ventilation" (Petrassi et al. 2012). Ideally, within the 5 minute timeframe of the initial hypoxic ventilatory response, one would want to assess the human response physiologically to acute hypoxia in order to assess the greatest effect on ventilation.

Human Mechanisms for Detecting Hypoxic Hypoxia

The ventilatory response to hypoxia is initiated by the carotid bodies (Teppema and Dahan 2010, Gonzalez et al. 1994). They are located bilaterally in the carotid bifurcations at the port of the brain circulation and have the highest blood flow-to-metabolism ratio in the body (Teppema and Dahan, 2010). As Parkes (2013) suggests they are ideally located to measure any breath that fails to match metabolic rate and therefore, can respond to a decrease in arterial blood oxygen (hypoxemia). In relation to this study, one would want to understand how sensitive the carotid bodies are in acute hypoxia to detecting a decrease in arterial blood oxygen and responding by stimulating ventilation in humans. This can be tested directly in humans as the carotid chemoreceptors are the only known chemoreceptors in man to be stimulated by hypoxia and in turn stimulate breathing (Parkes, 2013). A validation of this statement can be shown in humans who have undergone carotid denervation. Carotid denervation results in the loss of the increase in ventilation to a hypoxic stimulus (Wasserman et al.1986, Whipp and Davis 1979).

Background Cognitive Studies – Justifying the search for a Physiological Threshold

The human response to hypoxia has complex psychological and physiological mechanisms that are still not fully understood. As Petrassi et al. (2012) states: "Cognitive and Psychomotor deficits resulting from mild hypoxia can be difficult to quantify, are often not reproducible and sometimes produce conflicting results." In addition, cognitive and psychomotor studies have been inconsistent with their findings below ~15,000 feet (4572m) (Petrassi et al. 2012). Psychological studies have had difficulty explaining the cognitive effects of hypoxia particularly at an equivalent altitude associated with commercial airliners (~8,000 feet). Table 1 displays key cognitive studies conducted within the aviation medicine field and their conflicting findings.

Table 1). Compilation of key cognitive studies ranked by altitude. Author, Type of Cognitive task, altitude and their findings have been included. The table highlights the inconsistencies and contradictions found in hypoxic cognitive literature.

Author	**Details**	**Altitude**	**Results**
Crow (1971)	Short Term Memory Test	2,000 - 12,000 feet	No significant impairment to memorise digits.
Denison (1966)	Manikin Task	5,000 feet 8,000 feet	Increased time to complete task at both altitudes compared to sea level controls (1.5s to 3.3s)

Paul and Fraser (1994)	Repeat of Manikin Task	5,000 feet 8,000 feet 10,000 feet 12,000 feet	Contradicts Denison (1966), learning effect not modified by hypoxia. Better logical reasoning performance at 8,000 feet compared with 5,000 feet.
Ledwith (1970)	Reaction Time	5,000 feet	Reaction times became quicker as altitude increased. All reaction times were within 4s.
McCarthy (1995)	Signal detection orientation test	7,000 feet 12,000 feet	Delayed response time compared with sea level but no significant difference between the two altitudes.
Fowler (1985)	Repeat of Manikin Task	8,000 feet	Increased Reaction Times (no greater than 3 seconds).
Kelman (1969)	Card Sorting Task	8,000 feet	Participants sorted out cards faster at 8,000 feet compared with sea level.
Billings (1974)	Gedye Task (repeating sequence)	8,000 feet	An initial increase in time at 8,000 feet compared with sea level. As the task is repeated no difference detected.
Farmer (1992)	Manikin Task	8,005 feet	Hypoxia impairs learning and the

			performance impairment is sustained even at sea level oxygenation.
Berry (1989)	Recalling Digital Sequence, written and verbal fluency, trail making and visual search	9,000 feet	Only difference between sea level and 9,000 feet was a ~1 slower finger tap.
Li (2000)	Reaction Time Test	9,186 feet 11,811 feet 14,436 feet	Impaired reaction time at 11,811 feet and more so at 14,436 feet. No decrement at 9,186 feet. No effect on error rate up to 14,436 feet.
Terry (2001)	Cognitive and Memory Test	10,000 feet	Better scores at 10,000 feet compared with sea level.
Schlaepfer (1992)	Psychometric Tests	7,000 – 10,000 feet	Hypoxia improved performance, 25% less time to recognize brief letters.
Balldin (2007) Crow (1973) Fowler (1985) Hewett (2009) Pavlicek (2005)	Cognitive Function	10,000 feet 12,000 feet 12,000 feet 14,000 feet 15,000 feet	No effects on cognitive function found at all altitudes up to 15,000 feet.
Green and Morgan (1985)	Task Learning, logical reasoning task	12,000 feet	Trend of increasing percentage of errors with altitude.
Kida (1993)	Reaction Times to Auditory Stimulus	13,120 16,400 19,680	Reduction in reaction times for 6 participants at

			13,120 feet and 16,400 feet for 20 participants. Remaining 12 participants unaffected to max altitude of study (19,680 feet).
Hewett (2009)	Cog Screen Hypoxia Edition	14,000 feet	No cognitive deficit up to 14,000 feet
Kobrick (1970)	Reaction to Light Flashes	14,000 feet	0.7 seconds slower than at sea level to respond to random light flashes.
Rice (2005)	Cog Screen Hypoxia Edition	15,000 feet	12 or more errors for participants at 15,000 feet but no decrements at 12,000 or 10,000 feet.
Cahoon (1972)	Card Sorting Task	16,000 feet	12% longer to sort cards by shape and colour compared with sea level.
Hornbein (1989)	Psychometric Tests	17,000 – 26,000 feet	Long term visual memory worsened along with finger tapping ability as altitude increased.
Rahn (1951)	Hand Steadiness	18,000 feet 22,000 feet	Slight worsening of hand steadiness at 18,000 feet (x2 of score). 22,000 feet (x15 of score).
Stepanek (2013)	Rapid Number Reading Sequence	23,000 feet	Significant increase in number of errors per person, the effect was reversed

			when participants were returned to normoxia.
Lieberman (1995)	Psychometric Tests	24,000 feet	No difference in tasks except for increased comprehension time compared with sea level.
Kennedy (1989)	Psychometric Tests	28,000 feet	Short Term Memory down 12%, Pattern Recognition down 28% and grammatical reasoning down 43% compared with sea level.
Malle (2013)	Addition Task	30,000 feet	Percentage of correct responses fell significantly along with miscalculations.

As is evident from Table One, cognitive studies have produced a wide range of results and some individuals are affected at lower altitudes than others. Firstly, the manikin task conducted by Denison (1966), Fowler (1985) and Paul and Fraser (1994) assesses 3D spatial rotation, problem solving and attention. However, how relevant is this to pilots, aircrew and passengers? Although, the manikin task may replicate certain cognitive challenges faced by pilots, a more relevant experiment could have been conducted in a flight simulator, with a pilot performing routine flying procedures. Denison (1966) found that participants responded to the manikin task slower at altitudes of 5,000 and 8,000 feet compared with sea level controls. Ideally, Denison (1966) would use a paired design so that the same participants could be compared from sea level to altitude. This experimental design increases the variability between the control participants at sea level and the participants at altitude. On the contrary to Denison's findings, Paul and Fraser (1994) with a much greater participant size (n=144), found that hypoxia did not prevent learning and improvement of tasks in hypoxia at altitudes up to 12,000 feet. Paul and Fraser only detected an increased reaction time as altitude increased but presented a significant ($p=<0.0001$) improvement in the manikin task. Overall, these three studies show an increased reaction time (usually <1 second) as altitude increases but no reliable indication that this would be of any detriment to pilots operating an aircraft or any other individuals conducting aviation tasks. Clearly, there are questions of relevancy with the manikin tasks and disagreement between studies.

McCarthy (1995) used signal detection tests and found a delayed response time at 7,000 feet. There was no significant difference between the two altitudes and the accuracy of the test was only decreased at 12,000 feet. However, McCarthy measured the average HbO_2 at 7,000 feet to be 96.8% and 91.2% at 12,000 feet. This suggests the twelve participants did not receive the hypoxia associated with the altitudes in this study. One would expect a much more detrimental fall in HbO_2 levels at both altitudes. McCarthy did not measure $P_{et}CO_2$ but suggested these unusually high figures were the result of "hyperventilation induced hypocapnia." In addition, would a delay in a pilot's ability to detect certain signals affect their ability to fly an aircraft safely? What is of more interest is that despite an increase in altitude to 12,000 feet there was no significant detriment in response time compared with 7,000 feet.

Green and Morgan (1985) also contradict the work of Denison (1966) in that they found no effect on learning of a task at any altitude up to 12,000 feet. Green and Morgan assessed 150 participants on a logical reasoning task and found no detriment in number of statements attempted up to 12,000 feet. Although, there was an increasing percentage of errors as the hypoxia became more severe, it was only significant at 12,000 feet. However, again there is no evidence to suggest that based on the results of a logical reasoning test a pilot's ability to safely operate an aircraft is compromised. Furthermore, a dose response curve is needed, would there have been an altitude severe enough to prevent pilots from completing a logical reasoning task? In addition, Farmer (1992) showed that within the Manikin test at rest in a hypoxic condition equivalent to 8,000 feet participants' ability to learn was affected. This concurred with the study done by Denison (1966) and highlighted further disagreement between studies. Again, will pilots be affected by this inability to learn in hypoxia and will it be of any detriment to their ability to fly? One simply cannot reasonably presume if that is the case as the studies are not relevant enough from which to withdraw that conclusion and there is a clear inter study disagreement with this issue. How this will affect pilots but what does it mean for passengers and other aircrew roles?

Li (2000) managed to successfully replicate values of SaO_2 for a given altitude, reaching a SaO_2 of 74% for an altitude of 14,436 feet. Mean choice reaction time was significantly slower at altitudes of 11,811 feet and 14,436 feet but no more errors were found at any altitude compared with sea level. Li (2000) also measured finger tapping under hypoxic conditions; however, one cannot be sure as to why this may be a relevant measure for individuals performing tasks on an aircraft. Both Rice (2005) and Hewitt (2009) measured the effects of hypoxia on cognitive function. However, Hewitt (2009) states that they cannot be sure that the cognitive measures were sensitive enough to detect subtle changes. This would explain why Hewitt could not detect any cognitive performance detriments until 14,000 feet and Rice not until 15,000 feet. This confirms the argument that Petrassi et al. (2012) indicated, cognitive studies have had difficulty agreeing and presenting data of any cognitive detriments below ~15,000 feet. Either cognitive studies are not sensitive enough to detect small subtle changes at more moderate levels of hypoxia or the hypoxia is not severe enough.

Perhaps most telling of all experiments in moderate altitudes is the fact that some can have a recorded improvement from sea level, such as Terry (2001) who found that better cognitive and memory performance at 10,000 feet. A key experiment by Malle (2013) with 28 aircrew and 29 controls, assessed brain function at ~30,000 feet. The participants were exposed to this hypoxic stimulus for ~156 seconds. One would agree it is surprising that the participants can complete the test at such a high altitude, however, it is not certain that they were exposed to the hypoxia long enough with a SaO_2 mean at the end of the test of 64±1 %. They had to sum the last two digits of a sequence of numbers. The percentage of correct responses from a controlled state at sea level fell from an average of 95% to an average of 70%. A study by Rahn and Otis (1951) measured hand steadiness at both 18,000 feet and 22,000 feet. They found that hand steadiness at 18,000 feet was x2 of the absolute score, but would this be expected anyway if they were hyperventilating? At 22,000 feet the score worsened by x15 the absolute score indicating a possible cognitive effect at higher altitudes. Ernsting, Sharp and Harding (1988) have tried to sum the cognitive characteristics of hypoxia. They believe that psychomotor tasks show little decrement until 12,000-14,000 feet. However, where is the evidence for this assumption?

As a consequence of the inconsistencies seen within hypoxic cognitive studies, some researchers have focused their attention on to flight related tasks as shown in Table 2.

Table 2). Compilation of Flight Related Tasks in Hypoxic Hypoxia. Flight related data, ranked by altitude providing an insight into more relevant studies of the aviation medicine field.

Author	**Task**	**Equivalent Altitude**	**Results**
Smith (2007)	Aircraft Loadmasters	7,000 feet 9,000 feet	Exercise at 30W and 60W demonstrated symptoms of individuals at rest at 12,000 to 15,000 feet.
Nesthus (1997)	2Hrs of Flight Data	8,000 feet 10,000 feet 12,000 feet	More procedural errors at 10,000 and 12,000 feet.
Smith (2005)	Aircrew Operation (active)	8,426 feet	Difficulty with calculations, light headed, delayed reaction time and mental confusion.
Replogle (1971)	Unstable Tracking Task	12,000 feet 22,000 feet	Tracking Task sensitive to hypoxia at 22,000 feet but not at 12,000 feet. 12,000 feet produced large individual variation.
Gold (1972)	Simulator Study	12,300 feet 15,000 feet	Significant error rates for both airspeed and altitude for both 12,300 feet and 15,000 feet.

The five studies detailed in Table 2 are key flight related studies. However, a dose response curve needs to be created with flying performance ranked against severity of hypoxia, with the addition of cognitive affects to passengers and other aviation roles. Based upon the results from the cognitive and flight orientated tasks few have attempted to identify a threshold for when supplemental oxygen should be provided to prevent cognitive decline. Replogle (1971) demonstrated clearly that tracking tasks were sensitive to hypoxia, however, at a more moderate altitude of 12,000 feet individual variations exist. Also, of key importance, exercise can cause an exaggeration of hypoxic symptoms. Smith (2005, 2007) showed that aircrew and loadmasters experienced more hypoxic symptoms than pilots. Participants who exercised at 30 and 60 watts, at an altitude of 7,000 and 9,000 feet, experienced similar symptoms to participants at rest at an altitude of 12,000 and 15,000 feet. Crucially, future studies must ensure that a paired design is adopted into their scientific methodology. Allowing each participant to be their own control may help to counter the already large individual variation. An individual within the Smith (2006) study experienced symptoms as low as 6,000 feet but on average the majority experienced symptoms at a mean altitude of 8,426 feet. The relevance of these studies is a much needed step forward for the aviation cognitive research field. This data can be directly applied to a pilot or aircrews ability to operate and more research is needed in this field in order to provide key thresholds for hypoxia related stresses.

Overall, there are many studies that demonstrate the cognitive hypoxic stresses pilots, aircrew and passengers may experience. However, as previously highlighted, further relevant tests that can be reproduced in independent laboratories need to be undertaken. The studies need to be added to a dose response curve with key thresholds so that the commercial airline industry and branches of militaries globally can assess the safety of hypoxic exposure on humans. As more recent studies have demonstrated, more relevant studies are being undertaken but there are too few and the individual variation is large. The variation is especially large at moderate altitudes associated with commercial airliners (~8,000 feet). Essentially, 8,000 feet appears from a cognitive prospective to be a relatively safe compromise but not all studies agree with the effects of moderate altitude on cognitive function. Some studies even find better participant performances at these altitudes than sea level participants. Furthermore, despite the level of hypoxia all tasks were still completed by the participants.

As is clear from the evidence available to us, there needs to be a rationalization of the cognitive research related to aviation hypoxia. By discussing the data, it is clear a practical threshold for cognitive responses needs to be defined and combined with physiological data to fully understand hypoxia. In addition, the data also suggests there is a lack of agreement on a study design that should be undertaken to assess cognitive responses to hypoxia and the studies that have been conducted are either irrelevant or have not been validated by other laboratories. The review of the cognitive literature indicates that there is little evidence that would suggest a significant purpose as to why aircraft cabin altitude should be maintained below a maximum 8,000 feet. Within Figure 2, this research has placed some key studies in a dose response arrangement to highlight the difficulties with the available data to produce a relevant and accurate cognitive threshold to hypoxia.

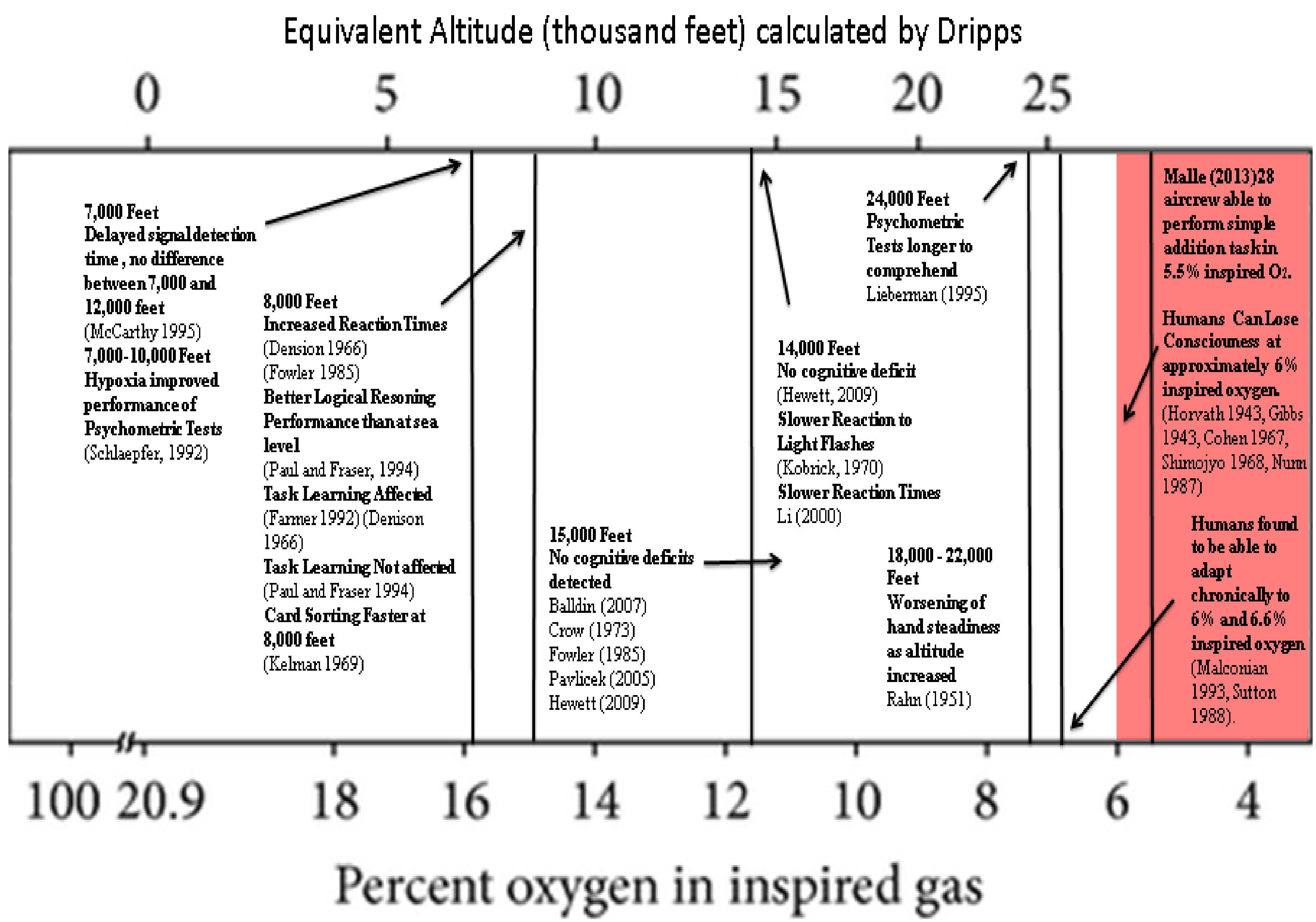


Fig 2) A diagram to show the difficulties identifying suitable thresholds and for determining why aeroplane cabin altitude should be set at a maximum of ~8000 feet. The diagram highlights the importance for a universally agreed cognitive test that is relavant to the airline industry.

Vision, Hearing and EEG – Neurophysiological Studies

Another consideration for the aviation medicine field is that of neurophysiology. Eyesight may can be affected by hypoxia and therefore be of concern to pilots and aircrew. Table three displays some of the key studies:

Table 3). Compilation of key Neurophysiology Studies ranked by altitude. The table indicates the subjective nature of neurophysiology studies.

Author	**Study**	**Altitude**	**Results**
McFarland (1971)	Dark Adaptation	7,000 feet	Slight impairment to dark rod adaptation.
McFarland and Evans (1939)	Light Sensitivity	7,400 feet	Decrease in visual light sensitivity and altered threshold for dark adaptation. (~2 minutes longer in hypoxia compared with sea level)
Connolly (2006) McFarland (1940)	Scotopic Sensitivity	9,000 feet	Impairments of scotopic sensitivity. (~14% slower dark adaptation)
Connolly (2008) Karakucuk (2004)	Photopic and Mesopic Test	9,000 feet	Impairments in both conditions of photopic and mesopic chromatic sensitivity.
Connolly (2008)	Foveal Contrast	9,000 feet	No change in foveal contrast sensitivity.
Fowler (1992)	EEG	12,000 feet	12-16% Visual Cortex EEG latency.
Deecke (1973)	Auditory Test	21,000 feet	8% latency of auditory cortex.

From the evidence in Table 3, it is clear there are some decrements to vision when participants are exposed to hypoxia. However, all participants can still maintain their vision and hearing. Even Ernsting, Sharp and Harding (1988) admit that there is a noticeable impairment of the sensitivity of the dark adapted eye at altitudes as low as 5,000 feet. Although the authors note, it is of “little consequence for aviation safety.” A more severe hypoxic stimulus would be needed to assess the true effect of hypoxia on vision, whereas, table three indicates that many studies focus on moderate altitudes. Furthermore, vision and hearing would be of importance to aircrew, however, it appears there is again no obvious threshold in which hypoxia affects brain function. In addition, can pilots still see easily landing and take-off signals? A relevant sight specific test is needed to assess if pilots can still visually recognize all possible light signals from ground sources. In addition, what does this mean for passengers and other aircrew? There appears to be no obvious threshold from a neurophysiology point of view in which brain function is impaired.

Overall, the research conducted from a cognitive and neurophysiology perspective does not provide any reasonable evidence of a threshold to support why aircraft cabins should be maintained at a maximum altitude of 8,000 feet. As Petrassi et al. (2012) states “Determination of a practical threshold is desirable for flight management and mission planning (including the need for supplemental oxygen with consideration of logistic requirements and aircraft performance effects). Not only if a threshold is established will there be a greater understanding of the cognitive and neurophysiological effects of hypoxia but it addresses a problem defined by McLoughlin (2017) as “the reproducibility crisis.” A central tenet of all scientific research is that it must be replicated by another entity. This is yet to occur on a scale necessary to understanding the cognitive effects of hypoxia. Indeed, there is a scarcity of evidence that suggests aeroplane cabins should be pressurised to ~8000 feet.

Ventilatory Responses to Acute Hypoxia

Dripps and Comroe (1947), as previously discussed, plotted a dose response curve (Figure 1) displaying the ventilatory response of participants exposed to hypoxia. However, the methodology and the sensitivity of their equipment did not enable them to detect small yet significant changes to ventilation. Prior to Dripps and Comroe (1947), there was much debate as to where the ventilatory threshold was located. Lutz and Schneider (1919) with agreement from Ellis (1919) suggested ventilatory stimulation was detectable at 18% O_2, whilst Boothby (1945) found 16% O_2 to be the threshold. However, many of these experiments were complicated by rebreathing methodologies in which concentrations of inspired gas were not maintained. In addition, slight changes to physiological variables could not be detected as breathing, heart rate and blood pressure were not constantly measured. Dripps and Comroe (1947) had a more robust scientific methodology than earlier studies, however, due to the scientific equipment, sensitive small changes that could have indicated a ventilatory threshold may not have been detected. Dripps and Comroe, unlike earlier studies, did take into account the psychological influences that could have impacted their results. Many previous studies such as the Lutz and Schneider (1919) used low pressure chambers that some participants “dreaded,” often causing participants to hyperventilate. This effect was negated by Dripps and Comroe using participants familiar with laboratory settings and allowed them to rest prior to the experiment. Dripps and Comroe could not continuously measure heart rate which was taken from the radial artery every thirty seconds and blood pressure measurements were abandoned due to the painful arm cuff inflation influencing participants breathing rates. Ideally, all physiological variables should have been measured continuously.

As stated by Rahn and Otis (1949), a greater response is seen by those participants exposed to hypoxia that are not acclimatized to high altitude. Therefore, careful adherence must be taken to ensure participants have similar backgrounds in terms of the altitude they reside at, smoking status, along with any other traits that may increase inter-individual variation. Table 4 comprises key studies where participants have inspired hypoxic mixtures and their results.

Table 4). Compilation of key ventilatory measurements for a given inspired oxygen percentage, ranked by equivalent altitude.

Author	**Breathing Response to Hypoxia**	**Equivalent Altitude (feet)**	**Participants (n)**	**Lmin^{-1}**
Sutton (1988)	40 days in 6.6% O2	6.6% O_2	8 (60w bicycle exercise)	PaO2 ~ 28mmHg
Goldberg (2017)	Hyperventilation at 75% SpO2.	Not recorded	170 Males	Average Increase of 0.43 (liter/minute/%SpO2)
Goldberg (2017)	Hyperventilation at 75% SpO2	Not recorded	169 Females	Average Increase of 0.22 (liter/minute/%SpO2)
Schneider (1919)	Hyperventilation found at 18% O_2	3,800 feet	<10	Unreliable due to experimental set up.
Ellis (1919)	Hyperventilation found at 18% O_2	3,800 feet	<10	Unreliable due to experimental set up.

Boothby (1945)	Hyperventilation found at 16% O_2	6,700 feet	<10	Unreliable due to experimental set up.
Fraser (1987)	No hyperventilation at 16% O2	6,700 feet	39	N/A
Steinman (2017)	No Hyperventilation detected	10,000 feet 15,000 feet	12	N/A
Lugliani (1971)	Some hyperventilation detected at 12% O_2 in non CB deneravted participants.	12,000 feet	7 (asthmatics) CB denervated	1 $L.min^{-1}$
Severinghaus (1966)	Some hyperventilation in 12% O_2	12,000 feet	7	1-5$L.min^{-1}$
Dripps and Comroe (1947)	Hyperventilation found at 12% O_2	13,900 feet	32	0.5 ($L.min^{-1}$) increase from rest
Connolly (2006, 2008)	No Hyperventilation detected at 11% or 14% O_2	14,000 feet	5 (2006) 12 (2008)	N/A
Rahn (1951)	Hyperventilation at 9.9% O_2	16,000 feet	8	Ve increased from 8.86$L.min^{-1}$ to 11.22$L.min^{-1}$.
Van Dorp (2007)	Hyperventilation at ~9% O_2	18,000 feet	22	11-17 ($L.min^{-1}$)
Stewart (2011)	Hyperventilation Found at 10% O2	18,200 feet	12	15 ($L.min^{-1}$)
Kety (1947)	10% O2 inspired – no measurable decrease in brain O2 consumption	18,200 feet	7	N/A

VanderPost (2002)	No hyperventilation at ~13% O2	18,200 feet	12	N/A
Guz (1966)	No Hyperventilation at 8% O2	23,000 feet	1	N/A
Cohen (1967)	Hyperventilation at 7% O_2	25,600 feet	9	22 ($L.min^{-1}$)
Gibbs (1943)	Breathing 6% O2 for less than 3 minutes caused confusion or loss of consciousness.	28,300 feet	8	N/A
Shimojyo (1968)	Psychiatric patients 12min of 6% O2	28,300 feet	7	PaO2 ~ 40mmHg= confusion and loss of consciousness in some (n=2)
Malconian (1993)	40 days in 6% Chronic O2	28,300 feet	6	Participants can adapt chronically to 6% O2 (Pa02 ~31mmHg)
Nunn (1987)	Literature Review – Patients lose consciousness at ~PaO2 27mmHg	>30,000 feet	N/A	N/A
Horvath (1943)	Participants lost consciousness breathing 4-5% O2	32,000 feet	11	N/A

As Table 4 suggests there is a large variation in results and responses. The main issue with many studies that apply hypoxia and measure ventilation is that the majority were not attempting to determine a threshold. Therefore, one has to take snapshots of the data to assess if the literature gives any indication of where a ventilatory hypoxic threshold may be located. However, as this research has shown within Table 4 not all previous physiological studies agree with each other as to what severity of hypoxia (inspired $\%O_2$) initiates an increase in ventilation. Based upon Figure 1 Dripps and Comroe (1947) indicate a small increase in ventilation around 10% inspired oxygen but not until 8% inspired oxygen does one see a more significant rise in ventilation, however, only approximately 5 $L.min^{-1}$.

Similar to the cognitive field, the physiology field also has conflicts as to which point ventilation is stimulated. Ideally, as discussed, a dose response curve needs to be designed as this research will attempt to show how key physiological systems respond to a given severity of hypoxia. In addition, many previous studies fail to outline how their equipment was calibrated which is essential to measuring small changes in ventilation. Producing a calibration graph allows one to assess if the equipment available is accurate enough to measure small changes and more importantly reflect on whether the results are true values or within the error range of the equipment. This research has outlined in Figure 3 the difficulty with identifying a ventilatory threshold and the individual studies that have recorded hyperventilation for a given inspired oxygen percentage.

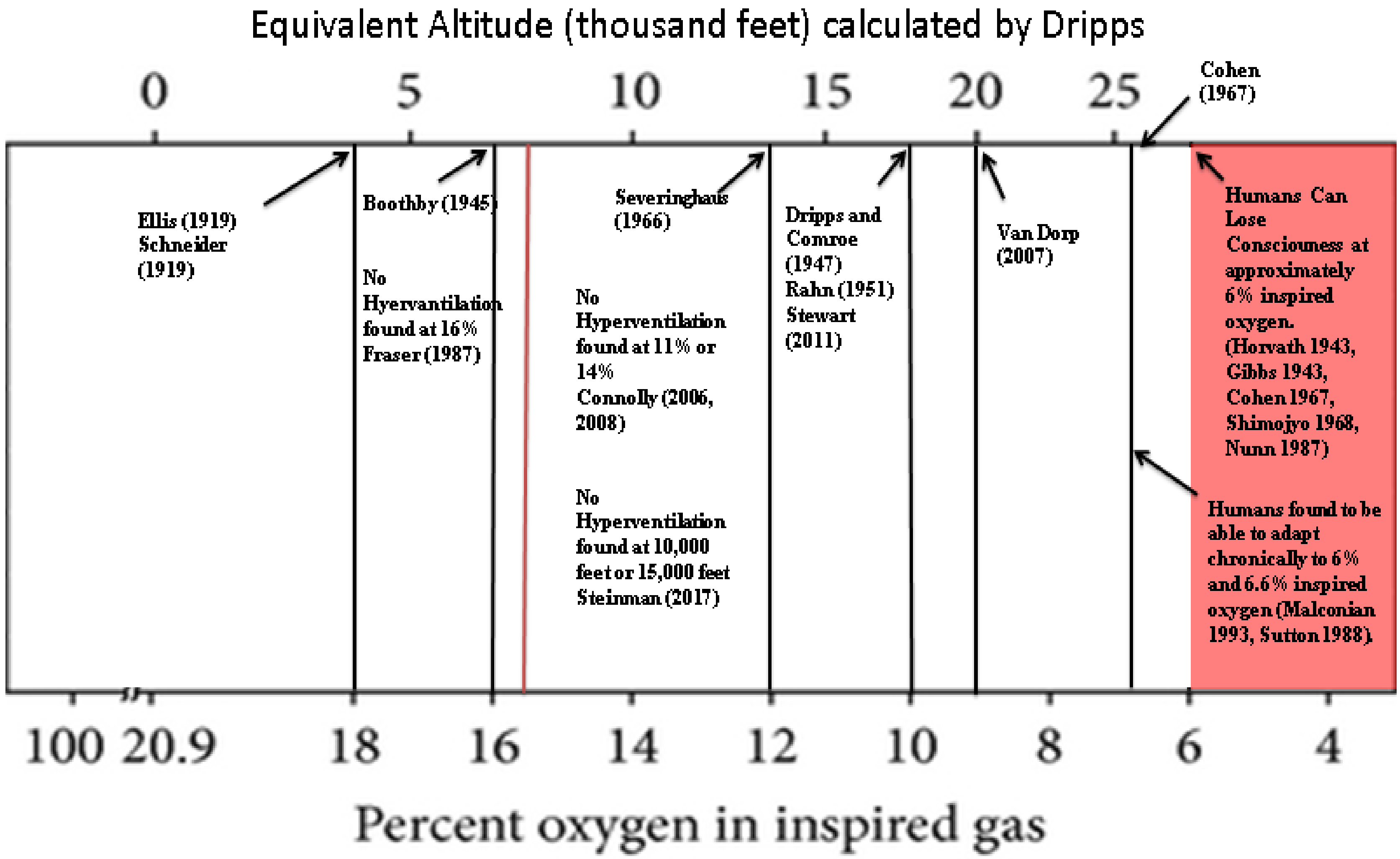
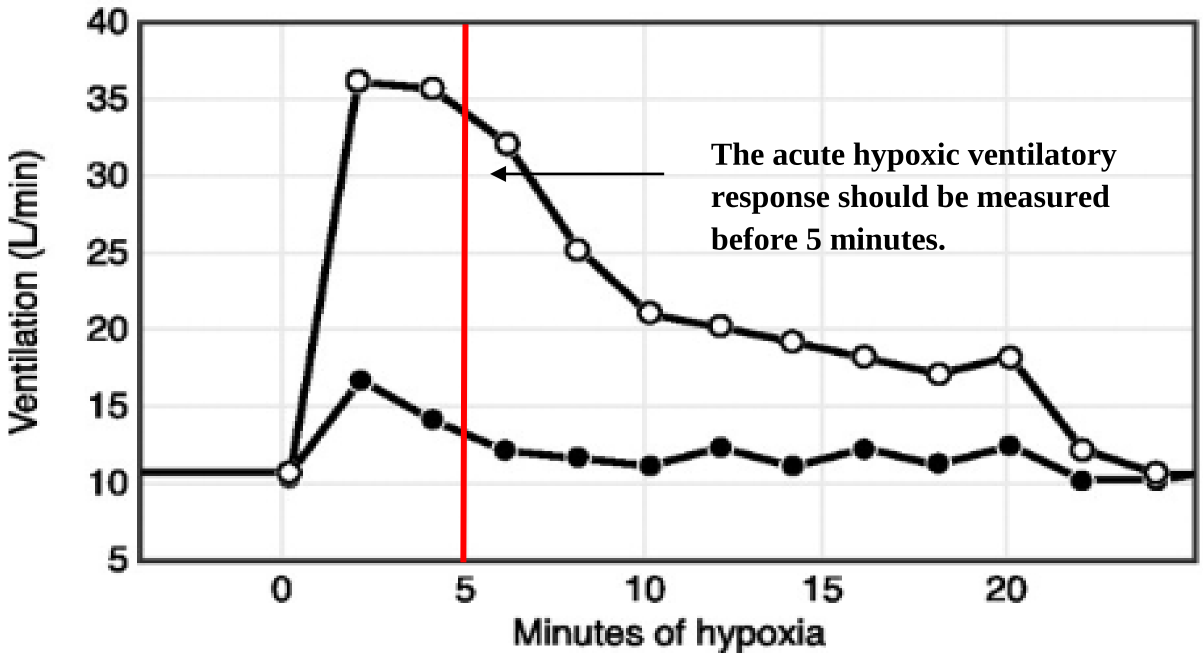


Fig 3) A diagram to show the difficulties identifying suitable thresholds and for determining why aeroplane cabin altitude should be set at a maximum of ~8000 feet. The diagram highlights the importance for a universally agreed ventilatory test that is relavant to the airline industry.

The Hypoxic Ventilatory Response - Where to measure the Threshold

Although a controversial mechanism, as many studies do not agree on the exact time course, hypoxic ventilatory decline must be taken into account when measuring the hypoxic ventilatory response. Figure 4 indicates the ventilatory response to hypoxia in 10 participants (Steinback and Poulin, 2007).

Figure 4 to show the mechanism of Hypoxic Ventilatory Decline. Steinback and Poulin (2007) hypoxia over a thirty minute time period and the ventilatory response. The dark circles represent poikilocapnic hypoxia and white circles represent isocapnic hypoxia.



Steinback and Poulin (2007) indicate that the point of measurement when assessing the ventilatory response to hypoxia is of critical importance (clear circles represent isocapnic hypoxia, dark circles represent poikilocapnic hypoxia). This is also in accordance with studies that have found hypoxic ventilatory decline to initiate at approximately five minutes (Duffin, 2007, Vovk et al. 2004, Powell et al. 1998, Bascom et al. 1990). As Figure 4 indicates the hypoxic ventilatory response to poikilocapnic hypoxia is smaller (Ainslie and Poulin, 2004), therefore, careful adherence must be taken to ensure representative measurements are being made.

The variability of the hypoxic ventilatory response in humans

Within participant variation, as previously discussed, should be considered when measuring the hypoxic ventilatory response. Sahn et al. (1977) suggests variations over a two hour period of measuring the hypoxic ventilatory response measured between 10 and 60% among participants. Furthermore, the hypoxic ventilatory response can vary as a result of (Teppema and Dahan, 2010):

1. Age

   Older age groups (64-79 years) have been shown to display a reduced hypoxic ventilatory response (Kronenberg and Drage 1973, Peterson et al. 1981). On the contrary, many studies have shown there is no difference between young (20-30 years) and older age groups (60-79 years) in the hypoxic ventilatory response (Ahmed et al. 1991, Pokorski and Marczak 2003, Pokorski et al. 2004 and Smith et al. 2001) Overall, it seems difficult to assess if age has any real effect on the hypoxic ventilatory response as the evidence is conflicting.

2. Metabolism

   Elevated metabolisms can increase the hypoxic ventilatory response (Regensteiner et al. 1989).

3. Circadian Rhythm

   Circadian Rhythm can influence the hypoxic ventilatory response depending on the time of the day and the metabolic need of the human body. Although, it has a relatively small influence on the adult human hypoxic ventilatory response (Stephenson et al. 2000).

4. Hormonal Status

   Testosterone has been shown to increase the hypoxic ventilatory response (Tatsumi et al. 1994, White et al. 1985). Progesterone has also shown to increase the hypoxic ventilatory response (Bayliss and Millhorn, 1992).

5. Pregnancy

   Pregnancy can cause hyperventilation because of an increase in metabolic rate and the stimulatory effects of progesterone (Regensteiner et al. 1989).

6. Psychological Factors (Anxiety)

   Making sure participants are accustomed to the protocol and the laboratory set up can help prevent anxiety and influencing responses.

7. Environmental Factors

   Previous exposure to altitude can affect the subsequent hypoxic ventilatory response (Teppema and Dahan, 2010).

8. Pharmacological Agents

Halothane has been noted to greatly reduce the initial hypoxic ventilatory response (Teppema and Dahan, 2010).

Experimental set ups, as a result of human variability, need to control as many variables as possible to minimise factors that could change a participant's hypoxic ventilatory response.

Cardiovascular responses to Acute Hypoxia

Cardiovascular responses to hypoxia provide valuable information that can be combined with the ventilatory responses to acute hypoxia to portray a detailed human response. Historically, early travellers to high altitude often complained of symptoms relating to the cardiovascular system. This became more prevalent as expeditions to altitude increased and the onset of high altitude ballooning around 1873. West et al. (2007) suggests it is well accepted that acute hypoxia causes an increase in cardiac output. This was also demonstrated in earlier studies where participants were exposed to hypoxia (Keys et al. 1943, Vogel and Harris 1967).

Acute hypoxia also causes an increase in heart rate (West et al. 2007) just as the case for cardiac output. As West et al. (2007) state there appears to be a linear relationship between heart rate and the level of hypoxia participants are exposed to, "the higher the altitude, the greater the increase in heart rate." Furthermore as Ernsting's Aviation Medicine 5th Edition (2016) suggests, there is an understanding that between 6,000 and 8,000 feet that heart rate increases. Compared with Ernsting's suggestion that ventilation is not stimulated until approximately 8,000 to 10,000 feet, heart rate appears to be considerably more sensitive to hypoxia than ventilation.

Vogel and Harris (1967) state there is no consistent change in stroke volume when participants are exposed to acute hypoxia. Within the acute hypoxia timeframe (<5 minutes) it would appear that stroke volume remains relatively constant with an increase in heart rate and therefore a resultant increase in cardiac output. In addition, many previous studies including that of Dripps and Comroe (1947) have failed to conduct continuous measurements of blood pressure. In reference to Kontos et al. (1967) and Vogel and Harris (1967) up to altitudes of 4,600m there is no change in mean blood pressure in humans.

As Ernsting's Aviation and Space Medicine 5th Edition (2016) states, acute hypoxia causes an immediate increase in both coronary and cerebral blood flow. However, when participants are exposed to severe acute hypoxia the majority of participants lose consciousness. The ventilatory and cardiovascular response appears inadequate to prevent this from happening (Horvath 1943, Gibbs 1943, Cohen 1967, Shimojyo 1968, Nunn 1987).

The cardiovascular system also undergoes a conflict when exposed to severe acute hypoxia. As participants hyperventilate when experiencing a lowering of arterial oxygen tension they often reduce their arterial carbon dioxide tension. As Ernsting's Aviation and Space Medicine 5th Edition (2016) states "a balance therefore exists between the vasodilating effect of hypoxia on the cerebral vessels and the vasoconstricting influence of a declining arterial carbon dioxide tension caused by the hypoxic drive to ventilation". As a result, one must consider the various effects and conflicts within the cardiovascular system and how they might impact ventilation. In particular, it is worth noting that during acute hypoxia the entire pulmonary vascular bed constricts which combined with an increase in cardiac output increases pulmonary arterial blood pressure (Ernsting's Aviation and Space Medicine 5th Edition, 2016). Whilst many previous studies measure blood pressure it may not give an accurate insight into what is occurring in essential organs such as the lungs. Displayed in Table 5 are some key studies that have measured heart rate and other cardiovascular variables in participants exposed to hypoxia:

Table 5) Cardiovascular Responses in Hypoxia containing heart rate and blood pressure, ranked by altitude.

Author	**Study**	**HR**	**Altitude**
Kronenberg and Drage (1973) N=8 young N=8 old	Heart Rate responses to Hypoxia in different age groups.	Average percentage increases in HR = 34% in young participants, in old participants = 12%.	PaO_2= 40 mmHg
Vogel and Harris (1967) N=16	Heart Rate responses to hypoxia	40-50% higher heart rates than resting values. Cardiac Output rose from 71 at 2,000 feet to 84 (ml/min/kg) at 15,000 feet.	2,000 feet 11,000 feet 15,000 feet
Steinback and Poulin (2008) N=10	Heart Rate responses to acute hypoxia	Average increase from 62.2 to 80.1 bpm.	3,350 feet
Steinback and Poulin (2008) N=10	Mean Blood Pressure Resonses to acute hypoxia	Average increase at 5 mins pf hypoxia percentage increase of 0.29.	3,350 feet
Ainslie and Poulin (2004) N=9	Heart Rate responses to acute hypoxia	Average percentage increase in hypoxia from resting values = 0.92.	3,350 feet
Naeije (2010) N=8	Heart Rate responses to acute hypoxia	Average increase of 20% from resting heart rate values at sea level.	11,500 feet
Reeves (1987) N=9	Heart Rate Responses to hypoxia	Average HR at sea level =64, at 18,500 feet = 86, at 23,000 feet = 95, at 26,800 feet = 99.	18,500 feet 23,000 feet 26,800 feet
Reeves (1987) N=9	Systemic arterial Pressure in hypoxia	Average BP at sea level = 96, at 18,500	18,500 feet 23,000 feet

		feet = 96, at 23,000 feet = 90, at 26,800 feet = 96.	26,800 feet

Carbon Dioxide and Ventilation

Similar to hypoxia, hypercapnia can cause a seemingly understated ventilatory response. Hypoxia at approximately 6% inspired O_2 only stimulates breathing to approximately 20 $Lmin^{-1}$ (Parkes 2013). Similarly, hypercapnia inspired at approximately 7% achieves only approximately 40 $L.min^{-1}$. By identifying the threshold at which carbon dioxide stimulates breathing it acts as a validation of this studies ability to measure accurately small changes to ventilation needed to identify a hypoxic threshold.

Lambertson et al. (1953) (Figure 5) tried to determine the ventilatory sensitivity of breathing at rest to CO_2. Lambertson gave participants 2.2%, 4.3% and 5.5%, however, breathing increased by approximately $4Lmin^{-1}$ when participants inspired 2.2% CO_2. By giving participants 2.2% Lambertson et al. (1953) would miss the threshold at which breathing is stimulated.

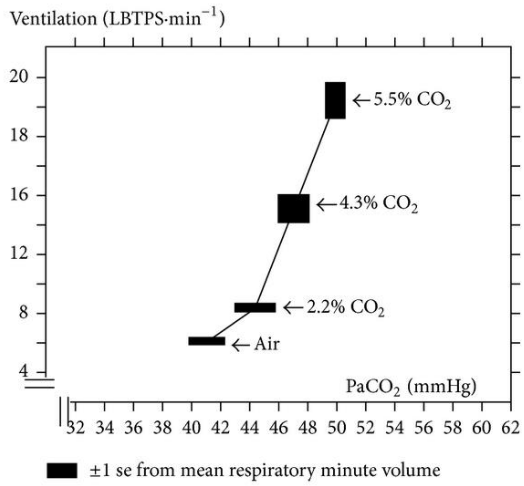


Figure 5) Sensitivity of breathing at rest to artificially raising $PaCO_2$ in Man. Minute ventilation and $PaCO_2$ (femoral) in 8 healthy men while inhaling 0–6% CO_2 in air at atmospheric pressure (mean slope is 2.5 $L.min^{-1}$ $mmHg^{-1}$ artificial $PaCO_2$ rise).

Kellogg (1963) also measured the ventilatory response to hypercapnia both at sea level and at altitude. At sea level the study found that the threshold for $PaCO_2$ increasing ventilation was between 34-38mmHg. Between these two points ventilation increased by approximately $2.5Lmin^{-1}$. Overall, very few studies have attempted to directly identify the point at which the human body can detect and adapt to artificial increases in arterial carbon dioxide. In addition, increasing inspired CO_2 is an artificial stimulus and it is commonly accepted that arterial CO_2 does not rise and even falls during heavy exercise (Parkes, 2013). Table 6 displays some previous studies and their measured ventilatory responses to CO_2.

Table 6).Compilation of key studies artificially raising inspired CO_2. A description of the study, ventilatory response and the CO_2 give to the participants is included.

Author	**Study**	**Ve (L.min^{-1})**	**CO_2**
Hirshman (1975) N=44	Measured the hypercapnic ventilatory response using the rebreathing method.	Increased by 2.69 (0.19)	~4% inspired CO_2
Bryne-Quinn (1971) N=10	Measured the hypercapnic ventilatory response using the rebreathing method.	Increased by 2.90 (0.15)	Varying and worsening CO_2 levels to ~5%.
Rebuck (1973) N=11	Measured the hypercapnic ventilatory response using the rebreathing method.	Increased by 1.94 (0.05)	Varying and worsening CO_2 levels to ~5%.
Forster (1969) N=10	Measured the hypercapnic ventilatory response using the rebreathing method.	Increased by 1.84 (0.26)	Varying and worsening CO_2 levels to ~5%.
Kronenberg and Drage (1973) N=8	Measured the hypercapnic ventilatory response using the rebreathing method.	Increased by 3.4 (0.5)	Varying and worsening CO_2 levels to ~5%.
Read (1966) N=21	Measured the hypercapnic ventilatory response using the rebreathing method.	Increased by 2.65 (0.27)	Varying and worsening CO_2 levels to ~5%.

Lambertsen (1953) N=8	Measured using set concentrations of inspired CO_2.	Increased by 4 at 2.2%	2.2%, 4.3% and 5.5% Inspired CO_2
Kellogg (1963) N=	Measured using set concentrations of inspired CO_2.	Increased by 2 between 34-38mmHg	Increased CO_2 until ventilation increased ($PaCO_2$ was between 34-38mmHg.

Acute Hypoxia – Overview

The effects of hypoxia and hypocapnia are of particular relevance during acute altitude exposure (Petrassi et al. 2012). During acute hypoxia, dependent upon the severity, a number of interactions occur between hypoxia, hypocapnia and other physiological variables. When the human body receives a large hypoxic stimulus of sufficient severity (usually breathing ambient air above 20,000 feet) sometimes loss of consciousness and eventually death can occur (Petrassi et al. 2012). This is less of a problem for aircraft with cabin pressurization systems but of considerable danger to fixed wing aircraft, rotary wing aircraft, balloons and gliders.

Some reviews have attempted to define the sensitivity of the carotid chemoreceptors, such as that of Tune (1964) who had suggested 10,000 feet to be the altitude at which motor performance deficits can be detected. More importantly for this study, Tune suggested that the physiological threshold for a hypoxic ventilatory response "usually initiated above 9,850 feet." However, was the scientific equipment and methodologies accurate enough to be able to make this claim? Overall, the general consensus appears to be an oversimplification of the human responses to hypoxic hypoxia and does not allow for the large variation between individuals. This study wanted to provide clear, evidence based data of the human response to hypoxia without generalizing the responses at specific altitudes.

Overall, this research has presented the various issues surrounding cognitive and neurophysiology research and the conflicting results. The key ventilatory studies have been reviewed and this research has made attempts to identify a ventilatory threshold using more modernized equipment and methodologies. With the dangerous nature of hypoxia it is of paramount importance to globally identify key physiological and cognitive responses. Especially for non-pressurized aircraft that are most at risk.

Typical Human Response to Hypoxia

As outlined by Ernsting's Aviation and Space Medicine 5th Edition (2016) the clinical picture of exposure to acute hypoxia up to approximately 10,000 feet includes:

- Resting participants show no symptoms of hypoxia.
- Performance of novel tasks may be impaired.

Compare Ernsting's (2016) clinical picture of a maximum of 10,000 feet to that of 10,000 to 15,000 feet:

- Resting Participants exhibit no or few signs and has virtually no symptoms.
- Ability to perform skilled tasks is impaired (usually participant is unaware).
- Prolonged exposure to 15,000 feet frequently causes a severe, generalized headache.

From this rather basic and uneventful human response to hypoxia at moderate altitudes one could assume that humans are relatively safe to fly up to 10,000 feet both from a physiological standpoint and a psychological one. So why are commercial airlines pressurizing cabins to a maximum altitude of 8,000 feet? Where is the scientific data allowing us to make this assumption?

Probably the most telling statement from Ernsting's (2016) suggests that above 8,000-10,000 feet "arterial oxygen tension falls to a level that stimulates respiration". Furthermore, Ernsting's suggests alveolar carbon dioxide tension does not fall until an altitude of ~10,000 feet, indicating that approximately 10,000 feet appears to be the point at which an increase in ventilation can be validated by a decrease of expiratory carbon dioxide ($P_{et}CO_2$) caused by participants hyperventilating.

This research has included a table to place into perspective the composition of air at various altitudes (Table 7)

Table 7) A guide to the partial pressure of oxygen at altitudes from sea level to 6km (~18,300 feet).

Height (km)	Height (feet)	Barometric Pressure (mmHg)	PiO_2 (mmHg)	PiO_2 (%)
0	0	760	159	21.0
0.3	1,000	731	153	20.2

0.7	2,000	704	147	19.5
1	3,048	674	141	18.6
1.3	4,000	652	137	18.0
1.6	5,000	627	131	17.3
2	6,096	596	125	16.5
2.3	7,000	579	121	16.0
2.6	8,000	556	116	15.4
3	9,144	526	110	14.5
3.3	10,000	511	107	14.1
3.6	11,000	490	103	13.5
4	12,192	462	97	12.8
4.3	13,000	450	94	12.4
4.6	14,000	430	90	11.9
5	15,240	405	85	11.2
5.2	16,000	393	82	10.9
5.6	17,000	376	79	10.4
6	18,288	354	74	9.8

Aims:

- Investigate at what altitude equivalent of FiO_2 did participants first experience an increase in respiratory drive.
- Determine if a hypoxic ventilatory threshold can be detected.
- Provide a validation to a hypoxic ventilatory threshold by measuring the point at which $P_{et}CO_2$ decreases and a validation of the hypoxia given to participants (SpO_2).

Methods

1) Participants

A total of 20 participants were included in this experiment. There were 11 females and 9 males. The age ranged from 18-24 for 19 participants with the inclusion of one 56 year old participant. All participants were non-smokers and at least 17 were engaged in regular physical activity (daily swimming). All participants provided informed, written consent. All experiments were carried out in according to the Declaration of Helsinki (American Physiological Society, 2002) and with approval of the local research ethics committee (Welcome Trust Clinical Research Facility, Queen Elizabeth Hospital Birmingham). All participants were evaluated during their visit to the research facility to ensure all physiological readings were within the normal range. This was also confirmed during the 15 mins of rest prior to the experiment beginning. All participants were sea level residents and had not travelled to an altitude greater than 1000m within the last year. The participants were told to relax and to ensure breathing was as autonomous as possible. This research requested participants to consume their typical calories during the day, prior to the experiment, without any substances that may affect normal ventilatory responses such as caffeine or alcohol. Participants arrived an hour prior to their experiment and were requested to only consume water in this period.

2) Protocol

Participants were all familiar with the laboratory settings and they visited the research facility to ensure they were comfortable with the experimental setup and any anxiety about the procedure was reduced. Participants lay semi-recumbent on a bed and breathed through a facemask connected to a capnograph to measure exhaled PCO_2 (Hewlett Packard) and Branta flowmeter (to measure breathing frequency, tidal volume at BTPS, minute ventilation and drive). Non-invasive measurements were made of the ECG (Neurolog), systolic, diastolic and mean blood pressure (Finapres 2300 Ohmeda) and oxygen saturation (SpO_2 Datex Ohmeda) and FiO_2 was measured using a Datex Ohmeda.

For 5 minute periods participants breathed hypoxic mixtures of 16.3%, 15.6%, 14.9%, 14.2% and 10% oxygen in random order with each separated by 5 minute periods of room air. As mentioned, this study decided on 5 minute exposures to hypoxia due to the mechanism of hypoxic ventilatory decline. This research chose the five inspired oxygen percentages after several experiments to determine where a hypoxic ventilatory threshold may be located. This required various trial and error experiments in order to pinpoint hypoxia doses that were close to a potential ventilatory threshold. Using this method this research was able to plot a dose response curve. This study wanted to provide a dose of hypoxia that did not stimulate respiration (16.3% O_2) and would most likely stimulate respiration (10% O_2).

All data was recorded and analysed using a CED1401 and Spike2 software (Cambridge Electronic Design, Cambridge, UK), where data was converted to lines of instantaneous measurements that were sampled at 1Hz. In each 5 minute period the last 1.5 minutes of data was averaged to produce each measurement at each FiO_2 level. This recorded the largest increase in ventilation within the acute hypoxia timeframe (<5 minutes). This avoided measuring a possible lower ventilatory response after approximately 5 minutes of hypoxia exposure in which hypoxic ventilatory decline may have occurred. The results of each participant was averaged and used for determining a significant increase in respiratory rate from rest (room air). This research adopted the same protocol with the carbon dioxide threshold experiment using inspired concentrations of 5%, 2.5%, 1.2%, 0.6% and 0.3% CO_2.

Participants were instructed to breathe as normal and were provided with noise cancelling headphones for music. This experimental set up allowed for changing inspired gas mixtures without the participants' knowledge. This research used a random number generator to change the order of hypoxic mixtures inspired. This study allowed for participants to acclimatize to the laboratory setting and place the facemask comfortably on their face for 15 minutes before the experiment began. Temperature within the Welcome Trust Clinical Research Facility was maintained at ~20 degrees centigrade.

Table 8) Example of an experiment conducted by this research. The order of the hypoxia given to participants was randomly generated before each experiment.

Condition	**Time**
Rest (Room Air, 21% oxygen)	15 (mins)
10% inspired oxygen	5 (mins)
Room Air	5 (mins)
14.2% inspired oxygen	5 (mins)
Room Air	5 (mins)
14.9% inspired oxygen	5 (mins)
Room Air	5 (mins)
15.6% inspired oxygen	5 (mins)
Room Air	5 (mins)
16.3% inspired oxygen	5 (mins)

Room Air	5 (mins)

3) Calibrations

The Branta flowmeter was calibrated using HR 3L and HR 0.1 L syringes (Hans Rudolph). Calibrations were linear over the range of 0.02-3L and the mean volume recovered was 5 ±2% of the actual volume. For each day the 0.1-3L "true" volumes were passed through the flowmeter and the reported volume noted. An average correction factor was calculated to convert the reported volume to the true volume. Figure 6 illustrates that the reported volumes had a linear relationship to the true volumes. Volumes were measured at recorded ATPS and converted using a standard table to BTPS.

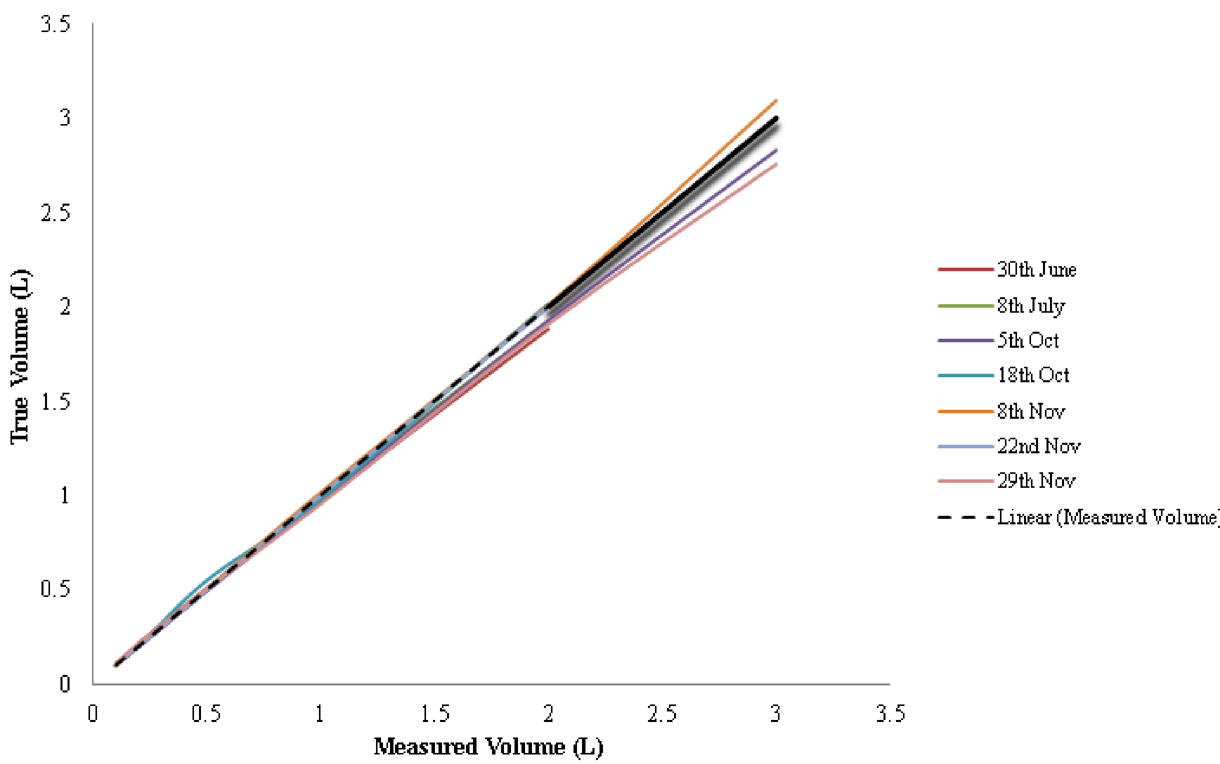


Figure 6) Calibration of Flowmeter. This research recorded calibration readings from the flowmeter before and after each day of experiments (coloured lines) plotted with the ideal (dashed) “syringe” volume. This figure illustrates that this study could accurately measure the participants’ respiratory rate using the flowmeter.

Statistics

Statistical analysis used Analysis of variance (F values were for minute ventilation, tidal volume, frequency and drive and for heart rate, blood pressure, SpO_2 and end tidal PCO_2) and Student's paired T-test. Significance was taken at $p<0.05$ for two tailed tests. Variance is given as standard error. Participant's resting data were compared with each dose of hypoxia and carbon dioxide. Data are expressed as mean ± SE.

Results – Ventilatory Hypoxia Threshold

For each variable (hypoxic hypoxia) statistical analysis was by repeated measures ANOVA with gas composition as the within participants factor and with significant F values for VE (14.2), Tv (16.6), Vt/Ti (10.2), frequency (3.7), CO2 peaks (5.6) and heart rate (70.5). There was no significant F value for BP. Within participants contrasts were used to compare the Eupnea values with subsequent values. Once a significant threshold had been identified vs. eupnea, this research tested whether there was a significantly linear increase in response with the appropriate within participant contrast.

Figure 7 acts as a validation for the level of hypoxia provided to the participants. Compared with room air all inspired hypoxic mixtures (16.3%, 15.6%, 14.9%, 14.2% and 10%) produced a significant reduction in SpO_2 ($p<0.05$).

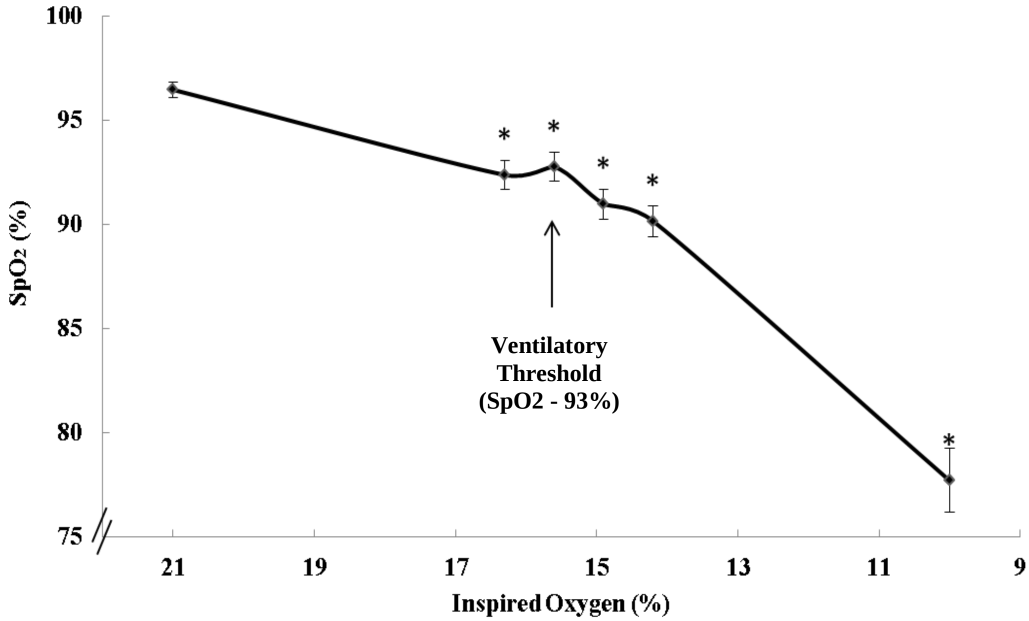


Figure 7) Average Measured SpO_2 (%).Inspired oxygen (%) and the effect on average (n=20) SpO_2. All values are mean ±SE. SpO_2 was measured and averaged across all participants within the last 1.5 minutes of hypoxic exposure. Asterisks indicate significant differences compared with 21% FiO_2 (Inspired Oxygen %).

Ventilation did not significantly increase with 16.3% inspired oxygen as opposed to 15.6%, 14.9%, 14.2% and 10% inspired oxygen where all four significantly increased when compared with resting ventilation. With regard to Figure 8, Dripps and Comroe’s measurements from 1947 have been superimposed. This research has detected a significant increase in instantaneous minute ventilation which identifies the participant’s ventilatory threshold to hypoxia to be 15.6% inspired oxygen. When comparing this with Dripps and Comroe’s threshold at 10% oxygen this research has shown a threshold difference of 5.6% inspired oxygen (equivalent altitude of 10,100 feet).

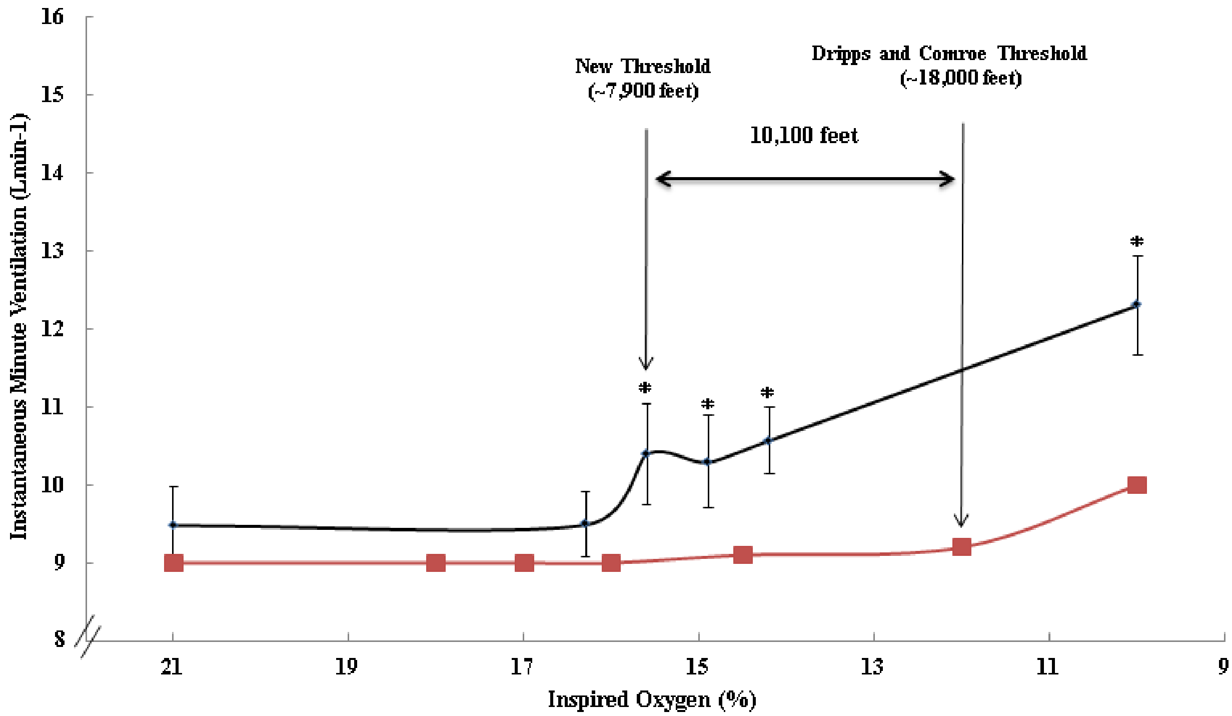


Figure 8) Average Instantaneous Minute Ventilation. Artificially changing FiO_2 and the subsequent effects on Average Instantaneous Minute Ventilation. All values are mean ±SE. Values were measured in the last 1.5 minutes of hypoxic exposure and averaged (n=20). The red line represents Dripps and Comroe's data (1947). Asterisks indicate significant changes compared with 21% FiO_2.

The finding in Figure 9 was validated by the $P_{et}CO_2$ result. This research found that 15.6%, 14.9%, 14.2% and 10% inspired oxygen all significantly reduced $P_{et}CO_2$. Figure 9 displays the participants $P_{et}CO_2$ for each inspired oxygen percentage.

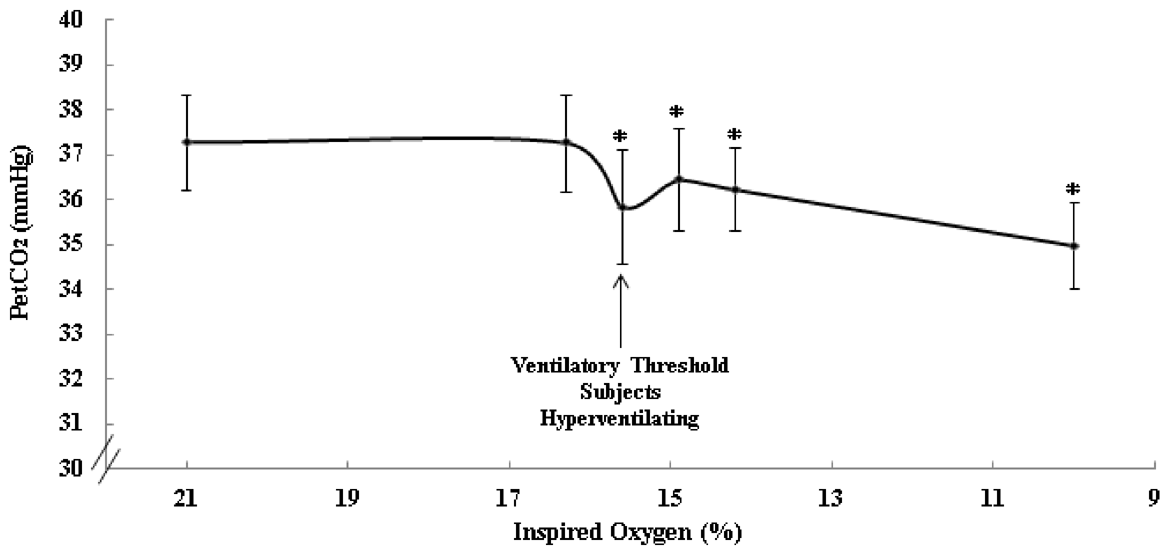


Figure 9) Average $P_{et}CO_2$. Inspired oxygen (%) and the subsequent effects on $P_{et}CO_2$. All values are mean ±SE. Values were measured within the last 1.5 minutes of hypoxic exposure and averaged (n=20). Asterisks indicate significant changes compared with 21% FiO_2.

Heart Rate was the most sensitive measure to changes in inspired oxygen mixtures. Heart Rate was significantly increased at all increments of hypoxia when compared with rest (Figure 10).

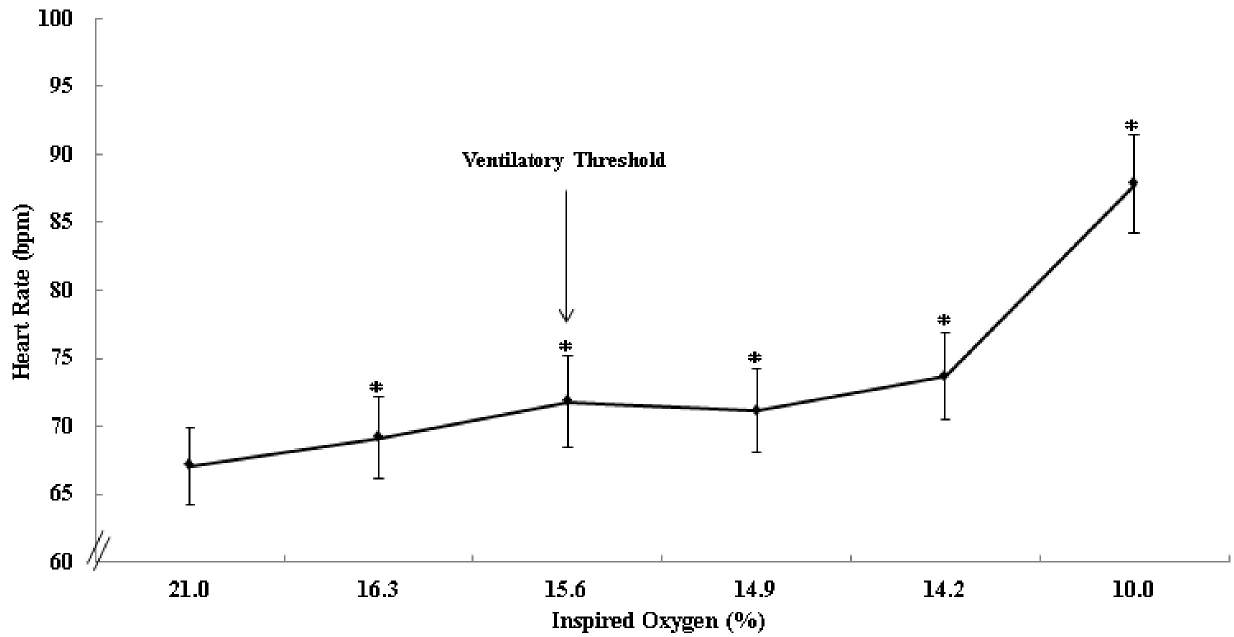


Figure 10). Average Heart Rate. Inspired oxygen (%) and the subsequent effects on average heart rate. All values are mean ±SE. Values were measured within the last 1.5 minutes of hypoxic exposure and averaged (n=20). Asterisks indicate significant changes compared with 21% FiO_2.

As a second measure of ventilation, this research recorded participant's drive to breathe (VT/Ti). The results display that only breathing 14.9%, 14.2% and 10% inspired oxygen were enough to significantly increase VT/Ti from room air values (FiO_2 21%) (Figure 11).

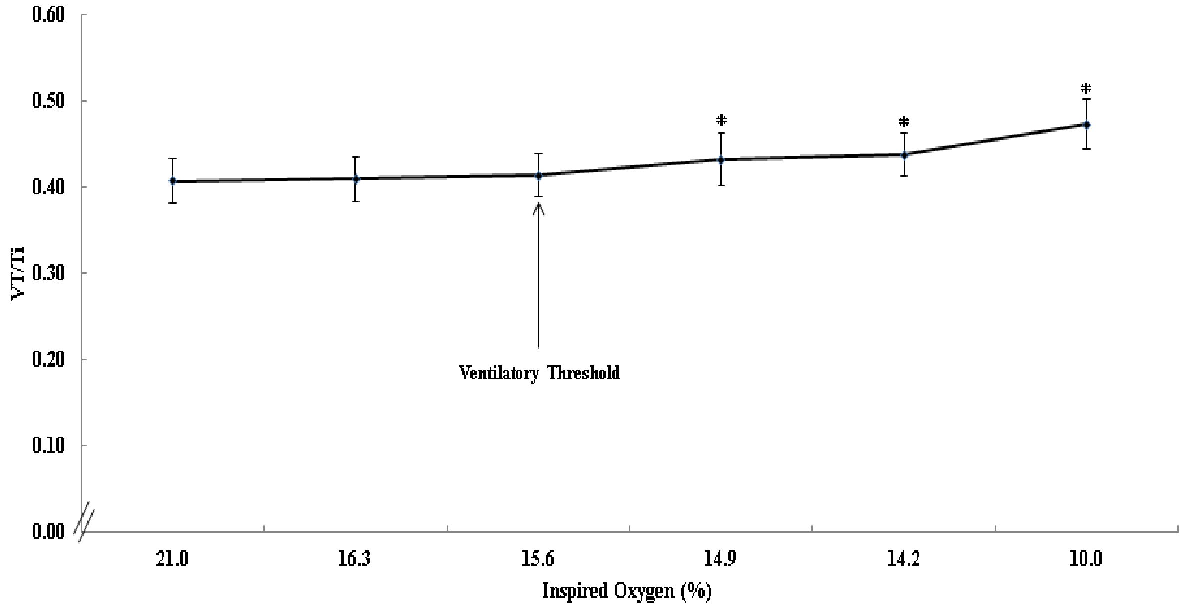


Figure 11) Average VT/Ti. Inspired oxygen (%)and the effects on average VT/Ti (n=20). All values are mean ±SE. Values were measured with the last 1.5 minutes of hypoxic exposure. Asterisks indicate significant changes compared with 21% FiO_2.

Along with VT/Ti this research also measured Frequency and Volume of breathing. Frequency (breaths per minute) (Figure 12) was only significantly higher than rest at 15.6% inspired oxygen. Tidal Volume (Lmin) (Figure 13) was significantly higher than rest at 14.2% and 10% inspired oxygen.

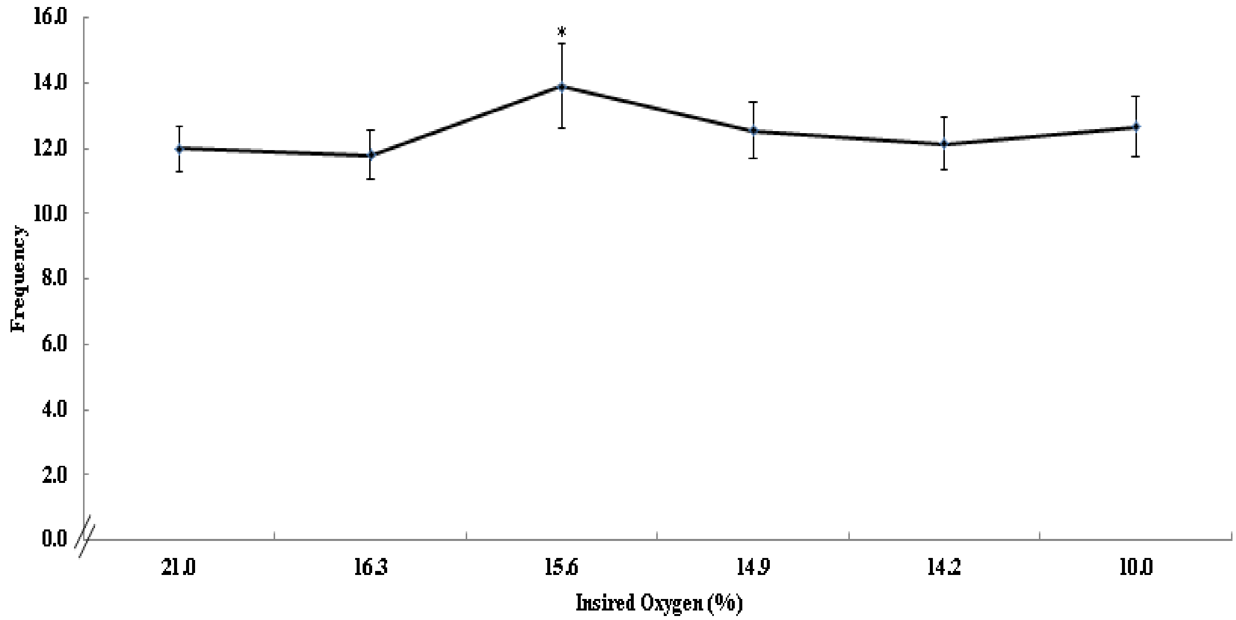


Figure 12). Average Frequency of Breathing (Number of Breaths per Minute). Inspired Oxygen (%) and the effects on average frequency (n=20). All values are mean ±SE. Values were measured with the last 1.5 minutes of hypoxic exposure. Asterisks indicate significant changes compared with 21% FiO_2.

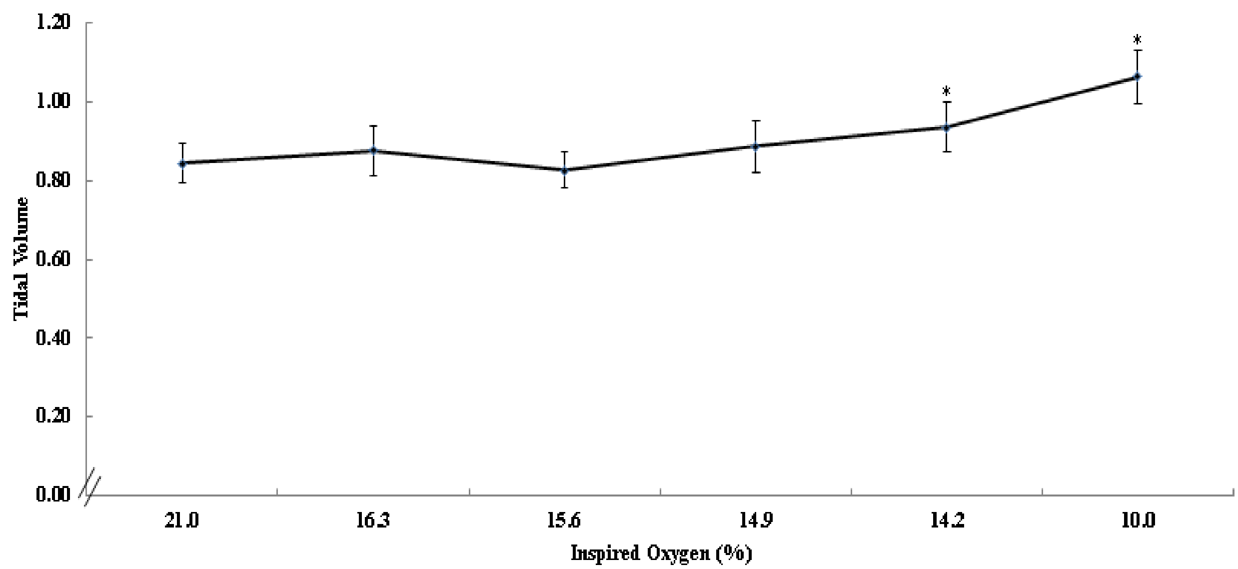


Figure 13). Average Tidal Volume (Litres). Inspired Oxygen (%) and its effects on average Tidal Volume (n=20). All values are mean ±SE. Values were measured with the last 1.5 minutes of hypoxic exposure. Asterisks indicate significant changes compared with 21% FiO_2.

Blood pressure was recorded continuously throughout all experiments. Figure 14 displays systolic, mean and diastolic blood pressure. This research found no significant differences for any given inspired oxygen percentage on any of the three measures.

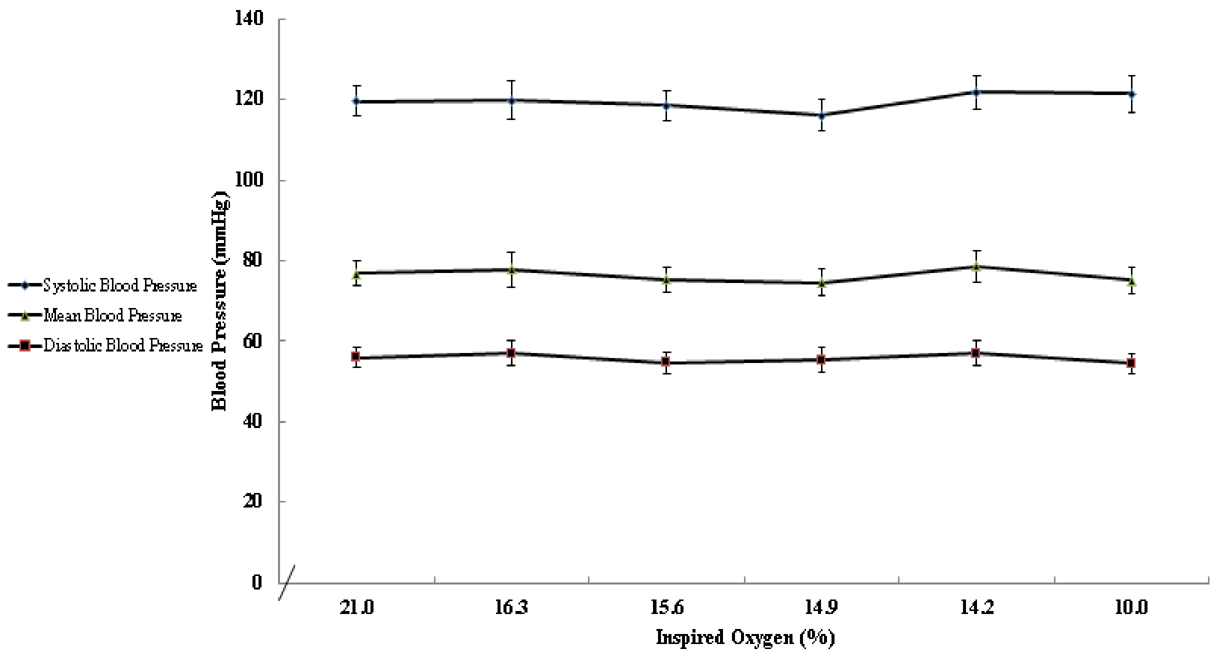


Figure 14) Inspired Oxygen (%) and the effects on average systolic, diastolic and mean blood pressure (n=20). All values were measured with the last 1.5 minutes of hypoxic exposure. Asterisks indicate significant changes compared with 21% FiO_2.

Results – Carbon Dioxide Threshold

For hypercapnia, statistical analysis was performed by repeated measures ANOVA within participant contrasts to compare each increment in $FiCO_2$ with the room air (control) condition.VE was significant and showed a significant linear effect after threshold at 1.2% $FiCO_2$. Tv showed a significant linear effect after threshold at 2.5% $FiCO_2$. VT/Ti and Frequency showed a significant linear effect after 1.2% $FiCO_2$. Blood pressure and Heart rate were both significant at 5% $FiCO_2$.

Inspired carbon dioxide applied to the participants acted as a secondary validation on the study design to accurately detect changes in $PetCO_2$ in the hypoxia threshold protocol. Figure 15 indicates the amount of CO_2 in mmHg for each protocol.

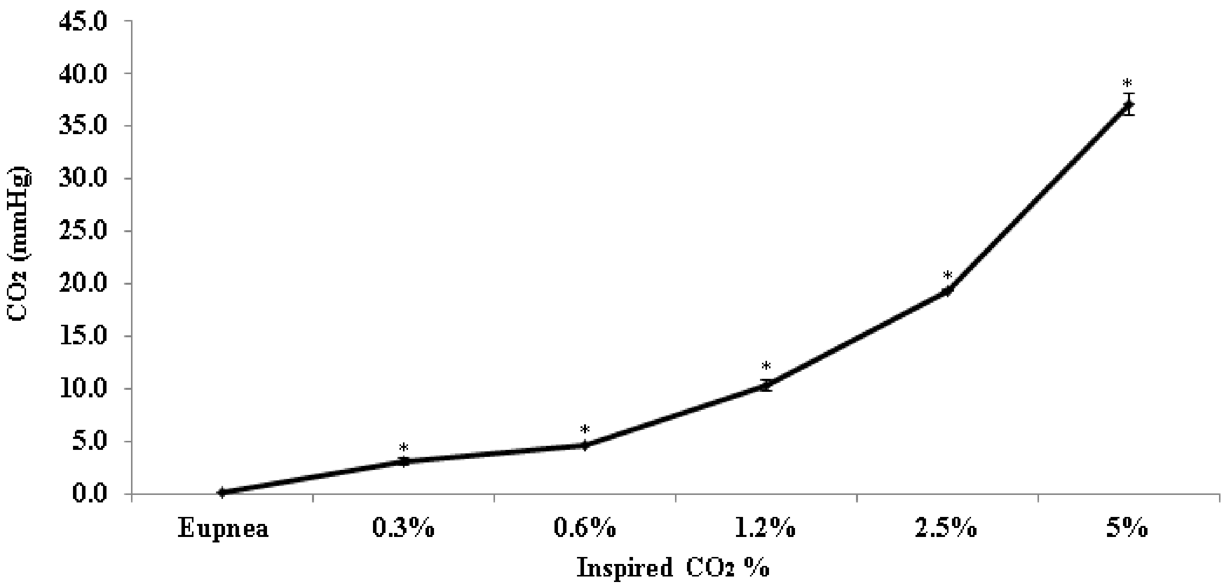


Figure 15) Inspired CO_2 and the resultant $PetCO_2$ (n=20). All values are mean ±SE. Values were measured with the last 1.5 minutes of hypercapnic exposure. All values were significantly higher compared with Eupnea (Room Air).

Within this particular protocol, this research detected that participants on average significantly increased their breathing at 1.2% inspired carbon dioxide along with 2.5% and 5% (Figure 16).

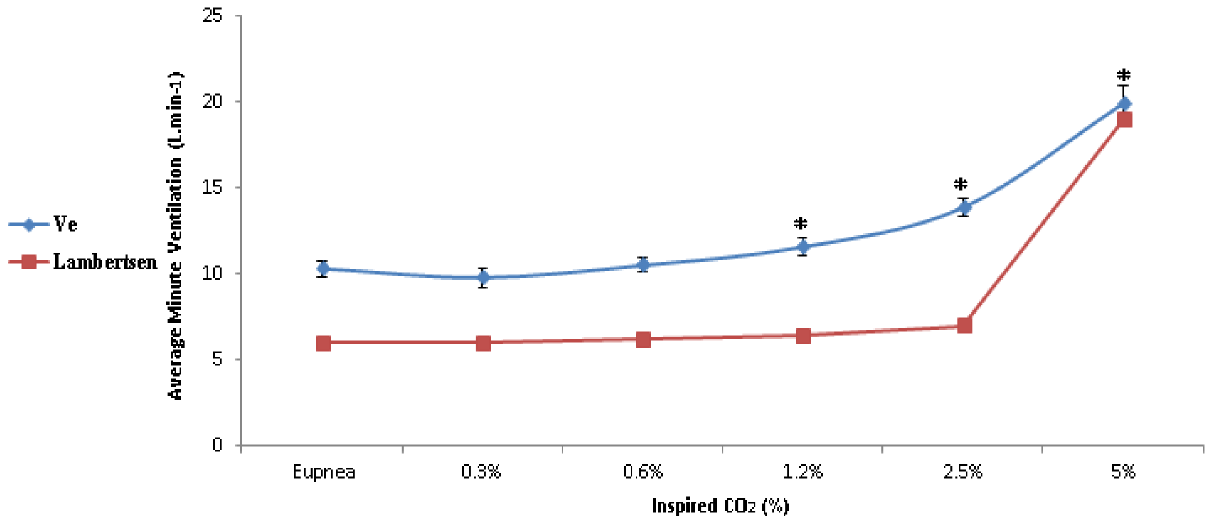


Figure 16) Average Instantaneous Minute Ventilation with Lambertsen et al. (1953). Inspired CO_2 (%) and the result on average Instantaneous Minute Ventilation, the red line indicates the results previously collected by Lambertsen et al. (1953) (n=20). All values are mean ±SE. Values were measured within the last 1.5 minutes of hypercapnic exposure. Asterisks indicate significant changes compared with Eupnea.

This research found, contrary to the hypoxia protocol, that VT/Ti appears to confirm the results of instantaneous minute ventilation as 1.2%, 2.5% and 5% inspired CO_2 all were significantly increased compared to eupnea (Figure 17).

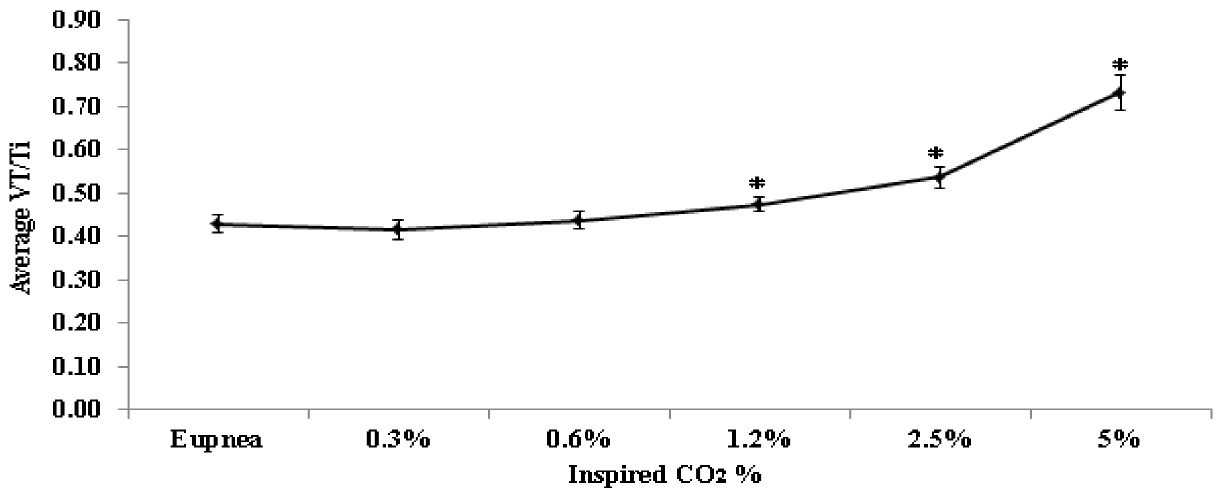


Figure 17) Inspired CO_2 (%) and the resultant average VT/Ti (n=20). All values are mean ±SE. Values were measured within the last 1.5 minutes of hypercapnic exposure. Asterisks indicate significant changes compared with Eupnea.

Tidal Volume (Figure 18) significantly increased compared with resting levels with inspired 2.5% and 5% CO_2. Frequency (Figure 19) increased significantly in 1.2%, 2.5% and 5% inspired CO_2.

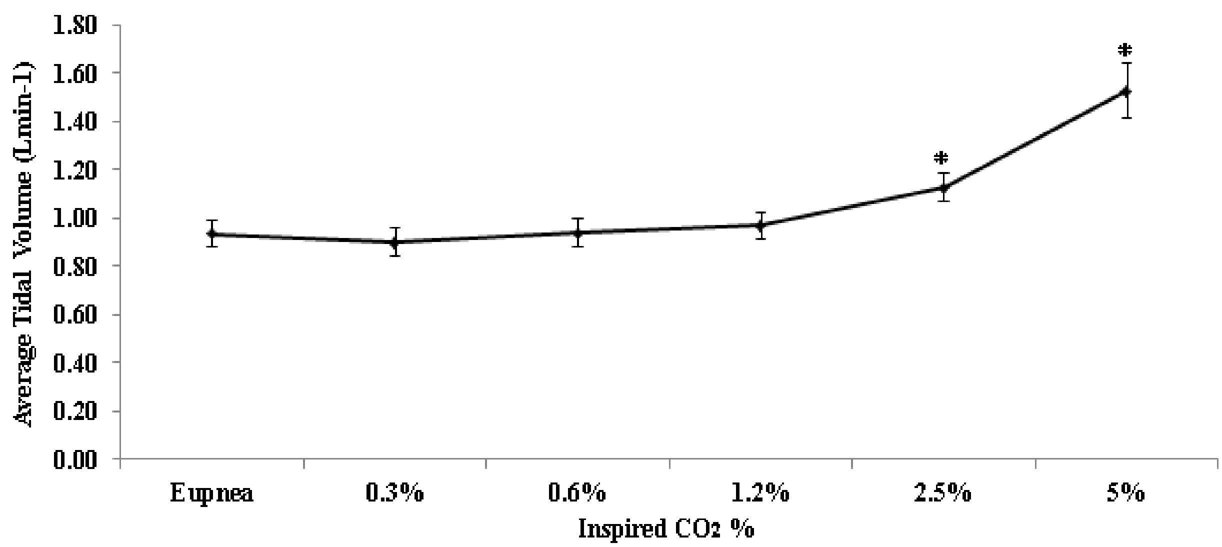


Fig 18) Inspired CO_2 (%) and the resultant average Tidal Volume (n=20). All values are mean ±SE. Values were measured within the last 1.5 minutes of hypercapnic exposure. Asterisks indicate significant changes compared with Eupnea.

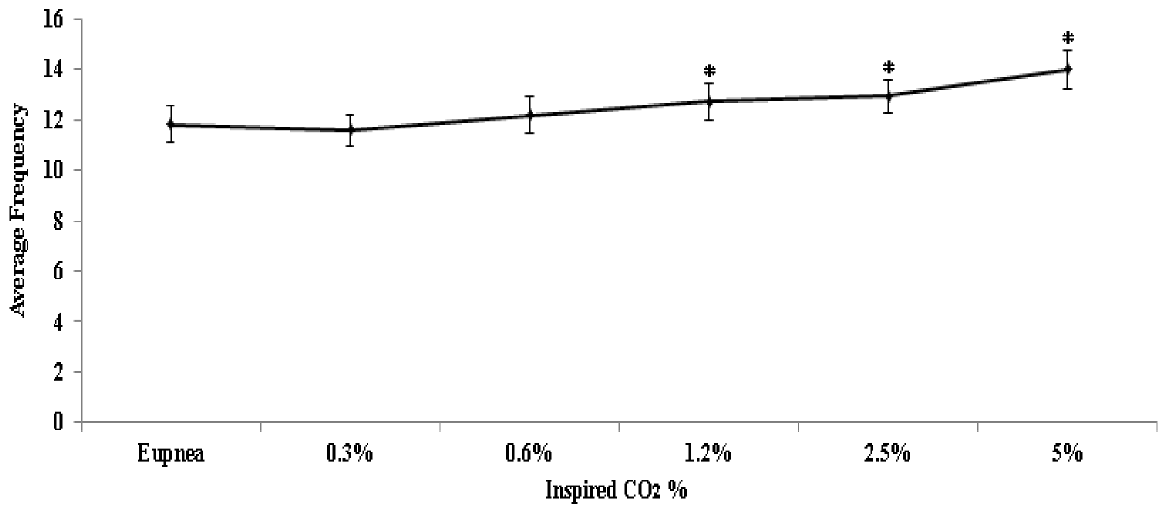


Figure 19) Inspired CO_2 and the resultant average frequency (n=20). All values are mean ±SE. Values were measured within the last 1.5 minutes of hypercapnic exposure. Asterisks indicate significant changes compared with Eupnea.

Blood pressure was measured constantly throughout the experiment and this study found that only until 5% inspired CO_2 did systolic, mean and diastolic pressure significantly increase compared to resting levels ($p<0.05$) (Figure 20).

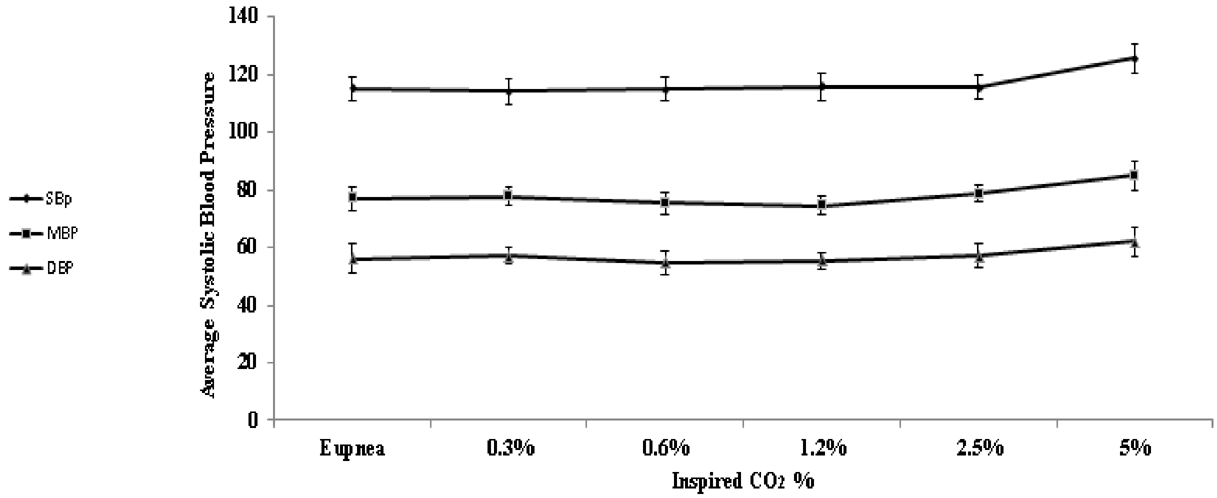


Figure 20) Average Blood Pressure. Inspired CO_2 (%) and the resultant Systolic, Diastolic and Mean Blood Pressure (n=20). All values were measured with the last 1.5 minutes of hypercapnic exposure. Asterisks indicate significant changes compared with Eupnea.

Heart Rate (Figure 21), unlike the hypoxia protocol, did not increase significantly until participants breathed 5% CO_2. There was variability as the inspired CO_2 concentrations increased from 1.2%, however, heart rate appears to be more sensitive to hypoxia.

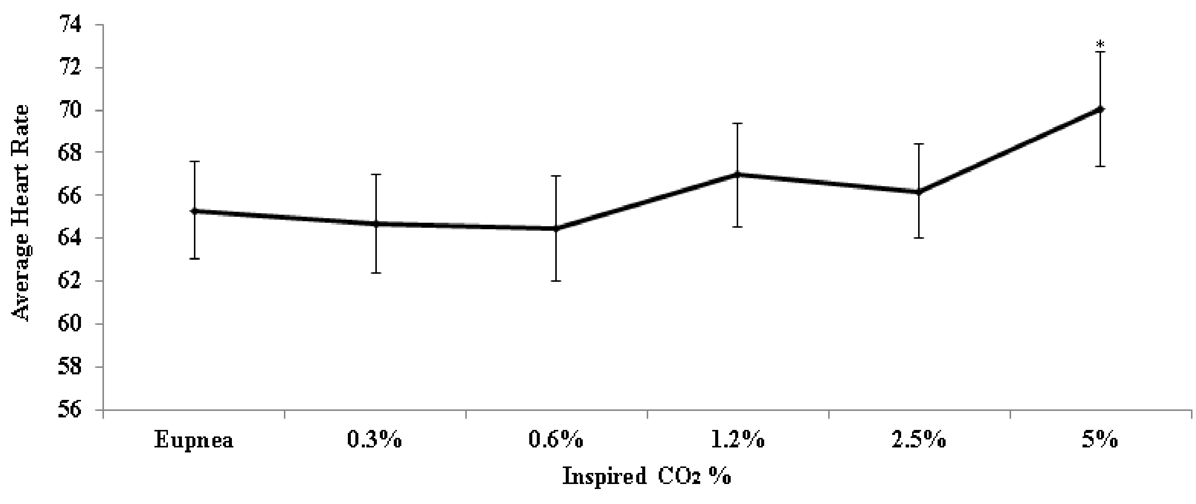


Figure 21) Inspired CO_2 and the resultant heart rate (n=20). All values are mean ±SE. Values were measured within the last 1.5 minutes of hypercapnic exposure. Asterisks indicate significant changes compared with Eupnea.

This study measured, with regard to the CO_2 threshold, expiratory CO_2 (Figure 22) and SpO_2 (Figure 23). Expiratory CO_2 (PetCO2) increased significantly at all inspired CO_2 concentrations apart from 0.6%. SpO_2 rose significantly when participants breathed 1.2%, 2.5% and 5% CO_2.

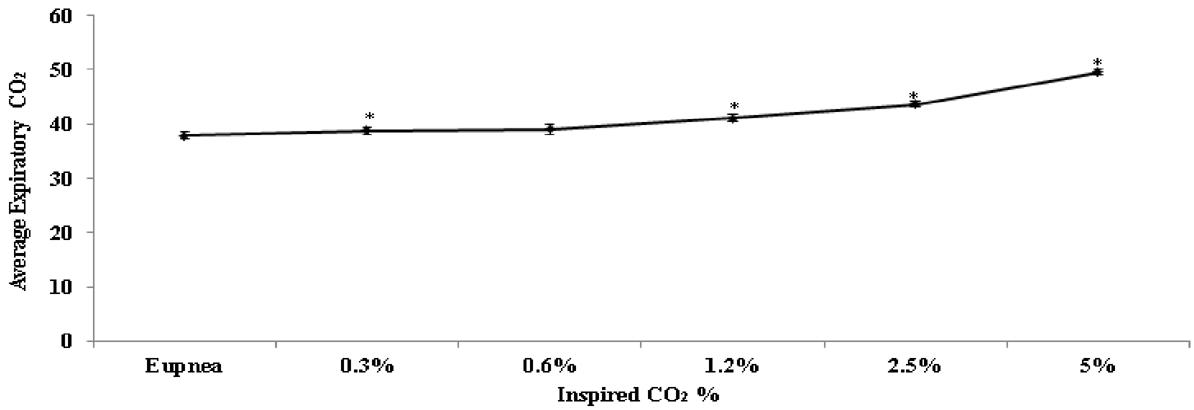


Figure 22) Inspired CO_2 and the resultant $P_{et}CO_2$ (n=20). All values are mean ±SE. Values were measured within the last 1.5 minutes of hypercapnic exposure. Asterisks indicate significant changes compared with Eupnea. 0.6% inspired CO_2 was not significantly increased from Eupnea.

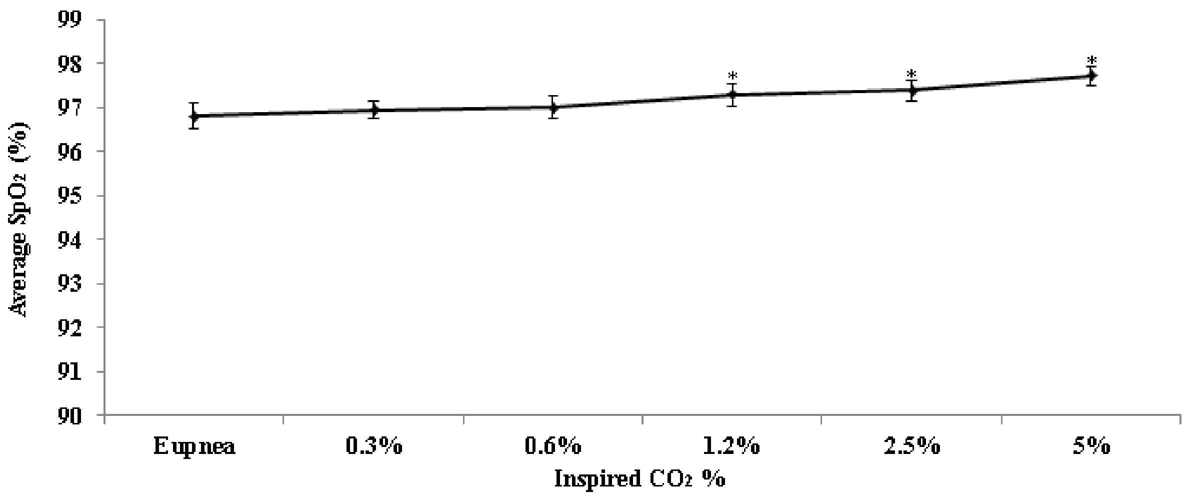


Figure 23) Inspired CO_2 (%) and the resultant SpO_2 (n=20). All values are mean ±SE. All values measured within the last 1.5 minutes of hypercapnic exposure. Asterisks indicate significant changes compared with Eupnea.

Discussion

Main Findings

Within this study, this research has provided a review of the aviation medicine field, both from a cognitive and physiological perspective. Psychological studies have failed to agree with each other and often lack consistency at moderate altitudes (Petrassi et al. 2012). In addition, this study has shown that humans are capable of detecting and responding to hypoxia at lower altitudes than seen in previous studies and literature. As this research presents, the threshold for the stimulation of breathing lies between 16.3% and 15.6% inspired oxygen. Compared with the Dripps and Comroe (1947) study, this study indicates that a significant increase in breathing can be detected at 15.6% inspired oxygen. Dripps and Comroe (1947) showed breathing to significantly increase at ~10% O_2. The different results are likely due to a more modern scientific methodology and statistical design. This research was calibrated and had the ability to measure small changes to respiration using a flowmeter. Furthermore, this also suggests that the modern threshold suggested in Petrassi et al. (2012), Ernsting's Aviation Medicine 5th Edition (2016) and Tune's review (1964) at ~10,000 feet underestimates the sensitivity of the human ventilatory response to hypoxia and therefore, how sensitive the carotid chemoreceptors are to detecting a decrease in PaO_2. This research has shown that there is a difference of 10,100 feet, in terms of equivalent altitude, when comparing this data with that of Dripps and Comroe (1947).

The question remains, what does this mean for aircraft pressurization? Previously, it would be fair to assume from the research available that 8,000 feet was a safe compromise. However, within this study has shown breathing can be stimulated at approximately 7,900 feet across a large participant size (n=20). Therefore, the 8,000 feet maximum altitude cabin pressure regulation now has physiological support and agrees with this study's findings.

Inter-participant Variations – Notoriously Variable Hypoxic Ventilatory Response

The range of the hypoxic response between participants varies considerably so every attempt was made to recruit from a similar background, in terms of age, physical activity and other smaller variables. As seen with other previous studies, "the coefficient of variation lies between 23% and 72%"in terms of hypoxic ventilatory response (West et al. 2007, Cunningham et al. 1964, Weil et al. 1970, Rebuck and Campbell 1974).

As many of the participants were swimmers it is worth considering the study of (Bjurstrom and Schoene 1986) who found this particular group to have a lower than average hypoxic ventilatory response. Furthermore, the majority of this study's participants were young (18-24). This is of importance because older participants have been shown to have an attenuated hypoxic ventilatory response (Kronenberg and Drage 1973, Chapman and Cherniak 1986, Poulin et al. 1993). Although, 19 of the participants were between the ages of 18-24, one subject was 56 years old. However, any age differences that impacted the results would be considerably small, especially due to the participant size (20). This cannot be quantified by how much or even if these variables had any effect on the measured acute hypoxic ventilatory response. This research is confident that the participant group was large enough to substantially negate any incorrect data that may have changed the results (McLoughlin, 2017). Sporting background appears to be hard to define as one cannot reliably estimate the overall effect on the hypoxic ventilatory response. When measuring acute responses to hypoxia these variables seem even less significant and could just be considered minor physiological variables between participants. However, this study more importantly, avoids a much larger inter participant variations as seen with psychological/cognitive studies. This is because each participant was their own control, and a paired design could be employed.

The participants were semi-recumbent and this provided a relaxed environment for the participants. This research wanted to ensure that the breathing measured was as autonomous as possible as opposed to voluntary. By using this method, one could measure participants in a similar state to what they would be experiencing on an aircraft. Not only is this considerably more relevant, it considerably lessens any psychological factors that may influence breathing. A concern of a participant being nervous is that they may naturally hyperventilate and therefore, the results may be influenced. The use of headphones allowed participants to cancel the noise from the research facility and allowed the researchers to change the inspire oxygen percentage without the subjects knowledge to prevent any anxiety that could have caused hyperventilating.

$P_{et}CO_2$ – Acute Hypoxia

A key validation of the significant increase in breathing detected at 15.6% O2 was that $P_{et}CO_2$ significantly decreased. This decrease indicates that participants were stimulated by a decrease in FiO_2 as they were hyperventilating. SpO_2 readings were included as validation of the hypoxic mixture given and the effect on arterial oxygen levels. Prior to the experiment participants were not tested for their haemoglobin so there is no guarantee that their levels were within the normal range, however, one could assume healthy, active and young individuals would be likely to have a normal haemoglobin level. All physiological systems were continuously measured allowing detection of the small and subtle changes associated with finding a hypoxia ventilatory threshold. The participant size further contributes to this finding as this research averaged across 20 participants with the exact same protocol, only changing the order of the level of inspired O_2. Petrassi et al. (2012) states the importance of not only using PaO_2 as a sole measure of hypoxia but in combination with $P_{et}CO_2$. This is important when educating passengers, aircrew and pilots on hypoxic hypoxia.

Cardiovascular Responses – Acute Hypoxia

The ability to continuously measure heart rate agreed with other studies that it is the most sensitive physiologically to hypoxia. All levels of hypoxia caused heart rate to significantly increase from that of resting levels. This was agreeable with previous studies and that “the higher the altitude, the greater the increase in heart rate” (West et al. 2007). In addition, one cannot suggest what this means for cardiac output and therefore one cannot be sure what this increase in heart rate means in terms of an acute physiological response to hypoxia. Cardiac output increased with the inhalation of lower oxygen mixtures in some of the following studies (Asmussen and Consalazio 1941, Keys et al. 1943, Honig and Tenney 1957, Vogel and Harris (1967). Furthermore, Vogel and Harris (1967) found no increase in stroke volume when participants inhaled low oxygen mixtures. Many studies find it difficult to assess the cardiovascular responses to acute hypoxia particularly in a short time frame and many focus on the changes purely from an acclimatization viewpoint over many days. Perhaps, therefore, what others are seeing with an increased cardiac output is an increase in blood flow to the brain and heart as a protective measure (David Gradwell in Ernsting’s, 2016). However, one cannot either confirm or deny these possibilities within the experiment having only measured heart rate. Moreover, this research cannot be sure of how much oxygen the brain extracts from cerebral blood flow and therefore, it is difficult for any study to assess whether this is a protective measure.

Furthermore, this study produced a secondary measure of the ventilatory response to hypoxia, VT/Ti. Despite this measure proving not to be significant at 15.6% inspired oxygen the other measures provide a good case for arguing against the VT/Ti result. The more severe levels of hypoxia are validated by the VT/Ti result. In addition, frequency of breathing did not increase, which suggests that the significant increase seen at 15.6% inspired O_2 was an anomaly as no significant linear effect after this point was found. Tidal volume increased when participants inspired 14.2% and 10% O_2, which suggests they were breathing deeper in order to address the deteriorating levels of oxygen in arterial blood. As previous studies have suggested, acute hypoxia causes essentially no change in mean systemic arterial blood pressure in humans (West el al. 2007). This was the case with systolic blood pressure as no significant change occurred, at the most severe hypoxia (10%) there was only a 4mmHg increase. This study did not measure the effects of hypoxia on the lungs specifically in terms of blood pressure. West et al (2007) suggest that an increase in pulmonary hypertension causes an increase in pulmonary vascular resistance when participants are exposed to acute hypoxia. Motely et al. (1947) showed a 13-23 mmHg increase in mean pulmonary artery pressure when breathing 10% O_2. Whilst this study measured systolic blood pressure, which did not rise as expected, it is possible more intricate mechanisms are taking place, such as an increase in pulmonary artery pressure, that measuring overall blood pressure overlooks.

Carbon Dioxide

The ability of this research to accurately measure the breathing threshold to carbon dioxide acts as a validation to the $PetCO_2$ measured during the hypoxia protocol. By displaying the sensitivity of the equipment at this level it supports the finding that 15.6% inspired O_2 decreases $P_{et}Co_2$ by 1mmHg. As one can see from the results, artificially adding CO_2 to inspired gas produces a rapid and large increase in ventilation. Considering the results the threshold at which the inspired CO_2 stimulates ventilation appears to be located between 0.6% and 1.2%.

In comparison with hypoxia, inspired CO_2 (1.2%, 2.5% and 5%) caused participants to breathe more frequently and with a greater tidal volume (2.5% and 5%). This could be due to the fact that carbon dioxide appears to be a greater stimulus to ventilation or the fact that the carotid, aortic and central chemoreceptors are all stimulated by an increased level of inspired CO_2 as opposed to the majority if not all hypoxia acting solely upon the carotid chemoreceptors. Whilst there is not evidence to suggest this, an understanding of the basic mechanism could highlight potential differences in ventilatory responses between hypoxic hypoxia and hypercapnia.

Unlike hypoxia, carbon dioxide does not seem to elicit an increase in heart rate until the level of inspired CO_2 is relatively high (5%). Moreover, the carbon dioxide in arterial blood rarely increases unless by artificially inspiring carbon dioxide. Systolic blood pressure was also found to increase at 5% inspired CO_2.

Conclusion

This research has outlined the need for further research in the acute hypoxia time domain. This research has demonstrated that humans appear to be able to detect hypoxia and respond by increasing ventilation at lower altitudes than previously indicated. Based on these results one would recommend that further research repeating this protocol be done. Most importantly, this research has provided the first physiological evidence for why aircraft cabin altitude should be maintained at a maximum of ~8,000 feet. Future studies should combine what research has been conducted both cognitive and physiological and plot a dose response curve to hypoxia. Hopefully, this study will rationalize aviation medicine research and be a part of setting safety limits for all areas of human hypoxic exposure.

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