 doi:10.20944/preprints202004.0291.v1

CO_2 Narcosis as a Root Cause of Unexplained Physiological Events in High Performance Aircraft

A Review

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Running Title: **CO_2 Narcosis as a Root Cause of Unexplained Physiological Events.**

Brief title: CO_2 Narcosis in Fighter Pilots

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Word Count Abstract:

Word count: 5,861

Number of References: 48

Number of Figures: 2

Financial support: None

Conflicts of interest: The author is founder and owner of GO2Altitude, a company that manufactures and distributes medical-grade normobaric hypoxia equipment for exercise and aviation training.

Author biography:

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 doi:10.20944/preprints202004.0291.v1

Abstract

Since 1991, there has been an alarming increase in the number of unexplained physiological events (UPEs) reported and experienced by pilots of jet fighters across different fleets. The UPEs have resulted in grounding some airframes, loss of aircraft, and even loss of life. There is no single agreed-upon root cause of UPEs that has been identified, and therefore there is no reliable corrective action.

This author analyzed the literature related to other industries where artificial hyperoxic gas mixes are employed and where similar adverse reports have been reported. I hypothesize that UPEs are caused by high-dose oxygen delivery in excess of officially approved oxygen schedules while airflow rates are often inadequate, at a time when the positive pressure breathing feature of their oxygen regulator is not used. In a setting where pulmonary vital capacity is adversely affected by G-maneuvers and oxygen- and G-induced atelectasis, tidal volume is reduced by flight gear, and effective gas exchange is not supported by adequate ventilation, these factors combine to produce respiratory acidosis, followed by acute respiratory distress syndrome, CO_2 narcosis, and coma.

Reports from field data related to incidents in F-18S/H, showing that emergency oxygen did not correct the hypoxia-like symptoms including long-lasting periods of incapacitation and prolonged headaches, lend support to our hypothesis.

Key words: respiratory acidosis; CO2 narcosis; acute respiratory distress syndrome; hyperoxia; unexplained physiological event.

 doi:10.20944/preprints202004.0291.v1

Background

Unexplained physiological events (UPEs) are syncopal or near-syncopal events experienced by pilots or crew in high-performance military fighter jets. Events have been reported in association with many aircraft employed by the US Navy (USN) and Airforce (USAF) for at least a decade. Incidents have involved the F-22 Raptor, the F-35A Joint Strike Fighter, the A-10 Thunderbolt, the T-45 Goshawk trainer, and the F/A-18 Hornet.

Because so many different aircraft were affected, experts within the armed services did not believe that the episodes were being caused by one specific problem. In his testimony to the House Armed Services Tactical Air and Land Forces Subcommittee in February, 2018, Lt. Gen. Mark Nowland, the Air Force Deputy Chief of Staff for Operations, said that “there is no single root cause tied to a manufacturing or design defect that would explain multiple physiological event incidents across airframes or within a specific airframe.” [22] UPEs are aircraft-agnostic, oxygen system-agnostic, engine-agnostic, and flight envelope-agnostic. They have been noted at all altitudes from very high to ground level. Interestingly, they have not been seen in transport aircraft, a condition in which pilots and passengers are breathing ambient pressurized air without additional life support gear or mask.

Despite many years of detailed research and incident reviews, lives and expensive military equipment continue to be lost. As yet, no single explanation exists that would guide revisions in equipment or protocols. This author sought to examine the available literature with a fresh perspective to understand the cause of UPEs. Knowledge of the root causes will help resolve this problem by means of changing procedures and reviewing specifications of aviation life support systems. This will help pilots regain trust in their oxygen system, improve their confidence in flying, and importantly, save aircrafts and lives.

History

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In 2010, an F-22 Raptor malfunctioned in mid-flight and was lost along with its pilot. The pilot's oxygen system was officially blamed for the loss of life and a US$334M aircraft. [36] However, UPEs continued to happen, and the entire fleet of F-22s was grounded for five months in 2011.

USAF Public Affairs published online on June 09, 2017 that the Luke USAF Base temporarily canceled F-35A local flying operations: "In order to synchronize operations and maintenance efforts toward safe flying operations we have cancelled local F-35A flying," said Brig. Gen. Brook Leonard, the 56th Fighter Wing commander. "The Airforce takes these physiological incidents seriously, and our focus is on the safety and well-being of our pilots. We are taking the necessary steps to find the root cause of these incidents."[9]

Numerous problems with UPEs grounded the 19th USAF T-6 Texan trainers in 2018. The lost flights resulting from these groundings caused a decrease of 10% in the number of graduating pilots in 2018. [27] Despite exhaustive, multi-year investigative work involving hundreds (if not thousands) of aviation specialists and with close involvement of aeromedical physicians, the root cause of the problem is still not decisively identified and UPEs continue to occur. Reports on UPEs were released to public domain by the USAF Scientific Advisory Board[41] and NASA Engineering and Safety Center.[31]

USAF Lt.General Steve Kwast, head of the Air Education and Training Command (AETC), said in a statement on Sept. 13, 2018, "so far, technical efforts to date and analysis of data collected have determined that pilots have been exposed to significantly changing levels of oxygen concentration." He further stated that "the varying levels of oxygen concentration, even though in excess of what the body typically needs, has caused physiological stress that most pilots on most days actually adapt to without noticing."[28] Kwast reported that a 6-month review by the AETC and the Airforce Materials Command (AFMC) had determined that these fluctuations caused physiological stress in T-6 pilots whose bodies were not able to adapt quickly enough. This, in turn, produced symptoms akin to hypoxia, which is a lack of sufficient oxygen in the body; hypocapnia, or insufficient carbon dioxide; and other "related conditions." Symptoms of these conditions can include headaches, disorientation,

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and even blacking out[44], all of which can be especially dangerous for a pilot in the air traveling above the speed of sound.

The USAF SAB report notes that: “Lost capabilities and expertise to perform the critical function of human systems integration led to atrophy of policies/standards and research and development expertise with respect to the integrity of the life support system. Three life support system-critical subsystems (Onboard Oxygen Generation System [OBOGS], Back-up Oxygen System [BOS], and Emergency Oxygen Subsystem [EOS]) were not classified as ‘safety-critical items’ and were integrated or eliminated without sufficient analysis.” The USAF SAB issued 14 different Recommendations in the report.[41]

Under the direction of Congress in 2017, the Secretary of the Navy initiated an independent review of the PEs. To conduct this review, the Navy requested the assistance of NASA (NASA Engineering and Safety Center (NESC)). The report included a review of the Navy’s UPE resolution efforts, factors that may reduce the UPE rate, and the performance of the relevant F/A-18 subsystems. In March 2017, the NESC assembled a multi-disciplinary team of individuals with a broad range of expertise. The NESC team began its investigation by visiting Navy Commands and F/A-18 component manufacturers across the country, 14 locations in all. The team gathered information, observed carrier operations, and spoke with Navy leaders, aircrew, manufacturers, and maintenance crews. An extraordinary amount of briefings, interviews, reports, data, and other information was studied and analyzed.

The NESC team formed conclusions as a result (published in the form of a NASA/NESC report).[31] In this report it was stated that UPEs are primarily a human-based phenomenon, but the bulk of investigation and corrective action has been directed to the aircraft. Secondly, hypoxia, determined by the team to be the most prevalent cause of UPEs, is not solely a condition of insufficient levels of oxygen in breathing gas; it is insufficient delivery of oxygen to tissues in the body. Thirdly, a key to reliable OBOGS performance is uniform operating conditions, which the F/A-18 design rarely provides. Fourthly, the F/A-18 program has a large amount of aircraft performance data, but a

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shortage of evidence directly related to the Human System. Next, the F/A-18 systems that support human health are complex, dynamic, and interactive, requiring a well-coordinated "systems approach" to design requirements, interfaces, and operations. Finally, UPEs will persist in the F/A-18 (and possibly other high-performance aircraft) if there is a piecemeal approach to human systems integration.

Reported Class A Mishaps (Loss of aircraft F/A-18), 1991-2012:

A Class A mishap is currently defined as $2,500,000 or more and/or aircraft destroyed, and/or fatality.[32]

1991: During a training flight, a Royal Australian Air Force (RAAF) pilot was seen by his wingman to be slumped forward at the controls and unresponsive to radio calls while the aircraft was apparently on autopilot. The aircraft later crashed. Hypoxia was considered a contributing factor.

2001: An F/A-18C OBOGS aircraft above 40,000' mean sea level (MSL) suffered bleed air leaks to both engines; all bleed air flow to the pilot via the environmental control system (ECS) and OBOGS was cut off. The pilot selected the emergency oxygen system, pulling its green ring, but the aircraft departed controlled flight and crashed. G-induced loss of consciousness (G-LOC) and over-breathing of emergency oxygen leading to temporary loss of blood flow to the brain (so-called "oxygen paradox") were cited as contributory. Navy and Marine Corps F/A-18 squadrons briefed the mishap report, stressing the differences between LOX and OBOGS aircraft; the importance of conducting an immediate emergency descent following cabin pressurization loss; the importance of immediate selection of emergency oxygen; and the effects of nutrition and rest on G tolerance. The Naval Air Systems Command (NAVAIR) published a schedule of expected cabin depressurization rate after bleed air loss and a revised Naval Air Training and Operating Procedures Standardization (NATOPS) bleed air failure procedure. The report resulted in the development of a simple cabin pressure warning system, which was implemented in 2006.

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2004: An F/A-18A+ LOX aircraft launched with a CANOPY caution light (canopy was not sealed). The pilot continued flight with this condition, likely became hypoxic and lost aircraft control. All tactical aircraft squadrons briefed the mishap report; discussed conduct of periodic verbal cabin pressure checks over the radio or intercom systems; stressed verification of cabin altitude below 10,000 ft. MSL prior to removing the oxygen mask for short periods to scratch or wipe off perspiration; and discussed recognition of hypoxic symptoms as part of Crew Resource Management (CRM) training. NAVAIR procured and implemented the use of the Reduced Oxygen Breathing Device (ROBD) for periodic aviation physiology training.

2004: During a flight, the pilot reported feeling unwell to the flight lead and was unable to perform required maneuvers in formation. Later, the flight lead detected increasing disorientation and decreasing communication from the affected pilot, who ultimately appeared to pass out and lost control of the aircraft, which crashed into the ocean. It was probable that a) cabin pressurization was lost, and b) the O_2 mask was not fully worn. The Navy sought to make the cabin pressure gauge more visible when pilots wear night vision goggles, relocate the gauge, provide specific mask training, add requirements to verify cabin altitude below 10,000 ft. MSL before mask removal, and devise improved communication techniques between aircraft when cognitive impairment is suspected.

2012: An F/A-18C OBOGS aircraft suffered a series of engine bleed air malfunctions, ending in a loss of bleed air to the ECS and OBOGS systems. The pilot ejected after losing orientation and sensory awareness. Maintenance and operating procedures were updated, and improved cabin pressure diagnostic testing equipment was provided to fleet squadrons. An Integrated Vehicle Health Management system was introduced to identify aircraft with a history of ECS and/or OBOGS problems.

Hypoxia as the cause of UPEs

The prevailing theory of what causes UPEs is hypoxia. The symptoms of progressive lethargy combined with confusion are reminiscent of a low oxygen state. After careful examination of the

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NASA NESC 2017 Report [31], this author summarized several unanswered questions and noted discrepancies, resulting in the current review.

Considerable attention has been focused on updating and improving the cabin environmental control systems across airframes to provide consistent pressure and oxygen levels. In fact, in their recent report, the NESC team's flight surgeons concluded that over 80% of UPEs list hypoxia as a contributing factor. However, memory unit (MU) data from those same flights showed that there was an adequate amount of oxygen flowing from the OBOGS. It is difficult to explain how an otherwise healthy pilot could develop hypoxia in the presence of normal or even increased oxygen flow.

Several reports, as well as personal communications between the author and pilots, aviation medical specialists, and aviation technicians, have pointed out that UPE reports were rare during an era in which Liquid Oxygen system (LOX) was used as the source of onboard oxygen. These numbers have increased since the introduction of OBOGS since the early 1990s. LOX Dewar bottles contained a limited amount of oxygen to sustain the crew during a single flight, requiring regular recharge. Therefore, oxygen was conserved by the designers of the oxygen regulator, a cockpit device that titrates oxygen delivery to the pilots. Oxygen was delivered in accordance with an aviation medicine approved "oxygen schedule". With introduction of OBOGS, a device that generates oxygen similar to the function of a medical oxygen concentrator, oxygen became unlimited, allowing for its liberal delivery and effectively abolishing oxygen schedules. This allowed the naïve presumption that flooding the pilot with O_2 will resolve all design and specification deficiencies. While OBOGS can supply high oxygen concentrations for breathing at all altitudes, military standards restrict the use of oxygen in concentrations "NOT to exceed 60% at cabin altitudes between 0 and 15,000ft or 75% at a cabin altitude of 20,000ft, except for momentary excursions…".[42] The aircraft types with reports of UPEs are all pressurized up to levels consistent with an altitude of 10,000ft, maintaining that pressure up to 23,000ft, with automatic delivery of 100% oxygen above 10,000ft.

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If the “hypoxia-like” symptoms were in fact strictly related to hypoxia, they should be immediately reversible upon administration of oxygen. This is commonly demonstrated during hypobaric training at ground level as well as in normobaric hypoxia training systems.[45,46] However, UPE symptoms frequently last for minutes, hours, or even days after onset despite oxygen therapy. In a Class-A mishap reported in 2001, the pilot reported hypoxia-like symptoms. He collapsed immediately when he switched to 100% emergency oxygen. This is the definition of the “oxygen paradox” in which emergency oxygen was counter-productive in the treatment of the UPE.

Some pilots have complained of variations in oxygen concentration and airflow during flight. Some have reported marked increases in the work of breathing when trying to breathe through the oxygen mask.[31] Reportedly, OBOGS and oxygen concentration vary with engine revolutions (throttle position), decreasing airflow to the mask at lower throttles.[14].

A report from 1987[40] proposed atelectasis due to acceleration as the cause of UPEs. Atelectasis is the collapse of a part of the lung and can involve small segments or the entire lung. Atelectatic areas do not inflate and cannot contribute to gas exchange in the lung. Tacker et al suggested that this was the mechanism leading to UPEs. However, there was no direct evidence in either this report or in the English literature that supports this theory. Tacker used an indirect measure, that of reduced vital capacity (VC), as a surrogate measure of atelectasis, another assumption that has not been supported by studies.[40] Fighter jet oxygen regulators are equipped with a Positive Pressure Breathing (PPB) option to be used as a countermeasure against atelectasis, but this option is not used by at least F18A/S aircrews.[31]

There are reports that suggest hyperventilation with hypocapnia as the cause of UPEs. The symptoms preceding a UPE are similar to those of hyperventilation which leads to hypocapnia, a condition that causes cerebral vasoconstriction with diminished blood flow to the brain.[33] This could manifest as confusion and loss of cognitive function. But the rapid ventilatory rate required for hypocapnia has not been seen after review of audio recordings nor from reports of crew members.

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Air contamination has been proposed as a cause of UPEs. However, many years of research have failed to identify any significant contamination of life support systems[12]

The net result is that some pilots are losing faith in their life supporting oxygen equipment. Many pilots report that they do not fly with the mask on at altitudes below 10,000 feet, and some avoid flying above 28,000 feet whenever possible. These pilots refer to flights at this altitude as the “mask-on-O-sphere”, implying that they would need to rely on their oxygen masks at this altitude. Citing a lack of trust in the system, pilots will sometimes refuse to fly “mask-on-O-sphere” flights.[31]

Interestingly, recent articles have raised concerns that the use of OBOGS with constant high oxygen might contribute to UPEs. In *Handbook of Aviation and Space Medicine* by Dr. Nicholas Green et al. (Chapter 15), it is noted that “100% O_2 may cause respiratory tract irritation, delayed otic barotrauma, [and] acceleration atelectasis.”[20]

In recent work studying the UPE, this analysis is based on over 30 years of experience in designing equipment and utilizing it for normobaric hypoxia training of athletes and pilots, and for therapeutic hypoxia. This academic and practical knowledge points to the fact that human physiology is very well equipped with protective mechanisms against short term hypoxic hypoxia and long-term moderate levels of hypoxia (as seen in populations that live at high altitudes).

Research has shown that hypoxia induces an increase in cardiac output and ventilatory rate as immediate responses. Long-term adaptation to hypoxia consists of activation of hypoxia-inducible factor 1 alpha (HIF-1α) along with transcription of over 30 genes.[38] In stark contrast, there are no normal apparent physiological mechanisms that were developed in human evolution to protect us from debilitating and toxic high oxygen environments, as these are not naturally found on Earth. A situation in which a person would need to breathe higher than 20.9% oxygen is highly artificial and therefore would result in significant, and not fully understood, physiological side effects.

This author searched the international literature to identify areas of human activity in which the use of hyperoxia is absolutely needed for human survival. The situations identified were unpressurized or

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partially pressurized aircraft cabins exposed to high altitude; spaceships; undersea vessels and diving; firefighting; and other environments not compatible with human life due to lack of oxygen. Other such areas are found in critical care medicine when a person is unable to provide adequate oxygen supply to their bodies and tissues. In each of these areas, an oxygen mask is worn and the FiO_2 exceeds 21%. Analysis evaluated any reported symptoms in these situations that occurred that were similar to the UPE symptoms that were reported by aircrew.

Respiratory physiology, hypoventilation, and hypercapnia

Animals breathe for two primary reasons:

1. To take in oxygen as an essential ingredient needed for generating energy in our cells that rely on aerobic metabolism; and
2. To eliminate carbon dioxide produced in the body through processes of metabolism.

The primary driver of inhalation is a mechanism called “hypercapnic ventilatory drive”, while “hypoxic ventilatory drive” is a secondary, back-up mechanism that stimulates breathing.[13,19] Hypercapnic drive forces stimulate exhalation in a very powerful primordial reflex. This is easily demonstrated in a typical individual who wishes to hold their breath for more than a minute. We are all aware of the importance of oxygen for life, but the role of CO_2 for our wellbeing is typically neglected given the perception that human respiration is passively eliminating CO_2 as a “waste gas”, rather than CO_2 being a driver of normal physiology. In fact, the aviation medical profession and the engineers who design breathing apparatuses may not perceive CO_2 as a threat.

But when CO_2 homeostasis is disrupted, it can lead to very serious consequences as described further below. Such disruption can occur under several scenarios of “abnormal” physiology, such as conditions accompanying certain diseases, or in professions and industries in which people require artificially high oxygen level air for breathing. The combination of CO_2 retention in the face of hyperoxia poses a very real danger.

This ominous situation is called oxygen-induced hypercapnia (or hypercarbia) (OIH). OIH is carbon dioxide intoxication which can lead to CO_2 narcosis. Development of hypercapnia due to oxygen use may occur rapidly.[48] The common outcome is rapidly developing respiratory acidosis[34], respiratory distress, acute respiratory failure, coma, and death. Research suggests that this mechanism is relevant in UPEs and explains their occurrence in high performance aircraft.

There are three known effects of hyperoxia-induced hypercarbia leading to CO_2 narcosis in animals:

a. A mismatch between regional pulmonary ventilation (V) and perfusion (Q), referred to as V/Q mismatch[44];
b. The Haldane effect, where high FiO_2 causes poor CO_2 extraction from cells[1]; and
c. Hypoventilation, given the suppression of the respiratory drive by high oxygen and saving on inhalation volume during insufficient air supply.[44]

As a result, high inspired oxygen can cause CO_2 retention, a condition commonly seen in patients with chronic obstructive pulmonary disease (COPD).[3,21] Any or all of these effects may be present in the environment of artificial lung ventilation or artificially high oxygenated air inhalation.[18] It is important to remember that hyperoxia-induced hypercapnia induces symptoms similar to those described by aviators as “hypoxia-like” and are manifested as a UPE.

It has been reported that pilots often struggle to pull out air from their oxygen masks because airflow from OBOGS and oxygen concentration is a function of throttle position.[14] The amount of compressed air delivered to the OBOGS is dependent on the revolutions (RPM) of the aircraft’s main engine, and the OBOGS does not function normally when the engine is idle or operating at low revolutions.

The NECS report further states that “the results indicate that the current military oxygen system flow rate specifications are inadequate for tactical aircraft performing ACM [aircraft maneuvers]. The results also suggest that current F-14 and F/A-18 oxygen systems may be inadequate for low altitude ACM”.[14]

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The literature shows that there is a lack of consistency between aircrafts using OBOGS in terms of implementation of a plenum in the breathing line. A plenum is a storage container or receiver of gas (air or O2) that can provide a fill-in source of breathing gas for a short time, such as the interruption of oxygen supply or brief increase in breathing demand that surpasses the available supply. Plenum volumes range from nearly 16,000 cu inches (262L) in an F-15E, 250 cu inches in the A-10, F-16, and T-6, 97 cu inches for the F-18, to 0 cu inches in the F-22. The smaller plenum volumes, particularly in OBOGS aircraft, mean the complicated human system is directly connected to the OBOGS without any buffer to compensate for system abnormalities on either side. A summary table of these OBOGS systems in USAF and USN aircraft can be found in the USAF SAB Report on Aircraft Oxygen Generation.[41]

The report[41] goes on to discuss the importance of ventilation and gas exchange for aviators:

> *Hypoventilation as a mechanism is defined as a decrease in the rate and/or depth of breathing such that minute ventilation is reduced. Typically, this mechanism leads to an outcome of hypercapnia, as the reduced ventilation leads to CO2 retention. In the medical community, most conditions that lead to hypoventilation revolve around some kind of respiratory disease (COPD, asthma, etc.) that limits the body's ability to effectively exchange gases. From an aviation perspective, the closest analogous scenario is when a pilot's lung volume is decreased or restricted in some manner, either by an additional medical mechanism or by tight-fitting life support gear. Additionally, increased breathing resistance has been shown in multiple studies to lead to hypoventilation in a large group of aviators.*

This author's assessment of the above passage is that:

a) Hypoventilation leads to CO_2 retention in the body. In a medical context, this same process is seen in people with COPD[44], as well as in anesthetized animals. In these situations, CO_2 retention is exacerbated by high oxygen.

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b) In an aviation environment, the same physiological mechanism is applicable. Ventilation is restricted by:

- Intermittently inadequate mask airflow (or no flow)

  A pilot's compensatory response is to subconsciously avoid increased air resistance by decreasing "minute volume" (VE), also known as breath-holding, and to reduce tidal volume (Vt) (shallow breaths).
- Resistance in mask valves
- Mask dead space
- Atelectasis reducing vital capacity in the lungs[40]
- Resistance to chest movements by aircrew flight equipment (dry suit, harness, survival vest, partial pressure suit, and full-coverage G-suit)
- High FiO_2 leading to hypoventilation and consequent hypercapnia leading to CO_2 narcosis[37]

I do not agree that hyperoxia causes hyperventilation, as suggested by several authors. In general, hyperoxia suppresses the respiratory drive, increasing the accumulation of CO_2. This has been well documented in the treatment of COPD patients in critical care.

The literature suggests that some COPD patients can be defined as CO_2-retainers while others are not.[1,37] Theories abound regarding why this is the case, and Poon et al have proposed that, in some people with chronic severe COPD, the brain learns to ignore those signals and to tolerate the relative hypercapnia in the presence of relative hypoxia.[35] The same likely applies to pilots, and may explain why some pilots have UPEs in a given situation while others do not. Chiang et al have demonstrated that the body's responsiveness to fluctuations in $PaCO_2$ can be suppressed over time by using repetitive breath-holding, ventilation restriction, and oxygen therapy.[10]

Hypocapnia and hypoxia are both relatively easy physiologic problems to fix. Holding one's breath for 10-30 seconds effectively reverses hypocapnia, and associated symptoms resolve quickly. Breathing "compensated for altitude" higher pO_2 air for 30-60 seconds eliminates hypoxia. Curiously, there

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have been UPEs that do not resolve even after "pulling the green ring" and breathing 100% emergency oxygen: this safety measure is not always effective. This emergency corrective action could very well trigger a cascade of events starting with suppression of respiration and ending in unconsciousness.

Based on the above analysis, the data disagree with prevailing theories that hyperoxia leads to hypocapnia through hyperventilation. This theory has been stated in several published reports related to UPE investigations. It was first mentioned in an opinion letter by Iscoe et al in 2005[23] and has somehow become commonly accepted dogma. Iscoe's assertion was based on a single patient with references to the literature from nearly 100 years ago. They did reference experimental data published by Becker et al in 1996 suggesting that hyperoxia caused hyperventilation in normal healthy subjects.[7] Becker's experimental set-up exposed subjects to what was effectively a Carbogen gas, a mixture of enriched O_2 and CO_2 that is known to cause hyperventilation, panic, and disorientation. Becker used a semi-closed breathing circuit while controlling the amount of re-inhaled CO_2 by the test subjects with the aim of clamping the end-tidal PCO_2. They even stated in their paper that "If isocapnia is not maintained, hyperventilation is attenuated by a decrease in arterial PCO_2." These experimental conditions are not seen in the pilot's environment, and the report is therefore not relevant to the discussion of UPEs. Further, this line of reasoning negates the argument that hyperoxia causes hypocapnia through hyperventilation, leading then to cerebral vasoconstriction, cerebral hypoxia, and loss of consciousness in UPEs seen in high performance aircraft. There are no supporting data.

CO_2 Narcosis as the Cause of UPEs

This author proposes that the cause of UPEs in high-performance aircraft is carbon dioxide narcosis. Ample evidence from critical care medicine, neonatal intensive care, flight medicine, and diving physiology support this assertion.[1-4,21,24,26,29,34,37,47,48]

CO_2 narcosis is a physiologic condition that results from elevated $PaCO_2$ in arterial blood. Common symptoms are lethargy, confusion, headache, blurred vision, impaired hearing, and loss of

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consciousness. Left untreated, this can lead to cerebral edema, convulsions, anoxic brain damage, and death.[16]

The physiologic mechanisms of CO_2 narcosis are poorly understood, as are the mechanisms behind medically-induced anesthesia. CO_2 is a lipid-soluble molecule that is acted upon by the enzyme carbonic anhydrase to form two acids, carbonic acid plus a hydrogen ion.[39] It is likely that CO_2 dissolves into the lipid-rich neuronal membrane, releasing acid into the neuron. Neuronal acidosis is associated with decreased production of excitatory neurotransmitters and increased production of inhibitory neurotransmitters, decreasing overall brain activity.[17]

Reversal of CO_2 narcosis requires lowering $PaCO_2$ to within physiologic limits. This usually happens relatively quickly in response to clinical maneuvers such as hyperventilating, assuming normal or near-normal lung function. Additional oxygen, including supra-physiologic levels of oxygen, does not reduce CO_2 levels. Indeed, oxygen is a known contributor to cellular and systemic oxidative stress and acidosis and likely aggravates the physiologic perturbations caused by excesses in $PaCO_2$.

A challenge in aviation medicine is that the above-mentioned “normal or near-normal lung function” may or may not exist during flight, even in healthy aviators. The G-forces experienced during aircraft maneuvers such as climbs, descents, and turns cause a temporary redistribution of blood flow in the lungs along with atelectasis, creating a V/Q mismatch and an increase in the amount of ventilatory dead space. Compression suits and parachute gear add to the work of breathing and promote atelectasis and poor gas exchange, hypocapnia, and inefficient ventilation and expelling of CO_2. Supraphysiologic oxygen supplies do not fix these issues. “Pulling on the green ring” is not going to help and may in fact aggravate CO_2 narcosis by suppressing ventilatory drive.

The presence or absence of CO_2 narcosis at the time of a UPE is hard to prove. Currently there are no easy ways to monitor $PaCO_2$ levels in real time in vivo. While expired end-tidal CO_2 ($etCO_2$) monitors have been in use in anesthesia for decades, these are often criticized for the relevance or importance of their readings, since shallow respirations will produce normal $etCO_2$ readings even in a sick person.[30]

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Intra-bronchial catheters have more recently been developed for use in extremely low birth weight premature infants. However, these are invasive, and unlikely to be of practical use for aviators.

There is poor correlation between end-tidal expired CO_2 and $PaCO_2$ because of the impacts of physiologic buffer systems[8] Hyperkalemia (elevated potassium) is frequently used as a surrogate marker of metabolic acidosis, but there is poor correlation between hyperkalemia and the respiratory acidosis that exists in hypercarbia.[43] It has also been noted that confusion and disorientation remain despite full arterial oxygen saturation.[47] In fact, PO_2 pulse oximetry similarly does not correlate well with hypercarbia.[15] Even the level of $PaCO_2$ in and of itself is insufficient to dictate who will or will not develop CO_2 narcosis symptoms, with other variables including serum bicarbonate, use of supplemental oxygen, use of opioids, and BMI being important.[48]

However, the reports of UPE symptoms are most consistent with CO_2 narcosis as an etiology. Gradual onset of confusion, headache, blurred vision, and impaired decision-making without complaints of hyperventilation are the hallmarks of anesthesia without hypoxia. As the syndrome is allowed to progress, stupor, cerebral edema, seizures, coma, and death ensue. Despite the rarity of UPEs, their unpredictability, their potential severe implications, and the technical challenges of identifying CO_2 narcosis, an in vivo in-man interventional study is likely imminent.

Because reports of UPEs are increasing, the incidence of respiratory acidosis leading to acute respiratory failure is likely also increasing. Experimental research should be directed towards monitoring of $PaCO_2$ in flight. This is necessary to confirm whether hypercapnia is common in pilots of high-performance aircraft while performing complex maneuvers and experiencing higher acceleration as their life-support system delivers unlimited hyperoxic air at variable flow rates. The current clinical method of measuring $PaCO_2$ is through the use of an arterial blood gas (ABG) machine, a device that requires arterial blood sampling and time. Other proposed methods of in vivo $PaCO_2$ measurement include colorimetric, photonic, and optical techniques. However, there is no commercially available wearable device that is suitable for continuous $PaCO_2$ monitoring in the

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cockpit. The development of such a device, specifically designed for use in aviation, is critically important as a primary indicator of the wellbeing of a pilot.

Researchers should abandon the pervasive dogma of “hyperoxia-induced hypocapnia”. This theory has prevented aviation research teams from investigating the role of hyperoxia-induced hypercapnia in UPEs, leading to respiratory acidosis, acute respiratory distress syndrome, and coma. This is “groupthink” that goes from one report to another, including reports from the pilots themselves, obscuring scientific and physiologic facts.[14]

To quote Confucius, “The hardest thing of all is to find a black cat in a dark room, especially if there is no cat.”

If one reads through the various articles that were used to build the case for this groupthink, their respective references are often irrelevant (breathing Carbogen gas) or uncheckable (publications from between 1918 and 1953). Significantly, the “seminal” article “Hyperoxia induced Hyperventilation” was published in the “Hypotheses and Opinions” section of the Canadian *Chest* journal with no statistical power based only one patient.[23]

In contrast, practical experience confirms textbook knowledge that hypoxic drive is dysfunctional in hyperoxic conditions.[46] In fact, thousands of training records in possession of RAAF AVMED demonstrate this fact during the typical hypoxia training routine. In these studies, the usual 2-7-minute hypoxia challenge (FiO_2=0.07) is alternated with hyperoxia recovery (FiO_2=0.36), a condition that was argued to be a more accurate physiological representation of the depressurization that occurs at 30,000ft and breathing 100% oxygen at that altitude.[5,6] Physiological training logs, which contain data on peripheral capillary oxygen saturation (SpO_2), heart rate (HR), and breathing rate (BR), clearly show that the BR is reduced by 20-25% once trainees are on “oxygen”. Figure 1 demonstrates the drop in ventilatory frequency (Vf) once hyperoxia (FiO_2=0.36) is introduced during oxygen recovery phase. [Fig.1 here]

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Statistical analysis of the RAAF practical training logged data collected from 2010 to 2020 is long overdue.

Experimental data on the effect of 15 minutes 100% oxygen administration is summarized in Figure 2[3]. [Fig.2 here] The graph shows that minute ventilation drops relatively acutely but recovers, while pCO_2 continues to climb.

Conclusions

Aviation Scientists and industry have not considered oxygen-induced hypercapnia (OIH) leading to respiratory acidosis and acute respiratory distress syndrome to be a threat to the pilot of high performance aircraft. In fact, classical thinking has focused on hypocapnia as the primary problem. If this hypothesis is true, OIH, potentially leading to CO_2 narcosis is the primary trigger of UPEs.

Standard teaching says that we breathe to take in oxygen, and that the expulsion of carbon dioxide is part of a passive elastic recoil function of the lungs. But experts in the field of pulmonary physiology point out that that elimination of the metabolic byproduct CO_2 is the primary driver of respiration[11,25], a driver that is modulated by excessive oxygen. The idea that "the more oxygen, the better" that has dominated the aviation industry must be eliminated. Instead, aviation should embrace safe levels of oxygen administration to ensure the pilot's efficient gas exchange, with almost instantaneous delivery of adequate airflow to the pilot as his or her physiology demands.

As stated by Elliott et al, "The ideal life support system for flight is one that provides the concentration and flow rate of gases that the human demands in a given situation—no more and no less."[14]

There are three mechanisms leading to hypercapnia and an increase in the threat of CO_2 narcosis, and there are means to deal with them:

1. Problem: V/Q mismatch, originated by oxygen- and G-induced atelectasis plus compression suit and gear

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Solution: Use the proven and effective AGSM (anti-G strain maneuver) and use of unassisted positive pressure as suggested by Tacker[40]

2. Problem: Haldane effect

   Solution: Titrated oxygen delivery in accordance with an oxygen schedule that recognizes that "more" is NOT "better".[2]

3. Problem: Hypoventilation

   Solution: Monitoring $PaCO_2$, and creation of assisted ventilation that requires creative re-thinking of current concept of oxygen life support systems.

Based on the theory of OIH leading to CO_2 narcosis, it is important to recognize the following limitations in current thinking and practices:

- Monitoring of exhaled PO_2 may be misleading, as this parameter can be normal or above normal if 100% oxygen is supplied in the presence of V/Q mismatch;
- Measurement of end-tidal CO_2 may be misleading, as normal values may be seen in the presence of shallow breathing even in the face of abnormal lung function;
- SpO_2 monitoring may be misleading, since SpO_2 can be within normal physiological range since it measures hemoglobin oxygen saturation, not tissue PCO_2; and
- Spirometry is not likely to be helpful, since it is not easily "insertable" into current military standards.

It is critical to reiterate that 100% Emergency Oxygen in a case of a CO_2-intoxicated person, especially at low altitudes, can be dangerous and lead to rapid loss of consciousness and seizures.

If manned combat aircraft are to be required for foreseeable future, oxygen life support systems must be designed that match to their demanding operational environment. These systems need to be re-designed and validated with essential help of aviation medical professionals and specialist biomedical engineers.

Policies regarding emergency oxygen corrective action also need to be critically reviewed.

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Figures

Figure 1: Typical subject graph (practical training report) of SpO_2, HR, ventilatory frequency (Vf) during routine hypoxia/reoxygenation, part of a hypoxia awareness training session using GO2Altitude hypoxicator.

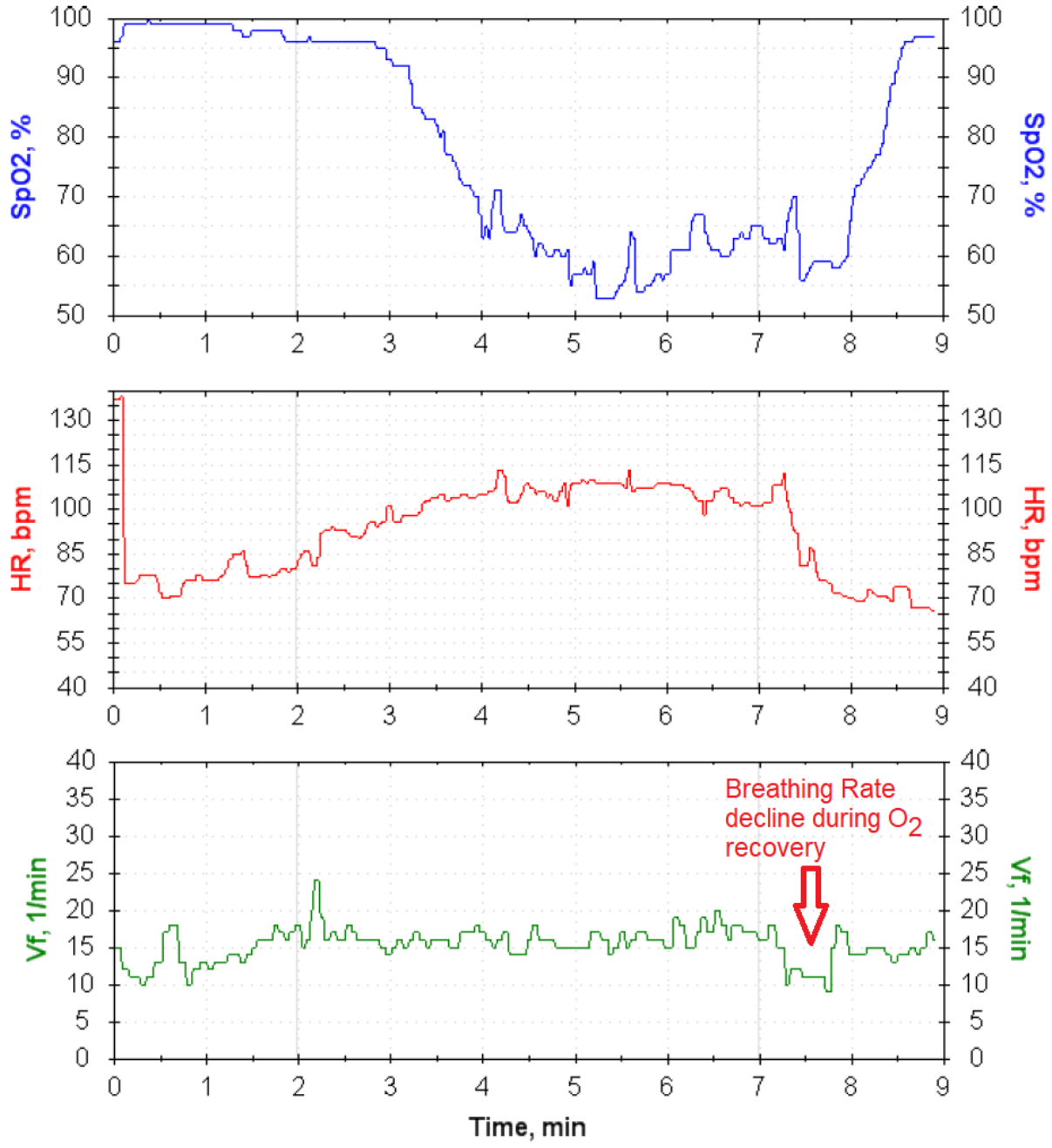

Fig.1

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Figure 2. Experimental data on the effect of 15 minutes 100% oxygen administration. Adapted from Abdo et al[1] and Aubier et al[3].

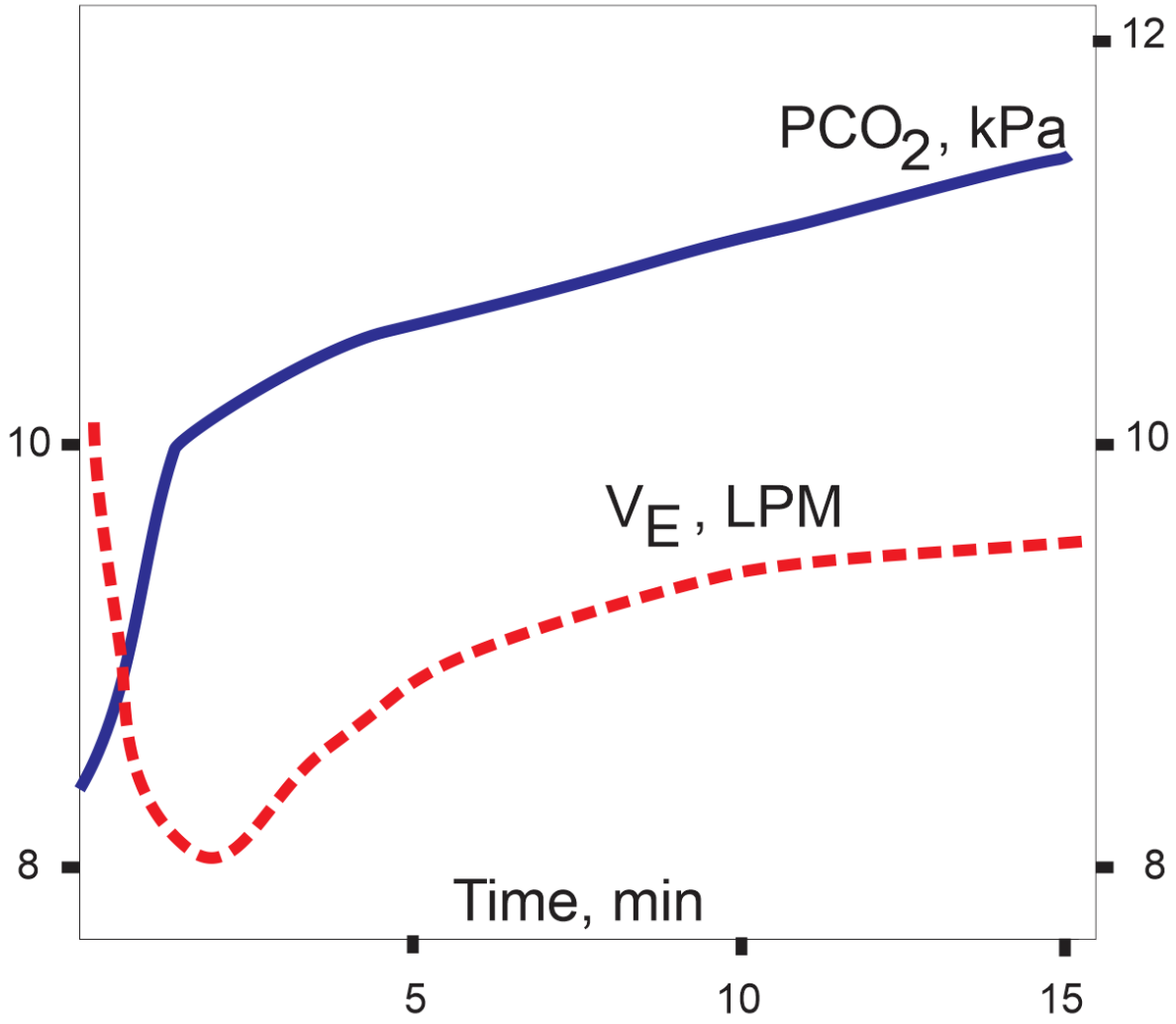

Fig.2