

**Liberal oxygen with unreliable unpredictable flowrate is the root cause of  
Unexplained Physiological Events in Combat aircraft**

**A Review**

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Running Title: **Liberal oxygen with fluctuating flow causing Unexplained Physiological Events in High Performance aircraft.**

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## Abstract

Over the last 20 years, there has been a significant increase in the number of unexplained physiological events (UPEs) reported by pilots of fighter jets across different fleets. The UPEs have resulted in grounding some types of aircraft, loss of airplanes, and even loss of life. Despite considerable research, no single agreed-upon root cause has been found that explains UPEs, and therefore no reliable corrective actions exist.

The purpose of this review was to analyze the literature related to other industries in which artificial hyperoxic gas mixes are employed and similar adverse reports have been reported. Based on analysis of the literature, it is hypothesized that UPEs are caused by unlimited delivery of high-dose oxygen in excess of officially approved oxygen schedules in the presence of inadequate airflow rates, at a time when the positive pressure breathing feature of their oxygen regulator system is not used. During flight maneuvers such as climbs, turns, and descents, pulmonary vital capacity is impaired by G-manuevers and oxygen- and G-induced atelectasis. At the same time, tidal volume is reduced by flight gear, and effective gas exchange is not supported by adequate ventilation. These factors combine to produce hypercarbia, respiratory acidosis, acute respiratory distress syndrome, CO<sub>2</sub> narcosis, and coma. In fact, 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 this hypothesis.

Key words: respiratory acidosis; CO<sub>2</sub> narcosis; acute respiratory distress syndrome; hyperoxia; unexplained physiological event.

*A complex system that is operated by a human, becomes useless if the operator is incapacitated.*

### Background

Pilots and crew of military aircraft are subjected to extremes of environmental stresses including changes in barometric pressure, changes in oxygen delivery, and gravitational forces. Some pilots and crew have experienced unexplained physiologic events (UPEs), defined as syncopal or near-syncopal events of unknown etiology. These events are known to have occurred in many types of aircraft used by the US Navy (USN) and Air Force (USAF) over at least the past decade. UPEs have been reported with the F-22 Raptor, the F-35A Joint Strike Fighter, the A-10 Thunderbolt, the T-45 Goshawk trainer, and the F/A-18 Super Hornet.

Given that a variety of different aircraft were involved, experts within the aeronautical medicine fields believed that the episodes were being caused by separate and distinct problems. 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.” (Hirsch, 2018) UPEs have occurred with a variety of aircrafts, oxygen systems, engines, and flight envelopes. Reports show UPEs are all altitudes, from very high elevations to ground level. Notably, physiologic events have not been noted in transport aircraft in which pilots and passengers breathe ambient (in pressurized cabin) air with no additional requirements for life support gear or masks.

Despite extensive research and countless hours of meetings with brilliant scientists in medicine and aeronautics, the loss of lives and expensive military equipment continues. There is no single and universally accepted explanation for UPEs that would guide redesign of aircraft or re-training of pilots. This author sought to examine the available literature with a fresh perspective to understand the cause of UPEs. It is hoped that the insights gained will lead to changes in procedures, protocols, sensors, and equipment that will help to save these young gifted military pilots’ lives.

## History

In 2010, an F-22 Raptor was lost along with its pilot due to a malfunction in flight. The cause was thought to be due to the pilot's oxygen system, resulting in loss of life and a US\$334M aircraft.(Ritsick, 2020) After this event, other UPEs continued to occur, resulting in the grounding of the entire fleet of F-22s for five months in 2011.

In 2017, the Luke USAF Base canceled F35A flights due to UPEs. On June 9, 2017, the USAF Public Affairs reported: "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 Air Force 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."(Carey, 2013)

In 2018, similar problems with UPEs resulted in grounding of 19th USAF T-6 Texan trainers. Eliminating these flights resulted in a decrease of 10% in the number of graduating pilots in 2018.(Losey, 2019) Despite extensive research and investigations by aviation specialists and aeromedical physicians, no root cause for the UPEs was determined. UPEs continued to happen, and reports on these events were released into the public domain by the USAF Scientific Advisory Board(United States Air Force, 2012) and NASA Engineering and Safety Center(National Aeronautics and Space Administration, 2017).

On September 13, 2018, USAF Lt. General Steve Kwast, head of the Air Education and Training Command (AETC), stated that "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 noted 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."(McCullough, 2018) He noted that a full 6-month evaluation by the AETC and the Air Force Materials Command (AFMC) had determined that these fluctuations resulted in excessive stress in the physiology of T-6 pilots and that their physiologic systems were not able to adapt quickly

enough. This resulted in symptoms akin to hypoxia, which is a lack of sufficient oxygen in the body; hypocapnia, or insufficient carbon dioxide; and other “related conditions.” Other related symptoms may include headaches, disorientation, and even blacking out.(West, 1971) These are all symptoms that may be highly dangerous for a pilot operating a heavily-armed aircraft traveling at supersonic speeds.

The USAF Scientific Advisory Board (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 over a dozen Recommendations for action in that report.(United States Air Force, 2012)

An independent review of UPEs was ordered by Congress in 2017, led by the Secretary of the Navy. The Navy enlisted the help of NASA’s Engineering and Safety Center (NESC). The resulting report described the Navy’s efforts towards resolution of UPEs, the factors that may reduce the rate of UPEs, and the performance of the relevant subsystems in the F/A-18. The NESC assembled a multi-disciplinary team of experts with a broad range of backgrounds. The NESC team began its work by visiting numerous Navy Commands and F/A-18 component manufacturers across the country. Team members gathered data, observed carrier operations, and spoke with Navy leaders, aircrew, manufacturers, and maintenance crews. Mountains of briefings, interviews, reports, data, and other information were studied and analyzed.

The net result of this team’s work was a NASA/NESC report that was published.(National Aeronautics and Space Administration, 2017) The team asserted that, while UPEs are primarily a human problem, most of the previous attention has been focused on the aircraft. Data indicated that hypoxia was the cause of most UPEs, although UPEs were not solely a result of insufficient levels of oxygen in the breathing gas. These was also insufficient delivery of oxygen to the tissues of the body. The report

stated that a key to reliable operation of OBOGS in fighter jets was uniform operating conditions, arguably seldom seen in combat aircraft such as the F/A-18 airframe. The team noted a paucity of data available related to the human in the pilot's seat in contrast to significant amounts of data from the systems surrounding the human. They noted that the complexity of the life support systems of the F/A-18 were highly complex, and the problem of UPEs required a well-designed systems approach in order to diagnose and fix the system problems leading to UPEs. Without a coordinated approach, important discoveries may be missed and UPEs will continue to occur.

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

A Class A mishap is currently defined as damage of USD\$2,500,000 or more and/or aircraft destroyed, and/or fatality.(Naval Safety Center, 2019)

1991: During a training flight, a Royal Australian Air Force (RAAF) pilot was noted 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, and all bleed air flow to the pilot from the environmental control system (ECS) and OBOGS was cut off. The pilot selected the emergency oxygen system, pulling its green ring, but the aircraft lost control and crashed. The cause of the incident was states as G-induced loss of consciousness (G-LOC) and over-breathing of emergency oxygen leading to temporary loss of blood flow to the brain (the so-called "oxygen paradox"). Navy and Marine Corps F/A-18 squadrons studied the report of the mishap, particularly the differences between LOX and OBOGS aircraft. The report emphasized 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 report resulted in a schedule of expected cabin depressurization rates after a bleed air loss that was published by the Naval Air Systems Command (NAVAIR). A revised Naval Air Training and Operating Procedures Standardization (NATOPS) bleed air failure procedure was approved, and a simple cabin pressure warning system was designed and implemented in 2006.

2004: An F/A-18A+ LOX aircraft launched with a CANOPY caution light (canopy was not sealed).

Despite the warning, the pilot continued flight and likely became hypoxic, losing aircraft control. All tactical aircraft squadrons reviewed the report of the mishap; discussed the 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 the Navy's Crew Resource Management (CRM) training. NAVAIR procured and implemented the use of the Reduced Oxygen Breathing Device (ROBD) for periodic aviation physiology training.

2004: A pilot reported feeling unwell to the flight lead during a flight and was not able to perform the required maneuvers in formation. Later, pilot became increasingly disoriented with decreasing communication, who ultimately passed out and lost control of the aircraft, which crashed into the ocean. It was surmised that a) cabin pressurization was lost, and b) the O<sub>2</sub> mask was not fully worn. After investigation, the Navy worked 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 became disoriented, lost sensory awareness, and ejected. 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.

The physiological event (PE) may be defined by reference to a sign or symptom of the pilot such as cognitive deficiency, drowsiness, confusion, visual or auditory disturbance, extended reaction times, or loss of consciousness.

Hypoxia as the cause of UPEs

The most common explanation of the cause of UPEs is hypoxia. Indeed, the common physical complaints of lethargy, drowsiness, and confusion strongly suggest hypoxia. However, upon review of the NASA NESC 2017 Report(National Aeronautics and Space Administration, 2017), several problems arise without hypoxia as an explanation. This dilemma prompted the current review.

Modern combat aircraft feature cabin environmental control systems that provide consistent pressure and oxygen levels across airframes. Yet in their recent report, the NESC team's flight surgeons pointed out that over 80% of UPEs list hypoxia as a contributing factor. This is despite the fact that the memory unit (MU) data from those same flights showed that there was an adequate amount of oxygen flowing from the OBOGS. How could an otherwise healthy young military pilot develop hypoxia in the presence of normal or even increased oxygen flow?

UPE reports were rare during the period of time when aircraft relied on Liquid Oxygen (LOX) systems were in use, and have been increasing since the introduction of OBOGS in the early 1990s. LOX Dewar bottles contained only enough oxygen to sustain the crew for one flight, requiring recharge at the end of it. To help these pilots complete their missions, oxygen regulators were designed to titrate oxygen delivery to the pilot. The regulators delivered oxygen in accordance with an aviation medicine approved "oxygen schedule".

OBOGS units are effectively the equivalent of a medical oxygen concentrator, making unlimited oxygen available to the pilot regardless of the military's oxygen schedule. Liberal delivery of oxygen was allowed and encouraged under the naïve presumption that extra oxygen is never a bad thing and that this would obviate all design and specification deficiencies in the aircraft. OBOGS can supply high oxygen concentrations for breathing at all altitudes, yet 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..."(United States Department of Defense, 2015) 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.



“Hypoxia-like” symptoms that are truly due to hypoxia should be immediately reversible upon administration of oxygen. This is commonly seen during hypobaric training at ground level as well as in normobaric hypoxia training systems.(Westerman, 2008, Westerman, 2010) In reality, UPE symptoms frequently last for minutes, hours, or even days after onset, even with oxygen therapy. In one Class-A mishap reported in 2001, the pilot reported hypoxia-like symptoms. He collapsed immediately when he switched to 100% emergency oxygen. This “oxygen paradox” shows that, in such cases, emergency oxygen was detrimental in the treatment of the UPE.

During flights, some pilots have complained of fluctuations in oxygen concentration and airflow. In fact, some have reported marked increases in the work of breathing when trying to breathe through the oxygen mask.(National Aeronautics and Space Administration, 2017) Reportedly, the effectiveness of the OBOGS and oxygen concentration vary with engine revolutions (throttle position), resulting in decreased airflow to the mask at lower throttles.(Elliott, 2019)

#### Other proposed causes of UPEs

Atelectasis due to acceleration has been proposed as a cause of UPEs.(Tacker, 1987) Atelectasis is the collapse of a portion of the lung and can involve small segments up to 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 Tacker’s report nor 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.(Tacker, 1987) Most 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 many aircrews.(National Aeronautics and Space Administration, 2017)

Some studies have proposed 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.(Novak, 1998) This could manifest as confusion and loss of cognitive function. However, audio recordings and testimony from

crew members did not reveal the rapid respiratory rate in the pilot that would be expected to accompany hyperventilation.

Investigators have proposed air contamination as the cause of UPEs. However, no studies to date have identified any significant contamination of life support systems.(Denola, 2011)

While experts and leaders are debating the exact cause of UPEs, in the background some pilots are losing faith in their life supporting oxygen equipment. There are reports from pilots that they avoid using their masks at altitudes below 10,000 feet, and others avoid flying above 28,000 feet whenever possible. Pilots refer to such high-altitude flights as the “mask-on-O-sphere”, implying that they would need to rely on their oxygen masks at this altitude. Because there is a waning level of trust in the system, some pilots will refuse to fly “mask-on-O-sphere” flights.(National Aeronautics and Space Administration, 2017)

In fact, recent articles have raised concerns that there may be a connection between the use of OBOGS with constant high oxygen and UPEs. In *Handbook of Aviation and Space Medicine* by Dr. Nicholas Green et al. (Chapter 15), it is noted that “100% O<sub>2</sub> may cause respiratory tract irritation, delayed otic barotrauma, [and] acceleration atelectasis.”(Green, 2019)

The current analysis is based on over 30 years of experience in designing equipment for use in 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). However, the converse is not true: humans (and animals) do not tolerate hyperoxia well.

Hypoxia is associated with an increase in cardiac output and ventilatory rate as immediate physiologic responses. Long-term adaptation to hypoxia consists of activation of hypoxia-inducible factor 1 alpha (HIF-1 $\alpha$ ) along with transcription of over 30 genes that help the body adapt to lower levels of inspired oxygen.(Semenza, 2006) 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. Any situation in which a person would need to breathe air that contains higher than 20.9% oxygen is highly artificial and may result in significant, and not fully understood, physiological adverse 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 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. Similar conditions are encountered in critical care medicine in which a patient is unable to provide adequate oxygen supply to their bodies and tissues. These settings require that an oxygen mask be worn with an  $\text{FiO}_2$  above 21%. The literature was searched for evidence of any reported symptoms in these scenarios that were similar to the symptoms of UPEs as reported by aircrew.

#### UPEs and diving physiology

Curiously, the underwater diving industry faced similar unexplained physiological episodes during WWII. John Scott Haldane described  $\text{CO}_2$  narcosis, saying it was a limiting factor for divers if ventilation of the helmet was insufficient.(Haldane, 1905) This resulted in accumulation of  $\text{CO}_2$ , exercise intolerance, and loss of consciousness (“deep water blackout”).

However, British Navy combat divers during WWII using oxygen rebreathers would occasionally lose consciousness in less than 6 meters of sea water (msw, 1.6 ATA). This was too shallow for oxygen toxicity according to previous experiments. This phenomenon was termed “shallow water blackout”, and it was thought to result from the narcotic properties of  $\text{CO}_2$  and exacerbated by high inspired oxygen partial pressures ( $\text{PiO}_2$ ).(Barlow, 1944, Gill, 2014) Gill’s paper describes two studies in the diving physiology context in which both studies sought to use oxygen for breathing to extend operational capabilities. The results of both studies concluded this was inadvisable due to safety concerns.(Gill, 2014) In these studies, air breath-holding or rebreathing, hypoxia led to extreme discomfort and voluntary termination. After administration of oxygen, hypoxia resolved, but

hypercapnia became more extreme and the ability to judge when an exposure should be ended safely was compromised. According to their studies, Barlow and Gill both concluded that an elevated end-tidal  $\text{CO}_2$  was the main cause of shallow water blackout.(Barlow, 1944, Gill, 2014)

In diving physiology, the physiological problem seems to be less about oxygen delivery and more about removal of  $\text{CO}_2$ .  $\text{CO}_2$  is highly soluble in human fluids and tissues, and readily diffuses from cells to blood. The nervous system senses arterial  $\text{pCO}_2$  ( $\text{PaCO}_2$ ) and adjusted breathing to maintain an even  $\text{PaCO}_2$  level around 40 mmHg. Venous  $\text{PCO}_2$  is around 45 mmHg as it enters the lungs. Because a large amount of carbon dioxide dissolves in blood, reducing  $\text{PCO}_2$  to 40 mmHg requires the removal of a large volume of  $\text{CO}_2$ . This requires highly efficient ventilation.  $\text{CO}_2$  diffuses from blood into a gas space (alveoli) and there achieves an equilibrium at around 40 mmHg.

The neurologic effect of elevated carbon dioxide is the depression of awareness to the point of complete loss of consciousness. In humans, acutely raising  $\text{PaCO}_2$  to the range of 70-75 mmHg reduces awareness, while a  $\text{PaCO}_2$  above 100-120 mmHg causes unresponsiveness. Inhalation of 30-40%  $\text{CO}_2$  produces surgical anesthesia in humans and animals, although this effect is often accompanied by seizures.

Warkander et al. studied  $\text{CO}_2$  accumulation during exercise at 6.8 ATA and described two subjects that required rescue from a wet pot (an experimental decompression simulator) due to severe  $\text{CO}_2$ -induced incapacitation. Both subjects had elevation of arterial  $\text{PCO}_2$  above 80-90 mmHg, and both were unaware of their incapacitation. In the same study, other subjects continued to function with similar elevation of arterial  $\text{PCO}_2$ . This suggests that  $\text{CO}_2$ -induced depression of awareness may vary greatly between individuals.(Warkander, 1990)

The single factor that limits the ability to increase ventilation is the rate at which gas can be exhaled from the lungs. As gas density increases, increased effort is required to exhale the gas (i.e., it takes more work to move a heavier gas). Oxygen is 14% more dense than Nitrogen, making 100%  $\text{O}_2$  about 11% denser than air, and this density interferes with the ability to breathe and eliminate  $\text{CO}_2$ . (See Table)

A number of studies have reported that divers have an abnormal respiratory response to CO<sub>2</sub>. (Earing, 2014, Florio, 1979) These findings suggest that chronic CO<sub>2</sub> rebreathing is not required for a diver to develop a depressed respiratory response to CO<sub>2</sub>. The depressed respiratory response to elevation of CO<sub>2</sub> appears to vary greatly between individuals, with some divers being normal and others having a very depressed CO<sub>2</sub> response. Divers may consciously reduce their rate of ventilation to conserve gas, which would lead to CO<sub>2</sub> accumulation. Because most diving mixes are relatively hyperoxic, hypoxia with reduced ventilation is unlikely.

Scuba regulators can add additional resistance to breathing, limiting the ability to eliminate CO<sub>2</sub>. Based on the above studies, breathing resistance should be kept to a minimum to reduce the possibility of CO<sub>2</sub> retention.

The primary cause for CO<sub>2</sub> elevation during diving, then, is exertion coupled with increased gas density. Stress increases the metabolic rate and can contribute to increased CO<sub>2</sub> production. Rebreathing expired gas containing CO<sub>2</sub> will also elevate PCO<sub>2</sub>. However, significant rebreathing seems unlikely with standard demand-valve scuba regulators, as they have minimal dead space. Devices with increased dead space, such as communication systems and full-face masks, may elevate CO<sub>2</sub> by rebreathing.

Increased CO<sub>2</sub> impairs mental and physical skills and may hamper self-rescue. Severe elevation of CO<sub>2</sub> can depress the level of awareness and prevent a diver from recognizing and reversing the process. Divers have become incapacitated and lost consciousness due to CO<sub>2</sub> retention without being aware of being in a life-threatening situation. Elevated CO<sub>2</sub> also increases the likelihood of hyperoxic seizures.

#### "Hypoxic training" (voluntary breath-holding) in swimmers and free divers

Numerous news stories have described tragic events occurring with experienced, often young, swimmers undergoing so-called hypoxic training. This is breath-holding training with the goal of extending a competitive swimmer's ability to stay underwater for longer periods of time. The results

can be fatal.(Boyd, 2015) An expose of the consequences of this training method was televised on *60 Minutes Australia* and can be viewed at <https://www.youtube.com/watch?v=IRdBz3fFkm8>.

What is not clear in these cases, however, is the actual physiology underlying the incidents. There is no physiologic data regarding hypoxia or hypercarbia in such victims. In the above-mentioned *60 Minutes* episode, it is proposed that the problem is hypoxia. In fact, the televised segment shows a depiction of oxygen levels dropping to critical levels as carbon dioxide levels rise. This focuses on the effects of hypoxia on the body rather than the effects of hypercarbia on respiratory drive. An inexperienced person attempting breath-holding is not able to hold their breath for longer than 60-90 seconds before hypercapnic drive forces them to gasp fresh air. Towards the end of this breath-holding challenge, the person's SpO<sub>2</sub> will typically not drop below 90%. At this level of hypoxia, it is unlikely that there would be significant hypoxia-related impairment of cognition. In fact, this level of hypoxia is similar to that experienced by a large population of people visiting or living in Aspen, CO (about 2,400m above sea level).

Poon et al described the mechanism of "submissive hypercapnia" in which a chronically hypoxic person can tolerate elevated PaCO<sub>2</sub> levels with little margin of error before the PaCO<sub>2</sub> rises to lethal levels.(Poon, 2015) It is possible that such breath-holding training, which essentially teaches the body to tolerate higher levels of PaCO<sub>2</sub>, dangerously narrows the physiologic buffer that drives respiration. An experimental study in a safe out-of-water condition of subjects performing breath-holding while simultaneously measuring PaCO<sub>2</sub> and SpO<sub>2</sub> would shed more light on the role of CO<sub>2</sub> narcosis in swimming, diving, and UPEs in fighter pilots.

Some cases have been attributed to drowning, or water in the lungs. However, some of these cases are strong and usually young gifted swimmers who died with no water in their lungs. The more likely explanation is a blackout resulting in apnea. The report by Boyd et al stated that the cause of breath-hold blackouts was well understood: hypoxia from prolonged breath-holding.(Boyd, 2015) A report of 58 cases of loss of consciousness during submersion made the same assertion.(Craig, 1976) No measures of PaCO<sub>2</sub> levels were available in these studies. Another method fraught with hazard is the

use of hyperventilation before submersion, thinking that this will “build up” some extra oxygen in the blood or “wash out” more CO<sub>2</sub>, delaying its accumulation to the point where the person has to breath and extending the diver’s time under water. The net effect is to blow off carbon dioxide to a level where the drive to breathe and self-protect is blunted.(Szpilman, 2016) Even the American Red Cross has defined shallow-water blackouts in terms of hypoxia, “where alternative causes of unconsciousness have been excluded”.(Bart, 2020) It is not clear from the text if one of the “alternative causes of unconsciousness” that was excluded was CO<sub>2</sub> narcosis. Health and athletic organizations including the American Red Cross, USA Swimming, and the YMCA have issued warnings against using pre-diving hyperventilation as a means of being able to remain submerged longer, arguing that it may increase death rates due to blackouts while submerged.

Vann et al reviewed the literature related to shallow water blackouts and noted that there were two subtypes of these events.(Vann, 2008) One type is described as loss of consciousness due to hypoxia, while the other results from the loss of respiratory drive due to elevated carbon dioxide. He noted that the urge to breathe was stronger when hypercarbia occurred in the presence of normoxia compared to hypercarbia occurring with hyperoxia. Hyperoxia blunts the normal rescue reflex for respiration that results from a build-up of carbon dioxide.

#### Respiratory physiology, hypoventilation, and hypercapnia

Respiration in animals accomplishes two physiologic outcomes:

1. An increase in blood oxygen as an essential ingredient needed for generating energy in our cells that rely on aerobic metabolism; and
2. A decrease in carbon dioxide, a waste product produced in the body through processes of metabolism.

It has been shown that the primary driver of inhalation is a mechanism called “hypercapnic ventilatory drive”, and “hypoxic ventilatory drive” is a secondary, back-up mechanism that stimulates breathing.(Dick, 1997, Goldberg, 2017) Hypercapnic drive forces exhalation in a very powerful, deep

brain stem, primordial reflex. This is easily demonstrated in a typical individual who wishes to hold their breath for more than a minute. Oxygen is obviously important for life, but the role of CO<sub>2</sub> for our wellbeing is typically neglected. While CO<sub>2</sub> is a driver of normal physiology and a critical component to acid-base equilibrium in normal physiology, there is a perception that CO<sub>2</sub> is only a “waste gas” and has no other function. As such, the aviation medical profession and the engineers who design breathing apparatuses may not understand the importance of maintaining a physiologic CO<sub>2</sub> balance.

When CO<sub>2</sub> homeostasis is disrupted, it can lead to very serious consequences for mammals. 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 as discussed above. In fact, the combination of CO<sub>2</sub> retention in the face of hyperoxia poses a very real danger.

This ominous situation is called oxygen-induced hypercapnia (or hypercarbia) (OIH). OIH is a process of carbon dioxide intoxication that can lead to CO<sub>2</sub> narcosis. Development of hypercapnia due to excessive oxygen use may occur rapidly.(Yang, 2018) The common outcome is rapidly developing respiratory acidosis(Ogino, 2016), 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 consequences of hyperoxia-induced hypercarbia leading to CO<sub>2</sub> narcosis in animals:

1. A mismatch between regional pulmonary ventilation (V) and pulmonary perfusion (Q), referred to as V/Q mismatch(West, 1971);
2. The Haldane effect, a biochemical effect where high FiO<sub>2</sub> causes poor CO<sub>2</sub> extraction from cells(Abdo, 2012); and
3. Hypoventilation, both from the suppression of respiratory drive by high oxygen and from the body’s attempt to save on inhalation volume during insufficient air supply.(West, 1971)



In medicine, it is well-recognized that high inspired oxygen can lead to CO<sub>2</sub> retention as seen in patients with chronic obstructive pulmonary disease (COPD).(Aubier, 1980, Hanson, 1996) Any or all of these effects may be present in the environment of artificial ventilation or artificially high oxygenated air inhalation.(Gill, 2014) The hyperoxia-induced hypercapnia induces symptoms similar to those described by aviators as “hypoxia-like” at the time of a UPE.

Another relevant ventilation parameter is tidal volume. Low tidal volumes may manifest as shallow breathing in a pilot, thereby limiting the turnover of gas in the lung air spaces (and especially the air spaces deeper within the lungs). CO<sub>2</sub> accumulation in the lung is increased during conditions of low tidal volume, and accordingly CO<sub>2</sub> tends to remain in the alveolar blood. Increasing tidal volume improves the turnover of gas in the lungs, and therefore increases the rate of expulsion of CO<sub>2</sub>. This in turn lowers the partial pressure of CO<sub>2</sub> in the lung air spaces, with equilibrium principles favoring exit of CO<sub>2</sub> from the blood into the air spaces. Decreased tidal volumes allow endogenous CO<sub>2</sub> levels to rise, leading to CO<sub>2</sub> narcosis with lethargy, confusion, headache, blurred vision, impaired hearing, and loss of consciousness. Left untreated, this can lead to cerebral edema, convulsions, anoxic brain damage, and death.(Fothergill, 1991)

Hypoventilation may result from the design of the aircraft’s OBOGS. Pilots have reported that they sometimes struggle to pull out air from their oxygen masks, since airflow from OBOGS and oxygen concentration is a function of throttle position.(Elliott, 2019) The OBOGS delivers compressed air at a rate that is related to the revolutions per minute (RPMs) of the aircraft’s main engine. The OBOGS does not function optimally when the engine is idle or operating at low RPMs.

The NECS report noted 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”.(Elliott, 2019)

There is inconsistency between aircrafts using OBOGS in terms of implementation of a plenum in the breathing circuit. A plenum is a storage container or receiver of gas (air or O<sub>2</sub>) that can provide a

short-term backup source of breathing gas, such as when the oxygen supply is interrupted or there is a 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. Smaller plenum volumes, particularly in OBOGS aircraft, mean that the complicated human system is more directly connected to the complex OBOGS with no 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.(United States Air Force, 2012)

The same USAF report(United States Air Force, 2012) 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 CO<sub>2</sub> 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.*

An alternative assessment of the literature, and the assertion of this author, is that:

- a) Hypoventilation leads to CO<sub>2</sub> retention in the body. In a medical context, this is the same process seen in people with COPD(West, 1971), as well as in anesthetized animals. In these situations, CO<sub>2</sub> retention is exacerbated by high oxygen.
- b) In an aviation environment, the same physiological mechanism applies. Ventilation is restricted by:

- Intermittently inadequate mask airflow (or no flow)

A pilot's compensatory response is to try to avoid increased air resistance by decreasing minute volume (VE) through breath-holding, and to reduce tidal volume (Vt) by taking shallow breaths

- Breathing resistance caused by mask valves
- Mask dead space
- Atelectasis reducing vital capacity in the lungs(Tacker, 1987)
- Resistance to chest movements by aircrew flight equipment (dry suit, harness, survival vest, partial pressure suit, and full-coverage G-suit)
- High FiO<sub>2</sub> leading to hypoventilation and consequent hypercapnia leading to CO<sub>2</sub> narcosis(Robinson, 2000)

It is also not proven that hyperoxia causes hyperventilation, as suggested by some authors. In general, hyperoxia suppresses the respiratory drive, increasing the accumulation of CO<sub>2</sub>. This has been well documented in the treatment of COPD patients in critical care.

In pulmonary medicine, some COPD patients can be defined as CO<sub>2</sub>-retainers while others are not.(Abdo, 2012, Robinson, 2000) Theories abound regarding why this is the case. Poon et al have proposed that, in some people with chronic severe COPD, the brainstem learns to ignore those signals and to tolerate the relative hypercapnia in the presence of relative hypoxia.(Poon, 2015) The same process likely applies to pilots, and may explain why some pilots have UPEs in a given situation while others do not. Chiang et al have shown that the body's responsiveness to fluctuations in PaCO<sub>2</sub> can be suppressed over time by using maneuvers such as repetitive breath-holding, ventilation restriction, and oxygen therapy.(Chiang, 2002)

Even if Poon's assertion about tolerance to hypercarbia is true, higher levels of carbon dioxide impair a pilot's ability to perform complex flight maneuvers. In a study of 30 commercial aircraft pilots, Allen et al studied the effects of rising inspired CO<sub>2</sub> on flight performance.(Allen, 2019) Pilots were given normobaric air to breathe, but the CO<sub>2</sub> content was altered by introducing varying amounts of

ultrapure CO<sub>2</sub> into the breathing mixture. Pilots performed maneuvers with significantly higher accuracy at lower levels of inspired CO<sub>2</sub> than at higher levels. The authors concluded that “there is a direct effect of carbon dioxide on performance, independent of ventilation, with implications for many other indoor environments that routinely experience CO<sub>2</sub> concentrations above 1000 ppm”.

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<sub>2</sub> air for 30-60 seconds eliminates hypoxia. Despite this, there have been UPEs that do not resolve even after “pulling the green ring” and breathing 100% emergency oxygen. This life-saving measure is not always effective. Such an emergency corrective action could very well trigger a cascade of events starting with suppression of respiration and ending in unconsciousness, not a good thing when travelling at 1,500 to 2,000 mph.

Based on the above analysis, it is not likely that hyperoxia leads to hypocapnia through hyperventilation. This assertion can be found in several published reports related to UPE investigations. One of the earliest such reports was in the form of an opinion letter by Iscoe et al in 2005(Iscoe, 2005) 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. The paper referenced experimental data published by Becker et al in 1996(Becker, 1996) suggesting that hyperoxia caused hyperventilation in normal healthy subjects. Becker’s experimental set-up exposed subjects to what was effectively a Carbogen gas, a mixture of enriched O<sub>2</sub> and CO<sub>2</sub> that is known to cause hyperventilation, panic, and disorientation in subjects. Becker used a semi-closed breathing circuit that controlled the amount of re-inhaled CO<sub>2</sub> with the aim of clamping the end-tidal PCO<sub>2</sub>. They even stated in their paper that “If isocapnia is not maintained, hyperventilation is attenuated by a decrease in arterial PCO<sub>2</sub>.” 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 that can

ultimately result in cerebral vasoconstriction, cerebral hypoxia, and loss of consciousness in UPEs seen in high-performance aircraft. There are no supporting data.

### CO<sub>2</sub> Narcosis as the Cause of UPEs

Based on a review of the literature, the most likely 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. (Abdo, 2012, Allerdet-Servent, 2019, Aubier, 1980, Barlow, 1944, Hanson, 1996, Jing, 2019, Lee, 2018, Merriman, 1955, Ogino, 2016, Robinson, 2000, Westlake, 1958, Yang, 2018)

As mentioned earlier, much research has been devoted to identifying contaminants entering the pilot's breathing apparatus. (Denola, 2011) In high performance military aircraft, the pressure required to drive gases into the pilot's breathing mask is typically provided by the aircraft engine. Some authorities have argued that combustion products from the engine were contaminating the breathing apparatus, affecting the pilot's neurological functioning. Other hypotheses center around the variation in engine revolutions (and especially where revolutions decrease intermittently at low throttle settings) and its effect on the OBOGS causing inadequate delivery of breathable gas to the pilot.

In contrast, it is proposed herein that hypoventilation is caused by suppression of the hypoxic ventilatory drive (mediated by the carotid body and aortic body centers) resulting from a combination of hyperoxic air breathing with accompanying hypercapnic respiratory drive suppression. The latter hypercapnic respiratory drive suppression may be due to a lack of available breathable gas, breath-holding (a habit particular to some pilots), obstruction to breathing caused by the resistance of valves in the breathing system, irregular breathing of the pilot caused by aircraft flight maneuvers, or added restriction of breathing caused by the weight of airman flight equipment and parachute gear bearing on the pilot's chest. The hypercapnia results in respiratory acidosis, acute respiratory distress, CO<sub>2</sub> narcosis, loss of consciousness, and coma. CO<sub>2</sub> narcosis may manifest as neurological and sensory effects such as drowsiness, dizziness, confusion, headache, loss of

consciousness, vision impairment, hearing impairment, muscle tremor, sweating, shortness of breath, and increased heart rate. Such effects in a pilot may be noted separately or seen together in various combinations. These effects and symptoms have been reported by pilots having UPEs, but the underlying cause has always been considered to be hypoxia (i.e. a lack of sufficient oxygen).

Hypercapnia is defined as an abnormally high level of carbon dioxide in the bloodstream and is seen in patients who have an underlying respiratory condition, or where a person is forced to breathe gases having relatively high levels of carbon dioxide. A pilot will typically not have any underlying respiratory conditions, and his/her breathing system does not deliver a carbon dioxide rich gas mixture (in fact, the gas mixture is devoid of or has relatively low levels of carbon dioxide). In a normal healthy fighter pilot with a normal life support system on board, what would be the source or cause of hypercapnia that would result in CO<sub>2</sub> narcosis?

As mentioned earlier, hypercapnia may be caused by any one or more of the following three potentially interrelated mechanisms:

- Impaired V/Q ratio (ventilation/perfusion) caused by atelectasis (i.e. a collapse or closure of all or part of a lung resulting in compromised gas exchange). In aviation, atelectasis can result from excessive acceleration forces that are applied to the pilot's thoracic cage during acceleration/deceleration or certain aircraft maneuvers and may be exacerbated by an anti-gravity suit. In addition, or perhaps alternatively, an impaired V/Q ratio may be caused by mask dead space which allows for some exhaled carbon dioxide-rich gas to be rebreathed, thereby limiting the amount of oxygen that is available to ventilate the lungs.
- The Haldane effect (inefficient CO<sub>2</sub> excretion from tissues)
- Hypoventilation due to
  - Insufficient oxygen flowrate from an oxygen regulator that forces pilots to limit inhalations, gradually suppressing their hypercapnic drive;
  - Weight of flight gear; and

#### □ Resistance to respiration.

The occurrence of UPEs is unpredictable. UPEs do not occur in all instances of a pilot breathing hyperoxic gases. Factors which interfere with normal ventilation of the lungs may contribute, such as G-forces imposed on the pilot, compression of the chest by heavy garments and equipment, some pilots being less efficient ventilators than others, tiredness and fatigue, chest wall deformities, weakness in the diaphragm muscles, respiratory infections, administration of some medications (such as analgesics), and metabolic processes that increase carbon dioxide production (such as thyrotoxicosis, increased catabolism from sepsis or hormone imbalance, overfeeding, metabolic acidosis). Furthermore, some individuals have an inherent predisposition for retaining carbon dioxide (so-called “carbon dioxide retainers”). Because these risk factors may occur infrequently within a population of pilots, one would expect a relatively low frequency of UPEs.

Furthermore, conditions aboard an aircraft that contribute to UPEs do not occur on all flights. For instance, executing certain aircraft maneuvers that are associated with significant acceleration/deceleration on a pilot may cause compression of the lungs and/or difficulty in respiration, leading to hypoventilation and hypercapnia.

Identifying the true cause of at least some UPEs would allow engineers to redesign and develop new, “PE-free” life support systems that would prevent UPEs from occurring. This may include new personal breathing systems for pilots, methods of treating and preventing UPEs in a pilot, screenings for at-risk pilots, and methods for training pilots how to ideally prevent, or at least recognize and recover from UPEs.

#### CO<sub>2</sub> narcosis

Over six decades ago, J. E. Merriman (Merriman, 1955) explained the mechanism of CO<sub>2</sub> narcosis syndrome, a condition that was becoming increasingly recognized by anesthesiologists in patients with severe respiratory insufficiency. In his words:

*Patients with chronic pulmonary emphysema, for example, have great difficulty ventilating their lungs. As a result, alveolar ventilation becomes inadequate, the PaCO<sub>2</sub> rises and the PaO<sub>2</sub> decreases. The high PaCO<sub>2</sub> results in respiratory acidosis, and the low PaO<sub>2</sub> produces arterial oxygen unsaturation and cyanosis.*

*The elevated PaCO<sub>2</sub> should act as a respiratory stimulant, but these patients are unable to increase their ventilation because of their increased pulmonary resistance. Finally the respiratory centre becomes completely insensitive to the PaCO<sub>2</sub> stimulus. What then controls the ventilation and respiration of these patients? They are now breathing only in response to their oxygen lack. A patient in such a precarious respiratory state may be admitted to the medical ward, possibly with a patch of pneumonia which has taken away a further portion of his functioning lung tissue. The unwary interne, who on examination finds a markedly dyspnoeic, deeply cyanosed patient with rales at both bases, may order morphine for the supposed pulmonary oedema, and oxygen as correction of the cyanosis. He is unfortunately "killing him with kindness" for he is making two mistakes. The morphine will depress the respiration rate, and thus further reduce alveolar ventilation. But more important, he has taken away this man's only stimulus to breathing. The oxygen therapy corrects the hypoxaemia, and alveolar ventilation is further reduced. The PaCO<sub>2</sub> soon rises to narcotic levels and the acidosis may cause respiratory arrest and death.*

Later, in 1958, Westlake(Westlake, 1958) described the mental disturbances associated with respiratory failure as a progressive deterioration in mental function with visual and auditory hallucinations, delusions, stupor, and coma. According to Westlake, the delivery of 100% oxygen in such cases results in transient improvement, and yet his patients remained confused and disoriented even while having full arterial oxygen saturation.(Westlake, 1958)

Westlake hypothesized that hypercapnia underlying respiratory failure causes cerebral vasodilation and increased intracranial pressure, resulting in a throbbing type of headache. The physiologic mechanisms of CO<sub>2</sub> narcosis are poorly understood, as are the mechanisms behind medically-induced anesthesia. It is known that CO<sub>2</sub> is a lipid-soluble molecule that is acted upon by the enzyme carbonic anhydrase to form two acids, carbonic acid plus a hydrogen ion.(Supuran, 2004) It is likely that CO<sub>2</sub> 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.(Giffard, 1990)

### CO<sub>2</sub> Narcosis in Anesthesiology



Anesthesiologists of the 1950s were acutely aware of the treacherous combination of suppression of ventilatory drive using analgesics and high oxygen. After induction of anesthesia and paralysis, inefficient ventilation and V/Q mismatch lead to the development of lung regions where V/Q mismatches increase, leading to deficient CO<sub>2</sub> elimination and hypercarbia.(Becker, 1996, Rehder, 1979)

The science of assisted ventilation developed alongside the use of general anesthesia as a response to the common occurrence of respiratory acidosis caused by impaired ventilation and gas exchange in patients undergoing surgery. With the invention and introduction of mechanical ventilators in 1960s, the problem of respiratory acidosis was finally able to be addressed. Even today, anesthesiologists learn that one of their main challenges is to avoid respiratory acidosis leading to acute respiratory distress syndrome (ARDS), coma, and death.(Kaynar, 2018) The duty of the mechanical ventilation operator is to manipulate FiO<sub>2</sub>, tidal volume (Vt), and constant positive air-pressure (CPAP) (in a non-invasive ventilation case) or positive end- expiratory pressure (PEEP) (when the patient is intubated) in order to avoid abnormal arterial blood pH that is a direct result of elevated PaCO<sub>2</sub>.(Hedenstierna, 1985)

Aviators face the same physiological threat of impaired normal gas exchange, as their lung VC is reduced by oxygen- and acceleration-induced atelectasis. The current approach to intervention involves unbridled use of hyperoxic air(National Aeronautics and Space Administration, 2017), despite oxygen schedules published in military standards. Current thinking is that providing unlimited amounts of oxygen to the pilot will compensate for all physiologic challenges that may be faced. There are situations in flight in which there is “low flow” or even “no flow”, and pilots are trained to adapt to these situations. Such training is encouraged instead of fixing the design of the oxygen regulator and OBOGS.

Medical science has shown, through millions of patients over the past several decades, the value of CPAP and PEEP during both surgery and post-anesthesia recovery.(Hedenstierna, 1985) Reports from aviation medicine has recommended the use of CPAP in the form of positive pressure breathing in

aviators, although this option is generally not selected by airframe management in combat aircraft such as the F-18/SH.(National Aeronautics and Space Administration, 2017) It is not clear whether pilots do not use positive pressure breathing because the masks interfere with communications or because they believe that the compression suit is sufficient. However, as we know from aeronautical physiology, the compression suit addresses only one of the two variables in V/Q mismatch, the perfusion to the lungs. This, combined with respiratory suppression caused by breathing hyperoxic air, alters the V/Q mismatch in unpredictable ways.

Anesthesiologists and Intensivists refer to “alveolar recruitment”, a ventilatory method using positive pressure that re-opens and recruits collapsed alveoli. Studies have shown that this approach helps eliminate excessive CO<sub>2</sub> and reduce CO<sub>2</sub> narcosis.(Claxton, 2003, Lumb, 2010, Mols, 2006, Tusman, 1999) The net effect would be the same in pilots, if they choose to use the positive pressure breathing as well as assisted ventilation functionality.

Nearly 100 years ago, Prausnitz recommended using CO<sub>2</sub> during general anesthesia as a means to prevent postoperative atelectasis(Prausnitz, 1928), while others have advocated the use of carbon dioxide as a short-acting anesthetic in animals.(Kohler, 1999) Today, carbon dioxide is used for animal stunning in some abattoirs.(Atkinson, 2012)

Reversal of CO<sub>2</sub> narcosis requires lowering PaCO<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub>.

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<sub>2</sub>.

Supraphysiologic oxygen supplies do not fix these issues. "Pulling on the green ring" is not going to help and may in fact aggravate CO<sub>2</sub> narcosis by suppressing ventilatory drive.

The presence or absence of CO<sub>2</sub> narcosis at the time of a UPE is difficult to prove empirically.

Currently there are no easy ways to monitor PaCO<sub>2</sub> levels in real time in vivo. While expired end-tidal CO<sub>2</sub> (etCO<sub>2</sub>) 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<sub>2</sub> readings even in a sick person.(Moses, 2009)

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<sub>2</sub> and PaCO<sub>2</sub> because of the impacts of physiologic buffer systems.(Campion, 2019) Hyperkalemia (elevated potassium) is frequently used as a surrogate biomarker of *metabolic* acidosis, but there is poor correlation between hyperkalemia and the *respiratory* acidosis that exists in hypercarbia.(Weinberg, 2019) It has also been noted that confusion and disorientation can continue despite full arterial oxygen saturation.(Westlake, 1958) In fact, PO<sub>2</sub> pulse oximetry does not correlate well with hypercarbia.(Fanari, 2019) Even the level of PaCO<sub>2</sub> in and of itself is insufficient to dictate who will or will not develop CO<sub>2</sub> narcosis symptoms, with other variables including serum bicarbonate, use of supplemental oxygen, use of opioids, and body mass index (BMI) being important variables.(Yang, 2018)

However, the reports of UPE symptoms are most consistent with CO<sub>2</sub> 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<sub>2</sub> narcosis, an in vivo human or animal interventional study is desperately needed.

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<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub> measurement include colorimetric, photonic, and optical techniques. However, there is no commercially available wearable device that is suitable for continuous PaCO<sub>2</sub> monitoring in the 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 oxygen-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.(Elliott, 2019)

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 well-engrained dogma, their respective references are often irrelevant (breathing Carbogen gas) or unverifiable (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 virtually no statistical power, being based only one patient.(Iscoe, 2005)

In contrast, practical experience confirms textbook knowledge that hypoxic drive is dysfunctional in hyperoxic conditions.(Westerman, 2008) In fact, thousands of training records in possession of Royal Australian Air Force (RAAF) Institute of Aviation Medicine 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(Bassovitch, 2012, Bassovitch, 2012) 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]

Experimental data on the effect of 15 minutes 100% oxygen administration is summarized in Figure 2.(Aubier, 1980) [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 the hypothesis of this report 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(Comroe, 1965, Kohler, 1999), 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.”(Elliott, 2019)

There are three mechanisms leading to hypercapnia and an increase in the threat of CO<sub>2</sub> narcosis, and potential solutions to deal with them:

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

Solution: Use the proven and effective AGSM (anti-G strain maneuver) and use of unassisted positive pressure as suggested by Tacker(Tacker, 1987)

2. Problem: Haldane effect

Solution: Titrated oxygen delivery in accordance with an oxygen schedule that recognizes that “more” is NOT “better”.(Allerdet-Servent, 2019)

3. Problem: Hypoventilation

Solution: Monitoring PaCO<sub>2</sub>, and development 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<sub>2</sub> narcosis, it is important to recognize the following limitations in current thinking and practices:

- ☐ Monitoring of exhaled PO<sub>2</sub> 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<sub>2</sub> may be misleading, as normal values may be seen in the presence of shallow breathing even in the face of abnormal lung function;
- ☐ SpO<sub>2</sub> monitoring may be misleading, since SpO<sub>2</sub> can be within normal physiological range since it measures hemoglobin oxygen saturation, not tissue PCO<sub>2</sub>; 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<sub>2</sub>-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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Tables and Figures

Table: Relative density of gasses in the atmosphere

Gas	Density (g/l of gas)
Nitrogen	1.1009
Helium	0.1573
Oxygen	1.2572
Argon	1.5696
CO <sub>2</sub>	1.9777

Figure 1: Typical subject graph (practical training report) of SpO<sub>2</sub>, HR, ventilatory frequency (Vf) during routine hypoxia/reoxygenation, part of a hypoxia awareness training session using GO2Altitude hypoxicator.

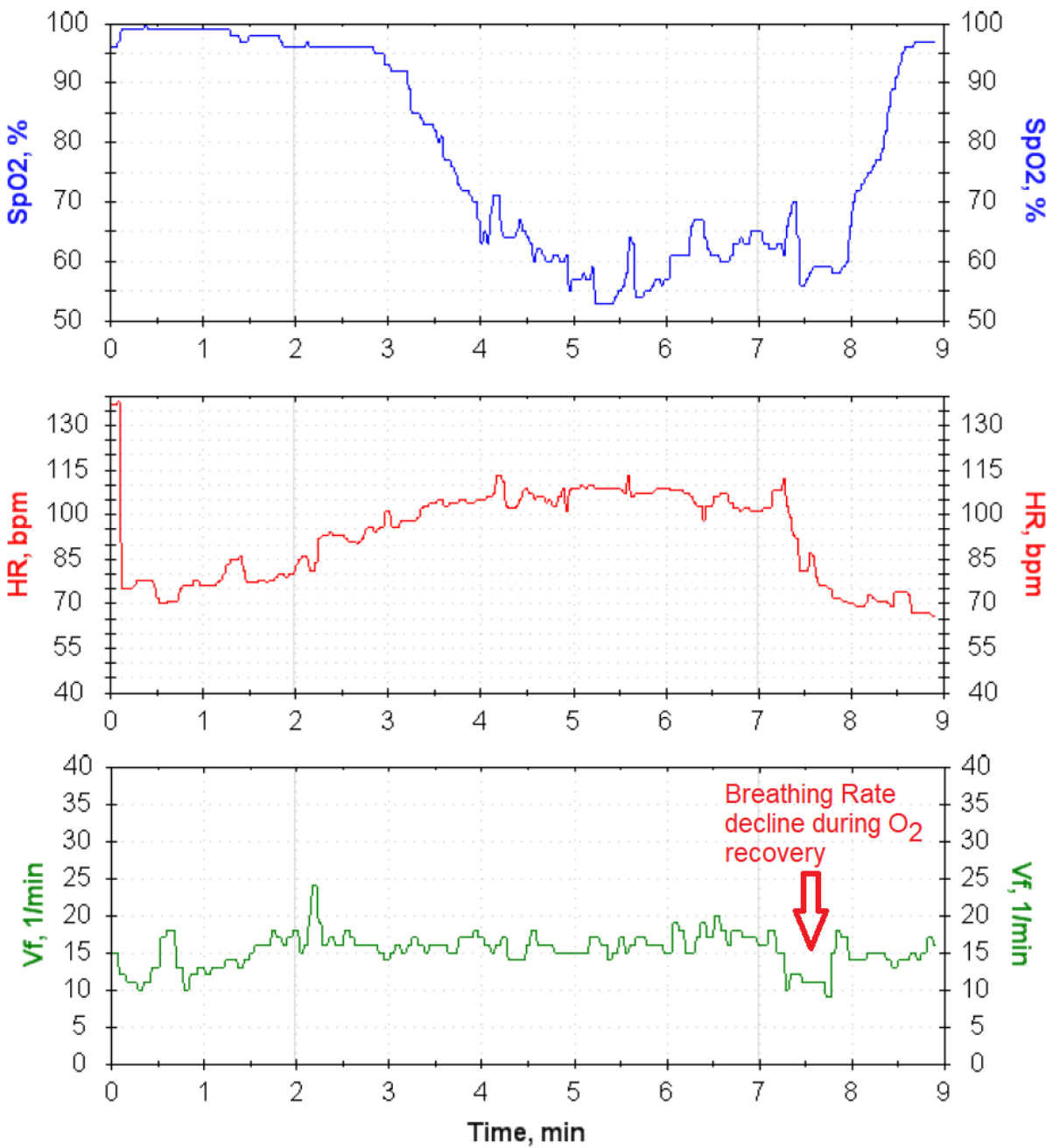


Fig.1

Figure 2. Experimental data on the effect of 15 minutes 100% oxygen administration. Adapted from Abdo et al(Abdo, 2012) and Aubier et al(Aubier, 1980).

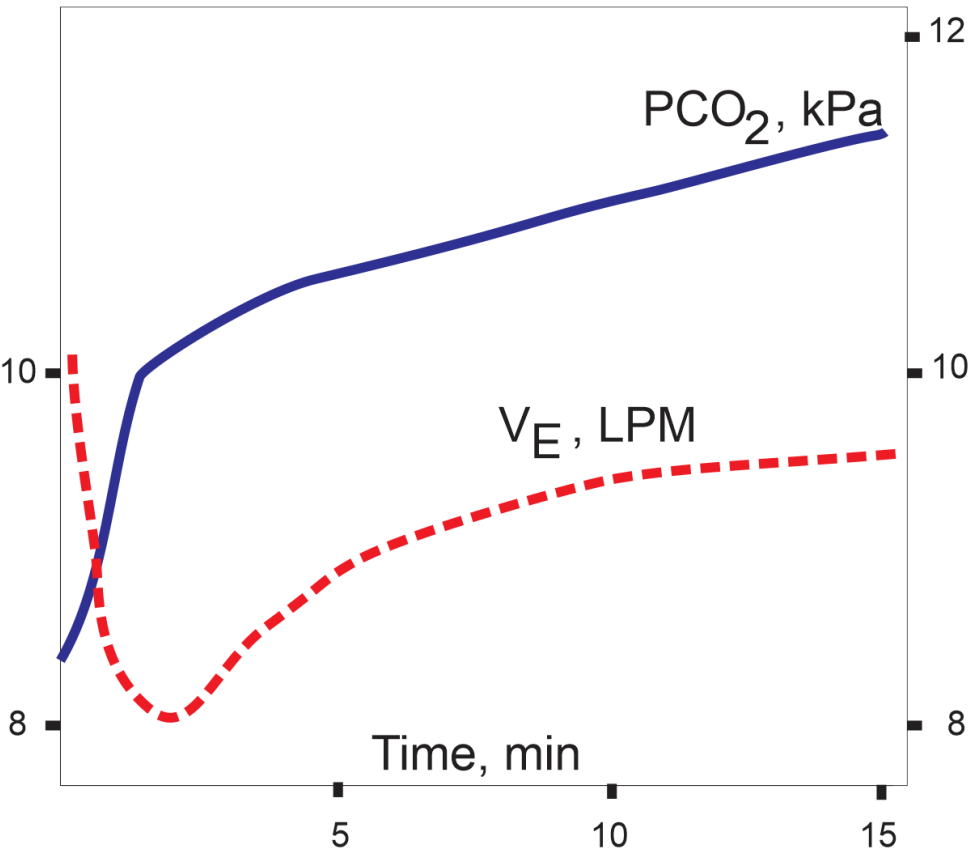


Fig.2