Symptoms of central nervous system oxygen toxicity during 100% oxygen breathing at normobaric pressure with increasing inspired levels of carbon dioxide: a case report

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Abstract

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The greatest danger faced by divers who use oxygen-enriched gas mixtures is central nervous system oxygen toxicity (CNS-OT). CNS-OT is characterised by convulsions resembling grand-mal epileptic seizures, which may terminate in drowning and death. Elevated arterial levels of carbon dioxide (CO_2) (hypercapnia) represent a major risk factor for CNS-OT when breathing hyperoxic gas mixtures. To reduce the risk of a diver being involved in a CNS-OT incident due to hypercapnia, candidates for combat diving are examined at our institute using a routine physiological training procedure, in which they are tested for CO_2 detection and retention. We present the case of a candidate for combat diving, who unexpectedly exhibited signs typical of CNS-OT while breathing pure oxygen under normobaric conditions with > 3 kPa inspired CO_2. Severe headache and nausea, as well as facial muscle twitching, appeared during one of these routine tests. Subsequent medical examination including neurological tests, magnetic resonance imaging and an electroencephalogram were unremarkable. To the best of our knowledge, an event such as this has never previously been published in the medical literature. We present a discussion of the case, and a review of the relevant literature regarding CO_2 as a risk factor for the development of CNS-OT.

Introduction

Central nervous system oxygen toxicity (CNS-OT) represents a major risk for combat and recreational divers who use oxygen-enriched mixtures as their breathing gas. CNS-OT is characterised by tunnel vision, tinnitus, headache, nausea, and twitching of the muscles of the face. Convulsions similar to epileptic seizures may also appear, as well as sudden loss of consciousness, sometimes without any warning symptoms.[1] CNS-OT may be observed at oxygen pressures above 200 kPa with the dry chamber.[2,3] However, the limit of concern for CNS-OT when using an oxygen rebreather underwater may well be less, as low as 146 kPa.[4] The cellular mechanisms underlying the development of CNS-OT include reactive oxygen species (ROS), which can oxidise specific cellular components, producing neurochemical alterations that conclude in neurotoxicity.[5,6] Reactive nitrogen species (RNS) also play a role,[7–11] as does nitric oxide (NO), which modifies GABA metabolism and may contribute to neuroexcitation and seizures.[12,13]

Elevated arterial levels of CO_2 (hypercapnia) due to CO_2 production/elimination mismatch during submerged exercise (termed CO_2 retention), an inherent tendency to retain CO_2, or failure of the CO_2 absorbent in the breathing apparatus, all carry an added risk of CNS-OT when breathing hyperoxic gas mixtures.[14] The correlation between elevated inspired PCO_2 (P_ICO_2) and an increased risk of CNS-OT has been well established in animal models.[15–19] This correlation has also been reported in divers with a low ventilatory response to inhaled CO_2 ('CO_2 retainers'), who may convulse while apparently within the safety limits for hyperoxic exposure.[20]

There are a number of possible mechanisms which might explain the higher risk of CNS-OT in the presence of elevated levels of CO_2. First, CO_2 induces cerebral vasodilatation, which increases the blood flow through neural tissues, and in turn increases the transfer of O_2 to these tissues. Second, hyperoxia, unlike normoxia, suppresses the sensitivity of peripheral CO_2 chemoreceptors to [H^+], which might lower the potential ventilation rate and result in higher

arterial levels of CO_2.[21] Third, at hyperbaric pressure, CO_2 retention may be presumed to increase the production of NO, which also results in cerebral vasodilatation.[22,23] Fourth, at hyperbaric pressure, there is increased production of RNS, such as peroxynitrite, due to the reaction of nitric oxide with superoxide. It may be presumed that in the presence of CO_2 retention, molecular CO_2 will react with peroxynitrite to generate the RNS nitrosoperoxocarboxylate ($ONO_2CO_2^-$), which may cause oxidation as well as nitration and nitrosylation reactions.[24] Finally, ROS production in the presence of CO_2/H^+, such as the Fenton reaction, might generate hydroxyl molecules.[24]

To reduce the risk of a diver being involved in a CNS-OT incident due to hypercapnia, candidates for diver training are examined at our institute using a routine physiological training procedure. In this test, subjects are checked for CO_2 retention and detection while breathing a hyperoxic gas mixture. We expect a candidate to be able to detect P_ICO_2 before it reaches 4 kPa (27 mmHg). Those unable to detect a rise in P_ICO_2 by the time it reaches this level, which is the detection threshold for conscious recognition of elevated CO_2, is defined as a poor CO_2 detectors. The assessment is performed using an electric scale board with a matrix of push-buttons related to five subjective symptoms typical of hypercapnia. CO_2 retention is defined as an end tidal PCO_2 ($P_{ET}CO_2$) in excess of 9.5 kPa (71 mmHg) when inhaling 6 kPa (45 mmHg) CO_2. We have previously shown that a diver who is defined as both a poor CO_2 detector and a CO_2 retainer is prone to suffer from CNS-OT.[25] The purpose of the present case report is to bring to light the uncommon event of an individual who displayed twitching of the facial muscles, a symptom of CNS-OT, while breathing 100% normobaric oxygen to which 3 kPa (22 mmHg) CO_2 had been added.

Methods

EXPERIMENTAL SYSTEM AND PROTOCOL

The CO_2 retention test is performed with the subject seated on a bicycle ergometer (Ergonomics 800, Sensormedics Corp., Yorba Linda, CA, USA). The experimental system and protocol have been described in detail in our previous studies.[25,26]

Before the test, subjects receive an oral lecture on the role of CO_2 in closed-circuit diving, the signs and symptoms of hypercapnia, and the nature of the test.

In the training and test protocols, the subject under examination inhales 100% oxygen while pedalling at a work rate of approximately 50 W. After 5 min, the CO_2 level in the inspired gas is arbitrarily cycled within a range of 0–5.6 kPa (0–42 mmHg). In the training session, the subject is provided with a digital display of the inspired CO_2 concentration, as well as being informed verbally, until he/she is able to sense the presence of CO_2 in the inspired gas without hints and signal accordingly.

The test session usually starts 15–30 min after training, when the subject's $P_{ET}CO_2$ has returned to baseline (pre-training) levels and any of the symptoms (such as headache or dizziness) which may have occurred during the training session have disappeared. It comprises the same procedure as the training session, but the gradual elevation of P_ICO_2 begins immediately after the start of oxygen breathing. The CO_2 level in the inspired gas is arbitrarily cycled two or three times within a range of 0–5.6 kPa. Subjects are not informed of the F_ICO_2, other than that it will at some point start to rise and that they should indicate on the electric board (with a matrix of push-buttons related to five subjective symptoms: hyperpnea, air hunger, headache, dizziness, and a warm sensation, each of which can be scored according to 5 degrees of intensity) the moment they detect it. This first detection is unsolicited. The minimum level of inspired CO_2 for which we consider a response to be a true detection is found for every subject individually, according to his/her detection repeatability during the test session.

Case report

A 19 year-old male diver on active duty in the Israel Navy, weighing 67 kg, height 1.73 m, came to our laboratory at the Naval Medical Institute to perform the routine physiological test designed to examine his CO_2 retention and detection traits. During his interview before the test, he complained of dizziness, headaches and nausea he had experienced during the series of dives using closed-circuit apparatus commenced two weeks earlier. The diver began the test as described above. During the training session, when the CO_2 in his inspired gas reached a level of 2 kPa ($P_{ET}CO_2$ 4.9 kPa), he complained of severe dizziness and headache. At the same time, with the inspired CO_2 somewhere in excess of 3 kPa ($P_{ET}CO_2$ 5.7 kPa) he also reported twitching of his facial muscles, especially around the mouth, which was indeed observed clearly by the medical staff. When the level of CO_2 in his inspired gas was reduced the twitching stopped, although the sensations of dizziness and headache remained. The level of CO_2 was raised and lowered between 0–4 kPa twice more, which resulted in reappearance of the facial muscle twitch. During the actual test, his sensitivity to inspired CO_2 was found to be very high. He had severe headache and dizziness at an inspired level of 2 kPa CO_2. This is considered quite low, the average value for CO_2 detection being 3 (SD 0.2) kPa. Most of the divers who undergo the test hardly have any sensation at all at an inspired level of CO_2 at 2 kPa. In most cases, when a candidate indicates any subjective change as a result of inspiring CO_2 at a level as low as 2–2.5 kPa, his/her $P_{ET}CO_2$ is usually lower than the average level for all divers who have participated in the test.[25] Therefore, the diver in the present case indeed seems to be particularly, if not uniquely sensitive to CO_2.

We asked the diver to repeat the test two weeks later in exactly the same format. The symptoms of dizziness, headache and twitching of the facial muscles appeared as they had on the first test, and the candidate was sent for medical investigation.

The diver's medical history was unremarkable. All aspects of the medical check-up he underwent to qualify for combat diving, performed prior to the CO_2 tolerance test, were normal. This included examination by a cardiologist, electrocardiogram, spirometry and blood analysis.

A detailed medical interview, conducted after the CO_2 test, revealed that the diver had experienced headaches, dizziness and nausea after many of his closed-circuit oxygen dives, and apparently had to terminate some of the dives as a result. The diver had never experienced these symptoms in any other situation apart from diving with an oxygen rebreather, even during very strenuous exercise.

The diver was examined by a senior neurologist, who noted no pathological findings. Magnetic resonance imaging did not show any abnormalities, and electroencephalography was interpreted as normal. A 24-hour EEG recording was performed, during which he underwent another CO_2 detection and retention test as described above. Despite normal findings on the continuous EEG recording, the same symptoms appeared once again.

Despite the fact that all the examinations he performed were found to be normal, providing no definite explanation for the events, it was decided that due to the diver's symptoms during oxygen breathing (appearing both in his prior oxygen dives and in the CO_2 detection and retention test), he would not continue to dive with oxygen-enriched mixtures. The decision was based on the likelihood of excessive risk for CNS-OT.

Discussion

The present case represents a very rare phenomenon, of a subject in whom breathing ~100% normobaric oxygen to which 3% CO_2 had been added (P_ICO_2 = 3 kPa, 22 mmHg) triggered signs often associated with CNS-OT. To the best of our knowledge, no signs or symptoms of CNS-OT have ever previously been reported during breathing of normobaric oxygen, even with the addition of CO_2 to the inspired gas.

In contrast to pulmonary oxygen toxicity, which may be observed with prolonged oxygen-enriched breathing in normobaric conditions, CNS-OT has always been related to breathing oxygen at hyperbaric pressure, both during a dry dive or clinical treatment in the hyperbaric chamber, and in the wet conditions of underwater diving. The breakthrough of CO_2 to the inspiratory limb of the breathing loop in the diving apparatus, or CO_2 retention, represent a major risk factor for CNS-OT with which divers may have to contend. For that reason, rebreather divers attend our laboratory for a training session to give them experience of hypercapnia. They thus have an opportunity to familiarise themselves with the sensations induced by CO_2, so that they will know when to abort the dive should the need arise. Seizures occurring underwater may have a fatal outcome.

This raises questions concerning other mechanisms which may result in physical hypersensitivity to oxygen. Chronic obstructive pulmonary disease can cause basic hyperpnoea, and increased susceptibility to oxygen toxicity.[27] Certain brain processes (against an epileptic or other epicenter), such as brain damage after carbon monoxide poisoning, may cause hypersensitivity to oxygen.[28] Therefore extra care should be taken with such patients when they undergo hyperbaric oxygen treatment. There may be a decrease in the CO_2 carrying capacity of venous haemoglobin, due to its being saturated with O_2 on hyperbaric exposure, which will bring about an increase in tissue and venous PCO_2.[22] The resultant hypercapnia-induced intracellular acidosis will make cells more susceptible to ROS. Molecular CO_2 reacts with peroxynitrite (ONOO-), a RNS that may also cause cellular damage.[24] Exercise may contribute to CNS-OT, most likely due to the increase in cerebral blood flow and metabolic rate.[13] In the present case, the diver was breathing 100% oxygen together with an elevated percentage of CO_2 when cycling on an exercise ergometer at 50 W, which is considered a low work rate.

The results of EEG and MRI studies in our diver did not indicate any abnormal brain pathology, including an epileptogenic focus expressed on exposure to oxygen in normobaric conditions. It is possible that more specific EEG or MRI testing could have shed light on delicate changes which standard tests were not sensitive enough to detect.

Arieli et al.[4] summarised CNS-OT symptoms reported from 2,527 dives. They found that the most prevalent symptoms after four-hours diving were headache and nausea. Moreover, the authors concluded that if facial twitching appears, the probability of losing consciousness is 700 times greater than in a diver who does not have that symptom. Our diver reported severe headache, dizziness and nausea, both on his O_2 dives and during his CO_2 test on 100% normobaric oxygen. These symptoms are by no means exclusive to hyperbaric hyperoxia but may also be observed in hypercapnia. It is thus plausible that our diver may have been highly sensitive not only to hyperoxia, but also to hypercapnia. Using a rebreather naturally places the diver in a situation where he is breathing hyperbaric oxygen, while also at a high risk of hypercapnia. The decision in the present case was therefore to disqualify this diver from diving with oxygen-enriched gas mixtures, due to a serious possibility that he might lose consciousness during an O_2 dive.

Conclusions

We have described a diver who is possibly at high risk for CNS-OT, manifesting in symptoms which developed

consistently in all hyperoxic conditions: wet hyperbaric and dry normobaric. These included severe headache, dizziness and nausea when using closed-circuit oxygen apparatus, and twitching of the facial muscles while breathing 100% normobaric oxygen to which 3% CO_2 had been added (P_ICO_2 = 3 kPa, 22 mmHg). We have experience going back many years testing CO_2 retention and detection.[25] Never before have we seen a symptom so typical of CNS-OT appear at normobaric pressure. We feel this exceptional event should be brought to the knowledge of the diving community to heighten awareness of the danger concealed in the use of oxygen rebreathers.

CNS-OT represents a grave danger for both combat and recreational divers. A major risk factor for the development of CNS-OT is an increase in the level of inhaled CO_2. This is why we conduct the test to determine our divers' ability to detect CO_2, and check the possibility that they may be CO_2 retainers, in all candidates for oxygen diving. In recent years, more and more civilians have begun using electronic rebreathers. It is therefore of great importance that divers be made aware of the potential danger of hypercapnia in accelerating the development of CNS-OT. A poor detector who also has a tendency to retain CO_2 may suffer from CNS-OT when using a rebreather, even at a depth considered safe.

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