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Introduction: Reactive oxygen species are involved in the functional changes necessary for synaptic plasticity, memory, and cognitive function. It is far from clear whether the increased excitability, and which forms of neuronal excitability, should be considered a part of the learning process or, rather, cellular manifestation of neuronal oxygen poisoning. It is yet to be elucidated whether oxygen (O_2)-induced learning and poisoning use the same or distinct cellular pathways. *Purpose:* We hypothesized that O_2-induced neuronal excitability might use the same or an intertwined signaling cascade as the poisoning cellular pathway. *Method:* Eighty-one healthy, young males, mean age 27.7 ± 4.1 (*SD*) years, were exposed in the hyperbaric chamber to 0.7 atmosphere absolute (ATA) O_2, 1.4 ATA O_2, and 2.8 ATA O_2. The critical flicker fusion frequency (CFFF), oxyhemoglobin saturation (SiO_2), and heart rate (HR) were measured before exposure, after 30 min of oxygen breathing while still at pressure and then after exposure. *Results:* Normobaric (0.7 ATA) O_2 exposure did not affect CFFF and HR. Medium hyperbaric O_2 exposure (1.4 ATA) decreased CFFF but HR remained unchanged. High hyperbaric O_2 exposure (2.8 ATA) increased CFFF and diminished HR. SiO_2 was similar in all investigated groups. A correlation between CFFF, HR, and SiO_2 was observed only at low oxygen (0.7 ATA). *Conclusions:* The effect of O_2 on neuronal excitability measured by CFFF in young healthy men was dose dependent: 0.7 ATA O_2 did not affect CFFF; CFFF were significantly jeopardized at 1.4 ATA O_2, while CFFF recovered at 2.8 ATA. With 2.8 ATA O_2, the CFFF and oxygen poisoning transduction pathways seemed to be intertwined.

Keywords: Neuronal excitability; Hyperbaric oxygen; Normobaric oxygen; Critical flicker fusion frequency; Oxygen poisoning.

Reactive oxygen species are involved in the functional changes necessary for synaptic plasticity, memory, and cognitive function (Massaad & Klann, 2011). Stimulation of presynaptic neurons followed by glutamate release and subsequent *N*-methyl-*D*-aspartate (NMDA) dependent postsynaptic depolarization are hallmarks of the induction of long-term potentiation, the cellular substrate for memory (Bliss & Lomo, 1973). Hyperbaric oxygenation (HBO) and normobaric reoxygenation increase excitability and activate oxygen-induced potentiation in CA1 hippocampal neurons (Garcia, Putnam, & Dean, 2010a). Interestingly, induction of neural plasticity by hyperoxic stimulation does not require changes in excitatory synaptic transmission (Garcia, Putnam, & Dean, 2010b). It is far from clear whether the increased excitability, and which forms of neuronal excitability, should be considered a part of the learning process or,

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rather, cellular manifestation of neuronal oxygen poisoning. It is yet to be elucidated whether oxygen (O_2)-induced learning and poisoning use the same or distinct cellular pathways.

The critical flicker fusion frequency (CFFF) is a recognized method to assess neuronal excitability influencing attention and alertness (A&A; Kahlbrock et al., 2012; Lu, Cai, Shen, Zhou, & Han, 2012). Not surprisingly, stimulants were found to significantly increase CFFF, while sedatives, hypnotics, and ethanol decreased CFFF (Hindmarch, 1982; J. M. Smith & Misiak, 1976). CFFF has been assessed in divers in various open-water conditions (Balestra, Lafère, & Germonpré, 2012; Lafère et al., 2010). The Lafere et al. (2010) and Balestra et al. (2012) studies, although very insightful, do not provide sufficient data to differentiate among different confounding effects on neuronal excitability and A&A, including: nitrogen narcosis; an effect of O_2; a bubble effect (decompression stress); and ambient pressure effect. CFFF is rather shown in these studies as a global index of central nervous system (CNS).

Recent studies on the nigro striatal dopaminergic pathway clearly indicated that single hyperbaric nitrogen exposure (up to 30 ATA) induces a reduction in presynaptic glutamate release (Vallée, Rostain, Boussuges, & Risso, 2009; Vallée, Rostain, & Risso, 2009; Vallée, Rostain, & Risso, 2010) and postsynaptic nitric oxide (NO) production (Vallée, Rissoe, & Blatteau, 2011). Repeated hyperbaric nitrogen exposures may disrupt NMDA receptor function and modulate gammaamino-butiric acid A (GABAA) receptors sensitivity decreasing the GABAergic input, at least in rats (Lavoute, Weiss, & Rostain, 2006; Lavoute, Weiss, Risso, & Rostain, 2012). HBO exposure (up to 5 ATA), in turn, seems not to affect glutamate level while depressing GABA inhibitory action in rats. The glutamate/GABA ratio favoring neuroexcitation might lead to oxygen seizures. Furthermore, increased postsynaptic NO production following NMDA activation actually amplifies glutamate release (Demchenko & Piantadosi, 2006). Glutamate and GABA regulate the excitability of virtually all neurons in brain and are mediators of many physiological processes including long-term potentiation (Bliss & Lomo, 1973; Maffei, 2011). Therefore, to study the effect of oxygen on neuronal excitability, it is absolutely critical to remove the confounding influence of hyperbaric nitrogen.

We hypothesized that O_2-induced neuronal excitability underlying neuronal excitability might use the same or an intertwined signaling cascade as the poisoning cellular pathway. Built on this assumption, we speculated that the response of neuronal excitability to oxygen might be dose dependent: dampened by medium (1.4 atmosphere absolute, ATA) O_2 exposure due to the narcotic effect of oxygen or protective cerebral vasoconstriction, while increased by high O_2 concentration (2.8 ATA) due to augmented overall neuronal excitability. The influence of O_2 on neuronal excitability is of high importance, taking into account the professions that are mostly affected: divers (professional, recreational, and military); high-altitude military pilots; and astronauts. The aim of this study was to assess the effect of short-term (30-min) normobaric (0.7 ATA) and hyperbaric (1.4 and 2.8 ATA) O_2 exposure on neuronal excitability using CFFF in highly trained individuals representative for the above-mentioned professionals.

METHOD

Participants

Eighty-one healthy, young males from the elite Special Forces unit of the Polish Army participated in the study. Sixteen subjects were exposed to 0.7 ATA O_2, 16 to 1.4 ATA O_2, and 65 to 2.8 ATA O_2. The 2.8 ATA O_2 exposure was achieved during oxygen tolerance tests conducted in the National Centre for Hyperbaric Medicine in Gdynia for military purposes. All subjects were males aged 22 to 27 years, mean 27.7 ± 4.1 (*SD*) years.

Materials and procedure

The study was approved by the Ethical Committee of the Medical University of Gdansk (NKEBN/548/2011-2012). All participants gave separate written informed consents for the O_2 exposures, the oxygen tolerance tests, and the CFFF test.

The O_2 exposures were conducted in a multiplace hyperbaric chamber at normobaric conditions (0.7 ATA O_2) and hyperbaric conditions: pressurized to 140 kPa(a) (1.4 ATA O_2) and 280 kPa(a) (2.8 ATA O_2) using compressed air (Table 1). Ambient temperature was kept between 24 and 27 °C. Subjects breathed 70% O_2 during normobaric exposure and 100% O_2 during hyperbaric exposures for 30 min while resting using a demand breathing regulator with low inspiratory and expiratory resistance. Subjects were observed continuously for signs and symptoms of CNS O_2 toxicity by a specialist in hyperbaric medicine who remained in the chamber during the whole test. After 30 minutes of breathing O_2, the chamber was decompressed to normobaric pressure over 10 min (Kot, Sicko, & Wozniak, 2003).

TABLE 1
Summary of O_2 exposures conducted in the study

O_2 exposure (partial pressure)	0.7 ATA	1.4 ATA	2.8 ATA
O_2 fraction in the breathing mixture	70%	100%	100%
Ambient pressure	101 kPa(a)	140 (kPa)	280 kPa(a)

Note. ATA = atmosphere absolute.

All subjects were assessed with the CFFF using a specific water- and pressure-tight device manufactured by Human Breathing Technology (Trieste, Italy). The device consists of a waterproof housing of 8 cm diameter containing a numeric (digital) frequency indicator with buttons for increasing and decreasing the frequency. A flexible cable is attached to this housing with a single blue light emitting diode (LED; color temperature 8000 °K) enclosed in a smaller cylindrical container to shield it from stray light and reflections. During CFFF measurement, the subject looked straight at the LED light at a distance individually adapted to his personal vision (generally around 50 cm) while the investigator pressed buttons to increase or decrease the flickering frequency of the LED. The test subject had no indication whatsoever of the actual flicker frequency. When the subject saw a change from fusion to flicker (or flicker to fusion), he signaled this to the investigator, who noted the actual frequency, which is the definition of CFFF (Rota-Bartelink, 1999; Tytla, Trope, & Buncic, 1990).

During each O_2 exposure, three CFFF measurements were performed: before starting the exposure (baseline); before the end of the exposure while still at pressure (HBO); and about 20 min after the exposure (in case of hyperbaric exposures, 10 min for decompression to normobaric conditions and 10 min of breathing normobaric air). Oxyhemoglobin saturation (SiO_2) and heart rate (HR) were measured at all measurement points with an ear-clip sensor (Datex-Ohmeda S5, Helsinki, Finland).

All results were analyzed using absolute values, but for easier readout they are presented in percentage values where 100% is taken as baseline. The normality of distribution of measured CFFF values was confirmed by the Kolmogorov–Smirnov test, so the results are presented as arithmetic mean and standard deviation. The differences between measurements were evaluated using a repeated measures analysis of variance and Scheffé test for post hoc analysis. Pearson product–moment correlation coefficients were estimated to assess interdependences between CFFF, HR, and SiO_2 values. Statistical significance was defined as $p < .05$. The statistical software package Statistica Version 10 (StatSoft, Inc., Tulsa, OK, USA, 2011) was used for calculations.

RESULTS

Normobaric hyperoxia (NBO; 0.7 ATA) exposure did not affect CFFF and HR. Medium HBO exposure (1.4 ATA) decreased CFFF while HR remained unchanged. High HBO exposure (2.8 ATA) increased CFFF and diminished HR. SiO_2 was similar in all investigated groups. Detailed results for CFFF and HR are presented in Figures 1 and 2, respectively. Significant interdependence between CFFF and HR ($r^2 = .50$, $p < .001$, Figure 3) and weak interdependence between CFFF and SiO_2 ($r^2 = .10$, $p = .03$) were found during NBO exposure (0.7 ATA). There were no interdependences between CFFF, HR, and SiO_2 during medium and high HBO exposures.

There was one case of cerebral O_2 toxicity in a 25-year-old subject, who reported severe vertigo and aural hallucinations after 13 minutes of breathing 2.8 ATA oxygen (during the oxygen tolerance test). After reporting those symptoms, O_2 was stopped, and he was observed carefully by the attending physician for more serious symptoms of O_2 toxicity whilst breathing chamber air [58.8 kPa(a)]. As there was no progress in symptoms, he was allowed to stay at pressure with the other subjects on that exposure and follow the general profile. Immediately after the incident, the diver was unable to concentrate on the CFFF test, so the following CFFF measurements were taken at the same time points as those for the other candidates, which were after 30 minutes of staying at pressure of 280 kPa(a) and after reaching normobaric pressure after decompression. His results were as follows: 46.0 Hz (baseline, 100%); 48.5 Hz (105.4%); and 42.0 Hz (91.3%).

DISCUSSION

The main finding of this study is that the effect of O_2 on neuronal excitability as estimated using CFFF is dose dependent. Furthermore, it seems that O_2-induced neuronal excitability and poisoning cellular pathways might be intertwined. To the best of our knowledge, this is the first study to assess the effect of acute administration of a wide

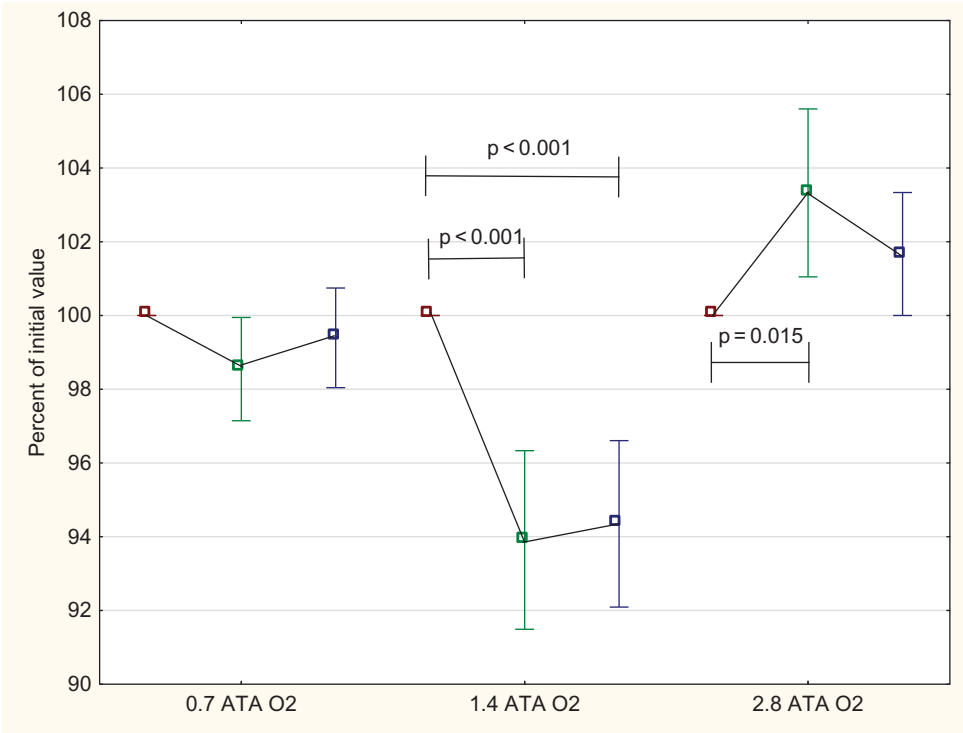

Figure 1. Relative changes of the critical flicker fusion frequency (CFFF; measured as percentage of initial value) between measurements at different oxygen exposures. For each oxygen exposure, three measurements are shown: (a) before starting exposure (baseline); (b) before the end of exposure while still under pressure (hyperbaric oxygenation, HBO); and (c) after exposure. ATA = atmosphere absolute.

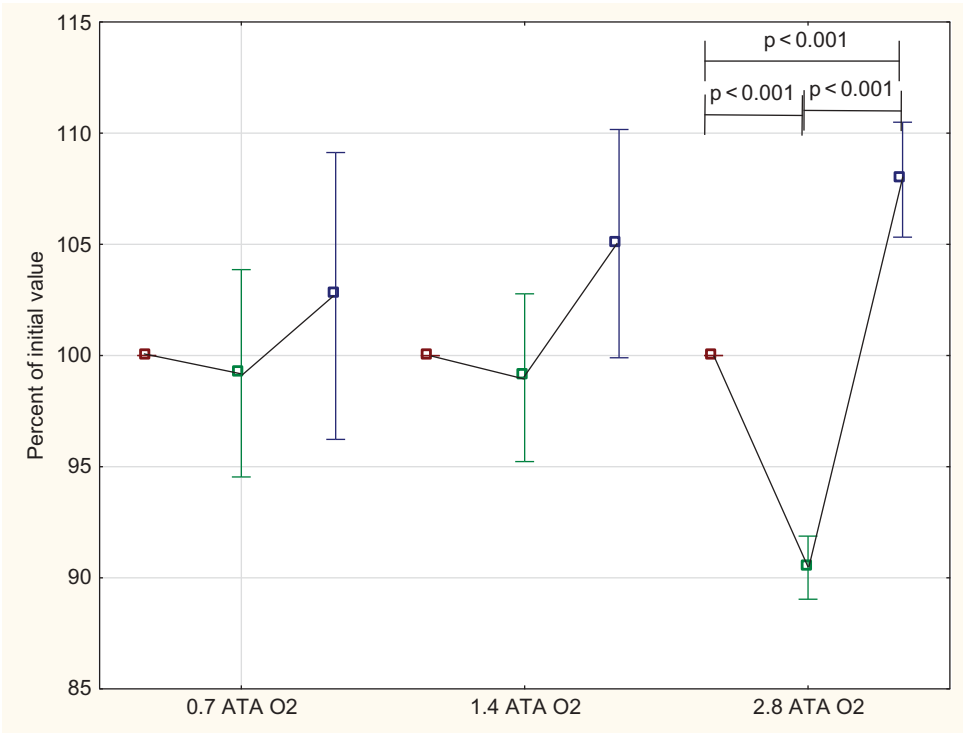

Figure 2. Relative changes of heart rate (HR; measured as percentage of initial value) between measurements at different oxygen exposures. For each oxygen exposure, three measurements are shown: (a) before starting exposure (baseline); (b) before the end of exposure while still under pressure (hyperbaric oxygenation, HBO); and (c) after exposure. ATA = atmosphere absolute.

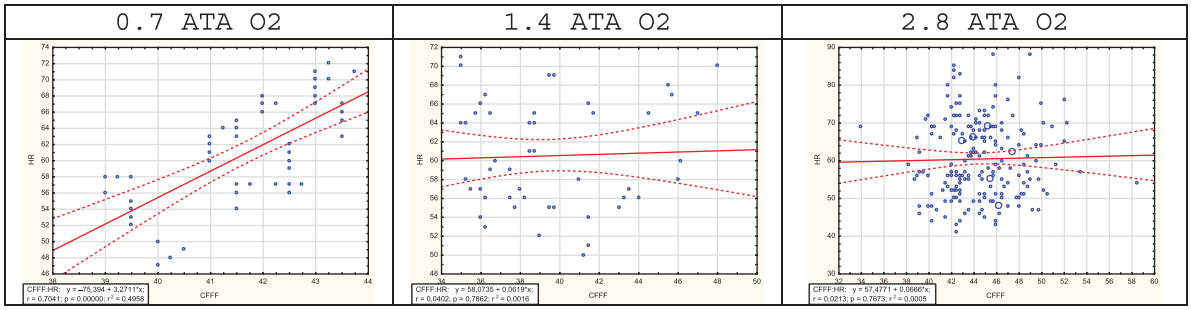

Figure 3. Correlation between heart rate (HR) and the critical flicker fusion frequency (CFFF) between measurements at different oxygen exposures. For each oxygen exposure, three measurements are shown: (a) before starting exposure (baseline); (b) before the end of exposure while still under pressure (hyperbaric oxygenation, HBO); and (c) after exposure. ATA = atmosphere absolute. To view a color version of this figure, please see the online issue of the Journal.

range of O_2 doses on neuronal excitability in human.

First, we would like to highlight a few methodological issues. In this study, we aimed to assess the effect of hyperoxia at three O_2 levels: 0.7 ATA, representative for therapeutic use and shallow dives; 1.4 ATA, encountered by professional and technical divers, close to the upper limit set for recreational divers; and 2.8 ATA, delivered during oxygen tolerance test to assess the immunity of the CNS to O_2 toxicity (Table 1). The 1.4-ATA and 2.8-ATA exposures were performed using 100% O_2 to eliminate any confounding effects of inert gases, like hyperbaric nitrogen narcosis. There might have still been some influence of the ambient pressure. However, in the 1.4-ATA HBO exposure, the ambient pressure was very low (1.4 ATA). Thus, it was unlikely to influence the results. In the 2.8-ATA HBO exposure, the ambient pressure decreased neural cell excitability (Garcia et al., 2010a, 2010b). Therefore, if there had been any influence of the ambient pressure, it might have caused an underestimation rather than an overestimation of the O_2-induced effect. In NBO conditions, the subjects breathed 0.3-ATA nitrogen. However, this partial pressure of nitrogen (PPN_2) is less than half of the normal value (PPN_2 of 0.8 ATA while breathing air at sea level), so it is safe to assume that such a nitrogen level does not induce any narcosis. Moreover, the main dose effect was observed between HBO 1.4 and 2.8 ATA at pure O_2.

Although it might be seen as a limitation, in this study we aimed at assessing the influence of NBO and HBO on neuronal excitability and A&A in highly trained individuals who are representative of the professional groups frequently exposed to NBO and HBO, like professional divers, high-altitude military pilots, and astronauts. For these reasons, the study results might not be representative for the wider population. But it should be taken into account that the oxygen tolerance test can be performed only in these professional groups. Groups at 0.7 and 1.4 HBO ATA were relatively small. Baseline values differed between sample groups and required normalization to 100%. Nevertheless, all participants were well matched in terms of profession, health status, and age group. Finally, the CFFF tests at 1.4 ATA HBO and 2.8 ATA HBO yielded quantitative (change in direction) rather than qualitative difference that would significantly strengthen the analysis.

Functional magnetic resonance (fMRI) studies showed that normobaric hyperoxia (NBO, 0.3 ATA O_2) during verbal or visuospatial tasks increased activation of brain areas associated with cognitive processing (Choi et al., 2010; Chung et al., 2004). There have been several reports demonstrating that short-term NBO (from 0.3 ATA to 1.0 ATA O_2) has a positive influence on cognitive abilities such as memory and visuospatial and verbal abilities (Chung et al., 2006; Moss & Scholey, 1996; Moss, Scholey, & Wesnes, 1998; Scholey, Moss, Neave, & Wesnes, 1999; Scholey, Moss, & Wesnes, 1998). Hemelryck, Rozloznik, Germonpre, Balestra, and Lafere (2013) demonstrated that under normobaric conditions, CFFF might show similar results to simple cognitive tests. In our study, however, exposure to NBO (0.7 ATA) did not produce any statistically significant change in A&A. Jammes et al. (2003) showed that HBO elicited neuromuscular hyperexcitability in normal volunteers, which was, however, attenuated in elite oxygen military divers due to frequent intermittent HBO exposures. There is no clear explanation for this long-term adaptation to HBO, but it has been suggested that changes in gene expression and molecular signaling may play a role (Dean, Mulkey, Garcia, Putnam, & Henderson, 2003). In this study, we recruited

subjects from the elite Special Forces unit of the Polish Army. Oxygen diving is included in their training curricula. Therefore, it is likely that the effect described by Jammes et al. (2003) took place. Several authors proposed that raised O_2 pressure might produce a narcotic effect (Hesser, Fagraeus, & Adolfson, 1978; R. A. Smith & Paton, 1976; Thomas, 1974). However, most of the reports refer to O_2 pressures above 3.0 ATA. The reports describing effects of HBO below 3.0 ATA are relatively rare (Dean et al., 2003). Hesser et al. (1978) suggested that 1.65 ATA HBO exerted a detrimental effect on cognition. Alternatively, cerebral vasoconstriction is a well-recognized mechanism that might protect brain from oxygen excess (Winklewski, Kot, Frydrychowski, Nuckowska, & Tkachenko, 2013). It has been shown by measurement of the cerebral blood flow velocity that such vasoconstriction is related to partial pressure of oxygen, but—on the other side—this effect is only about 15–20%, and the brain is still hyperoxygenated (Koch et al., 2013; Visser, Van Hulst, Wieneke, & Van Huffelen, 1996). Therefore, the relation between vasoconstriction and oxygen toxic effect remains unclear. Simultaneously, short-term HBO augments relative brain perfusion distribution mainly in the dominant hemisphere, with a cerebral blood flow increase in the neural networks involving dorsal and ventral attention pathways (Micarelli, Jacobsson, Larsson, Jonsson, & Pagani, 2013). Taken together, any protective mechanism, either molecular or vasoconstrictive, might explain no change in neuronal excitability at 0.7 ATA O_2 and CFFF reduction at 1.4 ATA O_2 in our professional group, while lack of such protective mechanisms may lead to CFFF increase in normal subjects at 1.0 ATA O_2 (Hemelryck et al., 2013). It is well established that severe HBO can cause neurotoxic effects from twitches to generalized seizures (Donald, 1947). In our study, the CFFF test was performed under the extreme but standardized conditions of the oxygen tolerance test. It has been recently demonstrated that the acute exposure of rat hippocampal slices to either HBO 2.84 ATA or 4.54 ATA stimulates synchronous orthodromic activity in CA1 neurons, which includes activation of oxygen-induced potentiation and, in some cases, hyperexcitability (Garcia et al., 2010a, 2010b). Obviously, it is not an easy task to translate results obtained from rat hippocampal slices to human brain. Nevertheless, we observed an increase in A&A after 30 minutes of HBO exposure at 2.8 ATA. This result suggests that at 2.8 ATA HBO, the narcotic effect of oxygen seen at 1.4 ATA is overcome by the overall CNS hyperexcitability. Interestingly, Lavoute, Weiss, Risso, and Rostain (2014) demonstrated biphasic oxygen effect on dopamine release in nigro striatal pathway in rats. It should be noted that dopamine release in nigro striatal pathway is regulated by the glutamate, GABA, NMDA, and NO interplay—that is, by the same factors as those that are involved in the long-term potentiation phenomenon. Furthermore, activation of NMDA receptors and subsequent NO production increase have been proposed to play a role in the neurotoxicity induced by hyperbaric exposure in primary rat cortical cultures (Huang et al., 2000). Taken together, this may indicate that oxygen-induced brain poisoning and increase in neuronal excitability measured by CFFF may use the same or intertwined cellular signaling pathways. When hyperoxia persists after an initial fall in cerebral blood flow due to vasoconstriction, there is a secondary increase in cerebral blood flow when the vasoconstriction is overwhelmed. As a consequence, toxic amounts of oxygen are delivered to the brain. Such secondary cerebral blood flow increase always precedes O_2-induced manifestations of brain poisoning, both in animals (Chavko, Braisted, Outsa, & Harabin, 1998; Demchenko, Boso, O'Neill, Bennett, & Piantadosi, 2000; Demchenko, Oury, Crapo, & Piantadosi, 2002; Demchenko, Ruehle, Allen, Vann, & Piantadosi, 2009) and in humans (Koch et al., 2008) and is caused by increased NO production. We may speculate that augmented neuronal excitability seen in CFFF may actually precede increase in cerebral blood flow and reflect disturbed glutamate/GABA balance amplified by augmented NO production.

In a series of studies in the 1970s, B. C. Lacey and J. I. Lacey (B. C. Lacey & Lacey, 1974; J. I. Lacey & Lacey, 1970) demonstrated that tasks requiring cognitive processing were associated with HR acceleration. Furthermore, memory improvements during muscle tension-induced arousal were accompanied by accelerated HR (Nielson, Radtke, & Jensen, 1996). Both HR and oxygen consumption were increased in subjects who played a video game or performed complex mental arithmetic (Turner & Carroll, 1985). It has been observed that HR acceleration is correlated with decrease of the response time of a visual matching task in childrn with attention deficit hyperactivity disorder (ADHD; Kim et al., 2014). Scholey et al. (1999) demonstrated that HR during cognitive testing was also accelerated in subjects exposed to NBO (1.0 ATA O_2). Similarly, we observed a correlation between CFFF and HR in low oxygen exposure (0.7 ATA). Furthermore, significant correlations were described between SiO_2 and cognitive performance during NBO exposures

(0.9–1.0 ATA O_2) in normal (Scholey et al., 1999) and elderly (Choi et al., 2013) adults. In this study, we observed a weak correlation between SiO_2 and CFFF in low oxygen (0.7 ATA).

Use of oxygen for modification of neuronal excitability is potentially of great interest not only in sport/recreational diving activities, but also in other high-demand physical and psychological tasks, including competitive sports, military, and aviation. Observed dose–reaction relations between oxygen and cognitive functions can be used for further studies in this field in humans, giving additional information on influence of oxygen on brain functions, including, for example, interaction with narcotic effect of nitrogen or pressure effect (high-pressure neurological syndrome). Oxygen pressure of 1.4 ATA is very frequent among recreational and professional divers. Our results, drawn from observation of the highly trained oxygen divers, indicate that such exposure is associated with a significant risk of oxygen-induced A&A deterioration, which persists for at least 30 minutes after the end of exposure.

CONCLUSIONS

We have proven that the effect of O_2 on neuronal excitability as measured by CFFF in young, healthy, and highly trained men is dose dependent: NBO at 0.7 ATA does not seem to affect CFFF, CFFF is significantly jeopardized at 1.4 ATA HBO, while CFFF recovers at 2.8 ATA. With 2.8 ATA HBO, the neuronal excitability and oxygen poisoning transduction pathways might be intertwined. In NBO, there was a dependency of CFFF on HR and SiO_2. Further studies are warranted to investigate the HBO influence on the CNS cognition and poisoning pathways.

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REFERENCES

Balestra, C., Lafère, P., & Germonpré, P. (2012). Persistence of critical flicker fusion frequency impairment after a 33 mfw SCUBA dive: Evidence of prolonged nitrogen narcosis? *European Journal of Applied Physiology*, *112*, 4063–4068.

Bliss, T. V., & Lomo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *Journal of Physiology*, *232*, 331–356.

Chavko, M., Braisted, J. C., Outsa, N. J., & Harabin, A. L. (1998). Role of cerebral blood flow in seizures from hyperbaric oxygen exposure. *Brain Research*, *791*, 75–82.

Choi, M. H., Kim, H. J., Kim, J. H., Kim, H. S., Choi, J. S., Yi, J. H., … Chung, S. C. (2013). Correlation between cognitive ability measured by response time of 1-back task and changes of SpO2 by supplying three different levels of oxygen in the elderly. *Geriatrics & Gerontology International*, *13*, 384–387.

Choi, M. H., Lee, S. J., Yang, J. W., Choi, J. S., Kim, H. S., Kim, H. J., … Chung, S. C. (2010). Activation of the limbic system under 30% oxygen during a visuospatial task: An fMRI study. *Neuroscience Letters*, *471*, 70–73.

Chung, S. C., Iwaki, S., Tack, G. R., Yi, J. H., You, J. H., & Kwon, J. H. (2006). Effect of 30% oxygen administration on verbal cognitive performance, blood oxygen saturation and heart rate. *Applied Psychophysiology and Biofeedback*, *31*, 281–293.

Chung, S. C., Tack, G. R., Lee, B., Eom, G. M., Lee, S. Y., & Sohn, J. H. (2004). The effect of 30% oxygen on visuospatial performance and brain activation: An fMRI study. *Brain and Cognition*, *56*, 279–285.

Dean, J. B., Mulkey, D. K., Garcia, A. J., III, Putnam, R. W., & Henderson, R. A., III (2003). Neuronal sensitivity to hyperoxia, hypercapnia, and inert gases at hyperbaric pressures. *Journal of Applied Physiology*, *95*, 883–909.

Demchenko, I. T., Boso, A. E., O'Neill, T. J., Bennett, P. B., & Piantadosi, C. A. (2000). Nitric oxide and cerebral blood flow responses to hyperbaric oxygen. *Journal of Applied Physiology*, *88*, 1381–1389.

Demchenko, I. T., Oury, T. D., Crapo, J. D., & Piantadosi, C. A. (2002). Regulation of the brain's vascular responses to oxygen. *Circulation Research*, *91*, 1031–1037.

Demchenko, I. T., & Piantadosi, C. A. (2006). Nitric oxide amplifies the excitatory to inhibitory neurotransmitter imbalance accelerating oxygen seizures. *Undersea & Hyperbaric Medicine*, *33*, 169–174.

Demchenko, I. T., Ruehle, A., Allen, B. W., Vann, R. D., & Piantadosi, C. A. (2009). Phosphodiesterase-5 inhibitors oppose hyperoxic vasoconstriction and accelerate seizure development in rats exposed to hyperbaric oxygen. *Journal of Applied Physiology*, *106*, 1234–1242.

Donald, K. W. (1947). Oxygen poisoning in man; signs and symptoms of oxygen poisoning. *British Medical Journal*, *1*, 712–717.

Garcia, A. J., III, Putnam, R. W., & Dean, J. B. (2010a). Hyperbaric hyperoxia and normobaric reoxygenation increase excitability and activate oxygen-induced potentiation in CA1 hippocampal neurons. *Journal of Applied Physiology*, *109*(3), 804–819.

Garcia, A. J., III, Putnam, R. W., & Dean, J. B. (2010b). Hyperoxic stimulation of synchronous orthodromic activity and induction of neural plasticity does not require changes in excitatory synaptic transmission. *Journal of Applied Physiology*, *109*, 820–829.

Hemelryck, W., Rozloznik, M., Germonpre, P., Balestra, C., & Lafere, P. (2013). Functional comparison between critical flicker fusion frequency and simple cognitive tests in subjects breathing air or

oxygen in normobaria. *Diving and Hyperbaric Medicine*, *43*, 138–142.

Hesser, C. M., Fagraeus, L., & Adolfson, J. (1978). Roles of nitrogen, oxygen, and carbon dioxide in compressed-air narcosis. *Undersea Biomedical Research*, *5*, 391–400.

Hindmarch, I. (1982). Critical flicker fusion frequency (CFFF): The effects of psychotropic compounds. *Pharmacopsychiatry*, *15*, 44–48.

Huang, K. L., Wu, J. N., Lin, H. C., Mao, S. P., Kang, B., & Wan, F. J. (2000). Prolonged exposure to hyperbaric oxygen induces neuronal damage in primary rat cortical cultures. *Neuroscience Letters*, *293*, 159–162.

Jammes, Y., Arbogast, S., Faucher, M., Montmayeur, A., Tagliarini, F., Meliet, J. L., & Robinet, C. (2003). Hyperbaric hyperoxia induces a neuromuscular hyperexcitability: Assessment of a reduced response in elite oxygen divers. *Clinical Physiology and Functional Imaging*, *23*, 149–154.

Kahlbrock, N., Butz, M., May, E. S., Brenner, M., Kircheis, G., Häussinger, D., & Schnitzler, A. (2012). Lowered frequency and impaired modulation of gamma band oscillations in a bimodal attention task are associated with reduced critical flicker frequency. *NeuroImage*, *61*, 216–227.

Kim, H. J., Kim, H. S., Choi, M. H., Lee, I. H., Hong, S. P., You, N. R., … Yi, J. H. (2014). Response time of visual matching task and heart rate in children with attention deficit hyperactivity disorder (ADHD). *Bio-medical Materials and Engineering*, *24*, 987–991.

Koch, A. E., Kähler, W., Wegner-Bröse, H., Weyer, D., Kuhtz-Buschbeck, J., Deuschl, G., & Eschenfelder, C. C. (2008). Monitoring of CBFV and time characteristics of oxygen-induced acute CNS toxicity in humans. *European Journal of Neurology*, *15*, 746–748.

Koch, A. E., Koch, I., Kowalski, J., Schipke, J. D., Winkler, B. E., Deuschl, G., … Kähler, W. (2013). Physical exercise might influence the risk of oxygen-induced acute neurotoxicity. *Undersea & Hyperbaric Medicine*, *40*, 155–163.

Kot, J., Sicko, Z., & Wozniak, M. (2003). Oxidative stress during oxygen tolerance test. *International Maritime Health*, *54*, 117–126.

Lacey, B. C., & Lacey, J. I. (1974). Studies of heartrate and other bodily processes in sensorimotor behaviour. In P. A. Obrist, A. H. Black, J. Brener, & L. V. DiCara (Eds.), *Cardiovascular psychophysiology*. Chicago, IL: Aldine.

Lacey, J. I., & Lacey, B. C. (1970). Some autonomic-central nervous system interrelationships. In P. Black (Ed.), *Physiological correlates of emotion*. New York, NY: Academic Press.

Lafère, P., Balestra, C., Hemelryck, W., Donda, N., Sakr, A., Taher, A., … Germonpré, P. (2010). Evaluation of critical flicker fusion frequency and perceived fatigue in divers after air and enriched air nitrox diving. *Diving and Hyperbaric Medicine*, *40*, 114–118.

Lavoute, C., Weiss, M., Risso, J. J., & Rostain, J. C. (2012). Mechanism of action of nitrogen pressure in controlling striatal dopamine level of freely moving rats is changed by recurrent exposures to nitrogen narcosis. *Neurochemical Research*, *37*, 655–664.

Lavoute, C., Weiss, M., Risso, J. J., & Rostain, J. C. (2014). Alteration of striatal dopamine levels under various partial pressure of oxygen in pre-convulsive and convulsive phases in freely-moving rats. *Neurochemical Research*, *39*, 287–294.

Lavoute, C., Weiss, M., & Rostain, J. C. (2006). Effects of NMDA administration in the substantia nigra pars compacta on the striatal dopamine release before and after repetitive exposures to nitrogen narcosis in rats. *Undersea & Hyperbaric Medicine*, *33*, 175–179.

Lu, S., Cai, Y., Shen, M., Zhou, Y., & Han, S. (2012). Alerting and orienting of attention without visual awareness. *Consciousness and Cognition*, *21*, 928–938.

Maffei, A. (2011). The many forms and functions of long-term plasticity at GABAergic synapses. *Neural Plasticity, 2011*, 9p.

Massaad, C. A., & Klann, E. (2011). Reactive oxygen species in the regulation of synaptic plasticity and memory. *Antioxidants & Redox Signaling*, *14*, 2013–2054.

Micarelli, A., Jacobsson, H., Larsson, S. A., Jonsson, C., & Pagani, M. (2013). Neurobiological insight into hyperbaric hyperoxia. *Acta Physiologica*, *209*, 69–76.

Moss, M. C., & Scholey, A. B. (1996). Oxygen administration enhances memory formation in healthy young adults. *Psychopharmacology*, *124*, 255–260.

Moss, M. C., Scholey, A. B., & Wesnes, K. (1998). Oxygen administration selectively enhances cognitive performance in healthy young adults: A placebo-controlled double-blind crossover study. *Psychopharmacology*, *138*, 27–33.

Nielson, K. A., Radtke, R. C., & Jensen, R. A. (1996). Arousal-induced modulation of memory storage processes in humans. *Neurobiology of Learning and Memory*, *66*, 133–142.

Rota-Bartelink, A. (1999). The diagnostic value of automated flicker threshold perimetry. *Current Opinion in Ophthalmology*, *10*, 135–139.

Scholey, A. B., Moss, M. C., Neave, N., & Wesnes, K. (1999). Cognitive performance, hyperoxia, and heart rate following oxygen administration in healthy young adults. *Physiology & Behavior*, *67*, 783–789.

Scholey, A. B., Moss, M. C., & Wesnes, K. (1998). Oxygen and cognitive performance: The temporal relationship between hyperoxia and enhanced memory. *Psychopharmacology*, *140*, 123–126.

Smith, J. M., & Misiak, H. (1976). Critical flicker frequency (CFF) and psychotropic drugs in normal human subjects—A review. *Psychopharmacologia*, *47*, 175–182.

Smith, R. A., & Paton, W. D. (1976). The anesthetic effect of oxygen. *Anesthesia and Analgesia*, *55*, 734–736.

Thomas, J. R. (1974). Combined effects of elevated pressures of nitrogen and oxygen on operant performance. *Undersea Biomedical Research*, *1*, 363–370.

Turner, J. R., & Carroll, D. (1985). Heart rate and oxygen consumption during mental arithmetic, a video game, and graded exercise: Further evidence of metabolically-exaggerated cardiac adjustments? *Psychophysiology*, *22*, 261–267.

Tytla, M. E., Trope, G. E., & Buncic, J. R. (1990). Flicker sensitivity in treated ocular hypertension. *Ophthalmology*, *97*, 36–43.

Vallée, N., Rissoe, J. J., & Blatteau, J. E. (2011). Effect of an hyperbaric nitrogen narcotic ambience on arginine and citrulline levels, the precursor and co-product of nitric oxide, in rat striatum. *Medical Gas Research*, *1*, 16.

Vallée, N., Rostain, J. C., Boussuges, A., & Risso, J. J. (2009). Comparison of nitrogen narcosis and helium pressure effects on striatal amino acids: A

microdialysis study in rats. *Neurochemical Research*, *34*, 835–844.

Vallée, N., Rostain, J. C., & Risso, J. J. (2009). How can an inert gas counterbalance a NMDA-induced glutamate release? *Journal of Applied Physiology*, *107*, 1951–1958.

Vallée, N., Rostain, J. C., & Risso, J. J. (2010). A pressurized nitrogen counterbalance to cortical glutamatergic pathway stimulation. *Neurochemical Research*, *35*, 718–726.

Visser, G. H., Van Hulst, R. A., Wieneke, G. H., & Van Huffelen, A. C. (1996). Transcranial Doppler sonographic measurements of middle cerebral artery flow velocity during hyperbaric oxygen exposures. *Undersea & Hyperbaric Medicine*, *23*, 157–165.

Winklewski, P. J., Kot, J., Frydrychowski, A. F., Nuckowska, M. K., & Tkachenko, Y. (2013). Effects of diving and oxygen on autonomic nervous system and cerebral blood flow. *Diving and Hyperbaric Medicine*, *43*, 148–156.