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Abstract	One of the possible risks incurred while diving is inert gas narcosis (IGN), yet its mechanism of action remains a matter of controversy. Although providing insights in the basic mechanisms of IGN, research has been primarily limited to animal studies. A human study, in real diving conditions, was needed. Twenty volunteers within strict biometrical criteria (male, age 30–40 years, BMI 20–23, non smoker) were selected. They performed a no-decompression dive to a depth of 33 mfw for 20 min and were assessed by the means of critical flicker fusion frequency (CFFF) measurement before the dive, during the dive upon arriving at the bottom, 5 min before the ascent, and 30 min after surfacing. After this late measurement, divers breathed oxygen for 15 min and were assessed a final time. Compared to the pre-dive value the mean value of each measurement was significantly different ($p < 0.001$). An increase of CFFF to 104 ± 5.1 % upon arriving to the bottom is followed by a decrease to 93.5 ± 4.3 %. This impairment of CFFF persisted 30 min after surfacing, still decreased to 96.3 ± 8.2 % compared to pre-dive CFFF. Post-dive measures made after 15 min of oxygen were not different from control (without nitrogen supersaturation), 124.4 ± 10.8 versus 124.2 ± 3.9 %. This simple study suggests that IGN (at least partially) depends on gas-protein interactions and that the cerebral impairment persists for at least 30 min after surfacing. This could be an important consideration in situations where precise and accurate judgment or actions are essential.

Keywords (separated by '-')	Diving - Inert gas narcosis - Critical flicker fusion frequency
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ORIGINAL ARTICLE

Persistence of critical flicker fusion frequency impairment after a 33 mfw SCUBA dive: evidence of prolonged nitrogen narcosis?

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Abstract One of the possible risks incurred while diving is inert gas narcosis (IGN), yet its mechanism of action remains a matter of controversy. Although providing insights in the basic mechanisms of IGN, research has been primarily limited to animal studies. A human study, in real diving conditions, was needed. Twenty volunteers within strict biometrical criteria (male, age 30–40 years, BMI 20–23, non smoker) were selected. They performed a no-decompression dive to a depth of 33 mfw for 20 min and were assessed by the means of critical flicker fusion frequency (CFFF) measurement before the dive, during the dive upon arriving at the bottom, 5 min before the ascent, and 30 min after surfacing. After this late measurement, divers breathed oxygen for 15 min and were assessed a final time. Compared to the pre-dive value the mean value of each measurement was significantly different ($p < 0.001$). An increase of CFFF to 104 ± 5.1 % upon arriving to the bottom is followed by a decrease to 93.5 ± 4.3 %. This impairment of CFFF persisted 30 min after surfacing, still decreased to 96.3 ± 8.2 % compared to pre-dive CFFF. Post-dive measures made after 15 min of oxygen were not different from control (without nitrogen supersaturation), 124.4 ± 10.8 versus 124.2 ± 3.9 %. This simple study suggests that IGN (at least partially) depends on gas-protein interactions and that the cerebral impairment persists for at least 30 min after surfacing. This could be an important consideration in situations where precise and accurate judgment or actions are essential.

Keywords Diving · Inert gas narcosis · Critical flicker fusion frequency

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Introduction

Although SCUBA (self-contained underwater breathing apparatus) diving is relatively safe, one of the possible risks incurred is inert gas narcosis (IGN), also called "nitrogen narcosis" or rapture of the depths.

IGN can provoke several troubles (Lowry 2005; Richardson et al. 2005) such as temporal and spatial disorientation, physical coordination alteration, mood disorders, loss of long term memory. Symptoms of IGN resemble alcohol intoxication or the early stage of anesthesia or hypoxia (Dean et al. 2003). As depth and pressure increase, the symptoms worsen and eventually lead to unconsciousness (Bennett 2004; Pastena et al. 2005).

Although in 1935 Behnke et al. (1935) correctly associated these phenomena to a raised partial pressure of nitrogen, its precise mechanism of action remains a matter of controversy. For long, inert gas narcosis was regarded as a pure biophysical phenomenon and it was assumed that breathed nitrogen did not interact biochemically with the cellular metabolism (Bennett 2004; Lowry 2005). The traditional view was that narcosis or anesthesia occurred

Journal : Large 421 | Dispatch : 26-3-2012 | Pages : 6
Article No. : 2391 | ☐ LE | ☐ TYPESET
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when the volume of a hydrophobic membrane site was caused to expand beyond a critical level by the absorption of molecules of a narcotic gas. The observation of the pressure reversal effect during general anesthesia has long supported this lipid theory (Jibu 2001; Wlodarczyk et al. 2006). However, results of the most recent animal studies have revealed that nitrogen narcosis could interact with the production, release and uptake of several brain neurotransmitters supporting a protein binding theory (Rostain et al. 2011).

In rats, neurochemical studies in the striatum have demonstrated that a rise in nitrogen partial pressure induced a decrease in dopamine release (Dedieu et al. 2004), a decrease of glutamate concentration (Vallee et al. 2009, 2010), and also enhanced gamma-aminobutyric acid (GABA-A) receptors activity (Balon et al. 2002; David et al. 2001; Lavoute et al. 2008).

Because of the paucity of the literature a human study in real diving conditions was needed to confirm that changes in human brains parallel the observations made in vivo in the rodent brain. However reliable indices to quantify the effects of inert gas narcosis are not yet available. Ideally, these indices should be reproducible, less subject- or investigator-dependent than a psychometric behavioral approach, based on observing a change in neurological parameters like electroencephalographic recordings (Pastena et al. 2005) but easy to implement underwater. The critical flicker fusion frequency (CFFF) seems to answer these needs. It is a tool that has already been used in the field of diving medicine research (Seki and Hugon 1976). The CFFF variations occur parallel to EEG modifications and may reveal neuropsychological troubles that are not apparent from subjective reports (Seki and Hugon 1976). The use of such measure is advocated by the particular characteristics of the CFFF: non invasive and of good reliability in cortical arousal (Hou et al. 2007; Rota-Baterlink 1999) as well as a good marker of cortical alteration to physical workload (Davranche and Pichon 2005; Luczak et al. 1995; Luczak and Sobolewski 2005), drug administration (Hindmarch 1982; Hunter et al. 1994), alcohol intoxication (Leigh 1982; Liu and Ho 2010; Schillaci and Fazio 1967), anesthesia (Salib et al. 1992; Sharma et al. 2011; Wernberg et al. 1980), hypoxia (Truszczynski et al. 2009) or in case of encephalopathy (Ali et al. 1994; Chang et al. 2007; Kircheis et al. 2002; Lauridsen et al. 2011). Using the CFFF, we performed an objective measurement of the effects of IGN in divers.

Materials and methods

After written informed consent and Ethics Committee approval (CE2008/66), 20 male experienced divers (Minimum certification "Autonomous Divers" according to European norm EN 14153-2 or ISO 24801-2 with at least 50 logged dives) volunteered for this study. They were selected from a large sports diver population in order to obtain a group of comparable age [30–40 years, 35.38 ± 3.59 (mean ± SD)], body composition (BMI between 20 and 25, 23.6 ± 1.15) and comparable health status: non smokers with regular but not excessive physical activity (aerobic exercise one to three times a week). Prior to entry into the study, they were assessed fit to dive. Divers needing visual correction underwater and divers taking any medications such as steroids, benzodiazepine, barbiturates, or psychoactive drugs were excluded. Participants were instructed not to dive 72 h prior to the experimental dive and not to drink any alcoholic or caffeine-containing beverages 4 h before the dive.

Each diver performed a dive to a depth of 33 mfw for 20 min in a pool environment (Nemo33, Brussels, Belgium) with a water temperature of 33 °C, thus needing no thermal protection suit. This depth-time profile falls within accepted "no-decompression limits" (NAVSEA 2008). Descent speed was at 15 m per minute and ascent speed was at 10 meters per minute to the surface, with no safety stop (none required according to the dive table used).

Divers were assessed with the CFFF using a specific watertight device built for the occasion by Human Breathing Technology (HBT, Trieste, Italy). The device consists of a rotating ring, surrounding a short cylindrical waterproof housing of 8 cm diameter containing the numeric (digital) frequency indicator. Attached to this housing is a flexible cable, on the end of which a single blue LED (Light Emitting Diode) (color temperature 8,000 K) is enclosed in a smaller cylindrical container (to shield it from stray light and reflections). While the subject to be tested is looking straight at the LED light at a distance individually adapted to his personal vision (generally around 50 cm), the investigator turns the dial slowly clockwise or anticlockwise in order to increase or decrease the flickering frequency of the LED. As there are no markings on the dial, nor a visible "starting position", the test subject has no indication whatsoever of the actual flicker frequency. When the subject sees a change from fusion to flicker (or flicker to fusion), he signals this to the investigator, who notes the actual frequency—which is the definition of CFFF (Rota-Baterlink 1999; Tytla et al. 1990). This test is carried out systematically three times in order to check its reproducibility. The average of the three measurements was noted as the actual individual CFFF. Divers were assessed immediately before the dive (baseline), upon arriving at the bottom, 5 min before the ascent (after 15 min at 33 mfw), and 30 min after surfacing. Once the late measurement was made, the diver breathed oxygen for 15 min (using a non-rebreather mask at a flow of 15 L per minute) and then CFFF was assessed a final time.

Journal : Large 421 Dispatch : 26-3-2012 Pages : 6
Article No. : 2391 LE TYPESET
MS Code : EJAP-D-11-00679 CP DISK

We furthermore performed a control experiment, where the same individuals were assessed with CFFF before and after 15 min of oxygen breathing without any dive scheduled or performed within a 3 days period in order to assess any oxygen effect in absence of nitrogen supersaturation.

Taking the initial value as 100 %, percentage variations were calculated allowing an appreciation of the magnitude of the change rather than the absolute values. Standard statistical analysis was performed after testing for normality, using GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA, USA) on a personal computer.

Results

All sets of data passed both Kolmogorov–Smirnov and Shapiro–Wilk normality tests, allowing us to assume a Gaussian distribution.

The evolution of CFFF during and after the dive is illustrated in Fig. 1. Compared to the pre-dive value (100 %) the mean value of each measurement is significantly different. An increase of CFFF to 104.0 ± 5.1 % when arriving to the bottom is followed 15 min later by a decrease to 93.5 ± 4.3 %. This impairment of CFFF persists 30 min after surfacing, being still decreased to 96.3 ± 8.2 % compared to the pre-dive CFFF (100 %). Each single measurement is statistically different from the baseline (one sample t test $p < 0.05$ or lower). Paired t test demonstrated a statistical difference between the first and second underwater measurement ($p < 0.001$), but no statistical difference between the second underwater measurement and the post-dive measurement ($p = 0.099$). After 15 min of oxygen breathing, CFFF increases significantly ($p < 0.0001$) and is 117.9 ± 9.8 % higher than the pre-dive CFFF (Paired t test, $p < 0.001$).

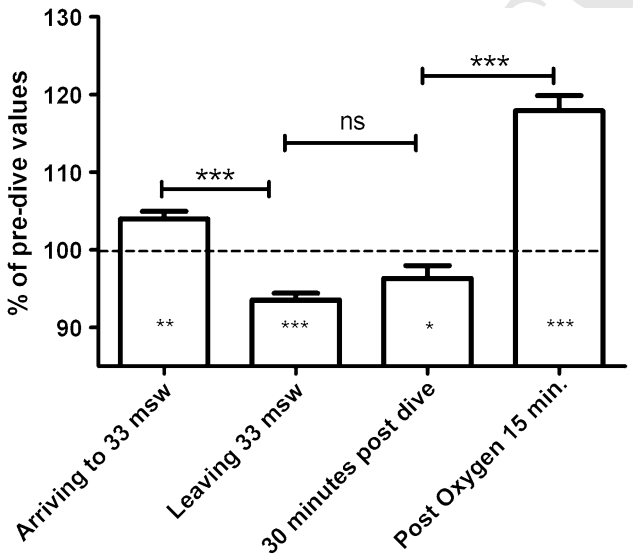

Fig. 1 Percentage variation of CFFF during and after a 20 min dive to 33 mfw/110 ffw. Pre-dive CFFF value is taken as 100 %. Each subject is compared to his own pre-dive value. (***$p < 0.001$; **$p < 0.01$; *$p < 0.05$; *ns* not significant) ($n = 20$)

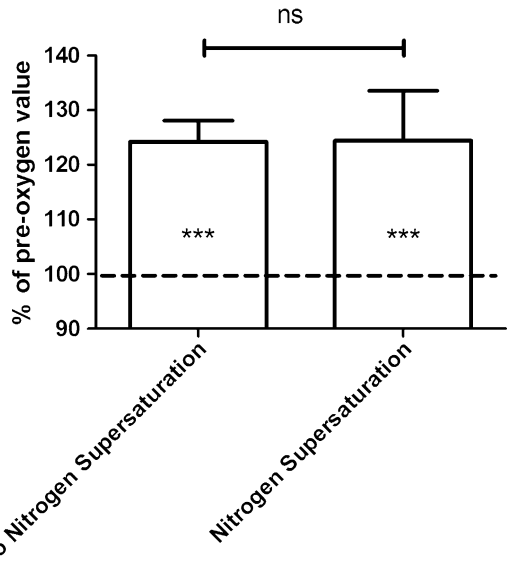

Fig. 2 Variation of CFFF after 15 min of oxygen breathing with and without diving. Pre-oxygen breathing CFFF value is taken as 100 % (when diving, pre-oxygen value is the post-dive value). Each subject is compared to his own pre-oxygen value. (***$p < 0.0001$; *ns* not significant) ($n = 20$)

When non nitrogen supersaturated (Fig. 2), compared to the pre-oxygen value (100 %), an increase of CFFF up to 124.2 ± 3.9 % was noted which was statistically significant (one sample t test, $p < 0.001$). When diving (with nitrogen supersaturation) we took the post-dive pre-oxygen value as a new baseline to compare the oxygen effect with the control experiment (without nitrogen supersaturation). With this new baseline, the increase (124.4 ± 10.8 % observed after oxygen breathing in the post-dive period) is statistically not different from the non nitrogen saturated increase (paired t test, $p = 0.72$). This suggests that the post-dive, post-oxygen increase of CFFF is due to a direct effect of oxygen rather than to a supplemental nitrogen washout effect by oxygen.

Discussion

Indices to quantify the effects of IGN can be roughly divided into two approaches.

The first is a behavioral approach, measuring task performance such as mental arithmetic, memory, reaction time and manual dexterity. Although these behavioral studies have confirmed a progressive deterioration with increasing pressure, many of these tests have been criticized because

Journal : Large 421 | Dispatch : 26-3-2012 | Pages : 6
Article No. : 2391 | LE | TYPESET
MS Code : EJAP-D-11-00679 | CP | DISK

of the influences of motivation, experience and learning on the test results (Lowry 2005).

The second approach relies on observing a change in objective, measurable neurological parameters. In this matter, even if there are some limitations (Rota-Baterlink 1999; Tytla et al. 1990), some authors have emphasized the advantages of CFFF assessment (Davranche and Pichon 2005; Luczak and Sobolewski 2005; Truszczynski et al. 2009) as an objective, quantitative, and important method for measuring alertness and arousal (Feshchenko et al. 1994; Ginsburg et al. 1982; Luczak and Sobolewski 2000; Railton et al. 2009). Moreover, CFFF seems to be a better way of testing cerebral arousal than the classical behavioral approach as in anesthesia, CFFF has been demonstrated to parallel brain impairment earlier than subjective symptoms (Salib et al. 1992; Wernberg et al. 1980) or behavioral tests (number connection test A and B, digit symbol test, serial dotting test, and line tracing test) (Sharma et al. 2011). When executed in standard conditions, the CFFF test makes it possible to measure in a longitudinal way the evolution of the state of cortical arousal in test subjects (Luczak and Sobolewski 2005). The construction of a waterproof housing for the CFFF test device, designed to keep the test subject fully blinded to the frequency read-out of the flickering LED, has allowed for the first time "real-life" measurements of CFFF while under water.

The results of this study are also unique because to our knowledge, it is the first time that effect of inert gas narcosis is measured for a period of time after surfacing. One of the most remarkable observations was undoubtedly that the CFFF results at the 30 min post-dive time point demonstrated impairment of cerebral arousal persisting long after surfacing. Indeed, based on the lipid theory (Jibu 2001; Wlodarczyk et al. 2006), diver's training programs advise that in the event of nitrogen narcosis, divers should ascend a few meters in order for the narcotic effects to dissipate rapidly. However, it is shown here that, even if subjective feelings of narcosis may rapidly abate, the cerebral impairment persists for at least 30 min after surfacing. This may be an important consideration in situations where precise and accurate judgment or actions are essential, such as in the hazardous situations in recreational diving or in professional (industrial, military) diving.

Recent observations suggest that there is a correlation between CFFF and post-dive perceived fatigue. In a previous study (Lafere et al. 2010) we have shown that in a large group of divers ($n = 219$), the change in perceived fatigue level after a single dive is significantly lower when enriched air Nitrox (EANx) was breathed rather than air which was demonstrated with a post-dive decrease of CFFF while breathing air and a slight post-dive increase while breathing EANx. The only difference between these two groups resided in the different proportion of oxygen/nitrogen in the breathing mixture, emphasizing the importance of the effect of these two gases on brain function. Indeed, electroencephalographic recordings of subjects exposed to compressed atmosphere in a pressure chamber in which the partial pressure of both oxygen and nitrogen were controlled, showed that any changes observed were related to the oxygen partial pressure and that the depressant effect of nitrogen is only revealed when a mixture containing a partial pressure of 0.2 ATA of oxygen is breathed (Pastena et al. 2005).

As oxygen seems to be the most important gas, it has to be remembered that hyperoxia has been shown to facilitate nerve conduction, possibly as a consequence of oxidative stress (Brerro-Saby et al. 2010). An enhanced production of reactive oxygen species (ROS) alters the conductance of potassium channels in excitable cells (Kovachich et al. 1981; Matalon et al. 2003). Oxygen is also known to interact with GABA neurotransmission by influencing the synthesis, secretion, and recapture of this neurotransmitter. Indeed, when rat hippocampal slices are deprived of oxygen and glucose, GABA levels increase rapidly and then normalize within 15 min of reoxygenation (Radomski and Watson 1973; Schwartz-Bloom and Sah 2001). Finally, oxygen acts on the production of ammonia (NH_3) by desamination of catecholamines, tending to decrease the cerebral concentration of GABA (Banister and Singh 1981). The consequence of all these mechanisms could be among others an increased inhibition of the inhibitory cerebral pathways.

These mechanisms have been studied in hyperbaric hyperoxia, and are able to provoke "hyperoxic" seizures as a result of imbalance between glutaminergic and GABAergic synaptic function (Demchenko and Piantadosi 2006). However, even in "normobaric hyperoxia" ($PpO_2 \leq 1$ ATA) this effect can be measured (Zhang et al. 1993). Abraini et al. (2003) have also emphasize the possible significant role of GABA (A) receptor as their results support a selective antagonism of the narcotic action of nitrogen.

The CFFF measurements, before and after oxygen breathing in non-divers, seem to confirm the effect of oxygen on cerebral arousal. CFFF increased by almost 25 % compared to baseline measurements. This same effect could be responsible for the increased CFFF observed in the beginning of the dive. While at 33 mfw depth, divers breathing air actually breathe a gas with a PpO_2 of 0.9 ATA (Dalton's Law: 21 % × 4.3 ATA), which is almost equivalent to breathing pure oxygen at surface. It could also be a good explanation for the effect of post-dive oxygen breathing, as the increase from the CFFF at 30 min post-dive is also 24.4 %. Although an accelerated nitrogen washout (denitrogenation) effect cannot formally be excluded, the similarity in CFFF increase is striking.

Journal : Large 421 | Dispatch : 26-3-2012 | Pages : 6
Article No. : 2391 | ☐ LE | ☐ TYPESET
MS Code : EJAP-D-11-00679 | ☑ CP | ☑ DISK

Moreover, the progressive reduction of the CFFF in the course of the dive seems to suggest a competition between the effect of oxygen and the effect of nitrogen. With time at depth, brain nitrogen concentrations increase up to a sufficient level within the effect-site and narcosis sets in, as measured by the reduction of CFFF after 15 min into the dive. Upon return to surface, blood nitrogen concentrations return to baseline, but the persistent reduction of CFFF shows that that the narcotic effects dissipate only slowly. Breathing oxygen after surfacing again decreases the inhibitory pathways, restoring CFFF to a supra-normal level.

Although these phenomena are quite complex, this study, carried out in real diving condition, provides an objective and reproducible measurement and makes it possible to suggest some conclusions, namely that nitrogen narcosis seems indeed to depend partly on a gas-protein interaction and that the system seems to be adaptive. Further studies may shed more light on the complex phenomena involved in the functional changes of the nervous system in the diving environment.

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Journal : Large 421 | Dispatch : 26-3-2012 | Pages : 6
Article No. : 2391 | LE | TYPESET
MS Code : EJAP-D-11-00679 | CP | DISK

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Journal : Large 421 | Dispatch : 26-3-2012 | Pages : 6
Article No. : 2391 | ☐ LE | ☐ TYPESET
MS Code : EJAP-D-11-00679 | ☑ CP | ☑ DISK