Early detection of diving-related cognitive impairment of different nitrogen-oxygen gas mixtures using critical flicker fusion frequency

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Abstract
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Introduction: Cognitive impairment related to inert gas narcosis (IGN) is a threat to diving safety and operations at depth that might be reduced by using enriched air nitrox (EANx) mixtures. Using critical flicker fusion frequency (CFFF), a possible early detection of cognitive abilities/cerebral arousal impairment when breathing different oxygen (O_2) fractions was investigated.
Methods: Eight male volunteers performed, in random order, two dry chamber dives breathing either air or EANx40 (40% O_2–60% nitrogen) for 20 minutes (min) at 0.4 MPa. Cognition and arousal were assessed before the dive; upon arrival at 0.4 MPa; after 15 min exposure at 0.4 MPa; on surfacing and 30 min post-dive using behavioural computer-based testing psychology experiment building language (PEBL) and by CFFF while continuously recording brain oxygenation with near-infrared spectroscopy.
Results: In both breathing conditions, CFFF and PEBL demonstrated a significant inverse correlation (Pearson r of -0.90, $P < 0.0001$), improved cognitive abilities/cerebral arousal occurred upon arrival at 0.4 MPa followed by a progressive deterioration. Initial brain activation was associated with a significant increase in oxyhaemoglobin (HbO_2) and a simultaneous decrease of deoxyhaemoglobin (HHb). The magnitude of the changes was significantly greater under EANx ($P = 0.038$).
Conclusions: Since changes were not related to haemodynamic variables, HbO_2 and HHb values indicate a significant, O_2-dependent activation in the prefrontal cortex. Owing to the correlation with some tests from the PEBL, CFFF could be a convenient measure of cognitive performance/ability in extreme environments, likely under the direct influence of oxygen partial pressure, a potent modulator of IGN symptoms.

Introduction

Although considered safe, there are some inherent risks to scuba diving. For instance, under hyperbaric conditions, nitrogen accumulates within the human body and is responsible for a neurologic syndrome that includes alterations of cognitive functions, motor control and mood states. Individual susceptibility varies widely but all divers eventually will be impaired.[1] As a consequence, these associated cognitive and motor impairments may increase the risks of injury and reduce working performance. According to *Project Stickybeak*, seeking to document all diving fatalities in Australia, inert gas narcosis (IGN) was directly responsible for 9% of those fatalities.[2]

No accurate depth of onset of IGN has ever been proven satisfactorily because of a wide individual variation in onset and/or divers' lack of insight into behavioural manifestations of narcosis in themselves during diving. For instance, it was demonstrated recently, that although objectively impaired as assessed by a computerized test battery, it was not possible for blinded divers to identify the gas they had just breathed.[3] Narcosis is not simply an objective measurable phenomenon; it also has a subjective facet.[4] Indeed, metacognitive awareness (defined as cognition about cognition) and cognitive performance can become dissociated.[5] However, although divers may be aware of this impairment, and could potentially compensate for it, the ability or willingness of divers to implement control procedures was not as good at deeper depths.[5] This has major safety implications. Indeed, individuals unable to either accurately assess whether they are impaired, or unable to implement compensatory control procedures in response to a preserved accurate metacognitive judgment, are at risk of failing to adopt compensatory strategies and behaviours to avoid accidents. Therefore, reliable indices to quantify the effects or identify pre-symptomatic effect of IGN are needed but not yet available.

Based on animal models,[6] it is now commonly accepted that the narcotic action of inert gases is responsible for an impairment of cognitive abilities and control, where cognitive control is defined as a system of processes that maintain the ability to interact with the environment in a goal-driven manner, with flexibility and constantly adapting behaviour to the changing environment.[7] Behavioural studies have indeed confirmed a progressive deterioration with increasing pressure. Although amenable to mitigation through study design, many of these tests have been criticized because of the influences of motivation, experience and learning which may improve task performances over the course of testing.[8] A computer-based cognitive approach may now be possible underwater,[9] although its assessment has been limited to shallow depth and might not be practical in operational circumstances. Hence there is a need for a simple, non-invasive but objective tool.

Since a recent study using event-related brain potentials suggested that cerebral arousal influenced both proactive and reactive cognitive control, an alternative measurement such as critical flicker fusion frequency (CFFF) may prove useful. Indeed, it has been demonstrated that CFFF could follow the recovery of cognitive function after propofol sedation earlier than psychometric testing.[10] This kind of correlation between mental state, CFFF and electroencephalography (EEG) has also been proposed recently in a world-class chess player, who showed parallel increases in CFFF threshold and theta Fz/alpha Pz ratio.[11] In another recent study CFFF and attentional performance were closely related, with a tight relationship between the CFFF and occipital gamma band activity both in frequency and power.[12] Under normobaric conditions, CFFF has been correlated to a computer-based assessment of cognitive function obtained from the psychology experiment building language battery test (PEBL), but with a less complicated set-up.[13]

Testing the CFFF device under hyperbaric condition was then an opportunity to question some divers' habits. Although air is the most commonly used breathing gas during diving, alternative gas mixtures, such as enriched air nitrox (EANx) are increasingly used in scuba diving. This alternative employs a lower nitrogen (N_2) content and higher oxygen (O_2) content than air, partly justified to reduce the risks of IGN. Interaction between O_2 and N_2 is poorly understood. One study suggests a correlation between individual sensitivity to nitrogen narcosis and protection by N_2 against cerebral O_2 toxicity in rats,[14] which allows the hypothesis of an individual O_2 limit in mixed-gas diving based on the diver's sensitivity to IGN. However, few comparative studies of air and EANx on IGN are available. Some human studies have reported worse psychomotor performance when using pure O_2 or EANx,[15] whilst others reported that narcotic impairment was the same, EANx and air being only differentiated on the basis of metacognitive assessment.[16]

The aims of this study were twofold; firstly, to understand cognitive performance variation under several standardized hyperbaric breathing conditions with different oxygen partial pressures (PO_2) and secondly, to investigate the value of CFFF under hyperbaric conditions as a potential early warning tool useful for the working diver.

Materials and methods

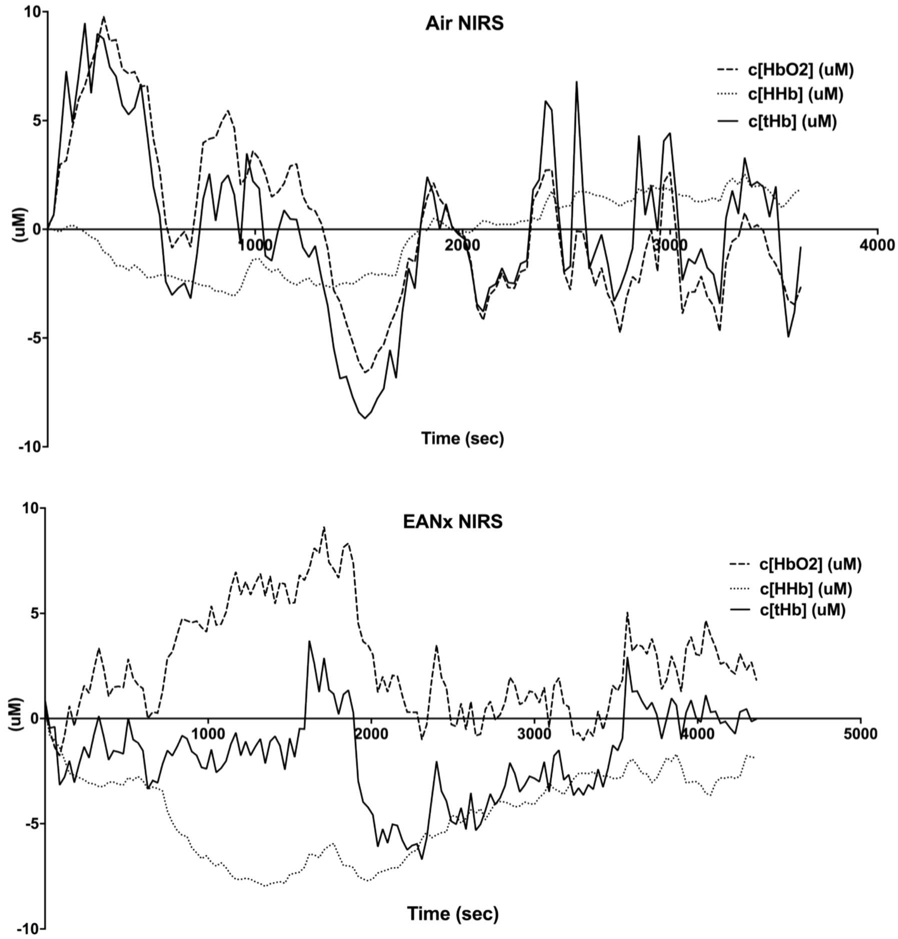
Experimental procedures were conducted in accordance with the Declaration of Helsinki and were approved by the Academic Ethical Committee of Brussels (Belgium) (Ethic committee B 200-2011-5). The study protocol has also passed all Clinical Trial Application validation rules (EudraCT Number: 2011-004596-37). All subjects were recruited from a large sports diver population (age between 30 and 40 years, body mass index (BMI) between 20 and 25 $kg{\cdot}m^{-2}$ and in good health) as described in detail previously.[8] Methods and potential risks were explained to the eight selected male volunteers (certified according to European norm EN 14153-2 or ISO 24801-2 and for EANx-diving) who gave their written, informed consent prior to the experiment. Divers taking psychoactive drugs, or who had dived 72 hours prior to the experimental dive or had imbibed alcoholic or caffeinated beverages within four hours before the experimental dive were excluded.

EXPERIMENTAL PROTOCOL

All dives were dry dives, simulated in the hyperbaric chamber (Haux-Starmed 2800, Haux-Life-Support Gmbh, Karlsbad-Ittersbach, Germany) at the Centre of Hyperbaric Oxygen Therapy, Military Hospital 'Queen Astrid', Brussels, Belgium. On separate occasions, each subject performed, in random order, either a compressed air dive or an EANx40 (40% oxygen–60% nitrogen) dive. The inspired gases were delivered via a tight-fitting mask connected to the Haux-Oxymaster system which includes inspiratory and expiratory regulators. To avoid any bias, gas composition was monitored using a Haux-Oxysearch (Haux-Life-Support Gmbh, Karlsbad-Ittersbach, Germany). Subjects were blinded to the breathing gas.

Figure 1

Example of time plot of cerebral oxygenation after elimination of artefacts measured through oxyhaemoglobin (HbO_2 – dashed line), deoxyhaemoglobin (HHb – dotted line) and total haemoglobin (tHb – solid line) while breathing either air or enriched-air nitrox (EANx); the average of each value is calculated on a sample of 120 seconds (test time) concurrent with other measures



The dive profile was designed to produce narcosis: a seven-minute (min) compression time to 0.405 MPa; a 22-min bottom time and a 12-min linear decompression (0.033 MPa·min^{-1}) to the surface including a 3-min safety stop at 0.13 MPa. This profile is within accepted 'no-decompression' and O_2 toxicity limits for both gas mixes. The profile was managed by an experienced chamber technician according to the procedure described previously.[3]

Divers were assessed, in the seated position, for higher cognitive functions using CFFF with a specifically designed watertight device (Human Breathing Technology, Trieste, Italy) as fully described previously,[8] and a computerized test battery (the psychology experiment building language - PEBL) specifically chosen to track deterioration in visual-perceptual organization, visual-motor coordination as well as integration, and visual memory. The tests (maths-processing, trail-making and perceptual vigilance) were chosen based on previous work.[3,13]

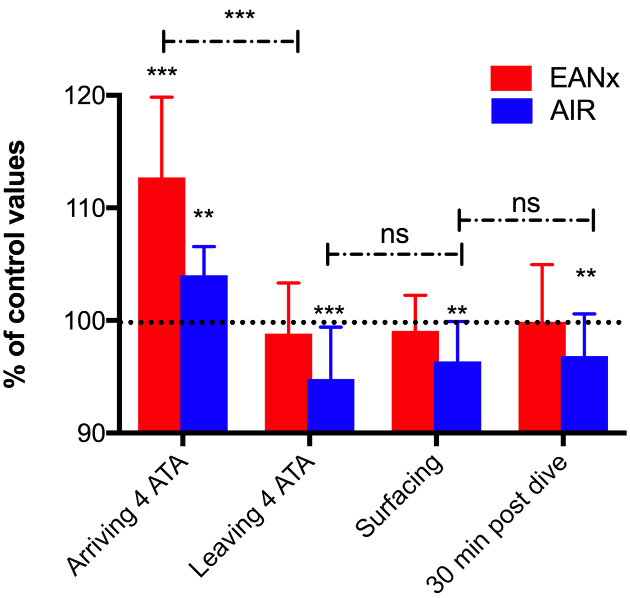
Divers were tested immediately before the dive (baseline), immediately upon arriving at 0.4 MPa, after 15 min at depth, when surfacing (i.e., at atmospheric pressure), and 30 min after surfacing. Since divers usually breathe EANx only during the dive, both baseline and 30 min post-dive measurements were made while breathing atmospheric air for all dives (air and EANx).

NEAR-INFRARED SPECTROSCOPY (NIRS)

Oxygenation of the prefrontal cortex, which plays an important role in cognitive control, in the ability to orchestrate thought and action in accordance with internal goals, was assessed with continuous recording of brain NIRS (Nimo [laser continuous wave near-infrared tissue oxymeter], NIROX srl, Brescia, Italy). NIRS data analysis is adapted from technical data established for functional magnetic resonance imaging (MRI). There are substantial differences between the two methods in particular the impact of the specific noise related to NIRS methodology. In the context of functional MRI related to task execution, error or noise is defined as all non-correlated activities in particular those related to head movements. They represent a critical obstacle to reliable statistical inference with a consequent

Figure 2

Percentage variation of CFFF during and after a dry chamber dive for 22 minutes at 0.4 MPa (4 ATA) breathing either air or enriched-air nitrox (EANx); pre-dive values normalized to 100%; each subject is compared to his own pre-dive value; ** $P < 0.01$; *** $P < 0.001$; ns – not significant ($n = 8$, means and SDs shown)



significant statistical bias toward false positives.[17] Therefore, for each individual recording (Figure 1), the curve was inspected to remove all artefacts in order to achieve effective statistical inference.[18] Then, the average of each value is calculated on a sample of 120 seconds concurrent with other measures. Functional challenge of the brain by task execution is accompanied by regional changes in cerebral blood flow, volume and oxygenation which can be monitored through the use of NIRS. When the brain is stimulated, in this case by the PEBL testing, this induces an increase in oxyhaemoglobin (HbO_2) and a decrease in deoxyhaemoglobin (HHb). According to the literature, brain activation is occurring when, compared to the baseline value, a two to threefold increase of HbO_2 accompanied by a similar decrease in HHb is observed.[19] Therefore, the whole literature reports HHb/HbO_2 changes as variations in percentage compared to a normalized baseline observation. We assumed the same method to report concurrent CFFF changes. The total O_2 index (TOI), defined as the ratio of oxygenated to total tissue haemoglobin, was also recorded. This measure reflects cerebral oxygenation to a high degree of sensitivity and specificity.[20]

ULTRASONIC MONITORING AND HAEMODYNAMICS

Finally, bubble load was evaluated 30 min post dive according to the Brubakk-Eftedal classification,[21] using a Vivid 7 echograph equipped with a GE 3S-RS sector array ultrasound probe (GE Healthcare, UK). The machine was used in harmonic imaging mode (2.0/4.0 MHz) to reduce noise in the cardiac cavities. Haemodynamic variables (blood pressure and heart beat) were also monitored through the whole experimentation.

STATISTICAL ANALYSIS

Since all data passed the Kolmogorov-Smirnov test, allowing us to assume a Gaussian distribution, they were analysed by means of repeated measures ANOVA with Bonferroni's multiple comparison tests comparing the effects of pressure (0.4 MPa vs. 15 min at 0.4 MPa vs. upon surfacing vs. 30 min post-dive) and breathing gas (Air vs. EANx), two-ways ANOVA and paired *t*-tests. After normalising the pre-dive values to 100%, percentage changes were calculated for each parameter, allowing an appreciation of the magnitude of change between each measurement rather than the absolute values. Existence of a correlation was assessed through a Pearson test and linear regression. All tests were performed using a standard computer statistical package, GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego California USA). A threshold of $P < 0.05$ was considered statistically significant. All data are presented as mean ± standard deviation (SD).

Results

The mean age of the eight subjects was 35.38 ± 3.59 years; BMI 23.68 ± 1.15 $kg{\cdot}m^{-2}$, weight 71.4 ± 9.5 kg and height 1.77 ± 0.06 m.

CRITICAL FLICKER FUSION FREQUENCY

The evolution of CFFF during and after the dive is illustrated in Figure 2. When breathing air, each single measurement is statistically different from the baseline (one-sided *t*-test $P < 0.01$ or lower), while with EANx, only the first measurement is statistically different from baseline (one sample t test, $P < 0.0001$). When breathing air, there was an increase in CFFF when arriving at maximal pressure (104 ± 9.8 % of baseline) followed 15 min later by a decrease (95 ± 4.6 % of baseline). This impairment in CFFF persisted when surfacing (97 ± 3.5 % of baseline) and 30 min after surfacing, being still decreased to 97 ± 3.8 % compared to the pre-dive CFFF (100 %). When breathing EANx, similar changes were seen, with an increase (113 ± 7.1 % of baseline) followed by a decrease. However, this decrease was followed by a return back to baseline (99 ± 3.3%).

Repeated measures ANOVA followed by paired t-tests with a Bonferroni adjustment demonstrated a statistical difference between the first and second measurement at 'depth' in both conditions ($P < 0.001$, F (9, 171) = 16.6), but no statistical difference between the following measurements ($P > 0.05$). A two-way ANOVA analysis shows that gas accounted for 11.6% of the total variance ($P = 0.0001$, F (1.56) = 17) while time accounted for 47% of the total variance ($P < 0.0001$, F (3.56) = 23.15). Gas mix had the same effect at all time values as interaction accounted for a mere 3% of the total variance ($P = 0.218$, F (3.56) = 1.52).

Figure 3

Correlation calculation and linear regression of the magnitude of CFFF change and time to complete in a math processing and a trail-making task during air (A) or enriched-air nitrox (EANx) (B) breathing under pressure (0.4 MPa)

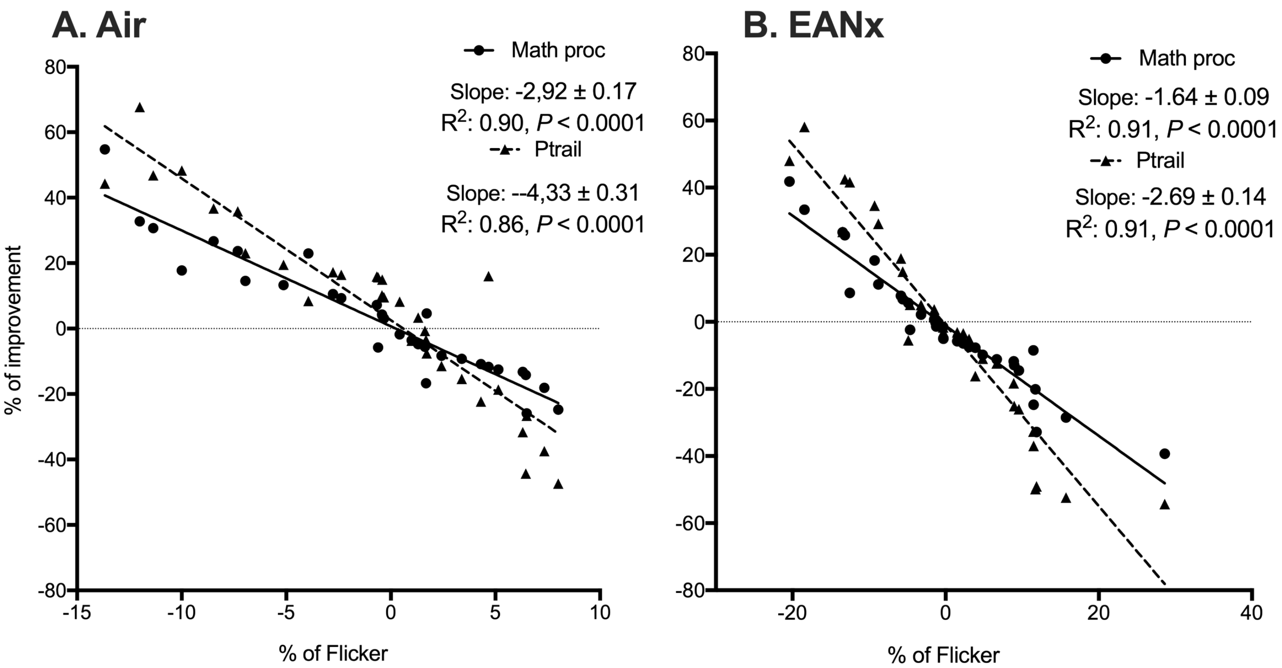
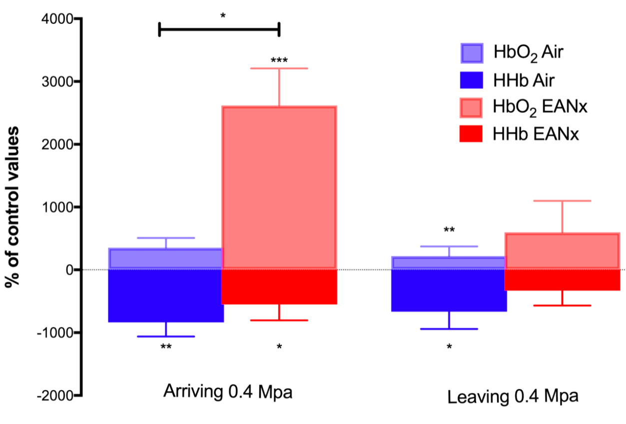


Figure 4

Variation of HbO_2 and HHb under pressure (0.4 MPa); pre-dive values normalized to 100%; each subject is compared to his own pre-dive value; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; ($n = 8$, means and SDs shown)



PSYCHOLOGY EXPERIMENT BUILDING LANGUAGE

PEBL results have already been published in detail elsewhere.[3] For all three tests (maths-processing, trail-making and perceptual vigilance) the error rates were stable throughout the whole experiment for both gas mixes. After an initial improvement in the times to complete the three tasks there were progressive deteriorations (increased time to complete) that lasted up to the 30-min post-dive test. The magnitude of CFFF changes and the times to completion in both the maths-processing and trail-making tasks were inversely correlated with air (Pearson r -0.90 and -0.86 respectively, $P < 0.0001$ in both tests; Figure 3A) and with EANx (Pearson r -0,91, $P < 0.0001$ in both tests; Figure 3B). This relation is further confirmed by linear regression (Figure 3).

NEAR-INFRARED SPECTROSCOPY

Arrival at maximal pressure is associated with a significant brain activation while breathing EANx was characterized by an increase in HbO_2 (2619 ± 590%, $P < 0.001$) and a simultaneous decrease in HHb (550 ± 253%, $P = 0.027$). These results are, by definition, associated with brain activation.[19] Similar activation is present while breathing air (HbO_2 354 ± 154% increase; HHb 836 ± 225% decrease). However, only the decrease of HHB is significant ($P < 0.01$, F (15, 72) = 1.377). The difference between the two gases is significant, EANx being associated with greater brain activation than air (ANOVA, $P = 0.038$, F (3, 19) = 0.785). Data collection beyond the measurements at depth was incomplete owing to a technical problem related to the Nimo Device buffer memory, with a loss of almost 40% of the data for the 30-min post dive measurement. Whilst there appears to be a trend thereafter characterized by a progressive return to baseline followed by brain inhibition, these data are not reported, only the two observations at depth being shown in Figure 4. The TOI remained stable throughout the experiment (Air: 2.22 ± 1.3 μM; EANx 2.89 ± 4 μM, $P = 0.343$).

ULTRASONIC MONITORING AND HAEMODYNAMICS

Precordial cardiac echography at 30 min post dive failed to demonstrate any bubble production (Grade 0, Brubakk-

Eftedal classification[21]). Heart rate and mean blood pressure were essentially identical for the two dives (P = 0.99, ANOVA, F (5, 33) = 0.03).

Discussion

Since IGN can eventually lead to unconsciousness, there is a need for underwater neurocognitive performance testing to identify pre-symptomatic cognitive impairment, affording the diver at depth a tool to improve their safety. This is especially true since subjective assessment (metacognition) does not meet the criteria of reliability[3] or alternatively does not guarantee proper implementation of appropriate goal-directed behaviour/coping strategies.[5] To investigate such a tool, one needs to assume a correlation between cognitive performance, measured with task performance such as mental arithmetic, memory, reaction time or manual dexterity (PEBL in this study) with physiological indexes that more accurately monitor mental workload/arousal (CFFF in this study). This correlation has already been demonstrated under normobaric conditions.[13] In the present study, the regression graph also shows a significant inverse correlation between CFFF and the time to completion of the chosen PEBL tasks under hyperbaric conditions. This correlation should come as no surprise, as a recent study using event-related brain potentials as indicators of the use of cognitive control, demonstrated that arousal has the potential to influence both proactive (active maintenance of contextual information to optimally bias attention, perception and action systems in a goal-driven manner) and retroactive control (retrieval of context information mobilized only as needed, especially after detection of a high interference event).[22] High arousal has been reported to decrease proactive control and increase reactive control compared to low arousal.[22]

Altogether, this suggests that these tests (PEBL and CFFF) might be considered comparable in providing assessment of cortical functions in both conditions, air and EANx. One study demonstrated that CFFF was a unique predictor of executive function across different age groups (means 21.7 vs. 72.4 years) and accounted for unique variance in performance above and beyond age and global cognitive status.[23] Nonetheless, even if there were a direct relationship between cortical arousal as measured by CFFF and cognitive performance, there is ample evidence of the nonlinear (inverted U-shape) relationship between arousal and cognitive performance (Yerkes-Dodson Law[24]), predicting declining performance at higher than optimal arousal levels, particularly in more complex cognitive tasks.[25] However, this should not be seen as a limitation in the case of scuba diving as arousal and cognitive performance deteriorate progressively during exposure to pressure rather than improving.

Although, the understanding of the result is simple: the lower the CFFF threshold, the lower the cerebral arousal, some limitations might apply. Indeed, since CFFF measurements are influenced by many factors (intensity of ambient light, flicker frequency modulation, the amplitude of the modulation, the average intensity of the illumination, the wavelength or colour of the LED and the position of the stimulus on the retina), no conclusions can be made on absolute values, hence the choice of assessing the magnitude of change. This also implies that this method, in its present form, is only suitable for studies where each candidate is his own control. Moreover, to compare studies or start multicentre experiments, a standardised, easily available device is required, which is lacking currently.

Because a small cohort was used, further research is needed to identify a clinically relevant cut-off for CFFF, namely a variation value, individually parameterized, indicating a cognitive impairment incompatible with safety of the monitored diver. Once identified, this cut-off could be implemented in a robotic system such as the ROAD project (Robotics for Assisted Diving)[26] or the CADDY project (Cognitive Autonomous Diving Buddy),[27] which aims to develop an intelligent system able to supervise in a semi-automatic way the activities performed by underwater operators. This would allow, as in other situations where safety is of concern, reliable monitoring and assessment of the current status and performance of operational divers.

The observed changes are characterized by an initial increase of cerebral arousal when arriving at 0.4 MPa, which is followed 15 min later by a progressive deterioration. However, although similar in form, there was a significant difference between the two gases, EANx being associated with greater brain activation than air and likely less late-dive/post-dive impairment. Therefore, we hypothesized that a higher fraction of inspired oxygen (EANx40, PO_2 = 162 kPa; air, PO_2 = 81 kPa at 0.4 MPa) had a beneficial effect on arousal and cognitive performance. Indeed, short-term normobaric O_2 (maximum 101 kPa O_2) influenced cognitive abilities such as memory, visuospatial and verbal abilities in a positive manner,[28] whilst functional MRI studies have demonstrated that normobaric hyperoxia (30 kPa O_2) during verbal or visual tasks increases the activation of brain areas associated with cognitive processing.[29]

In divers, an association between changes in response times and changes in CFFF suggest that divers susceptible to IGN may also be susceptible to the effects of elevated PO_2.[30] Also, even a small reduction in PN_2, associated with a conservative dive profile, resulted in a modest beneficial effect of EANx28 (28% O_2–72% N_2) on performance that may contribute to diving safety.[31] This hypothesis is supported by the NIRS measurements, although it could be argued that these results do not correspond to cerebral activation but to a variation in haemodynamics. However, measurements of blood pressure and heart rate did not vary throughout or between the two dives.

Since the TOI remained stable throughout the experiment, this indicates that total haemoglobin was neither increased nor decreased, which, in the absence of variation in total blood volume, means that cerebral haemodynamics remained constant. The 'oxygen hypothesis' (above) is also consistent with experimental models of neurotransmission. Although the exact mechanisms are still debated, based on animal studies on neurochemical data on IGN,[6] it is now accepted that inert gases exert their effects by influencing the synthesis, secretion and recapture of neurotransmitters, mainly dopamine, glutamate and gamma-aminobutyric acid (GABA),[6] whilst O_2 facilitates nerve conduction and interacts with GABA neurotransmission.[32] Recent data obtained from trainee pilots using magnetic resonance spectroscopy demonstrated that higher striatal concentrations of GABA and glutamate/glutamine were related to superior performance in action control allowing differentiation between high and normal performers.[33]

However, given the available data on the subject, it would be an error to consider that O_2 only elicits brain activation. According to one study, the effects on neuronal excitability measured by CFFF of changes in PO_2 could be dose-dependent.[34] Oxygen at 93 kPa resulted in partial recovery of motor and memory reaction times in some hyperbaric conditions while caused incapacitation with amnesia in others.[35] In this latter study, even high PN_2 (up to 0.57 MPa) was well tolerated providing neither hypercapnia nor hyperoxia were present. These findings and those from the present study are not mutually exclusive, despite differences in study protocols (e.g., exercise vs. at rest). Given these limitations, future research should combine a computer-based approach (which is now possible underwater[9]) with objective measurements such as CFFF to study the effects of different inspired gas mixes on human cognitive performance and brain cortical function.

Conclusions

Under hyperbaric conditions, CFFF testing provided a global assessment of cerebral arousal/workload and correlated with some psychometric tests from the PEBL. CFFF could provide a convenient measure of cognitive performance/abilities in extreme environments and is simple to use. However, some limitations may apply, and confounding factors need to be controlled to ensure accuracy of the measurement. Oxygen appeared to be an important modulator of IGN. In accordance with the neurochemical theory of IGN, the net effect on cerebral performance appears to depend on a balance between the activating effects of O_2 and the inhibitory effects of N_2. However, other factors, such as carbon dioxide retention may be important and require further study.

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