Investigating critical flicker fusion frequency for monitoring gas narcosis in divers

Xavier CE Vrijdag[1,2], Hanna van Waart[1], Jamie W Sleigh[1,3], Costantino Balestra[4], Simon J Mitchell[1,5]

[1] *Department of Anaesthesiology, University of Auckland, Auckland, New Zealand*
[2] *Deep Dive Dubai, Dubai, United Arab Emirates*
[3] *Department of Anaesthesia, Waikato Hospital, Hamilton, New Zealand*
[4] *Environmental, Occupational and Ageing (Integrative) Physiology Laboratory, Haute Ecole Bruxelles-Brabant (HE2B), Brussels, Belgium*
[5] *Department of Anaesthesia, Auckland City Hospital, Auckland, New Zealand*

Corresponding author: *Xavier Vrijdag, Department of Anaesthesiology, School of Medicine, University of Auckland, Private bag 92019, Auckland 1142, New Zealand*
x.vrijdag@auckland.ac.nz

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Abstract
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Introduction: Critical flicker fusion frequency (CFFF) has been used in various studies to measure the cognitive effects of gas mixtures at depth, sometimes with conflicting or apparently paradoxical results. This study aimed to evaluate a novel automatic CFFF method and investigate whether CFFF can be used to monitor gas-induced narcosis in divers.
Methods: Three hyperbaric chamber experiments were performed: 1) Automated and manual CFFF measurements during air breathing at 608 kPa (n = 16 subjects); 2) Manual CFFF measurements during air and heliox breathing at sea level (101.3 kPa) and 608 kPa (n = 12); 3) Manual CFFF measurements during oxygen breathing at sea level, 142 and 284 kPa (n = 10). All results were compared to breathing air at sea level.
Results: Only breathing oxygen at sea level, and at 284 kPa, caused a significant decrease in CFFF (2.5% and 2.6% respectively compared to breathing air at sea level. None of the other conditions showed a difference with sea level air breathing.
Conclusions: CFFF did not significantly change in our experiments when breathing air at 608 kPa compared to air breathing at sea level pressure using both devices. Based on our results CFFF does not seem to be a sensitive tool for measuring gas narcosis in divers in our laboratory setting.

Introduction

The critical flicker fusion frequency (CFFF) has been used to quantify cognitive impairment in various environments and during exposures to drugs. CFFF is based on the phenomenon that the participant can perceive a flickering light as non-flickering if the frequency is above the 'fusion frequency'. By increasing or decreasing the frequency of the flickering light the fusion frequency can be determined. A decrease in fusion frequency is supposedly correlated with cognitive impairment,[1] whereas an increase in fusion frequency is interpreted as indicating improvement. For example, various hypnotic drugs decrease the CFFF, while an increase in CFFF can be achieved with stimulating drugs.[2]

In hyperbaric environments (underwater or in a hyperbaric chamber), CFFF has been used in studies exposing participants to various gas mixtures and pressures to investigate the narcotic effects (or lack thereof) of gases such as nitrogen,[3–7] helium[5,8] and oxygen.[9,10]

The CFFF device used in previous research involved the investigator in having to change the flicker frequency, communicate with the participant and write down the fusion frequency. In most research, the test is repeated three times in order to check its consistency. This method is time consuming and it is difficult to achieve simultaneous measurements in multiple participants. An automatic method for the estimation of the CFFF has been proposed.[11] A computerised device which tested stimuli at six constant frequencies multiple times in random order, estimates the peak frequency of the fitted sigmoidal response curve as the flicker fusion frequency. The measurement took six minutes on average, which is similar to the commercially available devices that use a flickering stimulus of steadily increasing or decreasing frequency. The downside of these devices is

the need for a connection to a personal computer to control the flickering light and to store the results, making this impossible to use in the hyperbaric and diving environment.

The initial primary goal of this study was to evaluate a new automated CFFF device by comparing its measurements of gas narcosis to those obtained using a manual system, prior to adopting the former device for pending gas narcosis studies. The results obtained during this comparison were inconsistent with expected CFFF variations; and hence a further two experiments were conducted with a manual device used by others in previous studies to re-evaluate changes in CFFF during exposure to hyperbaric air, heliox and oxygen, and its consequent use as an objective measure of narcosis. This study is part of a larger programme investigating novel approaches to measuring gas narcosis in divers.

Methods

This paper describes three experiments: 1) Automated and manual CFFF measurements during air breathing at sea level pressure and at 608 kPa; 2) Manual CFFF measurements during air and heliox breathing at sea level pressure and at 608 kPa; 3) Manual CFFF measurements during oxygen breathing at sea level pressure, 142 and 284 kPa.

The first experiment with the novel automated CFFF device took place at the hyperbaric facility at Deep Dive Dubai, in March 2018. The study protocol was approved by the Dubai Scientific Research Ethics Committee of the Dubai Health Authority, United Arab Emirates (reference 10/2017_06).

The second and third experiments with the conventional manual CFFF device took place at the Slark Hyperbaric Unit, Waitemata District Health Board, Auckland, New Zealand, in January–August 2019. The protocol of this randomised, cross-over study was approved by the Health and Disability Ethics Committee, Auckland (reference 16/NTA/93), and was registered with the Australian New Zealand Clinical Trial Registry (ANZCTR) with the Universal Trial Number U1111-1181-9722. These CFFF measurements were a sub-study in a larger body of work investigating use of quantitative electroencephalography to measure gas-induced narcosis that will be reported elsewhere.

PARTICIPANTS

Participants were certified, healthy adult divers, aged between 18 and 60 years and had normal visual acuity, either corrected or uncorrected. Exclusions were use of recreational drugs, tobacco, psychoactive medication, excessive alcohol (> 21 standard drinks per week) or over five caffeine-containing beverages a day. Participants abstained from any caffeinated drink on the measurement day, and from alcohol for at least 24 hours before the measurement. They had at least six hours of sleep the night before the measurement. Experiments two and three had as an additional requirement that participants were certified technical divers that were trained to do decompression dives, using oxygen as decompression gas. All participants provided written informed consent.

AUTOMATED CFFF DEVICE

The first experiment utilised a CFFF device suitable for hyperbaric environments built by Probe Embedded Solutions (Enschede, the Netherlands). The device could be controlled from the backside by an operator using three buttons and a small screen. The participants' side only had a cold white LED. This device had two modes: manual and automatic.

In manual mode both the operator and the participant held the CFFF device. The participant was instructed to hold the base of the device with one hand and point the LED towards the eye. Care was taken to minimise movement of the device and head of the participant during the experiment. With the other hand the participant raised a finger when he/she could see the LED flicker and lowered the finger when the LED was perceived not to flicker.

The manual mode started with a flickering frequency of 50 Hz, which was above the normal perceivable flicker frequency. The frequency could be decreased or increased by 0.5 Hz by the operator. The current frequency was not shown on the screen to blind the operator. The operator started the measurement by lowering the frequency until the participant raised their finger. This was repeated three times, the second and third recording started at two Hz above the previous fusion frequency; again with the frequency lowered until the participant raised their finger.

The automatic CFFF mode was programmed on the same device. The participant held the CFFF device with a finger on the reverse-side button and pointed the LED towards the eye. They pushed the button every time they perceived the LED to flicker.

The automatic mode started with a flickering frequency of 40 Hz, which is near the normal perceived flicker fusion frequency. The frequency was either increased (push of button) or decreased (no action for 2 seconds) in 8 iterations by a decreasing frequency step (respectively 20, 10, 5, 2.5, 1.25, 0.67, 0.33, 0.17 Hz). This resulted in a theoretical minimum and maximum CFFF between 0.17 (all decreased) and 79.83 (all increased) Hz. This was automatically repeated three times with a 0.5 second LED off interval.

For both manual and automatic modes, after the three recordings the results were displayed on the device including the mean frequency of the three CFFF recordings. The results were stored on an SD card for offline analysis. At the end of the three recordings the operator checked the results for errors, values outside of the physiological range, and repeated measurements if needed.

MANUAL CFFF DEVICE

The second and third experiments used a device previously used in a hyperbaric study.[7] This device had a blue LED visible to the participant, with two buttons and a screen (which displayed the current flicker frequency), not visible to the participant. The buttons increased and decreased the flicker frequency in 0.25 Hz steps. The participant held the device stable and minimised head movement while looking at the flickering light. The device was set to a starting frequency of 30 Hz, which was below the normal perceived flicker fusion frequency, and the participant confirmed that he/she could see the light flickering. The participant increased the frequency by holding the button, until the light was no longer perceived to flicker. This was considered the fusion frequency, which was recorded by the operator. This measurement was repeated till three recordings were within 1 Hz of each other (Figure 1).

EXPERIMENT ONE – AIR

The hyperbaric chamber was a rectangular 10-person chamber (Oxyheal 5000, National City, CA, USA). All measurements (including baseline measurements) were conducted inside the hyperbaric chamber with comfortable ambient light intensity held constant to minimise any biasing influence of ambient light. Both CFFF modes were recorded in random order while breathing environmental air, at sea level pressure immediately before compression, and at least five minutes after reaching 608 kPa (equivalent to 50 metres' seawater [msw] depth) (Figure 2). Participants were compressed in groups of 2–4 persons. Decompression was according to the US Navy decompression tables, including 100% oxygen breathing from 193 kPa to sea level pressure.

EXPERIMENT TWO – AIR AND HELIOX

The hyperbaric chamber was a cylindrical 5-person chamber (W.E. Smith Engineering PTY LTD, Australia). All measurements were conducted inside the hyperbaric chamber with constant comfortable ambient light intensity. Participants returned for two sessions at least 48 hours apart, breathing either air or heliox (20.8% oxygen, balance helium) in randomised order. CFFF was recorded inside the

Figure 1

Flow diagram of critical fusion frequency manual (left) and automatic (middle) modes during experiment one and manual mode (right) during experiments two and three

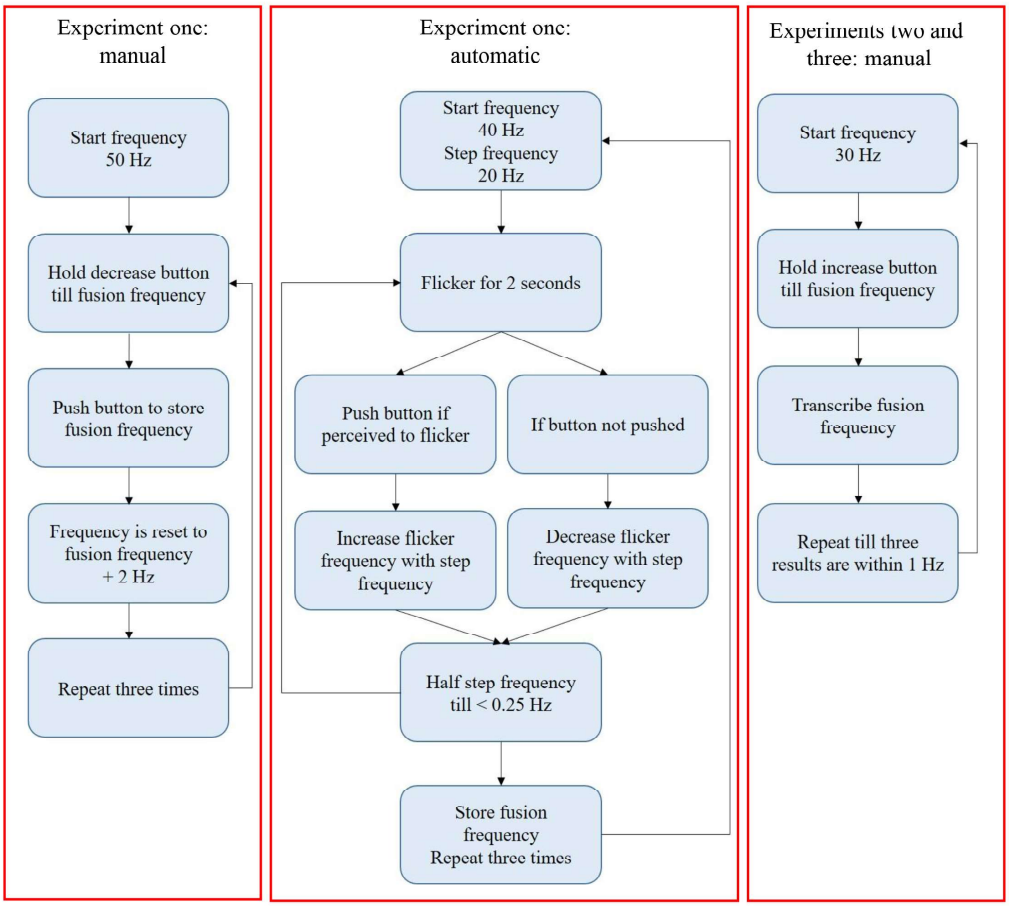
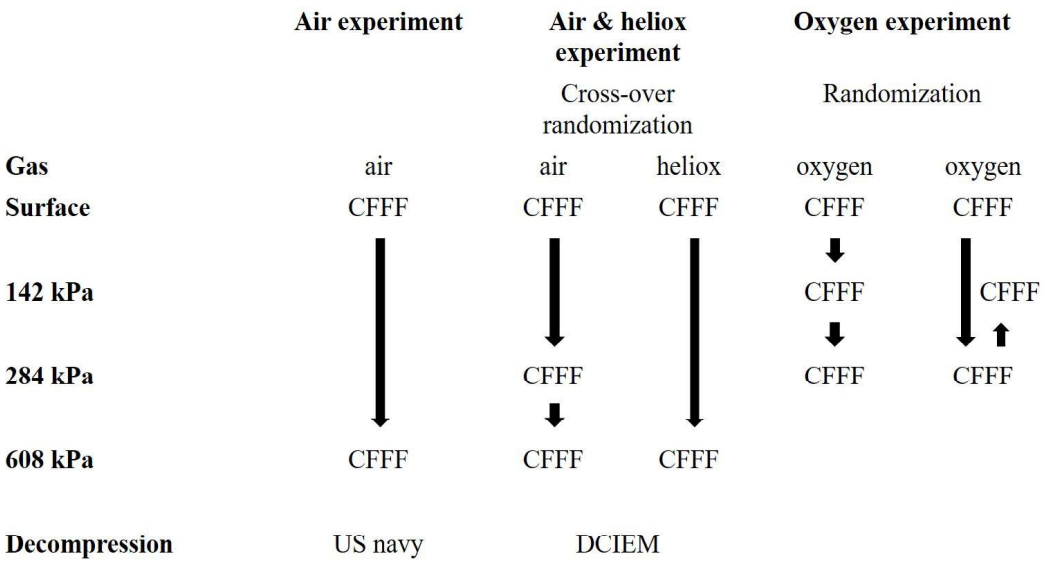


Figure 2
Diagram summarising procedures in all three experiments



hyperbaric chamber at sea level pressure immediately before compression. In the air sessions participants underwent a CFFF measurement at 284 kPa (equivalent to 18 msw depth) and 608 kPa. In the heliox sessions, participants breathed heliox for measurements at sea level pressure and continued breathing heliox during compression for a second measurement at 608 kPa (Figure 2). After each CFFF measurement end-tidal carbon dioxide was measured using a mainstream capnograph (EMMA, Masimo, Irvine, CA, USA). Measurements at 608 kPa were impossible due to device incompatibility, so readings were taken immediately after ascent to the first decompression stop at 284 kPa. The ascent took two minutes. Decompression was according to the DCIEM decompression tables, including 100% oxygen breathing from 193 kPa (equivalent to 9 msw depth) to sea level pressure.

EXPERIMENT THREE – OXYGEN

The same cylindrical 5-person hyperbaric chamber and ambient lighting intensity was used. A baseline CFFF measurement was taken at sea level pressure while breathing environmental air inside the hyperbaric chamber. Participants switched to 100% oxygen for a second sea level pressure measurement. The third and fourth measurement took place in randomised order at 142 (equivalent to 4 msw depth) and 284 kPa breathing oxygen (Figure 2).

In all experiments each measurement was preceded by a five-minute acclimatisation period for the pressure and/or gas mixture.[3] Again, end-tidal carbon dioxide was measured after each CFFF measurement at the measurement depth.

OUTCOMES

The primary outcome was the relative change (percentage) in mean CFFF (mean of the three recordings) of each exposure to a breathing gas and/or pressure compared to baseline air breathing at sea level pressure. Secondary outcome measures for studies two and three were the number of recordings per measurement required to achieve the required level of concordance and the end-tidal carbon dioxide after each measurement.

STATISTICAL ANALYSIS

All data were analysed with SPSS version 25 (IBM, Armonk, NY, USA). Descriptive statistics were generated to characterise the study participants. The relative CFFF value was calculated as percentage from baseline for each individual in each condition. All outcome measures were tested for normality with the Kolmogorov–Smirnov test. All data were normally distributed and were subsequently described by their mean and standard deviation (SD). Differences between relative (percentage) baseline and intervention measures were analysed with paired *t*-tests and reported as mean difference (MD) with 95% confidence intervals (95%CI). Statistical significance was set at $P < 0.05$.

Results

The 40 participants in this study had between 15 and 10,000 dives. Most were technical divers, although there were five non-technical divers in the first experiment. In all three experiments there was a high number of instructors and almost half of the participants had experience breathing

Table 1
Demographic data for subjects in all experiments

Parameter	Air experiment *n* = 16		Air - heliox experiment *n* = 12		Oxygen experiment *n* = 10	
	Mean	Range	Mean	Range	Mean	Range
Age (years)	35.3	20–54	35.8	24–55	36.4	24–49
Body mass index (kg·m^{-2})	23.8	19.1–29.3	26.7	19.5–31.9	26.6	19.5–35.5
Diving experience (years)	11.4	1–29	15.3	3–28	16.6	3–31
Dives	2,679	15–10,000	921	160–2,000	1,203	160–3,500
	n	%	*n*	%	*n*	%
Gender (male)	10	63	7	58	7	70
Certification						
Supervised diver	2	13	0	0	0	0
Autonomous diver	2	13	6	50	6	60
Dive Leader	1	6	1	8	1	10
Dive instructor	11	69	5	42	3	30
Technical diver	11	69	12	100	10	100
Narcotic experience (> 50 msw air)	8	50	7	58	4	40

air at 608 kPa or deeper. Sixteen participated in the air experiment, twelve in the air-heliox experiment and twelve in the oxygen experiment (Table 1). Owing to device failure, two participants were unable to perform the CFFF recordings in the oxygen experiment.

EXPERIMENT ONE – AIR

Neither the manual nor the automatic version of the CFFF measurements were significantly different during air breathing at 608 kPa compared to air breathing at sea level pressure (Table 2).

EXPERIMENT TWO – AIR AND HELIOX

The manual CFFF measurements were not significantly different in any of the air or heliox exposures compared to the air breathing at sea level pressure (Table 2). On average 3.8 (with up to six) CFFF recordings were needed to obtain results that met the requirement of having three recordings within 1 Hz. There was no significant difference in end-tidal carbon dioxide levels between the hyperbaric exposures and baseline air breathing.

EXPERIMENT THREE – OXYGEN

Breathing oxygen at sea level pressure and at 284 kPa caused a significant decrease in CFFF of 2.5 and 2.6%, respectively, compared with air breathing at sea level pressure. The CFFF measured during oxygen breathing at 142 kPa trended in the same direction (Table 2). On average 3.8 (with up to seven) CFFF recordings were needed to obtain results that met the requirement of having three recordings within 1 Hz. There was a significant decrease in end-tidal carbon dioxide level from baseline air breathing to oxygen breathing at 142 kPa (5.3 (SD 1.1) kPa at baseline to 4.6 (0.9) kPa, MD = 0.65 [95% CI 0.25–1.05], P = 0.005). End-tidal carbon dioxide levels in the other oxygen exposures were not significantly different from baseline air breathing.

Discussion

In both experiments one and two, CFFF measured by either method appeared insensitive to the known narcotic effects of nitrogen in air breathed at 608 kPa. Given that helium is a non-narcotic gas it is not surprising that there was no significant change in CFFF during heliox breathing at 608 kPa in experiment two, but the key point here is that CFFF also did not distinguish between the effects of air (79% nitrogen) and heliox (79% helium) when breathed at a pressure widely acknowledged to induce narcosis when air is breathed. In experiment three a reduction in CFFF was found when breathing oxygen at sea level and 284 kPa, with a similar trend at 142 kPa. As will be discussed below, the effects of oxygen were measured in an attempt to help interpret the results of experiments one and two. Summaries of the design and findings of other relevant studies are shown in Tables 3 and 4 respectively. Review of this literature reveals a complicated and often contradictory picture.

Several studies during air breathing conducted at 406 kPa (equivalent to 30 msw depth), have invoked nitrogen narcosis to explain a reduction in CFFF at this depth.[4,7,12] However, this result does not extrapolate to greater depth/pressures even though it is known that cognitive performance is further reduced with increased depth.[13] Several studies,

Table 2

Critical flicker fusion frequency (CFFF) measurements presented as mean absolute frequency (Hz) and percentage relative change compared to the baseline measurement (breathing air at sea level). * indicates significant difference compared with baseline; $P < 0.05$; MD = mean % difference between baseline and exposure; 95% CI = 95% confidence interval

Exposure	Sea level air CFFF (Hz (%))	Exposure CFFF (Hz (%))	Relative change	
			MD (%)	95% CI
Air experiment – automatic and manual CFFF				
608 kPa manual	43.9 (100)	44.0 (100.1)	0.1	-3.3 to 3.5
608 kPa automatic	44.8 (100)	43.9 (102.2)	2.2	-1.3 to 5.8
Air and heliox experiment – manual CFFF				
284 kPa air	37.9 (100)	38.1 (100.6)	0.6	-0.1 to 1.4
608 kPa air		38.4 (101.3)	1.3	-0.5 to 3.1
Sea level heliox		38.6 (101.9)	1.9	-1.0 to 4.8
608 kPa heliox		38.5 (101.6)	1.6	-0.9 to 4.0
Oxygen experiment – manual CFFF				
Sea level oxygen	37.9 (100)	36.9 (97.5)	-2.5	-4.1 to -0.8 *
142 kPa oxygen		37.3 (98.6)	-1.4	-3.7 to 0.9
284 kPa oxygen		36.9 (97.4)	-2.6	-4.3 to -0.9 *

including the present experiments, performed at 608 kPa while breathing air, did not show impairment, but instead showed either no change (the present study) or an increase in CFFF in two others.[5,6] The increase in CFFF seen in both latter studies was attributed to 'oxygen hyper-alertness', due to the increased partial pressure of inspired oxygen of 127 kPa during air breathing at 608 kPa. Oxygen hyper-alertness [14,15] is hypothesised to be caused by an increased availability of oxygen in the neuronal tissue,[16] which is postulated to cause accelerated nerve conduction.[17] This was also proposed as a mechanism to explain an increase in CFFF during normobaric 100% oxygen breathing.[10]

However, in contrast to Hemelryck et al.[10] the present results for 100% oxygen breathing at sea level pressure showed a small reduction in CFFF; while in another study by Kot et al.[9] 70% oxygen breathing at sea level did not produce any change.[9] Similarly, both the Kot study[9] and the present study showed a decrease in CFFF during oxygen breathing at higher pressures:142 kPa and 284 kPa in the present study; and 142 kPa in the study by Kot. This was explained by Kot as a manifestation of oxygen narcosis,[9] based on the concept that oxygen is twice as soluble in oil as nitrogen and hence should have a narcotic effect;[18] although probably not to the extent predicted by inspired partial pressure alone because it is metabolised in tissues.[19] To confuse matters further, Kot[9] reported an increase in CFFF when breathing oxygen at 284 kPa which was attributed to a hyperexcitability effect associated with cerebral oxygen toxicity.[20] After a latent period, oxygen can cause tonic-clonic seizures, but non-convulsive signs and symptoms appear to have a neuronal origin as well.[21] The present study demonstrated the opposite, consistent with all our results during oxygen breathing. Other than the uncertain oxygen narcosis hypothesis (which would not explain the similar result at sea level pressure) there is no obvious explanation for this.

Besides nitrogen and oxygen, carbon dioxide can influence cognitive impairment.[22,23] The relevant physiological pathway has been debated. Carbon dioxide may either have a direct narcotic effect or it might facilitate nitrogen and/or oxygen narcosis or hyper-alertness through cerebral vasodilation.[24] The present study recorded a decreasing trend in end-tidal carbon dioxide during oxygen breathing, essentially excluding any interference by hypercapnia in the relevant CFFF results. It was not possible to measure end-tidal carbon dioxide at 608 kPa in experiment two, and the possibility of a change in end-tidal carbon dioxide between leaving 608 kPa and arrival at 284 kPa where the measurement was made cannot be completely excluded, though there was no evidence of hypercapnia in the subjects.

In addition to the effects of the respired gas and the exposure pressure described above, other factors proposed to influence CFFF include: the prior diving or gas-exposure experience of the subjects;[5,9] subject fatigue;[12,25] the colour and intensity of the flickering light and intensity of the ambient light;[26] the latency of the measurement after beginning of the exposure;[3] the nature of the hyperbaric exposure (immersed or dry);[6,12] the definition of consistency in determining the result;[4] and others (Tables 3 and 4). All of these factors have been invoked to explain results that are inconsistent with an expected (or unexpected) narcotic effect, or the many inconsistencies between studies. This will mean that there may be debate about how the results of the present study were obtained or interpreted, but this would miss the wider point: namely, there is a substantial question-mark over the

Table 3
Details of studies reporting CFFF results in pressure exposures. HBT = Human Breathing Technology; NS = not specified; PES = Probe Embedded Solutions; ROAD = Robotics for Assisted Diving

Study	Environment	Device manufacturer	Light colour	Flicker / fusion	# recordings
Seki et al.[8]	Chamber	Shibata	NS	Flicker	Average of 5
Balestra et al.[4]	Pool	HBT	Blue	NS	Average of 3
Hemelryck et al.[10]	Surface	HBT	Blue	NS	Average of 3
Kot et al.[9]	Chamber	HBT	Blue	NS	NS
Tikkinen et al.[6]	Chamber	Schuhfried	White	Both	Average of 8
Lafere et al.[12]	Outdoor	HBT	Blue	Flicker	Average of 3
Lafere et al.[7]	Chamber	HBT	Blue	Flicker	Average of 3
Rocco et al.[5]	Outdoor	ROAD	Blue	Fusion	Average of 3
Present study (Experiment one)	Chamber	PES	White	Fusion	Average of 3
Present study (Experiments two and three)	Chamber	HBT	Blue	Flicker	Average of 3

Table 4
Results of studies reporting CFFF in pressure exposures. Results are percentage change in CFFF compared to baseline

Study	*n*	Exposure	Result (%)	Hypothesis
Seki et al.[8]	2	6.2 MPa, Heliox PO_2 38-52 kPa, 2 days	80	Extreme pressure
Balestra et al.[4]	20	430 kPa, air, 15 min	93.5	Nitrogen narcosis
Hemelryck et al.[10]	20	101 kPa, oxygen, 10 min	117	Hyper-alertness
Kot et al.[9]	16	101 kPa, 70% oxygen, 25 min	99	Oxygen narcosis
	16	140 kPa, oxygen, 25 min	94	Oxygen narcosis
	65	280 kPa, oxygen, 25 min	103	Oxygen toxicity
Tikkinen et al.[6]	30	608 kPa, air, 5 min	103	Hyper-alertness
Lafere et al.[12]	20	405 kPa, air, 15 min	94.5	Nitrogen narcosis
Lafere et al.[7]	8	405 kPa, air, 15 min	95	Nitrogen narcosis
	8	405 kPa, EAN40, 15 min	99	Hyper-alertness
Rocco et al.[5]	22	608 kPa, air, 15 min	105	Nitrogen narcosis Hyper-alertness
	18	608 kPa, Trimix 21/35, 15 min	107	
	11	608 kPa, Heliox 21/79, 15 min	111	

usefulness of an assessment modality that has produced so many conflicting findings across multiple studies, and which seems subject to influence by many variables and to difficulty in interpretation.

At a simplistic level the primary finding of this study is clear: in our hands CFFF failed to detect or quantify a narcotic effect known to be present (in the 608 kPa air exposures). Therefore, CFFF does not appear to be a candidate outcome measure for our programme of investigating gas narcosis in hyperbaric environments. Consistent with the 'wider point' articulated above, there is little merit in debating the fine detail of the methods, but several aspects are worth emphasising. First, the air exposures where a narcotic effect was expected were conducted with two different devices and (in experiment two) in collaboration with an author very experienced in using CFFF in diving research, who gave guidance on data collection and analysis methods, and provided the second manual CFFF device. Second, under-powering of these studies could explain the lack of statistically significant differences. These experiments had 10 to 16 participants per condition, similar to the number of participants in other studies, which varied between 8 and 30 per study condition with one outlier having 65 participants (Table 4). However statistical significance is largely irrelevant given that the measurement method seems unable to monitor gas narcosis on an individual level. Moreover, the fundamental direction of change was not consistent with the expected narcotic effects of air at high pressure. Thirdly, CFFF measurements were not recorded

until after an equilibration period with the respired gas of at least five minutes in every condition. In respect of nitrogen in the brain, based on a cerebral compartmental half-life of 1.2 minutes,[27] this should allow for ≥ 94% equilibration with the arterial PN_2. Finally, given the potential influence of many factors (discussed above) in affecting CFFF results, it is impossible to use absolute values to define normal or abnormal, and the use of subjects as their own controls in assessment of change between different conditions seems the most legitimate approach to utilising CFFF in this type of study; hence this approach was adopted here.

Conclusions

CFFF measured automatically or manually with different devices was insensitive to the narcotic effect of nitrogen in air at 608 kPa. The present programme requires a measurement method that provides robust and consistent quantification of the cognitive changes caused by gas narcosis in individual subjects. In this study CFFF does not appear to achieve this aim. Review of the relevant literature reveals inconsistent and sometimes paradoxical results with various groups attempting to sometimes explain their data using often contradictory hypotheses. It is concluded that CFFF may not be, in our laboratory setting, the optimal measurement method to monitor the effects of gas narcosis in divers.

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Conflicts of interest and funding

Professor Simon Mitchell is the Editor of *Diving and Hyperbaric Medicine*. He took no part in the peer-review and decision-making processes for this paper, which were managed entirely by the Deputy Editor, Dr Lesley Blogg. There were no other conflicts of interest.

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