Reply: Commentary on using critical flicker fusion frequency to measure gas narcosis

We wish to express our appreciation to Dr Jacek Kot and Dr Pawel Winklewski for their interest in our article.[1] We agree in general terms with the assertion that our critical flicker fusion frequency (CFFF) evaluations cannot be confidently extrapolated to measurements made after larger time intervals at pressure. However, as they point out, a 5-minute acclimatisation is sufficient for the onset of the phenomenon we were attempting to measure (nitrogen narcosis), based not only on kinetic models but also on studies that have shown onset after a 5-minute latency.[2,3] The remainder of their letter largely confirms our assertion that CFFF is confounded by so many other influences that it is likely incapable of reliably achieving our goal of isolating and measuring a short latency narcotic effect caused by hyperbaric nitrogen.

One such influence, emphasised by Kot and Winlewski, is the effect of elevated pressures of inspired oxygen, which can induce hyperexcitability. One point not noted in their letter is that hyperexcitability caused by oxygen has also been observed on arrival at elevated pressure.[2,4] Nevertheless, we agree that oxygen toxicity effects typically have an onset latency beyond the measurement period used in our study, but oxygen toxicity is obviously a different syndrome, and its measurement was not our goal. Therefore, we agree that studies comparing substantially different oxygen exposures might record very different findings when using an outcome measurement (such as CFFF) potentially affected by the duration of exposure to hyperbaric oxygen. This almost certainly explains the differences between our study and that of Kot et al.[5]

We note Kot and Winlewski's confident acceptance that oxygen is a narcotic gas and their invocation of the Meyer-Overton hypothesis in comparing narcotic potentials of gases. The Meyer-Overton hypothesis is still widely cited within the diving medicine community to predict the narcotic potency of the various gases used in diving. Conversely, in the field of anaesthesiology, progress has been made in understanding how narcotic agents cause their effect by binding to ligand-gated ion-channel proteins.[6] Related work has also helped explain why many gases, whose lipid solubility would predict a narcotic effect, have no such effect due to their incompatibility with receptor sites.[7] It has been shown that dopamine changes are only one among many neurophysiological pathways disturbed by oxygen,[8] both pre- and post-seizures. However, none of these pathways are similar to the pathways known to be implicated in the effect of narcotic agents. More recently, oxygen has been associated with the upregulating of the NMDA-receptor in a cellular model,[9] while nitrous oxide and ketamine inhibit the NMDA receptor.[10] This might explain the excitatory effect of hyperbaric oxygen. Hence, a narcotic effect of oxygen, preceding the hyperexcitability of oxygen seizures, seems very improbable.

In conclusion, we stand by our conclusion that research on CFFF as a measure of the narcotic effect exerted by hyperbaric gases has generated conflicting results, typically explained in each paper by invoking various confounding factors. We agree with Kot and Winlewski's conclusion that CFFF is poorly suited to monitoring hyperbaric gas narcosis. It is too sensitive to confounding effects that may obfuscate the cognitive impairment caused by gas narcosis.

References

1 Vrijdag XC, van Waart H, Sleigh JW, Balestra C, Mitchell SJ. Investigating critical flicker fusion frequency for monitoring gas narcosis in divers. Diving Hyperb Med. 2020;50:377–85. doi: 10.28920/dhm50.4.377-385. PMID: 33325019. PMCID: PMC7872789.

2 Balestra C, Lafère P, Germonpré P. Persistence of critical flicker fusion frequency impairment after a 33 mfw SCUBA dive: Evidence of prolonged nitrogen narcosis? Eur J Appl Physiol. 2012;112:4063–8. doi: 10.1007/s00421-012-2391-z. PMID: 22476770.

3 Bennett PB, Glass A. Electroencephalographic and other changes induced by high partial pressures of nitrogen. Electroencephalogr Clin Neurophysiol. 1961;13:91–8.

4 Rocco M, Pelaia P, Di Benedetto P, Conte G, Maggi L, Fiorelli S, et al. Inert gas narcosis in scuba diving, different gases

different reactions. Eur J Appl Physiol. 2019;119:247–55. doi: 10.1007/s00421-018-4020-y. PMID: 30350155.
5 Kot J, Winklewski PJ, Sicko Z, Tkachenko Y. Effect of oxygen on neuronal excitability measured by critical flicker fusion frequency is dose dependent. J Clin Exp Neuropsychol. 2015;37:276–84. doi: 10.1080/13803395.2015.1007118. PMID: 25715640.
6 Franks NP. General anaesthesia: From molecular targets to neuronal pathways of sleep and arousal. Nat Rev Neurosci. 2008;9:370–86. doi: 10.1038/nrn2372. PMID: 18425091.
7 Weir CJ. The molecular mechanisms of general anaesthesia: dissecting the GABAA receptor. Contin Educ Anaesth Crit Care Pain. 2006;6:49–53. doi: 10.1093/BJACEACCP/MKI068.
8 Rostain JC, Lavoute C. Dopamine, neurochemical processes, and oxygen toxicity at pressure. Compr Physiol. 2016;6:1339–44. doi: 10.1002/cphy.c140025. PMID: 27347895.
9 Bliznyuk A, Hollmann M, Grossman Y. The mechanism of NMDA receptor hyperexcitation in high pressure helium and hyperbaric oxygen. Front Physiol. 2020;11:1057. doi: 10.3389/fphys.2020.01057. PMID: 32982789. PMCID: PMC7478267.
10 Jevtović-Todorović V, Todorovć SM, Mennerick S, Powell S, Dikranian K, Benshoff N, et al. Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. Nat Med. 1998;4:460–3. doi: 10.1038/nm0498-460.

Submitted: 26 April 2021
Accepted: 26 April 2021

doi: 10.28920/dhm51.2.228-229. PMID: 34157743.

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

[1] Department of Anaesthesiology, University of Auckland, Auckland, New Zealand
[2] Department of Anaesthesia, Waikato Hospital, Hamilton, New Zealand
[3] Department of Anaesthesia, Auckland City Hospital, Auckland, New Zealand

Address for correspondence: *Xavier CE Vrijdag, Department of Anaesthesiology, School of Medicine, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand*
x.vrijdag@auckland.ac.nz

Key words
Critical flicker fusion frequency; Narcosis; Nitrogen; Oxygen; Letters (to the Editor)
