To survive a dive; cerebral oxygen delivery and our aquatic heritage

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Mammals, by definition, are air breathers. Yet, an aquatic phylogeny persists amongst all mammals of both terrestrial and marine origin, the so-called mammalian dive response. The mammalian dive response is hallmarked by powerful and functionally synergistic responses including bradycardia and peripheral vasoconstriction that collectively serve to preserve blood flow and oxygen delivery to the heart and brain. These autonomic changes make for some impressive breath-holds among some remarkable performers. Take the Cuvier's beaked whale (*Ziphius cavirostris*), the current marine mammal 'world record holder', capable of holding its breath for an astounding 137.5 minutes while diving almost 3 km below the ocean surface (Schorr *et al.*, 2014). Meanwhile, we humans, mere mortals by comparison, can achieve an impressive 11 min and 35 second breath-hold [*Association Internationale pour le Développement de l'Apnée (AIDA) certified*] despite our oversized brains limited by next to no O_2 reserves. Such feats would be impossible if not for the mammalian dive response.

The mammalian dive response becomes fully active when a breath hold is performed with underwater facial immersion or cooling thanks to facial trigeminal nerve (TGN) stimulation. The trigeminal nerve (Cranial Nerve V) has end-feet projecting across several regions of the brain, including vasomotor centres in the brainstem, and as such is the most complex of all cranial nerves. During a breath hold, TGN stimulation is thought to play a leading role in vagally-mediated bradycardia, and sympathetically-mediated peripheral vasoconstriction. Moreover, TGN stimulation has been identified as a potential stimulus for the increase in cerebral blood flow (CBF) observed during a breath hold, independent of other competing vasoactive stimuli encountered during the apnoea itself such as hypoxia, hypercapnia and elevated blood pressure. Indeed, experimental stimulation of the TGN causes marked cerebral vasodilatation in animals (Lapi *et al.,* 2016), and in select human cases such as during craniofacial surgery in anaesthetised patients (Schaller, 2005).

In this issue of *Experimental Physiology*, Alsalahi *et al.* (2020) combined no fewer than six experimental protocols in an attempt to isolate to what extent TGN stimulation per se (independent of increases in blood pressure and carbon dioxide) contributes to increased cerebral perfusion during breath holding in young healthy adults. They identified that TGN stimulation failed to alter cerebral perfusion with observed increases in CBF primarily attributable to the apnoea-induced pressor response and hypercapnia. Indeed, the increases in extra (internal carotid artery) and intracranial (middle cerebral artery) CBF were identical whether the breath hold was performed with, or without facial cooling, arguing against a regulatory role for TGN stimulation.

To what extent these findings force a reappraisal of current understanding remains unclear since Alsalahi *et al.* (2020) focused their attention on untrained apnoeists constrained by limited breath-hold times lasting less than 30 seconds on average. Despite all breath holds starting at functional residual capacity, their breath hold duration is unlikely to have generated arterial hypoxaemia of sufficient magnitude to have stimulated trigeminal-induced vasodilatation. Indeed, results from animal studies (mainly in rabbits) suggest that trigeminal-induced cerebral vasodilatation is evoked by activation of O_2-sensitive neurons in the rostral ventrolateral medulla (studies reviewed in Lapi *et al.,* 2016). Furthermore, arterial hypoxaemia triggers the carotid body mediated cardiovascular response (bradycardia) during breath holds in the seal (de Burgh Daly *et al.,* 1977). Thus, more marked hypoxaemia than that anticipated (albeit not measured) in the current study may be required to evoke TGN stimulation. Future studies of more prolonged breath holds in trained

apnoeists or alternatively, during the combination of facial cooling with hypoxic air breathing, would help address this hypothesis (Figure 1).

Furthermore, under the construct of trigeminal 'priming', some studies suggest that the mammalian dive response is sensitive to training. For example, a more pronounced breath hold induced-bradycardia response is observed following a relatively short two-week bout of training in previously naïve breath holders (Engan *et al.,* 2013), highlighting the functional significance of ontogeny and not just phylogeny. An additional study may therefore query whether the trigemino-cerebrovascular system becomes more sensitised through repetitive diving. Equally, the increase in the dive response may also be due to withdrawal of sympathetic activation associated with repeated cool/cold water immersion (habituation of the cold shock response). Regardless, in elite apnoeists, CBF can exceed 100 % of its baseline values, even without facial cooling. In this case, it is clear that the primary mechanism for the elevated CBF is not trigeminal mediated, rather, the extreme hypercapnia, hypoxaemia, and elevated blood pressure associated with the apnoea itself (Figure 1, A). Still, it remains to be determined how TG stimulation, or 'priming', contribute and interact with these potent cerebrovascular stimuli.

The Swedish born, Norwegian/US-based scientist, Per Scholander, was among the first to suggest that water might exert life-lengthening effects on humans and other animals by triggering the most powerful autonomic response known that he affectionately coined the 'Master Switch of Life'. While the current findings suggest that TGN stimulation may have little impact on the cerebrovascular response to short lasting (30 second) breath holds, its precise contribution to the maintenance of cerebral O_2 delivery in the face of profound hypoxaemia, and/or in the clinical setting where the maintenance of cerebral metabolism is paramount, remains to be defined.

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Legend

Figure 1. A. Summative contribution and suggested timeline of primary vasoactive stimuli that increase cerebral perfusion and substrate delivery during a breath hold (left). **B.** Follow-up experimentation focusing on more prolonged breath holds in trained apnoeists and/or during facial cooling while hypoxic air breathing will help further establish to what extent trigeminal nerve (TGN) activation compounds cerebral perfusion. **C.** Neuroanatomical projections of the trigeminal nerve and the primary pathways (highlighted in red) that collectively serve to increase cerebral blood flow. RVLM, rostral ventrolateral medullar. Figure modified from Chiluwal A *et al*., 2017.