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LETTER TO THE EDITOR

A more holistic view could contribute to our understanding of 'silent hypoxaemia' in Covid -19 patients

The article written by Simonson *et al.* (2021), 'Silent hypoxaemia in COVID-19 patients', provides a comprehensive and interesting review on how hypoxaemia is related to dyspnoea. However, we would like to address some points that need further clarification.

Firstly, the terms 'happy hypoxia' and 'silent hypoxia' are based on the clinician's perception of an expected response related to levels of oxygen saturation (S_{pO_2}; Tobin *et al.* 2020), which implies that the only symptom of hypoxaemia is dyspnoea. Dyspnoea, however, is complex and difficult to define, as it can be perceived in different ways – not only by 'air hunger' (Tobin, 1990). As dyspnoea is a subjective experience, it is difficult to match specific levels of arterial partial pressures of oxygen (P_{aO_2}) with this symptom. Indeed, a more appropriate term could be 'asymptomatic hypoxia', as we need to measure many variables including tissue hypoxia to be sure that it is 'silent'.

Humans have been dealing with hypoxia in many different ways across our evolution, both as breath-hold divers (Schagatay, 2009) and as indigenous permanent inhabitants of moderate to high altitude regions of the Tibetan plateau, the Andes, Eastern Africa and North America (Huang, 2014; Simonson, 2015; West, 2019), proving that humans can thrive even in conditions of hypoxia. In addition, even in critical care patients, some levels of hypoxaemia could be accepted (permissive hypoxaemia) if tissue oxygenation is not affected (Martin & Grocott, 2013; Panwar *et al.* 2016). The individual response to hypoxia is highly variable; therefore it is difficult to define a precise threshold value of P_{aO_2} and S_{pO_2} (Tobin *et al.* 2020). Another important factor is timing, as the concept of acclimatization plays an important role in the response to hypoxia in order to cope with the restricted supply of oxygen (West, 2006). In COVID-19 patients, dyspnoea typically occurs 8–12 days after the onset of symptoms (Li & Ma, 2020; Zhou *et al.* 2020). Since it has been shown that acclimatization to high altitude takes between 4 and 8 days (Rahn & Otis, 1949), it may be possible that a similar process occurs in COVID-19 patients, having to cope with hypoxia for several days, hence reducing their oxygen consumption accordingly (West, 2006).

Secondly, we would like to clarify some statements about breath-hold diving. In the review, the authors cite two references (Lindholm & Lundgren, 2006; Overgaard *et al.* 2006) to explain normal arterial partial pressures of carbon dioxide (P_{aCO_2}) at the end of a breath-hold. Parenthetically, hyperventilation is avoided nowadays in competitive breath-hold diving, as it is a risk factor for hypoxic syncope (Pearn *et al.* 2015). Regardless, Overgaard *et al.* (2006) found end-tidal partial pressures of carbon dioxide (P_{ET,CO_2}) at the end of breath-holding (at different lung volumes) ranging between 45.7 and 50.2 mmHg, which is not in the normal range. A classical study on exhaled gases (Liner & Linnarsson, 1994) found a baseline P_{ET,CO_2} of 39 mmHg, which, after a surface breath-hold, had gone up to 46 mmHg, while it was 45 mmHg after a simulated 20 m dive. Recently, P_{aCO_2} was measured at 40 m depth, and it was found that baseline values of 37.7 mmHg had increased to 42 mmHg at depth (Bosco *et al.* 2018), but these were not maximal-effort dives.

Competitive breath-hold divers repeatedly expose themselves to hypercapnia and hypoxia, which increases tolerance to these stimuli due to a blunted ventilatory response to hypercapnia and/or hypoxia (Ferretti *et al.* 1991). During a breath-hold, P_{aO_2} will continue to drop as long as apnoea is extended, while P_{aCO_2} concomitantly rises, causing hypoxia- and hypercapnia-induced chemoreceptor activity in carotid and aortic bodies (Parkes, 2006). The resulting neural activity causes involuntary contractions of the diaphragm and inspiratory muscles, known as involuntary breathing movements (IBM; Hentsch & Ulmer, 1984). While untrained individuals may terminate apnoea shortly after the onset of IBM's, competitive freedivers can consciously suppress this respiratory sensory information due to training-induced psychological tolerance until discomfort and/or signs of asphyxia (tunnel vision, hearing distortion) indicates them to break apnoea, before losing consciousness (Schagatay, 2009). Thus, in untrained individuals, the breaking point of apnoea will most likely be influenced by hypercapnia alone, while the combination of both hypoxia and, to a lesser extent, hypercapnia, will be the determining factor for competitive freedivers. Freedivers also possess a powerful "diving response" which efficiently reduces metabolism and oxygen consumption (Schagatay, 2009).

The responses to extreme hypoxia and hypercapnia are not only a feature of elite breath-hold divers, as studies show that this adaptation can be trained (Hentsch & Ulmer, 1984; Engan *et al.* 2013). Breath-holding therefore seems to be a good *in vivo* model to understand severe hypoxia, which may be useful to test hypotheses regarding the ventilatory drive on healthy individuals.

Additionally, when hypoxia occurs, an early response is the rapid splenic contraction which elevates haematocrit. This response has been observed during breath-holding (Baković *et al.* 2003; Schagatay *et al.* 2005), at high altitude (Purdy *et al.* 2019; Schagatay *et al.* 2020) and under hypobaric hypoxia (Richardson *et al.* 2008; Lodin-Sundström & Schagatay, 2010). It allows an increase in oxygen blood content by 10% without any changes in S_{pO_2}. So far, this response has not been studied in clinical situations related to hypoxia, but it was evident in drowning victims (Haffner *et al.* 1994) and could have importance in clinical conditions.

We would like to remark on an observation of the authors in regard to the lack of an excessive ventilatory response that could reduce self-induced lung injury (Mascheroni *et al.* 1988; Brochard *et al.* 2017). We believe that a more holistic view that includes our natural defence mechanisms against hypoxia would be fruitful for better understanding of asymptomatic hypoxaemia. We advocate for this more holistic view as organism survival can be addressed in multiple ways.

Eric Mulder, Frank Pernett and Erika Schagatay

Environmental Physiology Group, Department of Health Sciences, Mid Sweden University, Östersund, Sweden

Email: eric.mulder@miun.se

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Additional information

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None declared.

Author contributions

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