Published in final edited form as:

J Physiol. 2020 May ; 598(10): 1805–1806. doi:10.1113/JP279590.

Variability in hypoxic response: Could genetics play a role?

Tatum S. Simonson, **Atul Malhotra**

Section of Physiology, Division of Pulmonary, Critical Care, and Sleep Medicine, UC San Diego, La Jolla, CA, USA

Keywords

breathing; genetics; hypoxia

The biological response to hypoxia leads to important fundamental questions regarding health and disease. Some patients exposed to hypoxia develop a waxing and waning breathing pattern known as periodic breathing (PB). Similarly, patients with congestive heart failure can develop Cheyne Stokes breathing (CSB), which has been somewhat controversial as a result of uncertainty about its prognostic impact and its optimal therapy (Bradley *et al.* 2005). In this issue of *The Journal of Physiology,* the new findings reported by Lancaster *et al.* (2020) not only shed new light on these issues, but also raise broader questions about genetic susceptibility to various breathing patterns and their associated consequences.

In terms of control of breathing, loop gain is an engineering term that has been used to quantify the stability or instability of a negative feedback control system. A system with a high loop gain is one prone to instability, whereas a system with low loop gain is intrinsically stable (Khoo, 2000). The loop gain of the ventilatory control system is a function of factors including the controller (i.e. chemoresponsiveness), as well as a plant (based on the efficiency of CO_2 excretion). Hypoxia can contribute to instability depending on the hypoxic ventilatory response, which may vary based on genetic and other factors. Elevated loop gain is important clinically (e.g. CSB and PB at high altitude) because it maybe amenable to oxygen therapy or acetazolamide. Some cases may respond to new forms of non-invasive ventilation, such as adaptive or auto servoventilation (ASV), although outcome data are mixed. Elevated loop gain has also been associated with failure of upper airway surgery for obstructive sleep apnea (OSA) and the development of central apnea for OSA patients when given continuous positive airway pressure. Based on the crescendo-decrescendo breathing pattern in CSB, patients can experience hypoxia with reoxygenation leading to oxidative stress, recurrent arousals from sleep during periods of hyperpnea, and repetitive surges in catecholamines in response to pathophysiological stimuli. Thus, CSB

tsimonson@health.ucsd.edu.

Author contributions

Both authors contributed equally.

Additional information

Competing interests

No competing interests declared.

complications may involve many pathways, including autonomic, inflammatory and oxidative stress mediated.

Given the variable prognosis of CSB and the inconsistent results of therapeutic studies to eliminate CSB, there is probably individual variability in the occurrence of CSB and in its haemodynamic and neurocognitive consequences (Heinrich *et al.* 2019). Lancaster *etal.* (2020) report possible associations with oxidative stress genes, which, in theory, could determine which patient may be susceptible to CSB. In particular, the selected anti-oxidative genes play a role in defence against oxidative stress, and the NOTCH signalling pathway interacts with hypoxia sensing pathways and plays an important role in neurodevelopment.

The candidate-gene approach has been debated given the availability of genomics information (e.g. from genome-wide association studies) within the past decade, and a push to utilize knowledge from publicly available databases and *in silico* tools is warranted in such studies. Of note, we and others have prioritized candidate genes that may be important in mediating the biological response to hypoxia based on extensive genome analysis and known gene function. For example, *EGLN1* and *EPAS1* play an important role in determining the variability in response to hypobaric hypoxia at altitude (Simonson *et al.* 2010) and have been linked to the development of polycythemia and associated abnormalities. However, we are unclear as to how Lancaster *et al.* (2020) determined their candidate genes of interest given that the general categories mentioned encompass many potentially relevant genes, and we encourage further development in this area in such Studies

As with all exciting research, the new findings raise a number of questions for the scientist. First, are there other candidate genes which may be important in modulating the biological response to hypoxia? In theory, various genetic factors, gene-by-gene, gene-by-environment interactions and epigenetic changes may all have an important role in defining the variability seen in human cardiopulmonary physiology. Second, would the addition of -omics techniques (e.g. to identify pathways of interest) help to complement the new findings? For example, inflammatory pathways are often influenced by hypoxia but have not been adequately assessed in the context of control of breathing. Third, would sophisticated autonomic physiology assessments (e.g. muscle sympathetic nerve activity) help to elucidate the mechanism underlying the cardiorespiratory phase coherence found by Lancaster *et al.* (2020).

For the clinician, a number of issues also arise. First, could metabolomics or transcriptomics allow the identification of biomarkers for patients who are at a particular risk of complications and/or who will probably respond to a specific intervention (e.g., high risk for CSB complications may need ASV therapy?) Second, could cardiorespiratory phase coherence be used diagnostically to identify particular patients and/or using predictive analytics to prioritize high risk patients? Third, could pharmacological interventions such as anti-oxidant therapy be guided by knowledge regarding those patients who probably have oxidative-stress mediated complications? Newtherapeutic approaches for afflicted patients will probably only evolve as a result of further research into the underlying mechanisms.

Acknowledgments

Funding

Dr. Simonson is PI on NIH RO1 HL145470. Dr. Malhotra is PI on NIH RO1 HL085188, K24 HL132105, T32 HL134632 and has received income related to medical education from Merck and Livanova. ResMed, Inc. provided a philanthropic donation to the UC San Diego in support of a sleep center.

References

Bradley TD, Logan AG, Kimoff RJ, Sériès F, Morrison D, Ferguson K, Belenkie I, Pfeifer M, Fleetham J, Hanly P, Smilovitch M, Tomlinson G, Floras JS; CANPAP (2005) Continuous positive airway pressure for central sleep apnea and heart failure. N Engl J Med 353, 2025–2033 [PubMed: 16282177]

Heinrich EC, Djokic MA, Gilbertson D, DeYoung PN, Bosompra NO, Wu L, Anza-Ramirez C, Orr JE, Powell FL, Malhotra A & Simonson TS (2019). Cognitive function and mood at high altitude following acclimatization and use of supplemental oxygen and adaptive servoventilation sleep treatments. PLoS One 14,e0217089. [PubMed: 31188839]

Khoo M (2000). Determinants of ventilatory instability and variability. Respir Phsiol 122, 167–182.

Lancaster G, Debecec T, Millet G, Poussel M, Willis SJ, Mramor M, Goricar K, Osredkar D, DolZan V, Stefanovska A (2020). Relationship between cardiorespiratory phase coherence during hypoxia and genetic polymorphism in humans. J Physiol 598,2001–2019. [PubMed: 31957891]

Simonson TS, Yang Y, Huff CD, Yun H, Qin G, Witherspoon DJ, Bai Z, Lorenzo FR, Xing J, Jorde LB, Prchal JT & Ge R (2010). Genetic evidence for high-altitude adaptation in Tibet. Science 329, 72–75. [PubMed: 20466884]