

UC San Diego

UC San Diego Previously Published Works

Title

Variability in hypoxic response: Could genetics play a role?

Permalink

<https://escholarship.org/uc/item/7d1438gb>

Journal

The Journal of Physiology, 598(10)

ISSN

0022-3751

Authors

Simonson, Tatum S

Malhotra, Atul

Publication Date


2020-05-01

DOI

10.1113/jp279590

Peer reviewed

TRANSLATIONAL PERSPECTIVES

**Variability in hypoxic response:
Could genetics play a role?**Tatum S. Simonson 
and Atul MalhotraSection of Physiology, Division of
Pulmonary, Critical Care, and Sleep
Medicine, UC San Diego, La Jolla, CA,
USA

E-mail: tsimonson@health.ucsd.edu

Edited by: Laura Bennet & Frank Powell

Linked articles: This Perspectives article
highlights an article by Lancaster *et al.*
To read this paper, visit [https://doi.org/
10.1113/JP278829](https://doi.org/10.1113/JP278829).

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 CO₂ 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 may be 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 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 neuro-cognitive consequences (Heinrich *et al.* 2019). Lancaster *et al.* (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 neuro-development.

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? New therapeutic approaches for afflicted patients will probably only evolve as a result of further research into the underlying mechanisms.

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 Investigators. (2005). Continuous positive airway pressure for central sleep apnea and heart failure. *N Engl J Med* **353**, 2025–2033.

Heinrich EC, Djokic MA, Gilbertson D, DeYoung PN, Bosomptra 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.

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

Lancaster G, Debecq T, Millet G, Pousset M, Willis SJ, Mramor M, Goričar K, Osredkar D, Dolžan V, Stefanovska A (2020). Relationship between cardiorespiratory phase coherence during hypoxia and genetic polymorphism in humans. *J Physiol* **598**, 2001–2019.

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.

Additional information

Competing interests

No competing interests declared.

Author contributions

Both authors contributed equally.

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.

Keywords

breathing, genetics, hypoxia