frontiers in Physiology

GENERAL COMMENTARY
published: 22 May 2019
doi: 10.3389/fphys.2019.00609

Commentary: Intermittent Hypoxia Severity in Animal Models of Sleep Apnea

Jonathan C. Jun[1] and Erik R. Swenson[2]*

[1] Pulmonary and Critical Care Medicine, School of Medicine, Johns Hopkins University, Baltimore, MD, United States,
[2] Pulmonary and Critical Care Medicine, University of Washington, Seattle, WA, United States

Keywords: hypoxia, hemoglobin, dissociation, sleep apnea, altitude

A Commentary on

Intermittent Hypoxia Severity in Animal Models of Sleep Apnea
by Farre, R., Montserrat, J. M., Gozal, D., Almendros, I., and Navajas, D. (2018). Front. Physiol. 9:1556. doi: 10.3389/fphys.2018.01556

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Edited by:
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Reviewed by:
Andrew E. Beaudin,
University of Calgary, Canada

****Correspondence:***
Jonathan C. Jun
jjun2@Jhmi.edu

Specialty section:
This article was submitted to Respiratory Physiology, a section of the journal Frontiers in Physiology

Received: *01 April 2019*
Accepted: *29 April 2019*
Published: *22 May 2019*

Citation:
Jun JC and Swenson ER (2019) Commentary: Intermittent Hypoxia Severity in Animal Models of Sleep Apnea. Front. Physiol. 10:609. doi: 10.3389/fphys.2019.00609

Obstructive sleep apnea (OSA) is a common disorder that leads to problems including intermittent hypoxia (IH) and arousals from sleep. To simulate consequences of OSA, some studies expose rodents to IH with the intention of simulating the oxygen profile experienced by OSA patients. Some IH experiments induce hemoglobin oxygen saturation (SaO_2) to fall to 50–70% during the nadir phase. In a recent review, we stated that this degree of hypoxemia is more severe than that experienced by typical OSA patients (Chopra et al., 2015). Farre et al. challenged this statement (Farré et al., 2018), pointing out that small mammals such as rodents have a right-shifted oxyhemoglobin dissociation curve (ODC) compared to humans (Schmidt-Nielsen, 1970). They argue that the higher arterial partial oxygen pressure (PaO_2) for a given SaO_2 confers mice with "better oxygen reserve." To achieve PaO_2 nadir values similar to those experienced by severe OSA patients they contend, "SaO_2 in mice should be much lower than the SaO_2 observed in patients." We disagree with this statement, which relies on PaO_2 as an indicator of tissue oxygenation. Arterial O_2 content (CaO_2) is determined by classic formula:

$$CaO_2 = (1.34 \text{ x Hb x } SaO_2) + (0.003 \text{ x } PaO_2)$$

Systemic O_2 delivery (DO_2) is the product of blood flow (Q) and CaO_2. From these equations, it is apparent that PaO_2 as it determines the amount of dissolved O_2 gas, itself has a negligible contribution to CaO_2 or DO_2. As oxygenated blood reaches target tissues, O_2 dissociates from hemoglobin to maintain a favorable capillary-to-tissue PO_2 driving gradient. When O_2 diffuses into tissues, systemic capillary PaO_2 falls, and is replenished by upstream oxygenated hemoglobin. Aerobic metabolic processes then consume cell O_2. The balance between O_2 supply and demand determines the cellular PO_2. Therefore, cellular PO_2–the parameter that truly determines oxygen adequacy - depends upon DO_2, capillary density, and rates of O_2 utilization. A right-shifted ODC means that O_2 is unloaded from hemoglobin more rapidly, but this does not increase the total amount of O_2 delivered.

To propose that mice should have their SaO_2 lowered in order to achieve a PaO_2 equal to that of humans is tantamount to suggesting that one should load a truck to only half its capacity, because it unloads boxes twice as quickly. If we invoke this logic, and use the figure provided by Farre et al., mouse SaO_2 would have to be decreased to ~75% to match a normoxic human PaO_2 at ~65 mm Hg. Mice exposed to hypoxemia of this magnitude exhibit robust erythrocytosis (Fagan, 2001) and activate anaerobic metabolic pathways (Jun et al., 2012, 2014) indicating that mice are effectively hypoxic at a higher PaO_2 than humans. Their higher PaO_2 may be necessary to maintain adequate tissue PO_2 (as opposed to having "better oxygen reserve"), as mice have dramatically higher mass-specific metabolic rates than humans. Therefore, we should be targeting equivalent drops in SaO_2 between humans and rodents if the goal is to reduce distal O_2 delivery to the same extent.

Implicit in the argument by Farre et al. is that a right-shifted ODC is advantageous in mitigating effects of low SaO_2. There is no evidence that we could find to support this argument. A right-shifted ODC is advantageous in states such as shock or hemorrhage ensuring O_2 is maximally transferred to ischemic tissues (Agostoni et al., 1975; da Luz et al., 1975; Cornum et al., 1998; Morgan, 1999). Conversely, transfusion of blood depleted of 2,3 diphosphoglycerate to left-shift the ODC (Riggs et al., 1973) decreases tissue oxygen supply. These examples pertain to conditions when hemoglobin is fully O_2 saturated (i.e., SaO_2 is constant). What is the effect of shifting the ODC during hypoxemia (e.g., high altitude, OSA)? Here, effects of hemoglobin O_2 affinity are not straightforward. Left shifting the ODC increases O_2 uptake in the pulmonary capillaries, but compromises peripheral tissue O_2 unloading. At high altitude, this trade-off is advantageous for survival; the "tipping point" occurs when O_2 uptake becomes diffusion limited (Storz and Moriyama, 2008). Indeed, rats exposed to severe hypoxia survived longer with a left-shifted ODC (Eaton et al., 1974). The rightward ODC curve of rodents may actually be counter-productive in the setting of ambient hypoxia.

In conclusion, we should not "titrate" SaO_2 in different species to match their PaO_2, based on different hemoglobin O_2 affinities. We stand by our statement that IH experiments that lower the SaO_2 of mice to nadirs of 50–70% are severe. Our intent was not to dismiss the importance or validity of these IH models. We merely object to the claim that SaO_2 needs to be lowered more in mice than humans to simulate consequences of OSA.

AUTHOR CONTRIBUTIONS

JJ and ES collaboratively wrote the manuscript.

FUNDING

This manuscript was supported by NIH R01HL135483 and R03HL138068.

ACKNOWLEDGMENTS

Authors would like to thank Dr. Jerome Dempsey and Dr. Norberto Gonzalez who participated in discussions on this topic.

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