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## The ABC of hypoxia – what is the norm

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## Reviewer 2

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\*Only major points from review and responses included.

### Reviewer 2

The manuscript by Donnelly et al. provides an interesting and useful framework of precepts to harmonize the use of terms/concepts related to normo/hyper/hypo oxia in the biological literature. The proposition is relevant, timely and useful. In general the text is clear and easy to follow. However, there are some sections that could be rewritten or extended in the points dealt with therein in order to make the manuscript even clearer and accessible to a wider audience.

### Authors

First and foremost, we thank Dr Abdulkader for their careful reading and comments on our manuscript. We agree with Dr Abdulkader that certain areas require improvement to make our manuscript even clearer and accessible to a wider audience. We have addressed all comments in the manuscript and in our point-by-point responses below.

### Reviewer 2

While one can grasp the scope of the paper rather easily from the main text, the abstract is confusing and I could only entirely understand what the authors meant by reading it again after going through the whole text. Suggestion: "We here define ... three complementary precepts denoted by the capital letters A, B and C, that compose our proposed 'ABC of hypoxia': (A) ..." - or something to that effect.

## Authors

Dr Abdulkader is indeed correct in saying that the oxia categories ABC are used to define normoxic reference states and that they are denoted by capital letters. In writing A, B and C (i.e., in uppercase letters) we do not believe that it is necessary to make this more explicit and have not amended the text: "We here define the normoxic reference state by three complementary precepts: (A) ambient ..; (B) biological .; and (C) control .."

## Reviewer 2

Also, in the abstract, it is not clear that the lowercase abc refers to different - albeit related to - categories from ABC.

## Authors

In continuation to the above comment, we have decided to amend the text so that the lowercase abc is now replaced by  $\Delta A$ ,  $\Delta B$  and  $\Delta C$  to emphasize that the categories and deviations are different yet linked.

## Reviewer 2

Still in the abstract, I understood both types of categories as pertaining two kinds of conceptual framework: ABC deals with the level of description in which the "oxias" are defined upon, while the abc considers the mechanisms by which each "oxia" condition is brought about. Is it so? If that is correct, would the authors consider to be useful to rewrite the abstract to convey that?

## Authors

Dr Abdulkader is correct in distinguishing ABC from abc. We have updated our nomenclature to ABC and  $\Delta A$ ,  $\Delta B$  and  $\Delta C$ . Please see the amended text.

## Reviewer 2

Continuing in the abstract, but now considering the first sentence, the term "levels" seems to be rather too general: do they mean amount, concentration, partial pressure, availability etc.? Though they do discuss this issue later in the main text, they don't seem to settle on that.

## Authors

In the interest of space we have kept the term "levels" as it is in the abstract. However, we do fully agree with Dr Abdulkader that although we do discuss this later in the main text we do not clearly define it. We have now addressed this in section 2.5. Explaining that "we .. used the term 'oxygen levels' to relate equally to oxygen concentration and the partial pressure of oxygen" before discussing concentration and partial pressure in more detail.

## Reviewer 2

Lastly in the abstract: the definition of (c) is rather cryptic: what do the authors mean by "critical oxygen pressure in oxygen kinetics"? From what I gathered from the main text, the critical pO<sub>2</sub> could be understood as the pO<sub>2</sub> in which mitochondrial O<sub>2</sub> consumption is not maximal and O<sub>2</sub> concentration becomes rate limiting.

## Authors

Dr Abdulkader is correct the  $p_c$  is indeed the  $p_{O_2}$  above which the capacity for oxygen consumption is not compromised (i.e., maximal) as defined in C. A deviation from this at the level  $\Delta C$  is due to a shifting of the  $p_c$  caused by a pathological or toxicological mechanism or an environmental stress.

## Reviewer 2

Page 2, 3rd para., "respiratory control": please define the term, it can have different meanings to different people (for instance, in respiratory physiology it applies to the activity of the neural centers in the medulla that determine the activity of the respiratory muscles and thus alveolar ventilation).

## Authors

Here we use the term "respiratory control" generally. And, therefore, we have kept this term here before elaborating further later in the text.

## Reviewer 2

Page 3, last sentence of 1st para.: please rewrite the sentence as it may lead the reader to think that "ABC of oxygen" is a widespread term in the literature ("several articles"), while - at list from the references the authors list - it seems to have been used only in a series of companion articles published at the British Medical Journal.

## Authors

We have rewritten the sentence to this effect "Some previously published articles under the umbrella of ABC of oxygen (Bateman 1998; Leach 1998; Peacock 1998; Williams 1998; Wilmshurst 1998) use the ABC symbolically and provide overviews on specific areas related to normoxia, hypoxia, and hyperoxia."

## Reviewer 2

Page 4, first sentence of first para.: "compartmental normoxia as the  $p_{O_2}$  in any compartment ... under ambient normoxia" - shouldn't this refer to "ambient normoxia and basal oxygen demand". For instance, could not one think that a human doing strenuous aerobic leg cycle ergometer exercises at sea level (thus ambient normoxia) would have a "gastrocnemius muscle" compartmental hypoxia, rather than compartmental normoxia? This compartmental hypoxia could be evidenced by the fact that the exercising muscle would be under local control of its circulation by  $p_{O_2}$  reduction-induced vasodilation. In this example, since the contractile activity is sustained, there would not be c-type hypoxia and thus the muscle would be in C-type normoxia.

## Authors

Dr Abdulkader is indeed correct that this sentence should include reference to physiological activity in addition to ambient normoxia. We have rewritten accordingly. Regarding the oxygen partial pressure ranges corresponding to compartmental normoxia for a tissue, please refer to Figure 2 and the legend for explanations and clarifications.

**Reviewer 2**

Page 4, first sentence of last para. "Control of respiration by O<sub>2</sub> pressure pO<sub>2</sub> or O<sub>2</sub> concentration cO<sub>2</sub>..." and whole section 2.5. - The authors circumscribe the C/c-type oxias basically to considerations on mitochondrial O<sub>2</sub> consumption. As such, all processes involving oxygen in this level of description happen with oxygen as an aqueous solute, not as a gas. Though this may seem as rather obvious to the scientists in the cellular respiration field, to a neophyte or a freshman student the use of pO<sub>2</sub> in the cellular level can be confusing - at least that is my experience teaching respiratory physiology for more than 10 years. Though Henry's law is implied throughout section 2.5, I believe an explicit presentation of it could be helpful to this public.

**Authors**

In the revised version of the manuscript, we now explicitly state that oxygen as a gas or dissolved gas can be expressed in either concentration or partial pressure.

**Reviewer 2**

Lastly on section 2.5: the authors start it by stating that oxygen levels could be understood as concentration or partial pressure. But by the end of the section, I could not decide which would be the appropriate synonym of "level", or even if the term "level" should be used at all (see also my points 4 and 9 above). I believe it would be important that the authors took a stance on that. I think that would contribute to their excellent purpose of harmonizing the nomenclature and enhancing proper communication and understanding between the researchers on the biological effects of oxygen.

**Authors**

We have thoroughly rewritten section 2.5 to address these points.