Reviewer's report

Title: Ventilatory chemoreflexes and the apnea-hypopnea index in six-to-twelve year old children

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Reviewer: Karen Waters

Reviewer's report:

Overview:
This article has investigated ventilatory control in a group of 50 children (aged 6-12 years) with a range of severity of obstructive sleep apnoea (1.2-73 events, or 1.2-51 obstructive events per hour of sleep time). Studies included unattended, overnight polysomnography, P0.1, and ventilation at 4 levels of CO2 (air, the 3,5,& 7%), and four levels of O2 (air, hyperoxic, 16 and 14%). Outcome measures include RDI (continuous OAHI), “hypercapnic and hypoxic responses”, P0.1, and eupneic expired CO2.

The study extends an area of physiological study that is of interest in Pediatric sleep medicine. The outcomes are relevant to clinical medicine, because they guide further studies of possible clinically-significant abnormalities. As presented in the introduction, there is some current debate about whether abnormalities of ventilatory control are associated with obstructive sleep apnoea in children. Larger studies, such as this one, will substantially improve the information available regarding this issue, and the multi-faceted approach that this group have taken to studying the problem will help clarify the points at which the abnormalities (which they have detected) occur within the ventilatory control system.

In its current form, however, the article lacks clarity to the extent that I found the article difficult to read and interpret over several points. My suggestions regarding revision of the written article are aimed at enhancing the readers’ ability to interpret the science being reported.

GUIDELINES ----------

1. Is the question posed by the authors new and well defined?
   The authors have posed several questions in this manuscript. Some of these are more novel than others.
   If I interpret the abstract correctly, then the primary outcomes of the study were to be hypoxic and hypercapnic ventilatory responses. If that is the case, then the significant contribution of this manuscript is the large dataset that were studied.
   However, other questions have been studied, and have taken a higher profile in the results and discussion that are presented.

The only point where the hypothesis is currently stated is in the abstract.
Here, it is posed as: “the ventilatory response to chemoreceptor stimulation is inversely correlated with the OAHI”.

The results, as presented, suggest that the authors interpret the P0.1/ end-tidal O2 (figure 7) or P0.1, CO2 (figure 6) as the best indicator of ventilatory responsiveness. In this case, the inverse correlation is shown for hypoxic responses, but not for hypercapnic responses where the slope of the correlation changes depending on whether the outlier is or is not included.

On the other hand, the manuscript suggests that if eupneic CO2 is taken to somehow reflect the ventilatory responsiveness to CO2 (with higher eupneic CO2 reflecting lower CO2 sensitivity), then the same inverse correlation also exists for CO2 responsiveness.

2. Are the methods appropriate and well described, and are sufficient details provided to replicate
Several methodological issues are unclear. Although it is stated that steady-state gases were used, a time limit was set for the duration of the exposure (although some went “a bit longer”, and a pre-defined cut-off point for saturation was used to terminate tests. No data is presented to confirm that equilibration was achieved between inspired and expired gases (which would confirm that steady state was indeed achieved). The point at which measurements of ventilation were made does not clarify this point (whether steady state was achieved) since it was over “6-10 breaths during the last 30-40 seconds” of the experimental condition. In addition, as written “CO2 in hyperoxia ... or 16 and 14% O2 balance nitrogen”, suggests that hypercapnia was combined with hypoxia. This point needs better clarification, as the description is ambiguous, but methodologically, very important.

While the majority of the methods appear to be carefully explained, these unusual descriptions of the methods, and analyses make it difficult to interpret the results.

3. Are the data sound and well controlled?
No control subjects were used, but the use of continuous outcome measures in a large group (50 subjects) is perfectly acceptable as a study design.

The description “random selection” is not strictly true, since the authors then go on to describe the criteria used for sub-group selection, and this should be corrected.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
In the introduction, the background for the measurements is presented, with three outcomes:
“a) to examine the correlation between OAH1
b) P0.1, P0.1 in hypoxia and hypercapnia, and
c) to measure the CO2 set-point”.

In the results, the minute ventilation is presented at 3 levels of CO2, and two levels of hypoxia, with the hypoxic responses presented in a non-standard manner (slope derived using VE against expired O2, rather than against oxygen saturation).

The results do reflect physiological measurements of ventilatory responsiveness, but loose terminology in this manuscript makes it quite hard to read. For example, in the first paragraph of the discussion is the sentence, “Thus, the higher the OAH1 the greater the resting CO2 retention and the more sluggish the hypoxic responsiveness”. However, the results (measurements) presented are of “resting CO2”, and of “upper airway reflex responses during hypoxia”. The manuscript would benefit from some additional care with terminology, since great care has clearly been taken during the data acquisition.

5. Are the discussion and conclusions well balanced and adequately supported by the data?
From a background of the abstract, and methods, where the authors pay great attention to descriptions that suggest they are using well-established methods, they have proceeded to non-standard data analyses. The conclusions are relevant to, but also appear to have focussed on their positive study outcomes.

6. Do the title and abstract accurately convey what has been found?
Some results presented in the abstract do not appear in the manuscript. For example, the correlation of hypoxic sensitivity is presented as positive (r=0.31), but the lower panel of figure 2 shows a negative slope. The manuscript proper focuses much more on results for P0.1 than for ventilatory responses, yet it is the ventilatory responses that are presented in the abstract.

7. Is the writing acceptable?
The article needs substantial revision before it would be acceptable for publication. In particular, the abstract should better reflect the primary measures and outcomes of the study. In particular, the P0.1 should be highlighted in all sections of the manuscript if the authors think that it is important. The study methods need clarification before this reviewer can be satisfied that the measurements
and analyses were indeed methodologically sound. The manuscript currently presents one focus in the abstract, another in the introduction, and yet another in the results and discussion. The introduction and conclusion have the most alignment. Therefore, the manuscript would benefit from substantial revision to first define what focus the authors which to have, and then alignment of all components of the manuscript (abstract through to conclusion).

In summary: Revisions should be undertaken (as detailed above) before publication. The article would be appropriate for BMC Physiology.

This study is one component of a larger study. However, the interdigitation of the studies is clear from the presentation of the methods, and the separate description of these results is appropriate. There is no suggestion of duplication.

Level of interest -----------------
The article is of interest to physiologists and clinicians involved in Pediatric Sleep Medicine.

Minor points:
Methods: It is not usual to compare end-tidal O2 against VE to determine hypoxic ventilatory responses. The standard technique is saturation, which generates a linear correlation. This should be explained.

Page 5, last paragraph, 3rd line. The meaning of this sentence is not clear. As stated (“..50 subjects by randomly selecting children with respiratory disturbance index (RDI) values greater than or equal to 5, or less than 5.”) the selection was not random. In the context of the following sentence, it would be better stated “To ensure that equal numbers were represented in the groups with RDI values < or <= 5 events per hour random selections were undertaken within each category.” This is also pertinent when examining the distribution of the OAHI which is in figure 1 appears to be skewed. Thee usual statistical procedure is this case would be to transform the data (commonly, with OAHI, a log transformation is used). It is also not immediately clear to me why this distribution does not appear to be replicated in subsequent figures (4, 6, & 7). This should be clarified in the revisions.

I did not find the age-categorization in Table 1 helpful, apart from showing that it does not reflect the usual age-distribution of children evaluated in Pediatric sleep units. Can the authors explain why the data is presented this way?

What next?: Accept after minor essential revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

None.