Author's response to reviews

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

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Reviewer 1. We wish to thank the reviewer for a comprehensive review.

Reviewer 1 comments: (paraphrased, and underlined), followed by our response.

Discretionary revisions:

Page 2, L 1, Abstract. To change "ventilatory response to chemoreceptor" by "respiratory response to chemoreceptor"

We now use the term ventilatory drive throughout the test, for clarity.

Minor Essential revisions.

A new version of the rewritten manuscript should be recommended........

The paper has been extensively rewritten.

Abstract and Results. Correlation coefficient between OAHI and hypoxic chemosensitivity is a negative value.

This has been corrected.

The authors write that the P0.1 technique does not need to be scaled for size. However, it should be mentioned that muscle strength and lung volumes can modify this measurement.

The issue of muscle strength and P0.1 is highly controversial. Some studies do show that P0.1 is modified by muscle strength (namely, that as strength increases, P0.1 decreases (see recent study by Huang, Martin and Davenport, JAP) --which I personally find difficult to understand, based on a "first principles" standpoint. On the other hand, even extreme muscle weakness, evoked by curare, had no effect on P0.1 (Holle, Schoene and Pavlin, 1984). Nevertheless, we examined changes in P0.1 in response to hypercapnia and hypoxia within each subject, simply to get the slope of the response. The slope in a given subject would not be influenced by strength, which would only come into play in between-subject comparisons of absolute P0.1, which we did not do. As a result, this complex issue has been left out of this study for clarity, and because the paper is already very long; although, this is admittedly a fascinating issue.
Hypothesis study is not clearly defined.

The hypothesis has been changed, and it is now stated consistently in the abstract, introduction and discussion.

For this reviewer is not evident why the patients were classified according to ethnicity. I suggest the excellent discussion of the subject by Kaplan KB. JAMA 2003;289:1709-1716.

We did this because we need to insure (by NIH regulations) that our study-population reflects the Tucson population, which is 30% Hispanic. However, we did clearly note in the second sentence of Results, that there were no ethnicity/gender differences; so all data were treated as a single data set from an homogenous population.

There are a great variability in the VE and P0.1 response to CO2 or hypoxic stimulation. Have you data on intra-subject reproducibility?

We did reproducibility on only a few subjects early on, and the data is quite reproducible. This inter-subject variability is also noted in healthy adults, particularly evident in some of the original work on the method by Whitelaw.

Authors should include some comments about the possible underestimation of the chemosensitivity due to methodological aspects (facial mask, steady state, ...)

We include a few sentences addressing this issue at the end of the "critique of methods" section in the discussion.

Table 1 must be suppressed. Anthropometric data and sleep parameters of the groups must be provided in table 2.

We have incorporated the sleep data in Table 1 into Table 2, so now there is only one Table.

Figure 5 could be dropped

Since this is the only figure showing actual data, we prefer to retain the figure.

Major Compulsory Revisions

Abstract. The last sentence is not supported by the study data.

Thank you; we have altered the sentence appropriately.

The selection of subjects must be described in detail.

This has been done. See the first paragraph in Methods.

The paper shows that the respiratory response to chemoreceptor stimulation is related with OAHI. However, it would be useful if you tested the relationship between the chemosensitivity and other sleep parameters (arousal index, lowest SaO2 or time SaO2 < 90%, ...)

We did use SaO2 initially, but the change from normoxia to hypoxia was very small (low dynamic range), making the data less sensitive. Moreover, as explained in the revised manuscript. We analyzed our data using PETO2 for two reasons. First, in our hands the correlation between PETO2 and P0.1 was better than the SaO2-P0.1 relation. Second, the measurement of PETO2 is more precise and physically meaningful than the measurement of SaO2, which reflects an often-crude
estimate of SaO2 that can vary considerably depending on skin perfusion, movement artifact and other variables (26).

Generally, it is accepted that the P0.1/SaO2 relationship is more lineal than the P0.1/PETO2. Thus, why hypoxic chemosensitivity was assessed as P0.1/PETO2?

Please see above.

Results. There is some potential confounding sentences. Authors should clearly refer that the PETCO2 was not significantly higher in the group with high OSHI than in the children with low OAH (table 2). In contrast, a significant (but weak) relationship was found between PETCO2 and OAH. It is necessary to clarify these points and to justify these discrepancies.

These points have been clarified throughout the re-written manuscript.


The references have been added.

Reviewer 2. We wish to thank the reviewer for a comprehensive and thoughtful review.

Reviewer 2 comments (underlined), followed by our response.

The only point where the hypothesis is currently stated is in the abstract.

We have changed the hypothesis, and have stated consistently throughout the paper. We now use the term "ventilatory drive" rather than sensitivity, and agree that the latter is ambiguous.

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.

In reality the resting PETCO2-OAH slope is positive--kids with a high OAH retain CO2 and have a higher PETCO2. Nevertheless, we have tightened the language throughout the study, and refer to this phenomenon as CO2 retention", which is more commonly used and less ambiguous, because it avoids the complex and contentious issues surrounding the definition of the CO2 set point; we thank the reviewer for pointing this out.

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

First, the protocol section has been rewritten and is now much clearer. We agree that we cannot (nor did not) document a true steady state, and we now avoid use of this term. And second, we have
clarified the description of all other aspects of the hypercapnia and hypoxia experiments.

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

This has been corrected; please see the first paragraph in Methods.

In the introduction, the background for the measurements is presented, with three outcomes: "a) to examine the correlation between OAHI 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).

First, we now use the term CO2 retention rather than "set point", as discussed above. Second, We did use SaO2 initially, but the change from normoxia to hypoxia was very small (low dynamic range), making the data less sensitive. Moreover, as explained in the revised manuscript. We analyzed our data using PETO2 for two reasons. First, in our hands the correlation between PETO2 and P0.1 was better than the SaO2-P0.1 relation. Second, the measurement of PETO2 is more precise and physically meaningful than the measurement of SaO2, which reflects an often-crude estimate of SaO2 that can vary considerably depending on skin perfusion, movement artifact and other variables (26).

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.....

This is an excellent point, and we have rewritten the entire paper with great attention paid to the consistent use of terminology throughout the paper.

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.

This has been corrected.

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 ..... 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).

Again, the entire manuscript has been rewritten with this in mind; we appreciate that the reviewer took the time to point out these inconsistencies.

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.

This has been addressed above. We have also described our methods for computation of the
P0.1-PETO2 relation in more detail, in Methods.

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 has been corrected, and addressed above.

This is also pertinent when examining the distribution of the OAHI which is in figure 1 appears to be skewed. The 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?

WE agree, and think that Figure 1 is leading to confusion because it is designed with 4 OAHI points per bin. It is really not needed, and we have eliminated it. We have also put the RDI and OAHI data from old Table 1 into Table 2, so that now we have only one Table. The range of AAHI values is easily seen by looking at the regression analyses in several of the figures, and we have also included the range in the Table.