Author’s response to reviews

Title: Respiratory mechanics in infants with severe bronchiolitis on controlled mechanical ventilation

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Guillaume Emeriaud, MD PhD
BMC Pulmonary Medicine

Dear Dr. Emeriaud,

Thank you and Drs Essouri and Baudin for the interesting observations to our manuscript (ID: PULM-D-16-00476) entitled "Respiratory mechanics in infants with severe bronchiolitis on controlled mechanical ventilation". We have responded to your comments and those of the reviewers in a point-by-point manner. In the point-by-point response that follows, we have
I. Editor Comments:

…In addition, it would be important to clarify the place where the volume, flow, and pressure were recorded? Was it at the Y piece or at the ventilator level? If it was done on the ventilator, was the respiratory circuit compliance compensated for or not?

This could certainly have an impact on the calculation of VT (and therefore of Crs), and also on the Resistive components (of the patient or of the patient+ circuit). This should be clarified in the methods and the potential impact should be discussed in the methods.

R: Thank you for this comment. We added to the methods section that Flow was measured at the Y piece (proximal flow sensor) as recommended by the manufacturer for infants.

Finally, one important finding is that the resistive component does not seem to be the most important problem in bronchiolitis. This is interesting as those patients have frequently overdistended lungs. If this overdistension is not the consequence of high resistance, do the authors think that it could be the consequence of an adaptation of the ventilatory pattern, adopted to optimize the respiratory mechanics? For example, we recently described (Larouche A, Ped Pulm 2015) that patients with bronchiolitis have particularly high tonic diaphragmatic activity, which also suggests "voluntary" patient efforts to increase the lung volume (through expiratory braking)...  

I wonder if the authors could prudently speculate a bit more about the consequence of their findings: how could they explain the frequent overdistension?  

R: This is a very interesting observation. We agree with the reviewer that overdistension is very frequent in bronchiolitis. Overdistension might be the response to the pathophysiological condition instead of the primary problem in patients with significant respiratory effort. Unfortunatelly, in our study we cannot explore that hypothesis. Patients were under the effect of neuromuscular blockers. No patient effort or diaphragmatic tone was present at the time of measurements.
Reviewer reports:

II. Florent Baudin, M.D (Reviewer 1):

…However, as in my previous comment, I am not quite sure that the use of the "airway pressure" as a surrogate of the "work of breathing" is validated and I am not aware of any study that allows to express each component of WOB as a percentage of airway pressure? I suggest the authors to provide references to use such equivalence. If not, I suggest the authors to remove the term WOB and expressed each component as a percentage of the working pressure.

R: We agree with the reviewers that WOB and working pressure are not equivalent. Although, according to equation of motion (formula 1), in patients without effort (under neuromuclcular blockers) and considering negligible the inertance, there is a good approximation between the proximal airway pressure applied by the ventilator and WOB (Formula 2)

\[
\text{P}_{\text{vent}} + \text{P}_{\text{mus}} = \frac{\text{VT}}{\text{CRS}} + \text{Raw} \times V \text{I}
\]

+ PEEPTOT + inertance (1)

\[
\text{P}_{\text{vent}} = \frac{\text{VT}}{\text{CRS}} + \text{Raw} \times V \text{I}
\]

+ PEEPTOT (2)

Having clarified that, we agree with the reviewers that we did not measure WOB (Joules or power) and in order to avoid confusion, is more correct to express each component as a percentage of the working pressure.

The analysis of the compliance and resistances was more relevant. I also suggest the authors to compare their values with others studies or with the very few "normal values" available in infants (Papastamelos et al. J App Physiol.1995 / Am Rev Respir Dis Vol 147. pp 474-496, 1993/ Gerhardt J pediatr 1989;114:120-5 / Tepper et al. Am Rev respir dis 1984; 130:461-466 / …). In comparison with reference values, the airway resistances were low in this study (even in comparison with healthy children??) and the compliance was decreased. It reinforces the findings of the authors and their conclusion.

R: Thank you for these interesting references. Compliance of the respiratory system was decreased by 50% compared to normal reference values, supporting the restrictive component of bronchiolitis.
Data of RawE in healthy infants is scarce. Compared with premature newborns, our patients’ RawE was very low, and this difference was even higher when compared with BPD patients on spontaneous breathing. The low RAWE measured could be explained by positive pressure support and the suppression of respiratory effort with neuromuscular blockers.

In summary, the theoretical description of bronchiolitis, normal CRS (>1) and high RawE, was not observed in our series.

We added to the discussion these references.

There are probably several presentations of bronchiolitis and the population studied by the authors was only one of them. I appreciate the section added by the authors in the discussion.

R: We agree with the reviewer. It was highlighted in the limitations and also added to discussion.

Specific:

**Abstract page 3 - line 59 and page 12 line 22. "RawI was higher than RawE in 37.5 % of cases and I/E ratio was 1:1.04 (1:0.59-1.42 ) » What does mean I/E ratio (IT/ET ratio?) In their response, the authors wrote that the ET was 1.44 with RR = 28 => IT/ET ratio = 1/2 ? Please clarify this point.

R: Thank you for bringing this to our attention. We meant to describe the ratio between Inspiratory Time Constant (KTI) and Expiratory time constant (KTE). We changed to “KTI:KTE ratio”.

**Results: Page 12 - Line 7 and response. In volume control mode the flow is constant and a controlled variable. Therefore, the flow was either set by the physicians either calculated by the ventilator (after the settings of the slope, inspiratory pause, IT,…). Does the authors set the flow rate? If yes how (1L/Kg/min)?

R: This is a very interesting observation, considering the numerous commercially available mechanical ventilators currently in the market.

Engstrom® (GE Datex, Madison, Wisconsin USA) and Hamilton G5 or Galileo® (Hamilton, Bonaduz, Switzerland) were the ventilators used in the study. The volume-controlled mode
allows the physician to set the tidal volume and Inspiratory time. The ventilator software calculates inspiratory flow.

**Table 2:**
- Please add the median and IQR in the table
R: it was added.

- Please change commas by dots in column 2
R: it was changed.

**Figure 1 B:**
The quality was higher than previously but it remains difficult to read the words (auto PEEP, inspiratory pause,…). Please increase the size of police.
R: It was changed.

III. Sandrine Essouri (Reviewer 2):

…As suggest by reviewer 1, the driving pressure needed to overcome resistive and elastic loads isn't a surrogate of WOB. To avoid confusion for the reader, despite the explanation made once in the revised manuscript, it seems preferable to avoid WOB and speak of driving pressure to overcome resistive and elastic loads all over the manuscript.

R: Thank you for this interesting observation. Please see answer to reviewer #1.

For exclusion criteria, page 7 in the material and method section you write that patients with consolidation greater than 1 quadrant were excluded and in the discussion section, page 15, you write " We excluded patients with more than 2 quadrants of infiltrates". Please check.

R: Thank you for bringing this to our attention. It was corrected.
The reference 22 used in the discussion section "so our pathophysiological findings may differ from moderate or mild disease" is not the good one because this reference is a randomized controlled study on HNFC versus CPAP in bronchiolitis but does not address pathophysiology. Please correct it.

R: Reference was fixed, to the previous

Thank you for the opportunity to revise our manuscript. We feel that it has been strengthened considerably as a result of the suggested edits.

Sincerely

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