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 the reviewers for the constructive comments on 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 quoted the reviewer
Reviewer 1

The authors conducted a study to explore respiratory mechanics in children with severe bronchiolitis with mechanical ventilation. It is an interesting question and a simple exploration way of mechanics at the bedside. However, the authors made some approximations and I have some concerns with the conclusions of the authors.

As mentioned by the authors, there are 2 components of WOB: Resistive and elastic. On the other hand, the equation of motion explains the airway pressure in a patient without effort under mechanical ventilation (John West, respiratory physiology - the essentials). The authors express in percentage the equation of motion (Resistive, elastic and threshold component) to conclude on WOB. Airway pressure and WOB are not equivalent and not allow the authors to conclude on the WOB.

R: Thank you for this observation. We added to the methods section that patients were on mechanical ventilation without spontaneous breathing effort. We agree with the reviewer that Paw and WOB are not equivalent. Instead of calculating the WOB, we used the working pressure of the respiratory system as a surrogate marker of WOB. Working pressure of the respiratory system is the pressure needed to overcome frictional forces, elastic forces and impedance. We changed that in the methods section and we added the equation of motion. Each component of WOB was expressed as working pressure in cmH2O and as percentage of total working pressure of the respiratory system.

Moreover, each part of the equation of motion was influenced by the settings:

- The Resistive part (FLOW x RESITANCE) is linked with the Flow. The physician directly set inspiratory flow. If you increase flow then you increase PIP and the percentage of pressure due to resistive component without change the airway resistances of the children…

R: On the ventilatory mode that we used, we only set VT and IT; the ventilator calculates flow. As we previously emphasized, we standardized the MV parameters, VT was 7,9 ml/kg and IT
0,7''. In our view this is one of the high points of our paper, making a great difference with previous studies, where peak inspiratory pressure and VT were higher. We added this observation to the discussion.

- Elastic component and auto-peep may be also influenced by the settings (Respiratory rate, I/E). If the exhaled time is too short to allow total exhalation you increase auto-Peep (dynamic hyperinflation) and the end expiratory lung volume (EELV). In this study, the I/E ratio set by the authors (patient) was 1:1.04 that is short and may explain dynamic hyperinflation in children with obstructive disease. Moreover, the Pressure/volume curve is not linear. By increasing EELV, the range of Vt is shift on the right of the P/V curve where there is increased elastic loading (that may explain a part in the decrease of compliance).

R: Thank you for bringing this to our attention. TI and TE referred to inspiratory and expiratory time constants and IT referred to inspiratory time. In order to avoid confusion we changed inspiratory and expiratory time constants to KTI and KTE respectively through the manuscript. Having said that, the inspiratory time constant (KTI) and expiratory time constant (KTE) ratio was close to 1:1, but the mean respiratory rate was 28 breath per min and inspiratory time (IT) was 0.7''. So the mean expiratory time (ET) with these parameters was 1.44'' , with a I:E ratio close to 1:2. Also, measured Total PEEP was low, an indirect sign of nonexistent or minimal dynamic hyperinflation. We clarified this in the manuscript.

Secondly, Hammer et al (Pediatric Pulmonology 23:176-183 (1997)) previously describe the 2 patterns in RSV bronchiolitis (Obstructive and restrictive). The authors should discuss their results with comparison with the previous papers. In the paper of Hammer et al, Restrictive group was ARDS patients with alveolar disease whereas obstructive patient have over-distension. The P/F ratio was < 200 mmHg but we have no data on the x-ray. The authors should precisely describe their population of RSV intubated patient.

In the obstructive group (in Hammer et al.) compliance was at 0.57 ml/cmH2O/Kg that is very close to the data in this study (0.55 ml/cmH2O/Kg). Finally, the patients in this study were not so restrictive. The authors should discuss this point.

I suggest the authors to clearly describe the patients, the settings and to justify it and finally to review the approach of the analysis and the conclusion accordingly.
R: Thank you for mentioning the article of Hammer et al. One of the exclusion criteria in our study was patient with consolidation or atelectasis greater than 2/3 of one hemithorax. We reviewed chest x-rays of the included patients and none of them had more than 2 quadrants of opacities. Looking the results of Hammer et al., probably they were describing varied conditions/diseases under the name of bronchiolitis due to the wide inclusion criteria. It is very interesting that they did not describe ventilatory parameters used. Given the fact that in the mid 90’s (pre ARDSnet study and low VT era) ventilatory settings were totally different from the contemporary standard of care, affecting the results of pulmonary mechanics. Large VT can be associated with hyperinflation on x-ray and also dynamic hyperinflation and AutoPEEP. They did not describe timing of measurement. One of the strength of our study is that ventilatory parameters were very homogeneous and it was in accordance with current recommendations.

Ventilatory parameters of each subject were added to Table 2.

This reference was added to the manuscript and discussion addresses their results.

Others:

Page 7 - Line 31: The range of age was large. As physiology change in the first months of life, the authors should add this limitation in the discussion.

R: It was added to the limitations.

Page 10 - Line 59: QE was set and QI was measured. Why the authors make this comparison? Please clarify.

The ventilator mode (volume controlled) was only given in the abstract but not in the article. Please add a section to describe the mode and the settings.

R: Thank you for bringing this to our attention. We added to the methods section tan patients were placed on volume control mode. Also we changed the term Mechanical Ventilator setting to parameters to clarify that QE and QI were registered (and not set by the investigators).
Figure 1B: poor quality of the picture (not easy to read)

R: A 300 dpi picture was uploaded.

Table 1: Patient 16. Bronchiolitis is due to bacterial infection? Not clear.

R: It was changed to viral bronchiolitis with negative viral study (on Viral Immunofluorescence), but bacterial superinfection was diagnosed.

Reviewer 2:

I would like to congratulate the authors on their work addressing the physiopathology in infants with severe bronchiolitis.

This study investigates the respiratory mechanics of infants with severe bronchiolitis requiring invasive ventilation but important data and considerations are lacking making their results less credible and representative of patients with severe bronchiolitis.

This study investigates a very specific population of severe bronchiolitis and also among them the most severe patients. The study gives to the reader a strong description of respiratory mechanics but there is no clinical correlation and most important no description of the patients.

Introduction

1. line 25: Bronchiolitis is usually ....requiring mechanical ventilation... you need to precise that now, bronchiolitis even the most severe forms, are mainly managed with noninvasive ventilation. The percentage of patients needing invasive support is very low. Your manuscript will be strengthened by the adjunction of epidemiologic data of the specific population studied here.

R: In both centers about 2 percent of patients with bronchiolitis were admitted to ICU, and only 50% of them required mechanical ventilation. This was commented in the discussion.
2. A better characterization of respiratory mechanics in severe bronchiolitis is crucial... I totally agree with this point of view but the population studied in this study doesn't reflect most of bronchiolitis patients.

R: Thank you for this comment. We added to the discussion that these results represent only the patients with most severe form of bronchiolitis. In addition patients with significant respiratory comorbidity (like BPD, chronic lung disease) were excluded.

3. "ultimately, it may improve outcomes" Can you clarify because the mortality is very low and do you really think that it should improve other factors such as length of ventilatory support or length of PICU stay ?

R: It was changed specifying the usual outcomes in PICU

Materials and methods

4. Study population: when was this study performed? Give a brief description of the PICUs involved in the study, number of beds....

R: Thank you for this observation. We added to the manuscript that the study was done between May and August 2015 in two PICUs: Hospital Pereira Rossell is a 20 bed mixed medical surgical unit located in Montevideo, Uruguay, that takes care to all common PICU pathologies except cardiosurgery. Hospital El Carmen de Maipú is a 6 bed polyvalent unit and a referral center for acute respiratory failure in Santiago de Chile.

5. The authors should describe the criteria for invasive ventilation. Are they similar in each center?

R: Criteria for invasive ventilation for acute respiratory failure are very similar in both centers: Severe respiratory distress, persistent hypoxemia and hypercapnia with respiratory acidosis. Most patients failed non-invasive mechanical ventilation or high flow nasal cannula trial before deciding necessity of invasive ventilatory support. Other indications in both units are in accordance with general PICU guidelines, like apneas, shock, encephalopathy, impairment of
consciousness and coma. It would have been interesting to know the exact cause of intubation as well as other associated therapies. On our next study it will be definitely added.

6. Did you register clinical data and gaz exchange just before invasive ventilation?
R: unfortunately no gas exchange data was registered before intubation, most of patients did not have arterial gas sample before intubation. Reported data is the first arterial blood gas after intubation.

7. "Resistive component: PIM-PPL" you need to define PIM
R: This typo was fixed. We meant PIP.

Figure 1: autoPEEP was not measured in ZEEP ??
R: We agree that from the research methods standpoint autoPEEP is usually measured without extrinsic PEEP, from the clinical standpoint facing patients with severe acute respiratory failure it would be difficult to get approval from IRB.

Results
8. What was the percentage of bronchiolitis with oxygen support alone, highflow nasal canula, NIV and IV during the period study ?
R: Unfortunatelly we don’t have the exact data of the study period. About 2% of all admitted bronchiolitis were admitted to critical care bed, and only 50% of them were finally intubated.

9. PF ratio were obtained for all patients ? Did these patients have an invasive arterial line ?
R: Not all the patients had an arterial line. Most of the patients of Chile had invasive blood pressure monitoring, but that is not the standard of care in Uruguay. Although, usual practice is that after intubation at least an ABG is taken within the first hour after intubation.

10. In the studied population, how many patients have bacterial coinfection? It need to be added in the manuscript or table 1. Bacterial coinfection is a main factor of severity and may change the physiopathology.

R: It was added to Table 1. In one patient, there was a co-infection between RSV and pertussis, and in other patients viral immunofluorescence was negative, but a pneumococcal infection was diagnosed.

11. What are the ventilatory settings used?

R: thank you for bringing this to our attention. It was added to table 2.

12. line 41: IT of 0.7 s, you mean Ti?

R: thank you for your comments on this issue. In the manuscript we refer to the inspiratory constant as “Ti” and inspiratory time as “IT”. Because it may lead to confusion we changed to KTI the inspiratory constant and we kept IT as set inspiratory time.

13. no significant differences were found between Ti and Te. All patients were Under the effect of neuromuscular blocker as describe in material and methods thus Ti and Te depend on ventilatory settings rather than respiratory mechanics.

R: please see above. TI and TE referred to inspiratory and expiratory time constants. In order to avoid confusion we changed to KTI and KTE respectively through the manuscript.
14. Table 2: can you give the data for each patient instead of median. Is there a difference between the younger patients <2 months? When looking at table 1, we can separate patients less than 2 months with the higher PF ratio from intubated patients over 2 months who have the lowest PF ratio. For the oldest patients, PF ratio are lower and we can suppose that they have a P-ARDS, most of them have criteria, either PF ratio or OI, but what about chest X ray. Adding the results of coinfection and chest X ray would help.

R: We changed table 2 to a case-by-case ventilatory parameters data. An analysis of the patients as suggested by the reviewer was attempted. No differences were found when cases were compared by age and PF ratio. Although, it is a very good hypothesis for our next exploratory study. Thank you for this interesting feedback.

Discussion

15. "These observations place severe bronchiolitis as a primarily restrictive disease" The data presented in this study do not support such conclusion. The population needs to be better described as previously required.

R: Thank you for this observation. We changed this sentence in accordance to our results.

16. "These findings may seem unexpected and contradictory with the current understanding of severe bronchiolitis as a primarily obstructive airway disease." Your population may not reflect only bronchiolitis. The youngest patients may have an obstructive disease as previously demonstrated in physiopathology studies of patients with severe bronchiolitis needing respiratory support (NIV). Please refer to Milesi et al. and Essouri et al.

R: Please see previous point. We changed this statement in accordance to our results. We focus only on patients on Invasive mechanical ventilation, so they are the most severe bronchiolitis cases.

17. "but they are supported by Krieger et al" This study was published in 1964....since then there is a major gap in the management of invasive ventilation and ventilatory settings. You need to find more recent study to reinforce your results.
R: We agree this comment. Unfortunately there is very limited data of patients with severe bronchiolitis under mechanical ventilation. A good example is the article of Hammer et al. (Ped Pulmonol 1997, see reviewer #1) where lung mechanics and x-ray patterns were described, but ventilatory parameters were not reported.

16. As you well describe in a paragraph, your findings are similar to ARDS pathophysiology, the population studied may not reflect only bronchiolitis even if RSV was found in most cases.

R: We acknowledge that current definitions of PARDS are very loose and include a wide umbrella of conditions and diseases. In this case series we tried to focus on a single condition: patients with severe bronchiolitis that fail standard treatment and require invasive ventilation.

Conclusion
"according to our results traditional pharmacological and ventilatory strategies may need to be revised"

The design of the study does not allow such conclusion. There is no comparison between different ventilatory strategies and no outcomes measured.

R: We agree with this observation. We change this to “a better understanding of lung mechanics may lead to change the traditional ventilatory approach to severe bronchiolitis”

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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