Author’s response to reviews

Title: Comparative bench study evaluation of different infant interfaces for Non-Invasive Ventilation.

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Author’s response to reviews:

Dear Editor

Dear Reviewers

Thank you very much for your revision.

We provide here a point-by-point reply to your comments and queries.

We hope that, with the help of your revision, this version of the manuscript merits publication in BCM Pulmonary Medicine.

Best Regards

The authors
Editor Comments:

BMC Pulmonary Medicine operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Reviewer reports:

Juan Mayordomo-Colunga (Reviewer 1): Thank you very much for giving me the opportunity to review this bench study comparing different interfaces to deliver non-invasive ventilation (NIV) in infants. This topic is very important as interface is of utmost importance to achieve synchrony during NIV, and very few interfaces are available for infants. The present study suggests that a new nasal interface may have some advantages over another nasal mask. The main limitations of this work are related to the delivery of NIV in 'ideal' conditions: no unintentional leaks, use of pressure support ventilation without NIV mode (air leak compensation software), and steady respiratory rate. Authors adequately address these limitations in Limitations.

Major comments:

* Please clarify why the air leak compensation software was not used. Leaks are always present during NIV, especially in children (ill-fitting interfaces, non-cooperative patients, mouth opened...). Authors sealed the masks (and filled the mannequin mouth to reduce dead space) and that is not applicable in clinical practice. This may limit the usefulness of the results in daily practice. Please comment on this.

Thank you for the comment.

In our bench study we wanted to precisely evaluate the performance in terms of PTP trigger, PTP300 and 500 etc, and in terms of patient-ventilator interaction. We had therefore to eliminate all the factors that may deeply modify those measurements. Only by sealing the masks to the mannequin and by filling the mannequin mouth to reduce dead space we were thus able to evaluate the performance of each interface in optimal conditions, thus obtaining clear data on the specific characteristics of each interface.

* Pressure support used (13 cmH2O) is quite high. Please clarify why authors made this choice.

We simulated a 5.5 Kg BW infant, with a restrictive condition (mild Acute Respiratory Distress Syndrome , ARDS), with a Compliance of 0.8 ml/cmH2O/kg, respiratory system resistances of 25 cmH2O/L/sec and inspiratory muscle pressure (Pmus) at 12 cmH2O. The PS was increased, in step of 1 cmH2O, starting from 10 cmH2O. A value of 13 cmH2O allowed us, to obtain a Vt around 6-7 ml/kg during NIV .
We also thank the reviewer, because by answering to this comment we noticed a typing error was made in the previous version. Indeed the reported body weight of the infant was 3.5 Kg instead of 5.5 Kg, We now corrected this value in the new version.

* What do authors mean when they state that inspiratory trigger, pressurization time and trigger threshold were set 'to optimize patient-ventilator interaction'? Please explain this further.

Thank you for your comment. Both the inspiratory trigger and the expiratory trigger threshold values were chosen to reduce as much as possible the delay between the mannequin onset of the inspiration and the ventilator start of the assistance, on one side, and on the other the delay between the end of the mannequin inspiration and the end of the mechanical insufflation. An optimized setting reduced major asynchronies, such as ineffective efforts, double triggering etc. Thus, allowed us to perform a more precise evaluation on masks’ performance.

* Could authors please provide the name/brand of FPM? Reference 17 studied FP Zest, but that does not seem the one authors analyzed in their bench study.

Thank you. The name/brand of FPM is Fisher and Paykel Health Care Infant Nasal Mask, New Zealand. We now provided in the text the exact name (page 4 line 11).

* It would be very useful and informative providing a figure where most of the parameters analyzed could be seen graphically.

Thank you for the comment. We’ve now provided a new schematic representation (Figure 2), extrapolated from our data base and not connected to this bench study, in which we graphically showed the patient-ventilator interaction measurements. We decided to not insert the performance measurements to not overwhelm the figure. For a schematic representation of performance measurements we already cited the paper from Vignaux L (Vignaux L, Tassaux D, Jolliet P (2007)Performance of noninvasive ventilation modes on ICU ventilators during pressure support: a bench model study. Intensive Care Med 33:1444–1451 ) in the material and method section page 6 line 5.

* Results are summarized in the first paragraph of Discussion, but tidal volume delivery is not included. I believe VT is also important, especially in restrictive lung disease, as shown by Carteaux et al (Failure of Noninvasive Ventilation for De Novo Acute Hypoxemic Respiratory Failure: Role of Tidal Volume. Crit Care Med. 2016 Feb;44(2):282-90).

Thank you for the comment, we now better specify in the results section the result on VT (page 7 Lines 17-20). We also added, in the discussion section, a comment on this issue (page 8, line 24-25).

* Page 9, lines 24-28. Authors state that NIV in PICU is "delivered by high pressure ICU ventilators with active valves adopting a double circuit, without any intentional leak". That is not true in many PICUs, where NIV is delivered by dedicated NIV ventilators.
We thank the Reviewer for the comment. We agree that children can be noninvasively ventilated using intentional leaks ventilators namely ventilators that are coupled with masks with embedded "exhalation holes", also named as vented masks. We added the following sentence in the discussion section:

“In order to understand this issue, it is important to note that in PICU, CPAP is delivered through “leaking systems”, where intentional air leaks are an intrinsic feature of the CPAP system. In the same way, NIV can be administered using intentional leaks ventilators, namely ventilators that are coupled with masks provided with embedded "exhalation holes", also named as vented masks. Conversely, in our bench study, NIV was delivered by a high pressure ICU ventilator with active valves adopting a double circuit, without any intentional leak. For these reasons we used a non-vented mask.” (page 9 lines 14-20)

* It is surprising that Respireo showed better Swingtrigger and PTPtrigger than ET. Why do authors think this could be related to? It may seem that an interface with smaller dead space would show better performance. Please elaborate on this.

Thank you for the comment. A possible explanation is related to the higher respiratory resistance that the endotracheal tube generates compared to the Respireo mask. The high resistance increases the swing trigger and thus, even if the Delay trigger insp is shorter with the ET, it causes an higher PTPtrigger. We add a comment on this in the discussion section (page10 line 1-3)

* There are some relatively new total face masks specifically designed for 'small children', that are being used very frequently in many PICUs. They have the advantage of avoiding leaks through the mouth, apart from avoiding pressing the forehead and the nasal bridge. Maybe a comment about this should be added.

Thank you for this comment. This is an important aspect. Our study was strictly dedicated to the comparison of two nasal interfaces for NIV.

Recently, a total face mask for infants has been introduced in the market, with important potential advantages in terms of air leaks and tolerance. At the time this study was designed the total face mask for infants was not on the market yet. For this reason we decided to evaluate only nasal masks for infants. A new study comparing different interfaces for NIV in infants is in project in our Lab.

* Main limitations are adequately addressed. However, a direct comparison of different interfaces (not including ET) is not technically or ethically impossible. Several studies have used a crossover study (face mask Vs helmet for example).

Thank you for your comment. We decided to compare the standard nasal mask, widely diffuse in the PICU's with the gold standard for ventilation in infants recovering from a mild ARDS and with a new nasal mask. Clearly, the choice of using the ET as gold standard, obliged us to conduct a bench study. We have now modified the sentence explaining this aspect in the
limitations of the study (page 10 line 25). For sure, clinical study on different NIV interfaces may be conducted on infants.

Finally, the helmet with its large inner volume and compliance does not allow triggering in small children weighting 25-30 Kg BW provided NAVA is used.

Minor changes:

* Please include abbreviations in figures legends.

Thank you. Done

* Page 9, line 44. Please correct: tested the efficiency of face masks in the resuscitation of newborn infants [28, 29] 26, 29.

Thank you. Done

Nadir Yehya (Reviewer 2): This is a bench study comparing mannequin-ventilator interactions between 2 non-invasive interfaces, and an endotracheal tube, in a test lung. The study is direct, the results explained in a straightforward manner, and the authors acknowledge their limitations. The overall interest matter is very niche, but I feel important, as we lack data on many of these devices. I have a few thoughts.

1) The authors used non-parametric statistics to compare results, but chose to present their data as mean +/- SD. Do the authors need to do a Wilcoxon? There data look reasonably tightly distributed, as is common in bench studies. Parametric statistics are generally better powered.

Thank you for your comment. We agree on the fact that parametric statistics are generally better powered. As the reviewer stated, bench study data are often tightly distributed but we preferred to use Kruskal-Wallis test when comparing “non-biological” small data. Kruskal-Wallis test assumes that data have identical shape and dispersion, although in most case little departure from those assumptions do not affect the results. In case of parametric assumption, Kruskall-Wallis test is as powerful as classic ANOVA(1).

2) How is exhalation handled on the Respireo (exhalation holes on mask, at the Y piece)? Does this affect any measurements when comparing across interfaces.

We thank for the comment. As we have already detailed to Rev 1, we agree that children can be noninvasively ventilated using intentional leaks ventilators namely ventilators, that are coupled with masks provided with embedded "exhalation holes" also named as vented mask.
In our setup we used a non-vented mask coupled with a high pressure ICU ventilator with active valves adopting a double circuit, without any intentional leak. We already added a sentence to better explain this point (page 9 lines 14-20).

3) I am intrigued by the improved SwingTrigger and PTP for the Respireo, compared to the endotracheal tube. I would like for the authors to speak more about why this might be. They mention resistance of the ET. One of the issues with bench models is that they poorly capture the airflow dynamics at the pharynx (especially dynamic collapse), and may make the Respireo seem better. This can be added as a limitation.

Thank you for this interesting comment.

Accordingly also to what was requested from Rev 1, we added in the text the following sentence: “This result can be explained considering the higher inspiratory resistance generated by the ET compared to the Respireo mask, that determines a deeper Swing trigger and thus, an higher PTP trigger.”

We perfectly understand your point on possible upper airway collapse during the exhalation phase, but the swing trigger and PTP trigger are both measurements conducted at the very beginning of inspiration (protoinspiratory phase), where the only resistance to be considered is the inspiratory one. In this specific case, the ET clearly represents a more resistive interface, compared to the nasal mask connected to the natural airway.

1. Nahm FS: Nonparametric statistical tests for the continuous data: the basic concept and the practical use. Korean Journal of Anesthesiology 2016; 69:8–14