

## Peer Review File

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### Reviewer A

#### *Major concerns*

1. *I think that the esophageal pressures (ins. and exp.) in your patients are smaller, compared to other studies.*

*- I wonder if you measure the pressure correctly.*

*- You said patients' RASS was -4, but I wonder if they were really in deep sedated.*

*- These are the biggest concern in your manuscript.*

**Reply:** Thank you very much for the reviewer's valuable and inspiring comments.

When measuring the patients' Pes, we took the value at a time point at the end of inspiration or end of expiration. During this process, patients are often in a state of deep sedation or even muscle relaxation, and have no obvious spontaneous breathing. At the same time, the PEEP we applied was about 8 cmH<sub>2</sub>O, the fluctuation was relatively small. Therefore, we think that our measured Pes is basically reasonable. When it comes to the RASS scoring process, we assessed patients' sedation depth by our senior nursing staff and the scores were re-scored before each collection, excluding cases where the patient received invasive treatment, turning over, sputum suction and other operations affecting the scoring. Thus, we think our score is relatively reliable as well.

2. *How many sessions (or days) did your patients receive PPV?*

*- You didn't measure or observe your patients for long-time. So, I think, you cannot say PPV could exert a long-term protective effect on the lungs (the last sentence on Page 10 in the results). Even if so, you move this sentence to the Discussion.*

**Reply:** The reviewer made a good point.

Maybe because our expression is not precise enough, it is easy to be misunderstood that patients in our study just accepted PPV for 6 hours. In our study, the median sessions of the patients who accepted PPV were 2 times (can be seen in Table 1). And most of them accepted PPV and were observed for more than 12 hours or even 16 hours each time (the median time is 12 hours which has been added to Table 1). Due to the limitation of the actual clinical situation, there are still some patients who accepted PPV was about 6 hours, thus we take 6 hours as the dividing line and divided them into “PPV early stage” and “PPV middle/late stage”. Thus, we believe that our results still have reference value. Of course, we agree with your comments, we have revised the sentence mentioned and moved it to Discussion.

**Change in the text:** The median sessions of the patients accepted PPV and the median duration of patients receiving PPV has been added in **Table 1 (Page 36 to 37)**; the sentence mentioned has been revised and moved to **Discussion from line 444 to 447, Page 23**).

*Minor concerns*

1. In the results on “A stratified analysis according to patients’ outcome (death or survival) and Table 3”

- Were the parameters measured during PPV (or SPV)?

**Reply:** Many thanks to the reviewer.

In fact, in Table 3, we have divided patients into survival group and death group according to their final prognosis. Thus, the final statistical results include not only the data recorded during SPV, but also the data recorded during PPV, which is a comprehensive result.

2. In the results,

- Numbers were repeated too much. It can make readers confused. So, I want you to delete many numbers which were already represented in the Tables.

- What do you mean “B”?

- I think "Pspv vs. ppv" means P value between SPV and PPV groups. but it also makes readers confused. I don't think it is a way that we commonly used in articles.

**Reply:** Thanks to the reviewer for the suggestions.

We agree with the reviewer, we have simplified the description in the results section, only kept some important and significantly different indicators in the text part, and also deleted the overly complicated subscripts. If any further simplifications you think are needed, we can make further modifications as well.

In this study, each patient experienced multiple measurements in different prone positions, considering the internal correlation between each measurement of each patient, we use GEE model to control the unobservable differences over time. GEE model makes estimates based on changes within individuals, it works by averaging over all individuals and making guesses about the internal covariance structure. Statistical value B represented the coefficient values of variables in the GEE model to explain the relationship of outcome in different groups compared to control group.

**Change in the text:** The whole Result section (**From line 285 to 403, Page 16 to 21**).

3. In the results on "A stratified analysis according to patients' outcome (death or survival) and Table 3"

- I don't understand the last two sentences "The PFR and Vt ~~~ ". Which groups were comparators?

**Reply:** We feel sorry for the mistake in writing this sentence.

It should be " the Vt, EMGdi and PFR in the death group were significantly lower than the survival group ". We have now corrected it in the article.

**Change in the text:** From line 367 to 370 (**Page 19**).

4. In the 1st paragraph In the discussion (page 13), did you mean it based on your results or just cite another studies?

**Reply:** We apologize for the unclear presentation of this section in the context.

To correct this confusing expression, we have re-paragraphed the Discussion and made some adjustments to the order of content. Now the content in the first paragraph was cited from other studies and the discussion based on our result has been moved to the following paragraphs.

**Change in the text:** From line 418 to 432(Page 22 to 23).

5. In the last sentence on Page 13, what evidence did you based the sentence on?  
- I mean the sentence “Considering that ventilation still continued to improved in the gravity-dependent region~~”. You don’t represent any data on gravity dependent region.

**Reply:** We agree with the reviewer, and have removed the relevant descriptions.

**Change in the text:** the sentence mentioned has been removed.

6. In the following sentence (the 1st part on Page 14),  $P_{Leippv}$  at the early stage and  $P_{LeiPPv}$  at the middle/late stage were significantly different. But I found it was not significant in the Table 2 ( $P = 0.099$ )  
- In the same paragraph on Page 14, You said that  $V_t$  and inspiratory pressure need to be adjusted....and, PPV may be necessary to be switched back to SPV.  
I wonder what do you mean? In particular, switching back to SPV has any beneficial effects?

**Reply:** Thanks to the reviewer for the careful review and constructive comments to the manuscript.

We apologize for the wrong presentation. We have re-checked the data and fixed related errors. What we intended to express is that “ $\Delta P_{es}$  increased significantly during middle/late PPV, while  $P_{Lei}$  increased continuously during this period too, although there was still no significant differences in the latter”. After considering your comments, we agree with you that the relevant statements are not sufficiently rigorous and we have removed the relevant statement.

**Change in the text:** the sentence mentioned above has been removed.

7. In the Table 4, *Pesei* and *Pesee* in the NMB groups were much lower than those in the non-NMB groups. Is it right?

- It's because due to the effects of NMBs, it is anticipated that patients' spontaneous work decrease and so, *Pesei* and *Pesee* decrease.

**Reply:** Thanks for the reviewer's insightful comments.

We have to admit that this result also surprised us to some extent. However, we still believe that the experimental data obtained are reasonable. To those who accepted NMBAs, they have no spontaneous breathing and are in a state of fully controlled ventilation. In this situation, their esophageal pressure is affected by PEEP and Pplat. At the same time, we believe that patients who were not used NMBAs may have some degree of spontaneous breathing which caused the occurrence of man-machine asynchronous events—when the patient is in the spontaneous breathing, it may cause a negative trend in *Pes*, so the *Pesei* will be lower than that of the patient who accepted NMBAs. When the patient is in the end-expiratory stage, it may be due to the patients who did not receive NMBAs used auxiliary expiratory muscles, and there was also a situation of human-machine asynchrony. The *Pesee* of these patients was still higher than that of patients who did not accepted NMBAs, but the gap has narrowed at this time (In Table 3, we can find that there is no significant difference between the two *Pesee*). Of course, we also have to admit that the reasons of above phenomenon may need to be further explained by combining the  $\Delta E_{di}$ .

8. I think you need to explain the abbreviations (on page 7) in the manuscript.

- There are many abbreviations but with no explanations

- What do you mean by “PFR”?

**Reply:** Sincere thanks the reviewer for the kind reminder, and we absolutely agree with the reviewer's suggestion.

The full name of the above abbreviation has now been added to the article.

And “PFR” is the abbreviation of “ $PaO_2 / FiO_2$  ratio”, and it is also sometimes

abbreviated as “OI” (oxygenation index). The above full name has also been added to the article too.

**Change in the text: From line 204 to 215 (Page 11)**

*9. Your IRB No. indicated 2017 but your study started from 2016. So, you need correct it.*

**Reply:** Thanks for pointing out this issue, In fact, most of the experiments and data obtained in this study were carried out or obtained after 2017, and some experiments were indeed carried out before 2017. The reason for the above situation is that we previously conducted relevant research for this study on patients with AECOPD before 2017, and the relevant research also got approval from the hospital ethics committee. And the experiment method we carried out previously was similar to the present study which was purely physiological monitoring without intervention in the treatment protocol. At the same time as we were conducting previous related experiments, we also submitted a new ethical review application for this experimental application and obtained the new IRB number in 2017..

**Change in the text: Line 227, Page 12**

*10. I don't know why you didn't represent interquartile values in tables? You gave "B values" which I don't know in the many tables.*

**Reply:** The reviewer has hit a good point.

In this research, each patient experienced multiple measurements in different prone positions, considering the internal correlation between each measurement of each patient, we use GEE model to control the unobservable differences over time. GEE model makes estimates based on changes within individuals, it works by averaging over all individuals and making guesses about the internal covariance structure. Statistical value B represented the coefficient values of variables in the GEE model to explain the relationship of outcome in different groups compared to control group. We use the “marginal mean” in table, not the mean and interquartile values. Because the data from

longitudinal studies arise from repeated observation of the same individuals, the within-subject correlation among repeated measures must be accounted for during analysis; otherwise, inferences on model parameters could be erroneous because of underestimation of standard errors of parameter estimators and P values of tests. One analytical technique that accounts for within-subject dependence uses marginal mean modelling. We use The term ‘marginal’ indicates that the model for the mean response of a subject at a given time point depends only on the associated covariates and not on any subject-specific random effects or previous responses. [Roberts, G., Ren, Q. and Rao, J. (2009). *Using Marginal Mean Models for Data from Longitudinal Surveys with a Complex Design: Some Advances in Methods*. In *Methodology of Longitudinal Surveys* (eds R.M. Groves, G. Kalton, J.N.K. Rao, N. Schwarz, C. Skinner and P. Lynn). <https://doi.org/10.1002/9780470743874.ch20>]

## **Reviewer B**

*Major concerns:*

*1. The results section is very difficult to read because of the need to include values to at least 2 decimal places, regression coefficient for each variable, and then the p-value between the groups, and the long names of each variable. E.g. for oxygenation (Mean PaO<sub>2</sub>SPV = 95.34 mmHg, B = -11.61; PaO<sub>2</sub>PPV at the early stage = 109.46 mmHg, B = 2.509; PaO<sub>2</sub>PPV at the middle/late stage = 106.95 mmHg, B = 0; PSPV vs PPV at the early stage = 0.001 <0.05). This needs to be adjusted to improve readability. E.g. Due to the differences in body position, the early-PPV and middle/late-PPV PaO<sub>2</sub> were significantly higher than those in patients receiving SPV (95 vs 109 vs 107mmHg respectively; p<0.05).*

**Reply:** Many thanks to the reviewer and we feel sorry for the unclear description of the result section.

Thus, according to your suggestion, we have simplified the expression of the results section, only kept some important and significantly different indicators in the text part, and also deleted the complicated descriptions; the complete result can refer to tables. If any further simplifications you think are needed, we can make modifications as well, thanks again for your valuable advice.

**Change in the text:** The whole Result section (**From line 285 to 403, page 16 to 21**)

*2. There is no data outlining at what point the middle/late readings were taken beyond the description after 6 hours. If they were all taken at 6hrs, just 2 hours after the early stage readings, then the results are much less interesting. If they all represent values taken at 12-16hours then they would be more representative of middle/late stage and therefore more interesting. The authors should include a description to inform the reader.*

**Reply:** We agree with the reviewer. In fact, although due to the limitation of the actual clinical situation, the data collection time of this group of patients was not completely uniform, most of them still accepted PPV and were observed for more than 12 hours or even 16 hours each time (the median time is 12 hours which has been added to Table 1). Thus, we believe that our results are relatively representative.

**Change in the text: Table 1 (Page 36 to 37)**

*Minor comments:*

*Abstract:*

*Line 25: I question the use of “high-strength” to define duration of PPV. I would suggest stating the hours of PPV e.g. early PPV for 12-18 hours duration.*

**Reply:** We agree with reviewer and thanks for the suggestions.

We have revised and stating the hours of PPV instead of define it as “high-strength”.

**Change in the text: From line 26 to 27 (Page 3)**

*Line 28: What is unclear about the use of NMBAs, effect on resp mechanics, or prognosis, or both? State which.*

**Reply:** Thanks to the reviewer for the reminder.

It should be “impact on respiratory mechanics” and we have revised it.

**Change in the text: From line 30 to 32 (Page 3)**



*Line 41: PesSPV is reported as 7.46 cmH2O here but 7.45 in line 246.*

**Reply:** We feel sorry for this mistake and have checked the original data again.

It should be 7.46 and data reported in line 246 (now in line 338) which now has been revised.

**Change in the text: line 338 (Page 18).**

*Line 50: If 3 points are taken then you can't say Pes rose gradually. It could have immediately increased.*

**Reply:** We agree with the reviewer.

To make the expression more precise, we have now modified the original expression as “*the values of  $\Delta P_{es}$  measured in the PPV are greater than SPV*”.

The above corrections have also been made in the manuscript.

**Change in the text: From line 62 to 63 (Page 4)**

*Line 54: Is the statement that PPV could exert protective effects related to the use of NMBAs or separate, it is unclear whether the two comments are linked or not.*

**Reply:** Thanks for pointing out the issue.

We think there is a connection between the two. According to our result, although the oxygenation of the patients improved after PPV (Table 2), the  $\Delta P_{es}$  increased as well. What's more,  $\Delta P_{es}$ , EMG<sub>di</sub> can be seen higher in the death group (Table 3), which may mean that some respiratory mechanics like higher  $\Delta P_{es}$  suggest poor prognosis. However, we also find that with the use of NMBAs, the  $\Delta P_{es}$ , P<sub>Lei</sub>, DP and DPL of the patients above were significantly decreased (Table 4). Thus, we think that the rational combination of NMBAS and PPV in terms of respiratory mechanics may exert a synergistic protective effect on the lungs. In order to avoid confusing readers, we have made some changes to the corresponding content.

**Change in the text: From line 68 to 69 (Page 5)**

*Introduction:*

*Line 66: As per comment in abstract, suggest defining this as 'standard PPV' (12-18hours duration)*

**Reply:** Thanks for your suggestion. We have made some corrections.

**Change in the text: line 83 (Page 6)**

*Line 68: Counter-intuitively, meta-analysis data suggests that improved oxygenation with PPV is a delayed effect, with no improvement at 24hrs (DOI 10.23736/S0375-9393.21.15254-X) but is seen at 4 days (10.1513/AnnalsATS.201704-343OT).*

**Reply:** We agree with the reviewer and thanks for your kind guidance and provided reference.

Although the oxygenation improvement of some patients who accept PPV could be found in a relatively short period in some old studies (eg: DOI 10.1164/ajrccm.155.2.9032181. DOI: 10.1097/01.ccm.0000149853.47651.f0), and oxygenation of the patients in our study improved in PPV early stage and middle/late stage(compared with those in SPV), there are still some new study shows that that improved oxygenation with PPV is a delayed effect(as you kindly shows). In order to make the content more rigorous, we have made some changes to the presentation.

**Change in the text: line 85 to 86 (Page 6)**

*Line 72: I do not think prone position is non-physiological, I imagine almost everyone sleeps on their front for some part of the night. Its certainly not usual for Intensive care patients however.*

**Reply:** We agree with the reviewer that the prone position is non-physiological.

In fact, in some studies prone position is common in infants (DOI: 10.1001/archpedi.157.5.469). What we want to express in here is that the fully prone position for more than 12 hours is not a very routine position and may cause discomfort to the patients. We have made some revision in the corresponding parts of the article.

**Change in the text: line 91 to 92 (Page 6).**

*Line 78: I assume you mean the impact of NMBAs on resp mechanics during PPV in which case I suggest moving this sentence to the end of line 85*

**Reply:** Thanks for your corrections and we have revised and moved the sentence.

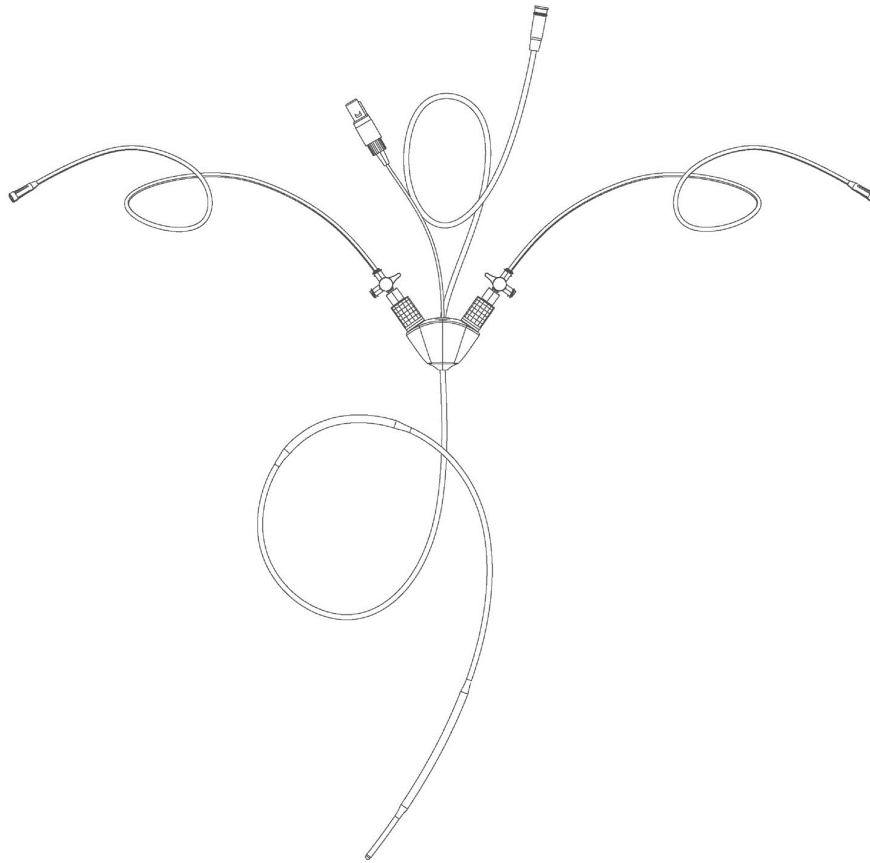
**Change in the text: line 105 to 107 (Page 7)**

*Line 92: Add a reference to this section which describes your development of the gastric tube.*

**Reply:** Thanks for your suggestion.

We have added some description of our development of the gastric tube: For conventional respiratory mechanics monitoring, an esophageal balloon catheter must be implanted to the patients each time, resulting in injury to the esophagus, affecting daily tube feeding and increasing the medical workload. What's worse, the stimulation above may interfere with the measurement of respiratory mechanics data in patients. In our study, we improved the problems above with the use of integrated four-channel multifunctional gastric tubes which have obtained the appearance patent in China (Patent NO. CN307246718S). Our catheter is composed of four sub-pipes for gastric feeding, detecting diaphragmatic electromyogram, measuring esophageal pressure, and measuring gastric pressure. When severe patients in ICU need indwelling gastric tube for therapeutic purposes, the integrated four-channel multifunctional gastric tubes can be used instead of the conventional gastric tube, with which we can continuously monitor the respiratory mechanics data of patients without repeated indwelling measurement catheters. We hope to make a more accurate assessment of continuous lung protection in patients with moderate to severe ARDS undergoing prone position ventilation.

And here is the schematic of the gastric tube:



The schematic of the integrated four-channel multifunctional gastric tubes  
(Patent NO. CN307246718S)

**Change in the text: line 109 to 124 (Page 7 to 8)**

*Methods:*

*Line 111: Given all patients were intubated, ventilated and sedated, could any have refused?*

**Reply:** Thanks for the good question.

There are some flaws in our statement in this section. In fact, because the patients enrolled were intubated, ventilated and sedated, we sought permission from the patient's family before enrolling the patient into the study. We have made revisions to the relevant expressions.

**Change in the text: line 150 to 151 (Page 9)**

*Line 113: Worth adding the name of the manufacturer(s) of the tube, or a reference to the development if it's one you are making in conjunction with industry or university.*

**Reply:** Thanks for your advice.

The tube was designed and manufactured by *Guangzhou Institute of Respiratory Health*, with the Patent NO. CN307246718S. The description and schematic diagram can be seen the question above.

**Change in the text: line 155 to 157 (Page 9)**

*Line 114: The sentence beginning 'a total of 22 patients...' is more a result than method, unless you had performed a power calculation which stipulated that 22 patients were to be enrolled? If not, move this sentence to the beginning of the results section (line 224).*

**Reply:** We absolutely agree with your comments.

The above sentence has been moved to the beginning of the results section.

**Change in the text: line 297 (Page 16)**

*Line 121: Here the authors state that the gastric tube was inserted when patients were at 30° , however in line 176 they state this was done after insertion. Could they clarify which is correct and remove the duplicated statement?*

**Reply:** Thanks for pointing out the issue.

When the patients enrolled were indwelled the gastric tube, we adjust their body position to make the head of the bed was raise to 30°C. However, when we recorded data, the patients' body position may be adjusted due to other treatment needs. Thus, we need to adjust their position again in order to make sure that patients are in the same position when the data are recorded otherwise the accuracy of data may be affected. To avoid misunderstanding, we have modified the relevant statements.

**Change in the text: line 234 to 236 (Page 13)**

*Line 133: By water do the authors mean gastric contents or did they specifically administer NG water through the tube?*

**Reply:** We are sorry for the wrong expression.

In fact, this step is a routine operation to ensure that the gastric tube is in the

stomach. Since there is gastric juice in the stomach, when we inject gas into the gastric tube, the gas will emit sound because it goes through the gastric juice. We have modified the above description.

**Change in the text: line 178 to 180 (Page 10)**

*Line 134: What is a lack of shade line?*

**Reply:** We would like to deliver our apology again.

This is also a description mistake. Here what we want to express that we can further confirm the location of the gastric tube by bedside X-ray inspection. We have modified the sentence.

**Change in the text: line 182 to 183 (Page 10)**

*Line 146: What were the ventilation settings between data recording sessions? Were ARDSnet lung protective values set for  $V_t$ , pH, PaO<sub>2</sub> etc? Presumably not given the pH in table 2 was normal rather than allowing permissive hypercapnia. Does that mean patients were being over-ventilated?*

**Reply:** Thanks for your comments and it really inspires us.

Yes, our clinicians referred to ARDSnet lung-protective strategy to set ventilator parameters. And the patients underwent the treatment of fluid resuscitation and adjustment of acid-base balance according to clinical condition. Thus, we believe that there are allowing permissive hypercapnia in the patients (we can find that the PaCO<sub>2</sub> of the patients were significantly higher than the normal range in Table 2). When it comes to the normal pH, we think that it was the comprehensive result of the above treatment measures, including fluid resuscitation and adjustment of acid-base balance and so on. In summary, we do not think that the patients were being over-ventilated.

**Change in the text: line 200 to 202 (Page 11)**

*Line 147: Was any assessment of depth of NMBA blockade performed, e.g. nerve stimulator? If patients were spontaneously breathing did they undergo the same protocol with IPPV?*

**Reply:** The reviewer raised a good question.

For patients who accept NMBA, our clinicians mainly evaluate the depth of NMBA blockade performed by whether the patient has obvious spontaneous breathing or human-machine asynchrony. There was no further evaluation with other means such as nerve stimulators. For patients with spontaneous breathing, we gave the same protocol with IPPV.

**Change in the text: line 198 to 199 (Page 11)**

*Line 166: Again this refers to a result & duplicates what's written in line 114.*

**Reply:** Thanks for the good reminder.

We have deleted the total number of patients and moved it to the result section.

**Change in the text: line 297 (Page 16)**

*Line 184: In the results section the authors should include the average time from onset of PPV that the middle/late stage values were taken. If they were all taken at 6hrs, just 2 hours after the early stage, then the results are much less interesting. If they all represent values taken at 12-16hours then they would be more representative.*

**Reply:** Thanks for the good question again.

As we replied at question 2 above, Due to the limitation of the actual clinical situation (such as patients receiving other treatment, clinical examinations, etc.), the data collection time of this group of patients was not completely uniform. But we still find that in the middle/late stage group, the median of data collection time point was 12 hours after the patients accepted PPV, we believe that the data obtained under this condition is stil representative. In order to give readers a better understanding of the above situation, we have added the above content to Table 1 and the result section of the article.

**Change in the text: line 302 to 303 (Page 16 )and Table 1 (Page 36)**

*Line 188: What was placed under the shoulders, presumably a pillow?*

**Reply:** Yes, it was a pillow. Thanks for your suggestion and we have modified the sentence.

**Change in the text: line 249 to 251 (Page 13)**

*Line 190: Do the authors mean venosus ductus here? I assume they are referring to central and peripheral lines, rather than foetal anatomy.*

**Reply:** We apologize for the mistake, and we have revised it. Thank you for your reminding.

**Change in the text: line 253 (Page 13)**

*Line 219: Have you included confidence intervals?*

**Reply:** Thanks for the good issue.

The sample size of the study was small which had mentioned in the discussion part, it may result in large fluctuations and large deviation in the confidence interval, so we use the marginal mean and coefficient B of the GEE model which can better reflect the correlation of the indicators and adjust for the repeated measurement.

**Change in the text: line 282 (Page 15)**

*Results:*

*Line 224: Worth adding the number and range of PPV events per patient from the table here.*

**Reply:** We agree with the reviewer's suggestions.

Adding the number and range of PPV events per patient could help the readers better understand more details of how patients receive PPV. However, most of the patients involved in this study received more than two times of PPV and the range of each patient received PPV of each time was various because of clinical situation. Thus, the content and table in this section may be overly complex and lengthy if we show the details of each patient. Of course, in order to let the readers understand the relevant content better according to your



suggestions, we supplemented the times and duration of PPV received by patients overall in Table 1.

**Change in the text: line 302 to 303 (Page 16 ) and Table 1 (Page 36 to 37)**

*Line 245: Given respiratory mechanics have been measured at 3 discrete time points, can you confidently state that the  $\Delta P_{es}$  was gradual?*

**Reply:** We agree with the reviewer. We have modified the expression here to make it more precise.

**Change in the text: line 337 to 338 (Page 18)**

*Line 249: I would suggest that an increase in  $P_{es}$  but within the normal range means that PPV is unlikely to be harmful rather than is protective per say.*

**Reply:** Thanks for your suggestions.

We think that your suggested expression is more precise and rigorous and we have modified the content according to your suggestion.

**Change in the text:** we modified the sentence and move it to **line 444 to 447 (Page 23, Discussion section).**

*Line 265: Difficulty breathing or difficulty ventilating? Given the use of IPPV I assume most patients weren't breathing.*

**Reply:** We agree with the reviewer.

The presentation of “difficulty breathing” has been modified to “difficulty ventilating”.

**Change in the text: line 370 to 372 (Page 19)**

*Line 270: This is an interesting finding as it suggests that monitoring respiratory mechanics can be used to decide who are non-responders preventing further futile attempts at repeat PPV.*

**Reply:** Thanks to the reviewer's approval of our work and good suggestion.

We hope that in further research, after incorporating more clinical data, more respiratory mechanics can be screened to help us predict the patients'

responsiveness to PPV.

**Change in the text: line 486 to 491 (Page 25)**

*Line 274: This result surprised me. Surely the use of NMBAs would lead to reduced end inspiratory esophageal pressures as chest wall compliance is better, even in the prone position. Or is this entirely down to altered diaphragmatic activity?*

**Reply:** Thanks for the reviewer's insightful advice.

In our clinical experience, the compliance of the anterior chest wall is decreased due to the compression during PPV while the compliance of the lung is increased due to the improvement of lung homogeneity. Although the using of NMBAs may improve the chest wall compliance, we think that to those who were accept NMBAs and not breathing spontaneously, their P<sub>esoi</sub> was affected by P<sub>plat</sub> and P<sub>peak</sub> mainly. Of course, to those who were not been used with NMBAs, their diaphragmatic and accessory respiratory muscle activity may affect the result too.

**Change in the text: --**

*Discussion:*

*Line 300: Was the reduced RR because minute ventilation could be reduced to maintain a target pH or PaCO<sub>2</sub> in which case surely PPV does affect ventilation?*

**Reply:** We agree with the reviewer's comments.

And combining with the result of Table 2, we think that the differences in patients' breathing rates may be due to patients' conditions, patient responsiveness to PPV and many other factors as you kindly proposed. Thus, we have removed relevant expressions.

**Change in the text: line 424 to 428 (Page 22 to 23)**

*Line 303: As per comment above regarding non-physiological.*

**Reply:** Thanks for your suggestion.

We have revised the expression of this sentence.

**Change in the text: line 431 to 432 (Page 23)**

*Line 310: Surely the respiratory embarrassment was relieved by accompanying deep sedation and paralysis rather than the improved oxygenation?*

**Reply:** We agree with the reviewer.

Both the use of deep sedation and paralysis and the improved oxygenation could relieve the respiratory embarrassment. We have modified the sentence.

**Change in the text: line 440 to 442 (Page 23)**

### **Reviewer C**

*The authors conducted an observational study on prone positioning for intubated ARDS patients, using the esophageal catheter developed in their institution. Even though it is interesting, there are lots of issues need to be addressed before publication:*

*Major:*

*To be frank, I did not get the points of the findings in this study. That being said, I don't know what this study contributes to the current understanding of prone positioning for intubated patients. I suggest the authors rethink this question and re-analyze their data. One thought is to compare the patient responses to the consecutive prone positioning sessions between patients who survived or died. The authors can take a look at the study on the responses to consecutive prone sessions: Weiss T, Cerda F, Scott B, et al. Prone Positioning for Patients Intubated for Severe Acute Respiratory Distress Syndrome (ARDS) Secondary to COVID-19: A Cohort Study. *Br J Anaesth.* 2021; 126(1):48-55. Secondly, the current way the authors presented is too complicated, I suggest the authors simplify their findings.*

**Reply:** Thank you very much for the reviewer's good suggestion and comments.

The studies you recommended for our reference really inspired our thinking and helped us a lot to further improve our article. Perhaps our inadequacies in the writing and presentation of our articles prevent the readers from getting the main points of our articles well. In our study, we monitored respiratory mechanics data in different time periods during patients receiving PPV in the ICU. We got the following findings: firstly, PPV may improve the oxygenation of the patients while  $\Delta P_{es}$  still fluctuated within a normal range. Secondly, we performed a stratified analysis according to patient outcome

(death/survival), showing that there were differences in respiratory mechanics between the two groups, which may help us find those who are non-responders preventing further futile attempts at repeat PPV. At last, with the significant differences of the patients accept NMBAs or not in respiratory mechanics, we found that the rational use of NMBAs may have protective effects during PPV. To make it easier for readers to understand our research, in this revision, we have made some simplifications to the content of the Results section. At the same time, we have also made some changes to the word order and content of the discussion section, hoping to improve the logic of the article. Once again, we sincerely appreciate your valuable suggestions, and if you have any other suggestions, please let us know.

**Change in the text: the whole Result section (From line 285 to 403) and line 404 to 506 (Page 22 to 26, Discussion section)**

*Others:*

*1. Abstract*

*a. What does delta Pesspv mean? Please provide the calculation formula*

**Reply:** Thanks for pointing out the issue.

$\Delta P_{es}$  means “esophageal pressure swings” and it is an index that indirectly reflects the activity of the diaphragm and accessory respiratory muscles. The calculation formula of  $\Delta P_{es}$  is “ $|P_{es_{max}} - P_{es_{min}}|$ ” and we have added this formula to the Methods section of the article.

**Change in the text: line 36 (Page 3) and line 221 (Page 12)**

*b. How come the numbers are only one number? It should be mean and SD.*

**Reply:** Thanks for the suggestion.

We feel sorry that didn't express clearly that the mean represented “marginal mean”, each patient experienced multiple measurements in different prone positions, so the study can't simply just calculated the mean of each patient by averaging every measurements, we use the marginal mean which was adjusted

by internal correlation of each patient.

**Change in the text: --**

*c. "When NMBAs were used, the  $\Delta$ Pes and DPL were significantly decreased, suggesting that PPV could exert a long-term protective effect on the lungs, and more dynamic monitoring is needed": I don't think the sentences before "suggesting" suggests the sentences after.*

**Reply:** Thanks for the good suggestions.

We agree with you and admit that the sentence may be not rigorous enough. According to our result, although the oxygenation of the patients improved after PPV(Table 2), the  $\Delta$ Pes increased as well. What's more,  $\Delta$ Pes, EMGdi can be seen higher in the death group(Table 3),which may mean that some respiratory mechanics like higher  $\Delta$ Pes suggest poor prognosis. However, we also find that with the use of NMBAs, the  $\Delta$ Pes, PLei, DP and DPL of the patients above were significantly decreased(Table 4). Thus, it should be the rational combination of NMBAS and PPV in terms of respiratory mechanics exert a synergistic protective effect on the lungs. We have made some modification to the corresponding content.

**Change in the text: line 68 to 69 (Page 5)**

## *2. Introduction*

*a. "high-strength (12-18 h every day)": due to the PROSEVA findings, the standard practice for prone positioning for intubated patients is minimally 16 hours/day, more importantly, 12 hours/day prone positioning has been found to be less effective in improving survival. Thus, why did the authors use prone positioning for less than 16 hours/day? Also, 12-18 hour/day is not "high" strength.*

**Reply:** Thanks to the reviewer for raising the good questions.

Due to the limitation of the actual clinical situation (such as patients receiving other treatments, clinical examinations, etc.) and medical human resources, the duration of patients accepting PPV in our study cannot be completely uniform. However, there were still a considerable number of patients accepted more

than 12hours or even 16hours PPV (the median time is 12 hours which has been added to Table 1). Thus, we choose to divide patients by PPV early stage and middle/late stage. Of course, we also acknowledge that our monitoring time was relatively short compared to some other studies. Also, we agree with that “high strength” is not rigorous, and it has been corrected to “PPV with duration of 12-18hours”.

**Change in the text: line 83 (Page 6)**

*3. Methods:*

*a. Trial registration: was the trial registered in somewhere? If so, please provide the detailed information.*

**Reply:** The clinical trial registration and ethical permission of was approved by the First Affiliated Hospital of Guangzhou Medical University (No.2017-034).

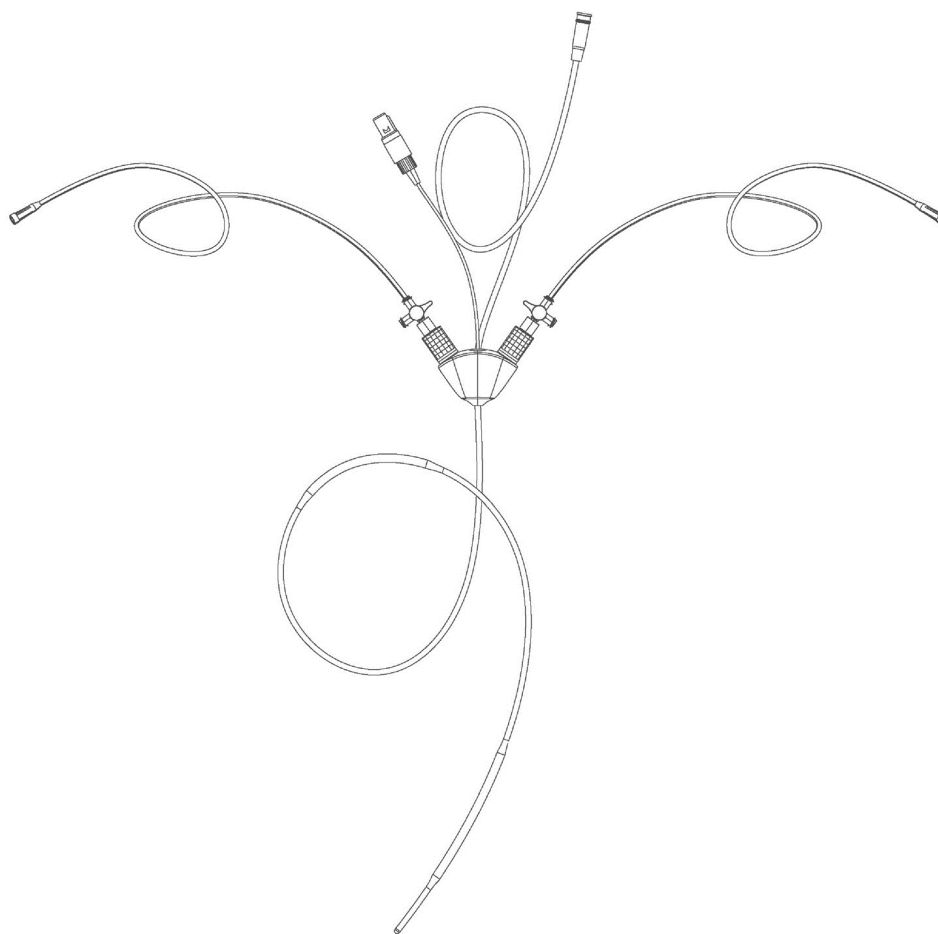
**Change in the text: line 158 to 160 (Page 9)**

*b. “four-channel multifunctional gastric tube”: please provide the manufacturer information for this product. additionally, since this product is developed by the authors' institution, the readers are not familiar with it. i suggest the authors add some introduction, including the FDA approval, along with its use in previous research.*

**Reply:** Thanks for your suggestion; and we have added some description of our development of the gastric tube: For conventional respiratory mechanics monitoring, an esophageal balloon catheter must be implanted to the patients each time, resulting in injury to the esophagus, affecting daily tube feeding and increasing the medical workload. What’s worse, the stimulation above may interfere with the measurement of respiratory mechanics data in patients. In our study, we improved the problems above with the use of integrated four-channel multifunctional gastric tubes which have obtained the appearance patent in China (Patent NO. CN307246718S). Our catheter is composed of four sub-pipes for gastric feeding, detecting diaphragmatic electromyogram, measuring esophageal pressure, and measuring gastric pressure. When severe

patients in ICU need indwelling gastric tube for therapeutic purposes, the integrated four-channel multifunctional gastric tubes can be used instead of the conventional gastric tube, with which we can continuously monitor the respiratory mechanics data of patients without repeated indwelling measurement catheters. We hope to make a more accurate assessment of continuous lung protection in patients with moderate to severe ARDS undergoing prone position ventilation.

And here is the schematic of the gastric tube:



the schematic of the integrated four-channel multifunctional gastric tubes  
(Patent NO. CN307246718S)

**Change in the text: line 109 to 124 (Page 7 to 8) and line 155 to 157 (Page 9)**

*c. “DP, Pesei, Pese, ΔPes, PLei, PLee and DPL”: first-time use, please list the full name.*

**Reply:** We have added the full name of the above abbreviations in the Methods section according to the reviewer's suggestion:

driving pressure (DP), inspiratory esophageal pressure (Pesei), expiratory esophageal pressure (Pesee), esophageal pressure swings ( $\Delta P_{es}$ ), inspiratory transpulmonary pressure (PLe<sub>i</sub>), expiratory transpulmonary pressure (PLe<sub>e</sub>) and transpulmonary driving pressure (DPL).

**Change in the text: line 204 to 215 (Page 11)**

d. *"The trachea cannula": do you mean "endotracheal tube"?*

**Reply:** We have corrected the phrase according to your suggestion.

**Change in the text: line 252 (Page 13)**

4. Results:

a. *"16 of the pulmonary ARDS were due to severe pneumonia": were any of the patients diagnosed with COVID-19?*

**Reply:** Thank you for the good question, none of the patients included in the trial were diagnosed with COVID-19.

**Change in the text: --**

b. *"the average time to admission to the ICU was 0.5 days": what admission? Hospital admission?*

**Reply:** Thanks for the good question.

We apologize for our unclear expression in English. It should be "the duration of the overall patient from hospital admission to ICU admission". To simplify the content of this section, we have removed the original sentence and presented this data in Table 1.

**Change in the text: Table 1 (Page 36 to 37)**

c. *"Some patients were transferred with invasive ventilation from other hospitals.": how long were patients intubated before transportation? Also, how long were the overall patients intubated before prone positioning started?*



**Reply:** The reviewer has made a good point.

The duration of the patients intubated before transportation is about 7 days.

And the medium duration of the overall patient intubated before PPV start is 5 days.

**Change in the text: Table 1 (Page 36)**

*d. "Mean PaO<sub>2</sub>SPV = 95.34 mmHg, B = -11.61": what does "B" mean?*

**Reply:** Thanks for pointing out the issue.

In this research, each patient experienced multiple measurements in different prone positions, considering the internal correlation between each measurement of each patient, we use GEE model to control the unobservable differences over time. GEE model makes estimates based on changes within individuals, it works by averaging over all individuals and making guesses about the internal covariance structure. Statistical value B represented the coefficient values of variables in the GEE model to explain the relationship of outcome in different groups compared to control group.

**Change in the text: --**