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Name of Journal: *World Journal of Critical Care Medicine*

ESPS Manuscript NO: 22031

Manuscript Type: REVIEW

Responses to the Reviewers' comments

We thank the Reviewer for his/her time and effort regarding this manuscript.

We do hope that the revised form of this submission will satisfy the high standards of the Reviewer and that he/she will consent to its publication. All comments raised have been addressed.

In our responses to Reviewer, we have inserted his/her original comments in italics followed by our related detailed response

Reviewer # 1

Minor Comments

1. Line 217. I suggest to include some references related to protein S100 and Caspase

Following the Reviewer's comment we quoted reference [10] for protein S100 and we added a new reference ([34] of our revised manuscript) for Caspase

2. Line 272 and 320. I understand that a few years ago, patients were ventilated with a strategy to target low levels of PCO₂ in order to "preserve brain integrity".

However, this strategy is no longer used. I suggest a further discussion concerning this topic

In compliance with the Reviewer's comment we have further elaborated our related text to emphasize that intense hypocapnia should be avoided. Instead, in clinical practice mild hypocapnia is still applied for the management of intracranial hypertension Please see lines 362-364 of our revised manuscript

3. I agree with the sentence: "Ventilation/perfusion (V/Q) mismatch and shunt, the main pathophysiological mechanisms of hypoxemia [60] ensuing from airway closure and atelectasis that are commonly developed in dependent lung zones with sedation and anesthesia, even in healthy adults [61][51], might explain oxygenation impairment" however, sedation and anesthesia may not be a specifically explanation for the brain injured patients' hypoxemia. Therefore I suggest removing this sentence.

Thank you for this comment. This sentence has been removed and the related text has been rephrased. Please see lines 318-322 of our revised manuscript

4. I suggest including the following references: ME Quilez, Crit Care 2011; 15: R124 and A. Gonzalez-Lopez, AJRCCM 2013; 188: 693

We followed Reviewer's recommendation and elaborated our text to include these two references. Please see lines 333-336 of our revised manuscript

Responses to the Editor

Dear Editor,

Thank you very much for giving us the opportunity to revise our article for possible publication in your distinguished journal.

Below are our responses to your comments

1. Page 1: Please offer the postcode

Postcodes have been added. Please see page 1 of our revised manuscript

2. Page2: Please offer a signed pdf file with all the authors

A signed conflict-of-interest statement has been provided as a separate pdf file (file name: 22031-Conflict-of-interest statement)

Page2: Author names should be given first, then author title...

Thank you for this comment. Done as requested

3. Page 3. Please offer the audio core tip

An audio core tip file has been added as a separate file (file name 22031-Audio core tip)

Step 1. Step 1. Please revise your manuscript according to the reviewers' comments.

All Editor's and Reviewers' comments have been addressed in the revised manuscript.

Step 2. Please update the manuscript according to the Guidelines and Requirements for Manuscript Revision-Review.

This has been done

Step 3. Please provide an Audio Core Tip

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Step 4. Please subject the manuscript to *CrossCheck* analysis and the final title to Google Scholar search, and store screenshot images of the results

We are providing the Google Scholar test for the title (file name: 22031-Google Scholar) as well as the iThinkcate CrossCheck results (file name: 22031-CrossCheck). The overall similarity index is 49% . However, this is mainly due to standard phrasing. In fact, this high percentage is made up of 143 x (<1%) matches.

Step 5. Please provide the files related to academic rules and norms

This has been done

Step 6. Please revise the language of your manuscript.

We are providing a language editing certificate of Miss Elli Angellidou (M.A. in English) regarding the revised version of our manuscript (file name: 22031-Language certificate)

Step 7. Please sign the Copyright Assignment form

We are providing the signed Copyright Assignment form (file name: 22031-Copyright assignment)

Step 8. Submit the revised manuscript and all related documents

We are providing the following files

1. 22031-Revised manuscript
2. 22031-Answering reviewers
3. 22031-Copyright assignment
4. 22031-Audio core tip
5. 22031- Conflict of interest statement
6. 22031 Google Scholar
7. 22031-CrossCheck
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We hope that the revised manuscript will satisfy the high standards of your Journal and that you will consent to its publication

Sincerely yours

Antonia Koutsoukou MD, PhD