

Author Response Letter to Reviewers' Comments

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Reviewer Code: 00646232, and 00467399

Scientific Editor: Li-Jun Cui

Dear Editor,

We, the authors, appreciate your care and valuable comments on our manuscript mentioned above. I have attached the manuscript revised according to the reviewer and editor comments. The changes are highlighted in the revised manuscript.

Point-by-point responses to the reviewers' comments are listed down in this letter. I hope these changes meet your expectations.

Regards,

Emad M Fathi

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Author's Response to the Reviewer's Comment

Reviewer's code: 00646232

Reviewer's Comment:

I reviewed with interest this well written review article. The article is comprehensive and covering a wide range of tools used to monitor the hemodynamics in septic shock. The article is general is good. I have few comments I embedded in the manuscript itself that I guess it could help to improve the quality of this good work.

Authors' Response:

Dear reviewer,

Thank you for your kind overall evaluation and your valuable time spent on our manuscript. Your comments are revised and corrections are done accordingly as below.

Point-by-point responses:

- **Comment 1: You mean CO or cardiac index??**
 - **Response:** We had changed CO and SVR to CI and SVRI as no need to be mentioned earlier.
- **Comment 2: Use of abbreviation without previously mentioned in detail**
 - **Response:** CO and SVR have been changed to CI and SVRI and the abbreviations are mentioned later at their proper position.
- **Comment 3: Pulmonary artery catheter (PAC)**
 - **Response:** (PAC) pulmonary artery catheter has been changed to Pulmonary artery catheter (PAC).
- **Comment 4: Correct**
 - **Response:** the sentence has been corrected so, the idea of relating CO to children size becomes clearer.
- **Comment 5: 2- Dimensional**
 - **Response:** Two-Dimensional has preceded the abbreviation "2-D"
- **Comment 6: transesophageal echocardiography is an invasive maneuver**
 - **Response:** The sentence has been modified to show that transesophageal 2-D echocardiography is invasive rather than the transthoracic one.
- **Comment 7: most of the machine calculate it**
 - **Response:** You are right that the machine calculate LVOT. By unintended mistake, LVOT is mentioned instead of SV. So we have changed it to be SV which is actually not a ready calculation by the machine and needs to be calculated manually after obtaining LVOT and VTI values by 2D-

echocardiography. The final formula for calculation “ $\text{Pi (LVOT diameter/2)}^2 \times \text{LVOT VTI}$ ” has also, been added to figure 3.

- **Comment 8: no need of this phrase**
 - **Response:** Devices names are removed

- **Comment 9: you mean 2 D echocardiography**
 - **Response:** “2-D” has been added before echocardiography at that position and later on.

- **Comment 10: Corrected flow time (FTc)**
 - **Response:** “flow time corrected” has been changed to “corrected flow time”

- **Comment 11: Electrical cardiometry**
 - **Response:** added “Electrical” before cardiometry.

- **Comment 12: I think it will be better to be explained like that: Bioimpedance measurements detect electrical changes occurring with altering fluid levels in the thorax. Levels change as the left ventricular contracts and blood flows into the thoracic aorta. This causes a corresponding change in resistance within the thorax because the fluid level in the aorta increases. This change in impedance can be measured as a change in voltage passing between electrodes placed on a patient’s chest. Bioimpedance measures the amplitude of the voltage change across the thorax**
 - **Response:** the above-mentioned theory describes the mechanism of action behind the electrical bioimpedance. The theory mentioned in the manuscript describes the mechanism of electrical cardiometry. Actually, we had put the previous title of this section “electrical bioimpedance” as a general one, to include electrical cardiometry under it. As you know, the electrical bioimpedance did not get acceptance or FDA approval. Therefore, to avoid confusion, we have changed the whole section title to be “electrical cardiometry” which is FDA approved and accepted for use. Therefore, the mechanism of action mentioned in the manuscript will now match.

- **Comment 13: No need to mention it**
 - **Response:** Devices names are removed

- **Comment 14: No need for that**
 - **Response:** Devices names are removed

- **Comment 15: Plz add: Bioreactance tracks the phase of the electrical currents traversing the chest. The underlying scientific phenomenon is that the higher the cardiac stroke volume, the more significant these phase shifts become.**
 - **Response:** thank you for the addition. The mechanism of action of bioreactance has been added.

- **Comment 16: Kupersztych-Hagege et al 2013 showed that Bioreactance is not reliable for estimating cardiac output. Moreover, it could not predict fluid responsiveness through the passive leg raising in critically ill patients.**
 - **Response:** you are right there is no consensus agreement about its use. Comment added and reference replaced the previous one.

- **Comment 17: and may vary at different doses**
 - **Response:** The sentence “and may be different at different doses” has been changed to “may vary at different doses”

Reviewer Code: 00467399

Reviewer’s Comment:

The article deals with a non-invasive procedure to monitor the hemodynamics of children in the presence of septic shock. The manuscript is well written and easy to read. It provides appropriate information on a rather complex topic. However this reviewer wishes to call the attention of the authors on some points. In the introduction the description of cold and warm septic shock is reported and it is underlined that both are responsible for a reduced perfusion of the various organs. Although the hemodynamic pattern of the two type of shock is clearly described, the paragraph should be enriched by a few words on the upstream pathophysiology of each of them. In the first paragraph of the section on the challenges in the management of septic shock, the different use of dopamine/epinephrine and norepinephrine depending on the type of shock is reported without explaining the reason of the choice. It is true that the reason is indicated at the end of the article before the conclusion. However, it would be useful for the reader to find the explanation at the beginning of the article. Obviously, this change involves a corresponding opposite change at the end of the manuscript. Strictly speaking, cardiac index (CI) is not an index of cardiac contractility because it is related with cardiac output, which matches with afterload and resistance. Actually, CI represents the overall final effect of cardiac activity. Thus the title and the first paragraph of section 2 (Assessment of contractility) should be modified accordingly. In the second paragraph of section 2, different values of CI are reported for children with and without septic shock. Although easy to guess, the reason should be explained. On lines 8 and 9 of the same paragraph we read “measure the CI in fluid resistance and catecholamine resistance shock towards the end of the septic shock”. What does “towards the end of the septic shock” mean? And how can it be predicted? In section 3

(Assessment of afterload), par. 1, end of line 2. SVR is likely to be changed in SVRI. SVR as such is not independent of body size. Minor points. Please check whether all abbreviations are explained in the relevant table.

Authors' Response: Thank you so much for your overall evaluation of our manuscript and really valuable comments. Please allow us to segment your comment into points for proper response.

Point-by-point responses included under each segmented comment paragraph

- **In the introduction, the description of cold and warm septic shock is reported and it is underlined that both are responsible for a reduced perfusion of the various organs. Although the hemodynamic pattern of the two type of shock is clearly described, the paragraph should be enriched by a few words on the upstream pathophysiology of each of them.**
 - **Response:** We have added more on the pathophysiology of cold and warm shock patterns and modified the introduction accordingly.
- **In the first paragraph of the section on the challenges in the management of septic shock, the different use of dopamine/epinephrine and norepinephrine depending on the type of shock is reported without explaining the reason of the choice. It is true that the reason is indicated at the end of the article before the conclusion. However, it would be useful for the reader to find the explanation at the beginning of the article. Obviously, this change involves a corresponding opposite change at the end of the manuscript.**
 - **Response:** We have added a sentence to direct the reader attention to our recommendation at the section titled "Suggested therapy guided by hemodynamic monitoring". We preferred to describe noninvasive methods for assessing the hemodynamic status of septic shock before discussing the therapeutic options so, the choice rationale will be easily understood.
- **Strictly speaking, cardiac index (CI) is not an index of cardiac contractility because it is related with cardiac output, which matches with afterload and resistance. Actually, CI represents the overall final effect of cardiac activity. Thus the title and the first paragraph of section 2 (Assessment of contractility) should be modified accordingly.**
 - **Response:** Thank you for drawing our attention to this valuable note. Changes and modifications are done.
- **In the second paragraph of section 2, different values of CI are reported for children with and without septic shock. Although easy to guess, the reason should be explained.**

- **Response:** The sentence has been modified and explained.
- **On lines 8 and 9 of the same paragraph, we read, “measure the CI in fluid resistance and catecholamine resistance shock towards the end of the septic shock”. What does “towards the end of the septic shock” mean? And how can it be predicted?**
 - **Response:** The sentence includes the word “**algorithm**” at its end “measure the CI in fluid resistance and catecholamine resistance shock towards the end of the septic shock **algorithm**”. We were talking about the SSC algorithm of septic shock management. We have reformatted the sentence to avoid confusion.
- **In section 3 (Assessment of afterload), par. 1, end of line 2. SVR is likely to be changed in SVRI. SVR as such is not independent of body size. Minor points.**
 - **Response:** The paragraph has been modified to be clearer to the reader. Thus, SVR has been mentioned first with its formula of calculation, and then moved to SVRI calculation.
- **Please check whether all abbreviations are explained in the relevant table.**
 - **Authors’ response:** They are revised.