Author’s response to reviews

Title: Computer-controlled closed-loop drug infusion system for automated hemodynamic resuscitation in endotoxin-induced shock

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Author’s response to reviews:

Response to Reviewers' comments:

Reviewer reports:

Joseph Rinehart (Reviewer 1): Much better reporting of the results of the study after the author's revision. Thank you. I have just a few minor suggestions:

Response: We thank Dr. Rinehart for his detailed review of our manuscript and constructive comments.

P5L19 - Did the authors mean Vaso[constrictor]?

Response: We apologize for the confusing description. In this section, we mean vaso[dilator], which was used in our previous system to reduce abnormally increased systemic arterial resistance in the closed-loop hemodynamic control in acute heart failure (not in endotoxin shock!). To avoid confusion, we rewrote 3rd paragraph in Introduction section in the revised manuscript as follows,

Third paragraph in Introduction section (Line 7, Page 5)
Since acute heart failure is characterized with abnormally increased R and V, and with depressed S, our system was previously designed to control R with a vasodilator, V with diuretics (or fluids), and S with an inotrope, thereby controlling AP, CO, and PWP [9-11].

P13L9 - please remove 'the' from the first sentence: "…in all 8 animals…"
Response: Following the reviewer’s suggestion, we removed ‘the’ from the sentence as follows,

First paragraph in Results section (Line 3, Page 13)
Intravenous LPS induced endotoxin shock in all 8 animals (Baseline vs Shock in Table 1).

P13L45 - P14L37 - The individual descriptions of animals from group A and group B are not as strong as the group reporting in P14L38 - P15L24. I would personally recommend moving these sections (P13L45-P14L37) to the end of the current results, putting them after the summary results of the full cohort and the comparisons between group A and group B.
Response: Following the reviewer’s suggestion, in the revised manuscript, we moved the sections (P13L45-P14L37 in previous version) behind the summary results of the full cohort and the comparisons between group A and group B. Since the order of the figures was changed, we corrected the number of figures and explanatory descriptions in Results sections and other sections including Figure Legends as appropriate.

Please review Results section (Line 18, Page 13)
P16L4 - Please report the p-value and coefficient for this correlation here in the results
Response: Following the reviewer’s suggestion, we reported the p-value and coefficient for this correlation in the revised manuscript as follows,

Sixth paragraph in Results section (Line 1, Page 16)
In Group B, CO measured less invasively by our system and COTD were significantly correlated (P < 0.001) with large Spearman correlation efficient (ρ = 0.68) (Fig. 6).
Response: We thank again Dr. Rinehart very much for his extensive review of our manuscript and highly constructive comments.

Michael Kinsky (Reviewer 3): the authors have done a good job in responding to critiques

Response: We thank Dr. Kinsky for his detailed review of our manuscript and constructive comments.

There are 2 minor points

Firstly, recommend the title to change to: Computer-controlled closed-loop drug infusion system for automated hemodynamic resuscitation in endotoxin-induced shock

Response: Following the reviewer’s recommendation, we removed the word “septic” from the title as follows,

Title of the revised manuscript

Computer-controlled closed-loop drug infusion system for automated hemodynamic resuscitation in endotoxin-induced shock

Secondly, insert the response language into the limitations section in regards to the increased hematocrit - Other possible mechanisms include enhanced recruitment of red blood cells into the systemic circulation from the spleen stimulated by endotoxin itself and/or by noradrenaline used for resuscitation. A specific limitation we had is that we did not perform a splenectomy, and/or evaluations of plasma volume/total blood volume using the dye-dilution methods, which would have better defined the increase in hematocrit.

Response: Following the reviewer’s suggestion, we first rewrote 4th paragraph in Discussion section as follows,

Fourth paragraph in Discussion section (Line 23, Page 18)
The persistent elevation of Ht might be attributable to other mechanisms such as enhanced recruitment of red blood cells from spleen stimulated by endotoxin, or by infused NA [30, 31]. The mechanisms of the persistent elevation of Ht remain to be unveiled. In any way, infusion of large amount of fluids was associated with poor prognosis in sepsis patients [32].

Response (continued): Following the reviewer’s suggestion, we inserted the response language into the limitations section as follows,

Final paragraph in Limitation section (Line 7, Page 23)

A specific limitation we had is that we did not perform a splenectomy, and/or evaluations of plasma volume/total blood volume using the dye-dilution methods, which would have better unveiled the mechanisms of the persistent increase in Ht [30, 31].

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Response: We thank again Dr. Kinsky very much for his extensive review of our manuscript and highly constructive comments.