Reviewer’s report

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

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Reviewer: Michael Kinsky

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BANE-D-17-00124

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

Uemura and authors demonstrate that acute LPS-induced shock can be successfully resuscitated with the use of autonomous closed-loop devices in an experimental animal preparation. The authors track various physiological parameters through the course of a presumed hyperdynamic and hypovolemic shock conditions and influence these parameters through the administration of vasopressors and fluid. They use two treatment groups to demonstrate that their resuscitation approach can work with less invasive input parameters. While the overall study design is quite elegant and elaborate, and the presented capabilities of the closed-loop system represent an exciting next step in the field of automated resuscitation, the authors fall short of taking full advantage of the data they gather, specifically interpretation. Given the changes in Frank Starling slope there seems to be clear evidence of acute cardiac depression, in addition to afterload and preload alterations as in a situation of endotoxin-induced shock; this finding is not appreciated enough by the author group in the discussion of their findings, let alone addressed by their experimental approach itself, as this would need to introduce inotrope drugs to the model as an additional variable. Additionally, other parameters are not discussed despite having the appropriate experimental design e.g., pulmonary artery pressure / right heart function. Substantial changes are necessary to make this interesting contribution ready for publication.

Comments:

- How is CO calculated/monitored in group B? Publication 17 indicates that CO measurement needs calibration with COref, which could not have been obtained without the aortic flow probe in group B. Please comment.

- Estimation of PWP from CVD is an approximation. The one-time estimation does not take into account changes in PWP during the experiment. As clearly the authors show an incredible amount of cardiovascular dynamics.
- The term septic shock is not equivalent to LPS-induced shock. Please clarify.

- Provide more detail regarding the increase in Hct? Should the spleen have been removed during the extensive preparation procedures as well or blood volume be calculated differently? For example, why not use indocyanine green or radio-isotopes? While on one calculation, a Hct increase from 30% to 41% could represent a vascular volume contraction of > 25%; as mentioned release of red cell mass from spleen and liver is also plausible. This reviewer has difficulty in reconciling the Hct at the end of the study [39%] along with volume repletion. Other mechanisms need to explored and/or discussed in limitations.

- No control group receiving some sort of manual resuscitation is presented in this experiment, which is ok for a proof-of-concept but will be needed in the future to make inferences on how the approach compares clinically to established practice.

- Is there a better way to produce the figures? The main focus should be on the time between shock induction and reaching steady state resuscitation, there is little information thereafter that is not discussed with the mention of the small deviations from target in the results section. Maybe focus the graphs on that first period.

- Cardiac determinants of CO [afterload/preload/contractility] are not accounted for in the model. Please discuss.

- The authors placed a pulmonary artery catheter - which can provide PAOP [PWP]; how did PWP calculated compare to PWP measured. Furthermore, LPS infusion is noted to increase thromboxane and other mediators that greatly influence pulmonary artery pressure [PAP] - what was the PAP before, during and after the LPS infusion? Did it dramatically increase? Did NA infusion make it worse? Was there evidence of right heart dysfunction? Could this explain the cardiac dysfunction apparent in your model - evidence by increased filling pressures / lower stroke volume?

- Please discuss, in limitations, the interaction of fluid infusion and NA - as both models uses CO as primary variable. Additionally, fluid could also reduce afterload [especially crystalloid]; which could induce an erroneous feedback loop with NA.

- Please mention that one time LPS-infusion is not an indisputable model of septic shock and that there is criticism regarding its accuracy in simulating actual septic shock.

- "By using this system to automatically support the macro-circulatory status, care providers may be able to spend more time on patient-specific treatments to improve micro-circulation, thereby potentially improving patient outcomes." How would caretakers specifically spend time on improving microcirculation? Please elaborate or delete this sentence. The general notion that time and resources could be saved is enough in the reviewers opinion.
Finally, it is difficult to state that this model was effectual in resuscitation as lactate remained elevated - please discuss the value of this endpoint as a global index of resuscitation and why lactate was not restored to basal levels? Additionally, the infusion of fluid seemed to linear - while this may have been what the model predicted; it does not seem to be clinically apparent and oversimplified. Please provide the total amount of fluid in mL/kg used for resuscitation.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

**Yes**

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

**Yes**

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

**Yes**

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If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

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