Reviewer’s report

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

Version: 0 Date: 25 May 2017

Reviewer: Joseph Rinehart

Reviewer's report:

The authors are reporting on the results of a series of animal experiments studying the ability of a novel-closed-loop system to resuscitate appropriately from septic shock. The system is capable of management of both vasopressor infusion rate and crystalloid resuscitation, and in this study both ran under full closed-loop control. The concept is novel; I am not aware of any other dual-loop systems managing both vasopressors and volume resuscitation simultaneously. As I am very active in this space myself I think the topic is of interest to the anesthesiology community and the future of our specialty and that work like the authors have performed is an essential step in the validation of a controller. The current manuscript could be much improved before publication, however.

Major Comments:

1. The main issue with the current manuscript is the statistical methodology and reporting. Specific comments follow, but overall there is a lot of loose language in the results (terms like "reasonable" or "close to" are used without definition or qualification), there are no statistical comparisons presented in the results section, and significant differences are stated but not supported. Even if all of these were resolved, however, the underlying statistical approach itself is very weak. I would propose two possible approaches to resolving this problem:

a. The first would be to re-frame this manuscript as a case-report. With only 8 animals it is a small sample appropriate for this format and narrative descriptions of the cases themselves (as the authors have presently in the results) more acceptable. The narratives in this case should be expanded to include all of the animals in each group (as opposed to reporting on a single animal as the authors currently do in the results), and group-wise summary measures reported where possible. Comparisons between the groups should still be made. If this is the approach taken, the authors should strictly limit conclusions drawn to "feasibility" and should not draw any specific safety or performance conclusions in the manuscript.

b. The second option (which could result in a stronger publication), would be to revise the statistical methodology to a more robust reporting for this type of study. Reporting of at least
Varvel's criteria would be my suggestion (PMID 1588504). For examples of practical application of this approach in published studies see PMID 28368936 or PMID 16931977. If the authors revise their analysis of the performance in this manner, they may be able to make more performance-related conclusions from this work, which would obviously be stronger. All 8 animals could be included in an overall assessment, but obviously with the two different subgroups it would be better to assess each group individually (else why bother having the subgroups).

Specific comments:

P6L58 - P7L4 - These rules appear to be "on/off" rules rather than "adjustments" to ongoing rates. The authors need to report what portion of operation time in the cases the system was infusing fluid, what the total volume infused for each animal was, what triggered infusion in the animals at what point. Overall reporting on this dimension of the system is almost non-existent.

P7L34 - rather than "make the system clinically feasible", I believe the authors intend "test the clinical feasibility"?

Statistical methodology - using mean and SD to report and ANOVA to test in n=8 (or actually n=4 in two different groups) animals istoo few data points to assume the normality of the distribution of the sample mean. The variables should be tested for normality using something like Shapiro-Wilk if mean ± SD and ANOVA are to be used. Otherwise (or if the distributions are shown to violate normality by Shapiro-Wilk), non-parametric reporting with median & quartiles is preferred and repeated measures testing would be by the Friedman test.

Results

P12L11 - "decreased significantly". Here and throughout results, please provide numerical data to support any report of "significance". This should include median and 25th, 75th quartiles (assuming non-parametric reporting) for both groups being compared (in this case before & after induction of sepsis), and a specific p-value. Ideally the 95% confidence interval of the difference between the groups would be included as well for robust reporting.

P12L24 - P13 - These two paragraphs describe individual cases (one animal from each group). This would be borderline if the authors intended to submit a "case report", but these paragraphs do not constitute statistical reporting of the results of an experiment. Please instead provide statistical summaries (medians & quartiles) of each group of four animals, and statistical comparisons where appropriate.
This paragraph is now reporting some summary measures better, but there are still many uses of vague terminology like "reasonable accuracy and stability" (P13L26) that are undefined and unsupported by any tests or measures. What did the authors define "reasonable" accuracy?

No comparisons between group A and group B are reported. No statistical test results are reported in the results.

Discussion

Again, the authors use vague terminology like "stably and accurately" and "showed good performance", but these terms and the criteria used to establish them are not defined in the manuscript. See comments above about evaluating performance, also.

The authors have not discussed weaning in the present manuscript. If this work was done previously it should be cited (the cited reference appears to be from a different group).

Table 1 - The exact p-values should be reported for each comparison. How much volume (total) was given during the resuscitation? Moreover, there are two distinct subgroups being combined in this table; what were the differences? Why are they being grouped all together?

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.

No

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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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I am personally working on a closed-loop vasopressor research program of my own.

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