Reviewer’s report

Title: Assessment of cerebral circulation in a porcine model of intravenously given E. coli induced fulminant sepsis

Version: 0 Date: 05 Nov 2016

Reviewer: Tobias Hilbert

Reviewer’s report:

In their article, the authors describe the results of a study analyzing the impact of globally changing hemodynamic parameters on cerebral blood flow velocity during sepsis developed from E. coli infusion in a porcine model. During development of septic shock, systemic hemodynamics were altered significantly, with decreasing blood pressure and an increase in heart rate, while SVRI and SVV both increased compared to the baseline, accompanied by a decline in cardiac index. Despite significantly decreasing diastolic TCD blood flow velocities (TCDBFV), mean TCDBFV remained stable during development of septic shock. TCD pulsatility index showed a significant increase, which correlated with decreasing MAP. The authors interpreted this as an increase in cerebrovascular resistance (CVR).

Study and paper are well structured, and the results are presented in a sound and clear way. However, some points have to be mentioned:

- The introduction section gives a brief overview on the recent literature, demonstrating that both in experimental as well as in clinical sepsis, the impact of septic shock on cerebral hemodynamics is elusive and the results so far are contradictory. How exactly augment the results of the presented study the already existing knowledge? Please discuss your findings critically on the background of the recent literature.

- The authors measured blood flow velocities, which in fact do not necessarily represent CBF. The latter depends on variables not recorded during this study, such as intracranial pressure. This limitation must be critically discussed.

- It has been demonstrated that increasing TCD PI may be positively or also negatively correlated with CVR, depending on surrounding conditions (see de Riva et al., Neurocrit Care. 2012 Aug;17(1):58-66). However, the authors of the herein presented study assume a strict correlation of increasing PI with increasing CVR. Please revise your discussion accordingly, implementing a variable association between PI and CVR. Additionally, the observed decrease in pH, likewise influencing CVR, should also be considered in the discussion section.

- Please discuss why induction of sepsis led to increasing SVRI, as others have reported contrary results (e.g., see Ridings et al., J Invest Surg. 1995 Mar-Apr;8(2):115-22).

Some other minor points should furthermore be advanced:
- Is there a reason for including 9 individuals into the control and 10 into the sepsis group? Were there animals excluded from the analysis retrospectively?

- p7, 3rd paragraph: "… at a minimum of xy °C." Please revise.

- Please explain when exactly the second measurement (T2) was performed (in relation to the infusion of bacteria).

- Please indicate if baseline parameters between control and sepsis group differed significantly. There seem to be differences in, e.g., SVRI (4084 vs. 2658) and SVV (15 vs. 10). If so, please explain why. Were control animals possibly volume depleted prior to beginning of the experiment?

- Table 1 and 2 should be presented in the same way, with pulse rate values at the top.

- p10, 3rd paragraph: according to Table 2, SVV showed no decline but rather an increase during development of septic shock.

**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

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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