Author's response to reviews

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

Authors:

Levente Molnár (mollevi86@gmail.com)
Norbert Németh (nemeth@med.unideb.hu)
Mariann Berhés (bermarjan@yahoo.co.uk)
Endre Hajdú (h11endre@gmail.com)
Lóránd Papp (csorilori@hotmail.com)
Ábel Molnár (abelmolnar@yahoo.com)
Judit Szabó (jszabo@med.unideb.hu)
Ádám Deák (deak.adam@med.unideb.hu)
Béla Fülesdi (fulesdi@dote.hu)

Version: 3 Date: 01 May 2017

Author’s response to reviews:

Dear Dr Schaefer,

Thank you very much for allowing us to revise our manuscript entitled „BANE-D-16-00306 Assessment of cerebral circulation in a porcine model of intravenously given E. coli induced fulminant sepsis” (Levente Molnár; Norbert Németh; Mariann Berhés; Endre Hajdú; Lóránd Papp; Ábel Molnár; Judit Szabó; Ádám Deák; Béla Fülesdi). In the following we respond point-by-point to the reviewer’s comments. Responses are marked with bold+italic in the response and are marked with red within the manuscript text.

RESPONSES TO THE EDITOR:

1. First it is unclear to me whether PICCO measurement algorithm established in humans can be adopted to a porcine model. The authors need to provide evidence that using PICCO in swine is suitable. Doing this the best way would be to compare PICCO results with a second tool for Monitoring hemodynamics like the pulmonary artery catheter.

2. In the methods section you do not explain how and how often the central venous pressure was measured. For calculation SVRI CVP is crucial. Changes in CVP might be the reason for differences in SVRI. Please provide measured CVP values for each time Point when SVRI was calculated. Did CVP differ between control and septic animals? Did the animals obtain cristalloids or other infusions during the Experiment? Did the amount of Urine produced during the Experiment differ between Groups?

Central venous pressure was only used for calibration of the PiCCo measurements and CVP values were not registered during the study, therefore we are unable to privode them unfortunately. Accoring to our opinion and the clinical guidelines, volumetric parameters provided by the PiCCo monitor reflect more sensitively the actual fluid status, therefore we did not pay attention to collect CVP data. CVP at baseline was 0-3 cmHgmm in both animal groups. As we described in the Methods section, we did not administer fluids in any of the groups, because we intended to assess the pathophysiology of the developing sepsis without therpeutic intervention.

3. Please indicate which formula for calculation of Body surface was used in swine as it is known that this defers from humans (at least 5-10%)? How where the PICCO calculations adjusted to the porcine model? Is the PICCO sistem suitable for us in infants with 20kg Body weight?

Thank you for this comment. We now included a sentence as follows: „The Meeh’s formula was used for calculation of body surface area in pigs (BSA=8.58xBW).” We used a PiCCo monitor that allows already monitoring of children. Additionally we added to the methods section the type of cathether that was used: 4F, 8cm PiCCO®-Catheter.

Addtional changes in the manuscript: for the sake of clarity, we ommitted the data of three animals (Nr 1,4,8) from the previous analysis, because these were the ones that were misleading. As we run the same (but hemostasis-focused) experimental sepsis model, in frame of this we repeated the measurements in 3 randomly selected control animals, as suggested by reviewer 1. Accordingly, the entire statistics was recalculated and the discussion section was modified.

RESPONSE TO REVIEWER 1.
1. I still do see a problem with the resting SVRI values significantly differing between control and septic animals. The authors discuss their finding of increasing pulsatility index on the background of "a more potent vasoconstrictor activity in this early phase of experimental shock" that "overwhelms autoregulatory vasodilation". They argue with a "strong vasoconstrictor activity present causing an increased SVRI". However, since resting SVRI values in septic animals are almost halve that of control animals, the increasing SVRI under septic conditions may be questioned. The authors should either reproduce their results by presenting cohorts with homogenous resting conditions, or at least restructure their discussion by avoiding references to changing SVRI values.

Thank you very much for your comments, we also do completely see the reason of your criticism. In our recent response we selected those animals that where selected in a different period and hypothesized that this might be the reason for the enormously increased SVRI among these animals. As we were also not satisfied with the data, in frame of our (hemostasis-based) running study we repeated the measurements in 3, randomly selected control animals, as you suggested and omitted the data of animals Nr 1,4,8 from the previous study. We now did a recalculation of the entire statistics of control animals and the data provided reflect already this analysis. Again, thank you very much for your important criticism.

2. Please decide to use either a non-parametric (Mann-Whitney U) or a parametric test (Students T) to compare variables of the two groups instead of using both tests. Since the data are not normally distributed, a non-parametric test should be used in general.

Thank you for this comment. In fact, there are a couple of data that show normal distribution, but the majority are not normally distributed. As suggested, we added to the methods section: „As the majority of the parameters did not show normal distributions, data are presented as medians and interquartile ranges and parameters were compared by the appropriate non-parametric tests.”

3. Furthermore, correlations (Fig. 1) between not normally distributed data should be analyzed using a rank correlation method such as Spearman's Rho instead of product-moment correlation.

You are completely right, thank you. We re-analyzed the ata as suggested and Spearman’s correlation coefficients and p-values are presented.

4. p6, l19 should be "...the inclusion of 20 animals was planned..." instead of "... were planned...".

We corrected it, as suggested, thank you.

Again, thank you very much for the thorough review and the useful suggestions to our manuscript. We hope that along with the present changes, the material will meet the requirements of the journal.
With compliments

Béla Fülesdi MD, PhD, DSc
Professor and chairman
Department of Anesthesiology and Intensive Care
University of Debrecen