Author’s response to reviews

Title: Tissue oxygenation as a target for goal-directed therapy in high-risk surgery: a pilot study

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Tissue oxygenation as a target for goal-directed therapy in high-risk surgery: a pilot study

Dear editor,

We would like to thank you and the reviewers for the positive response to our manuscript, and for the excellent feedback, which we thought was most constructive and helpful.

Hereby we would like to respond to the comments and questions raised.

Response to reviewer Marie Bosman comments:

Dear reviewer,

It is unfortunate that you could not download the flowchart. To the best of our knowledge no insufficiency occurred during the submission process.

In answer to your first question whether administration of dobutamine was allowed in the control group:

Use of dobutamine was not allowed in the control group. As a matter of fact, one patient had to be excluded due to protocol violation after use of dobutamine in the control group. To
clarify this more explicitly, in the methods we added “No dobutamine was to be administered in the control group.”

In answer to your question on the meaning of the number 80-85 in tissue oxygenation:

Numbers described in healthy volunteers or in non-shock surgical patients vary between 80 and 85%. We used a threshold of 80%, based on literature and recommendations. As mentioned in our present work we suggest the use of a higher threshold, or at least we wonder if this could make a difference in outcome. Flipside to that coin is excessive use of fluids and vasoactive medication, e.g. ill-treatment.

Based on yet unpublished work we suspect that StO2 measurements mostly convey information on microcirculatory integrity (microcirculatory DO2 / VO2 balance) The microcirculatory autoregulation of the thenar muscles adapts blood flow so that tissue oxygen saturation is maintained at a steady level under short-term CI variation. Only a persisting and sufficiently large change in systemic oxygen balance or an insult to the microcirculatory functioning (e.g. sepsis or vasoactive medication) is reflected in StO2.

Indeed, StO2 only partially reflects systemic measurements. The clinical question remains whether StO2 can be used as a mirror for organ (dys-) function and as a result also could predict postoperative morbidity.

Of note, there was no significant difference in vasoactive medication use between groups.

Finally, in answer to your question on place of tissue oxygenation measurement in superficial tissue in pathophysiologic circumstances, e.g. hypovolemia:

Peripheral hypovolemic vasoconstriction could be a justification to use these measurement sites (forearm; thenar eminence) as an early warning system. The main research question is
whether the goal-directed StO2 based treatment is correct and well dosed. Based on the present pilot study we are unable to answer that question. In the discussion we added

“Of note, flipside to that coin may be increased use of fluids and vasoactive medication.”

And

“Nevertheless, in general we suspect that StO2 measurements mostly convey information on microcirculatory integrity. It is possible that only persisting change of systemic oxygen balance and sufficiently large change in systemic oxygen balance is reflected in thenar StO2. The ultimate clinical question is whether the goal-directed StO2 based treatment is correct and well dosed. Based on the present study we are unable to answer that question.”

Response to reviewer Omar Adel Omar comments:

Dear reviewer,

Thank you very much for your kind comment. We fully agree that larger studies are needed. Also, we understand your concern on how such studies should be funded. However, we would like to underline here again that the funding used for this pilot study was unrestricted. As it is important to stress that our results are preliminary and aimed to facilitate further research, rather than to give a clear clinical message, we added to the discussion: “While our results tend to indicate an advantage of StO2 based goal-directed therapy, the limited power of this pilot restricts any clear recommendations before further larger studies are conducted.”
Again, we thank you for your constructive comments. We trust that the changes we have made will be acceptable to you and the reviewers.

We look forward to your reply.

On behalf of all coauthors,

Yours sincerely,

Paul van Beest, MD PhD