

Responses to Reviewer 2:

Thank you very much for your comments and suggestions they have greatly improved the manuscript. We have addressed the issues in the revised manuscript version. Most importantly, we have added the mean SOFA score data of both groups and numbers of patients with SIRS symptoms to be able to compare at least some of the clinical outcomes.

Abstract. Thrombotic activation. This term is not correct. The coagulation parameter tested is the TAT complexes. The others are inflammation or platelet activation markers. All of these parameters reflect thrombin generation and inhibition, platelet activation, which may increase the risk of thrombosis.

Response: Thank you for pointing this out. The term “thrombotic activation” was replaced by “coagulation-associated activation”.

Results: eventhough, the study was not designed and powered to evaluate the clinical outcome, it would be interesting to have few data on the outcome of the patients in the two groups (development of SIRS ..)

Response: We absolutely agree with you on this and have added the SIRS and SOFA score to the manuscript.

The discussion should be revised.

- In their discussion, the authors make lot of assumptions on different mechanisms of inflammation activation that are not always supported by their results. Some parts of the discussion should therefore be shorten.

Response: We have rewritten and shortened the discussion to more appropriately reflect the data and focussed more on the different activation through HLM and material.

- Proposed mechanisms are mainly focused on monocyte activation while other cells can largely contribute to the inflammation state. Hemostasis and inflammation are intimately linked, and induce and amplify one another. Indeed, the interaction of platelets with leucocytes is a key step in both system activation which facilitates leukocyte extravasation to the site of inflammation and initiation of vascular inflammation (Mansour A et al, J Clin Med 2020). This issue should be addressed.

Response: Thank you for this valuable comment, you are correct, we have focussed too much on monocyte and neutrophil activation and left out the crosstalk between platelets and leukocytes.

- In cardiac surgery, the sucked blood may be processed in a cell saver, which would remove cytokines, platelets and cell fragments. In this context, the differences between material may be less relevant. This should be considered in the discussion.

Response: We have stressed more clearly that the effect of materials used during CPB surgery only applies if a cell saver is not used (explanation in introduction and discussion). It is common practice to reperfuse directly into the HLM without cell saver when the anticoagulation is high to save time and blood transfusions. For exactly these cases, we have performed the study to investigate if the natural material may have a negative impact.

- Page 14, line 421 : the sentence “The strong increase of TAT...thus preventing thrombin formation less efficiently”. The increase of TAT in blood from taken from the swabs is more than likely due to activation of coagulation upon contact with swabs rather than an effect of protamine...

Response: In line 421, we meant the huge differences in TAT-levels during HLM and in blood taken from swabs are likely due to protamine antagonizing heparin. Of course, the differences between groups are due to the material, but TAT levels are very high – this is not observed during normal operations due to the anticoagulation. We have clarified this now.