Author’s response to reviews

Title: Tissue oxygen saturation as an early indicator of delayed lactate clearance after cardiac surgery: A prospective observational study

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Version: 1 Date: 13 Sep 2015

Author’s response to reviews:

Dear editors, dear reviewers,

Thank you for the important comments on our manuscript “Tissue oxygen saturation as an early indicator of delayed lactate clearance after cardiac surgery: A prospective observational study”. We resubmit our revised manuscript according to your notes and answer them point by point:

Reviewer #1:

- This is a prospective observational study: the authors should have followed the STROBE checklist for observational studies. Please, revise the paper accordingly.

We revised the paper according to the STROBE checklist [1] and integrated missing items in our manuscript, e.g. recruitment of patients, relevant dates or a more detailed description of the statistical methods.

- There is no sample size calculation.
We agree that a sample size calculation is an important measure to enhance the significance of a study. When we designed our study protocol, we tried to assume a reasonable patient number from available literature in the field of StO2, which included between 16 and 46 patients [2-5]. Additionally, we performed a power analysis (G* power 3.1 [6]) and calculated a sample size of 34 to detect a correlation between StO2 and lactate as a metabolic parameter of tissue perfusion and oxygen metabolism (coefficient of determination $r^2=0.16$, $\alpha$ error 0.05, power 0.8). As power analysis is more common for prospective controlled studies than for uncontrolled observational studies, we considered not to present the results of our power analysis and only cross-reference to other observational studies about StO2 in the manuscript (page 4, line 10). When the reviewers and editors recommend the integration of the power analysis, we would mention the power analysis in the manuscript of course.

My main concern is that on-pump and off-pump surgery were included in the same analysis. In fact, on-pump and off-pump cardiac surgery are associated with distinct alterations in microcirculatory perfusion. Microcirculatory perfusion seems to remain unaltered throughout off-pump surgery. In contrast, microvascular perfusion declined after initiation of cardiopulmonary bypass and did not recover in the early postoperative phase. The authors should comment on that. I suggest to compare on-pump and off-pump aorto-coronary bypass in a separate subgroup analysis.

We consent with the reviewer that the cardiopulmonary bypass causes specific changes in micro- and macrocirculation. We performed a post-hoc analysis of StO2 for an on-pump and off-pump subgroup, but there was only a significant difference before surgery between groups (* $p<0.05$). Significant changes within groups were observed and are marked with †, ‡, and § ($p<0.05$).

<table>
<thead>
<tr>
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<th>T -1</th>
<th>T 0</th>
<th>T 1</th>
<th>T 4</th>
<th>T d1</th>
</tr>
</thead>
<tbody>
<tr>
<td>StO2 (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>off-pump</td>
<td>82 (4)*,†</td>
<td>83 (7)‡</td>
<td>76 (7)</td>
<td>73 (5)†,‡</td>
<td>81 (3)</td>
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<tr>
<td>StO2 (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>on-pump</td>
<td>86 (4)*,†</td>
<td>87 (5)‡</td>
<td>77 (7)†,‡,§</td>
<td>76 (7)†,‡,§</td>
<td>85 (5)§</td>
</tr>
</tbody>
</table>

The minimum StO2 was 71% (3%) for off-pump and 74% (6%) for operation with CPB without statistical significance. We additionally analysed the lactate clearance for both groups at T d1: -56% (68%) for off-pump and -49% (76%) for on-pump surgery (no significance).

In two recent prospective studies, microdialysis of the deltoideus muscle was compared for off-pump and on-pump surgery and significant changes were observed between both procedures. One study suggested a compromised muscle energy metabolism during CPB because of a significantly higher lactate-pyruvate-ratio and glycerol level as well as a lower pyruvate level for CPB-group [7]. In contrast, however, the other study demonstrated higher lactate-pyruvate-ratio...
and lower pyruvate concentration for off-pump surgery the first day after surgery, indicating a higher risk of tissue hypoperfusion for off-pump surgery [8].

To consider the important hint of the reviewer in our manuscript, we integrated Min-StO2 and Lactate clearance at T d1 for the subgroups off-pump and on-pump in results (page 7, line 14). We comment on our results of the subgroup analysis in the context of the microdialysis studies in the discussion (page 8, line 9).

- Another concern is the lack of very important outcome variables such as aortic cross-clamping time and cardiopulmonary bypass time which have been demonstrated to be predictors of immediate postoperative morbidity and mortality.

Thank you for this important hint and we agree that type of operation and duration of cardiopulmonary bypass as well as cardiac ischemia are important variables influencing the outcome after surgery. We therefore included an additional table presenting this data together with different outcome variables separately for both subgroups (table 5).

- In the discussion section on page 7, the authors state: "Although recovery of StO2 occurred at day 1, increased lactate concentration and base deficit persisted probably due to delayed metabolism/wash-out of accumulated acid metabolites" This sentence sounds like an authors' assumption. I agree with the authors but this statement needs experimental supporting data or more references.

We endorse the reviewer that this statement has to be proved with additional references. To support our assumption we now describe the pathophysiology in more detail and include additional references (page 9, line 5).

- Discussion section, page 8: "Only StO2 combines advantages..." I suggest to modify this sentence as follows: "Our study demonstrates that StO2 combines..."

The sentence was modified according to the recommendation (page 10, line 15).

- Other missing data regards long-term outcomes, e.g., length of intubation, length of ICU stay, or ICU mortality.

As this data were recorded during the study, we present them now in table 5 for both subgroups.

Reviewer #2

- The main objective of the study is to explore the association between early StO2 measurements and lactate evolution. Although the authors do find a positive association between these two variables, I have some concerns when generalizing these results, since according to the results displayed in table 1 and 2, the studied population does not seem a very critical population, and their global lactate values are persistently within a normal range.
As the authors expose, both hyperlactatemia (lactate > 3 mmol/L) and lactate clearance (time from maximum lactate to lactate of 1.5 mmol/L) have been associated with poor outcome (Maillet et al. Chest 2003; Lindsay et al. Ann Thorac Surg 2013, respectively). However, the present population seems to have low lactate values, and thus that would be a great limitation when trying to generalize the utility of StO2 as a predictor of lactate disturbances, and being so, as an outcome tool.

Did the authors analyze separately those patients with hyperlactatemia at some point of the study? How many patients showed hyperlactatemia during their evolution?

Thank you for your worthwhile comments about the observed lactate levels in our study.

As the reviewer mentioned, the evaluation of the study population with regard to the perioperative risk is crucial. We have chosen the EURO Score as validated prospective score for cardiac surgery to estimate the perioperative risk profile of our patients. For our study population a mean EURO Score of 6 (4) with an median of 7 and a range of 0-12 was observed. Additionally EURO Score calculates a predicted operative mortality with a mean of 10.4 % (10.2 %) and a median of 6.1 % (range 0.9-35.2 %) for our study. An American study evaluated the EURO Score in 401,684 cardiac surgery patients describing a mean predicted mortality of 3.994 % [9], whereas the predicted mortality in our study was 2.6-fold higher demonstrating an even more critical population.

Nevertheless maximum lactat levels after surgery were <1.0 mmol/l in 10 % (4), 1-1.9 mmol/l in 57.5 %, 2-2.9 mmol/l in 20 % and >3.0 mmol/l in 12.5 %, representing a maximum lactate above the normal range of <2.0 mmol/l in 1/3 of the patients. To address the comment of the reviewer, we analysed all patients with a maximum lactate level ≥2.0 mmol/l separately. Univariate regression analysis was performed with this subgroup of 13 patients.

<table>
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<tr>
<th>Factor</th>
<th>Univariate analysis</th>
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<th>Multivariate analysis</th>
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<tbody>
<tr>
<td></td>
<td>Coefficient</td>
<td>95% Confidence Interval</td>
<td>r</td>
<td>P</td>
<td>Coefficient</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>Minimum StO2</td>
<td>3.440</td>
<td>0.6255 to 6.255</td>
<td>0.63</td>
<td>&lt;0.05</td>
<td>0.140</td>
<td>0.033 to 0.247</td>
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<tr>
<td>Minimum cardiac index</td>
<td>0.049</td>
<td>-0.223 to 0.320</td>
<td>0.12</td>
<td>n.s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum SvO2</td>
<td>1.186</td>
<td>-4.974 to 7.347</td>
<td>0.13</td>
<td>n. s.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum MAP</td>
<td>-0.679</td>
<td>-5.858 to 4.500</td>
<td>-0.09</td>
<td>n. s.</td>
<td></td>
<td></td>
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<tr>
<td>Overall</td>
<td></td>
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</table>

Univariate regression analysis was performed with this subgroup of 13 patients.
As you can see, we could demonstrate a relationship between minimum StO₂ and lactate clearance at T d1 for patients with higher lactate levels, as it was already demonstrated in table 3 of the manuscript for the 40 patients. Although a small patient number of 13 are limiting the statistical power of this additional analysis, we suggest, that these results confirm the significance of our regression analysis in table 3 of the manuscript. We added the sentence “After identification of 13 patients with a maximum lactate concentration higher than 2.0 mmol·l⁻¹, univariate analysis demonstrated also a significant correlation of minimum StO₂ with lactate clearance at T d1 (r=0.63, p<0.05).” to the results section to include this important aspect (page 7, line 20).

- According to reference #2 of the text, early hyperlactatemia is associated with increased mortality, whereas late hyperlactatemia lacks this association, and seems more related to catecholamine infusion. The authors should enhance the discussion on that matter.

We agree with the reviewer, that this paper should be additionally discussed in the context of lactate kinetics after cardiac surgery. We integrated the key points of this study in the discussion section of the revised manuscript (page 9, line 19).

- Did those patients with hyperlactatemia receive more interventions than the others? How did that affect to lactate clearance? I wonder that patients with elevated lactate were probably actively resuscitated, and that might have influenced lactate clearance.

The patients were resuscitated according to local clinical standard after the operation: Global parameters of haemodynamics as well as venous oxygen saturation or lactate concentration were used to guide volume replacement and catecholamine therapy. Nevertheless, infusion of cristalloide as well as colloid solution was not different between a maximum lactate <2.0 mmol/l and ≥2.0 mmol/l or with between effective lactate clearance or not. Altogether minimum StO₂ seems to be an additional information during the early postoperative course with regard to lactate clearance at T d1, although lactate concentration was used as a parameter to guide postoperative haemodynamic therapy.

- Results section, page 6, line 16-18: "...lactate concentration and base deficit were persistently impaired". It does not seem so when looking at table 2.

We agree with the reviewer, that we used a not-quite-correct term in this sentence. Mean lactate concentration was within reference range (<2.0 mmol/l) and base deficit just slightly increased (reference range -2 to +2) at T d1, although both were significantly higher at T d1 compared to T -1. We changed the sentence accordingly in the results section (page 6, line 24).

- According to the previous exposed concern, I think it would be very interesting to add the use and rate of catecholamine infusion as covariates in the regression analyses. The authors already used several covariates, which might be of limited value when analyzing such a limited population.
The idea of our regression analysis was to compare standard hemodynamic parameters (mean arterial blood pressure and central venous/mixed venous oxygen saturation) as well as cardiac output, a parameter of extended hemodynamic monitoring, with the novel parameter StO2 as risk indicator for low lactate clearance. Nevertheless it seems interesting to add catecholamine infusion to this analysis and we performed an additional regression analysis. Univariate analysis of mean dose of epinephrine and norepinephrine as well as maximum dose of these catecholamines demonstrated no significant effect and multivariate analysis resulted in no additional significant parameters also.

- I am not quite sure that the association between StO2 < 75% and increase in CK-MB and troponin are clinically significant. As it happened with lactate values, both, CK-MB and troponin, were pretty low.

Mean CK-MB was about 10 times higher than the cut-off <3.7 µg/l and the troponin T values were about 20-40 fold higher than the cut-off <0.03 µg/l. Nevertheless, most of the patients presented with CK-MB and troponin T levels within the expected range after heart surgery resulting from surgical myocardial trauma and cardiac ischemia related to cross-clamping. We agree with the reviewer, that the clinical significance of the observed differences in CK-MB and troponin T remains debatable, but we didn’t want to omit these statistically significant data.

- Conclusions section. I would eliminate the first sentence: "StO2 demonstrated to be a fast and non-invasive indicator of the tissue oxygenation status". In the present study, StO2 was a mere non-invasive measurement of tissue oxygenation, period.

We deleted the first sentence of the conclusion and added the sentence “StO2 was a non-invasive measurement of tissue oxygenation, according to your important comment (page 11, line 4).

- Conclusions section. "A StO2 below ... 75% ... was an excellent predictor...". I would suggest to eliminate "excellent". The AUC is statistically and clinically relevant, but not excellent.

Thank you for your comment. We agree and changed the sentence accordingly (page 11, line 4).

- Table 1 should be improved. It should be clearly displayed Euroscore "value" and "%". The type of operation should be displayed also in %.

We revised table 1 according to the comment. “Value” and “%” of Euroscore are clearly displayed and percent values of type of operation were added.

- Figure 3 should be better explained.

We tried to describe the figure more precisely. Different subgroups, calculation of lactate clearance and statistical analysis are now described in more detail.
Fluid management followed a local in-house standard using Ringer’s solution as full electrolyte solution and 6% hydroxyethyl starch 130/0.4 (HES) as volume substitute solution.

Intraoperative administration of Ringer’s solution was significantly different with 740 (430) ml for StO2>74% and 1250 (560) ml for StO2<75% (p<0.05), but HES application demonstrated no difference, 540 (410) ml for StO2>74% and 650 (390) ml for StO2<75%. Postoperative and total fluid administration demonstrated no significant differences between subgroups at T d1.

Transesophageal echocardiography (TEE) was routinely used intraoperative for patients with valve surgery to address valvular function and for patients with hemodynamic instability. Postoperative TEE was used in case of severe cardiac failure or hemodynamic instability, but not as standard monitoring.

I miss some statements regarding the signal quality, artefacts, or measurement failure. Please add.

Thank you for this comment. We added a description in the Methods section, how to achieve sufficient signal quality and to avoid measurement failure (page 5, line 1).

Please also discuss the StO2 measurement in the mucosal (i.e. sublingual, buccal) v.s. transcutaneous (i.e. thenar) microcirculation in this context.

Thank you for the reference to this monitoring technique. We integrated buccal StO2 in our discussion describing results from a study with children having a congenital cyanotic heart disease undergoing a cardiac surgical procedure (page 9, line 12).

The authors twice mention the SOFA score, though without reporting any data. Please report the score values.

An additional table with outcome data was integrated (table 5) presenting data of SOFA score as well as length of stay, ventilation time or characteristics of cardiopulmonary bypass.

The authors measured StO2 different oxygen delivery conditions (FiO2 ranging from 1.0 and 0.3). Considerably different oxygen levels may secondary influence StO2.

This may have influenced the StO2. Please also report PaO2 values and discuss.
We report the values of PaO2 now in table 1. The data of StO2, PaO2 and FiO2 are now discussed (page 8, line 25) and the possible influence of arterial oxygen level could be excluded supported by a study of Ikossi et al. [4]

- Line 50: Which test was used for correction of multiple testing?

We confirmed normal distribution with the Kolmogorov-Smirnov test and tested between different time points with repeated measures ANOVA. When statistical significance was detected, we used a Tukey multiple comparisons post test for dependent samples as post-test. We generally revised the section statistical analysis for a better understanding (page 6, line 6).

Editorial Requests

Ethics:

If your study involves humans, human data or animals, then your article should contain an ethics statement which includes the name of the committee that approved your study.

If ethics was not required for your study, then this should be clearly stated and a rationale provided.

In methods section the vote of our local ethics committee is described.

Consent:

If your article is a prospective study involving human participants then your article should include a statement detailing consent for participation.

If individual clinical data is presented in your article, then you must clarify whether consent for publication of these data was obtained.

We describe the process of receiving written informed consent including study participation and publication in the methods section.

Availability of supporting data:

BioMed Central strongly encourages all data sets on which the conclusions of the paper rely be either deposited in publicly available repositories (where available and appropriate) or presented in the main papers or additional supporting files, in machine-readable format whenever possible. Authors must include an Availability of Data and Materials section in their article detailing where the data supporting their findings can be found. The Accession Numbers of any nucleic acid sequences, protein sequences or atomic coordinates cited in the manuscript must be provided and include the corresponding database name.
The relying data of our conclusions are presented in the tables, the figures and the results section of the manuscript.

Authors Contributions:

Your 'Authors Contributions' section must detail the individual contribution for each individual author listed on your manuscript.

Individual author’s contributions are included in the manuscript

References


