Reviewer’s report

Title: Surfactant Replacement or Open Lung Concept? Comparison of two treatment strategies in an experimental model of neonatal ARDS

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Reviewer: Martin Krause

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Hilgendorff et al.: Surfactant replacement or open lung concept?

Major

Hilgendorff et al describe lung function parameters, gas exchange, histology scores, surfactant composition and mediator expression in a newborn piglet lavage model of acute lung injury. While some of the post-mortem lung examinations contribute to the wealth of knowledge about neonatal lung disease, several major drawbacks of this study must be addressed:

1. Above all, the study design is not clear to this reviewer. The study clearly lacks a control group with lavage and without further interventions. Many of the findings cannot be correctly interpreted without the results of a control group. A second control group without lavage would have been nice, too, especially for the interpretation of the surfactant component analysis.

2. Then, what is the rational of comparing surfactant administration and an open lung volume ventilatory strategy, as both components belong to good clinical practice in neonatal respiratory failure (or to be more specific, an adequate FRC). Why did the authors not plan another group combining the features of both kinds of interventions?

3. Group sizes are at the lowest end of statistical feasibility.

4. Another delicate aspect is the lack of a comparable degree of lung injury between the three groups. E.g., the difference in Cdyn after airway lavage is huge (range 100 to 216%) which is a significant difference even in these small groups. Many down-stream results support the assumption of differences in initial lung injury, as for instance the histology score.

5. Interventions were carried out at different time points (surfactant administration immediately after lavage, lung recruitment one hour after lavage). This makes it hard to do two-factorial ANOVA by the use of the same time points.

6. The analysis of surfactant composition generates many data that are not clear at first view (maybe also due to small group size), but are later not adequately discussed.

7. Last but not least: the title of the manuscript “surfactant replacement or open lung concept” does not find an answer in the conclusion. Is it really “or”, or is it “and”?
Minor

Abstract
Measurements and results: inadequate data presentation, please give numbers and p-values. VEI not explained.

Introduction
Please reword first sentence.

Page 4, end of first paragraph: to this reviewer, it is not clear why surfactant therapy and OLC should be any contradiction. OLC maneuver is generally not considered as a first line therapeutic option in neonatal respiratory failure, however, most neonatologists do aim at adequate lung volumes (i.e. adequate functional residual capacity) and simultaneously support of gas exchange by surfactant administration.

Page 4, second paragraph, references 11-14: none of these studies has investigated neonatal ARDS. Reference 16 is dealing with RDS in premature babies.

Materials and Methods
Page 5, second paragraph, age: 6+/-5 days is a huge variation in a porcine neonatal model. How about variations/occurrence in surfactant pool and patent ductus?

Page 5, second paragraph: probably, a 3 mm inner diameter ETT was used.

Page 5, last paragraph: 50 mL/kg lavage fluid is probably beyond TLC, when adding FRC (approximately 25 mL/kg in a piglet) and VT (6-10 ml/kg). Did the authors aim at additional lung damage by non-physiologic stretch?

Page 7, 2nd paragraph: why were piglets excluded with a PaO2<60 kPa?

Page 7/8, decrease in PEEP: increasing PaCO2, decreasing PaO2 and decreasing blood pressure can also all occur due to alveolar collapse. Where do the authors know that overdistension took place?

Page 8, 2nd paragraph: why was surfactant administration carried out immediately after repeated airway lavage, whereas alveolar recruitment in the OLC group was not done before one hour after completion of lavage?

Results
Page 12, 1st paragraph: please provide number of lavages and the amount of lavage fluid that could be aspirated from the airways.

Page 12, 2nd paragraph: no signs of hemodynamic compromise. Why do the authors mention decreasing blood pressure in the methods section but did not occur?

Page 12, 1st paragraph, Table 2a: this reviewer is concerned about the differences in PaO2, Cdyn and VT between the three groups at T=0. The differences in Cdyn vary between 100% and 216%. The same applies to VT; why
were these huge VTs used? It seems as if the mon SP-B group received a lesser lung injury than the other two groups. The presentation of the statistics is not clear: do the asterisks present the results of the post-hoc tests? Please clarify.

Page 12, 5th paragraph: “…significantly improved over the time course…” Cannot find the statistical test that supports this statement.

Page 12, last paragraph: two-way ANOVA testing includes reporting group differences, time factor, and interaction between these factors. Please specify. Does ANOVA testing also include the time points “H” and “T=0”? How do the authors deal with significant differences between groups in PaO2 at T=0 when performing ANOVA for the following 5 time points (especially time factor)? It seems to this reviewer that the time differences in interventions (OLC at 1 hour, surfactant immediately) does not justify to perform ANOVAs with the inclusion of the time points T=0 and 1h.

Page 13, 2nd paragraph: the text mentions a significant difference for deltaP (p=0.001). Table 2a and Table 2b do not. Significant VT differences mentioned in text, but not in Table 2a.

Page 13, 3rd paragraph: differences in VEI not given in Table 2a.

Page 13, data presentation: Table 2a and Figures 1 and 2 present the same data. Please stick either with the tables or the graphs.

Page 13, last paragraph: what is the reason for the difference in histology score for the middle lobe? This reviewer would expect some more detail in how the individual scores are composed, and how the individual interventions influence the different scoring. The bar graph in figure 3 is not necessary.

Page 14, 1st paragraph: figure 4 data are the same as can be found in Table 3, however, figure 3 presents box-plots (non-Gaussian population), Table 3 means +/- SD (Gaussian population). Please reconcile and omit the one or the other. The text mentions a phospholipid/protein ratio, the table a protein/phospholipid-ratio. What are normal levels in PC and PG, as there is no control group? Why is PS not detectable in the two surfactant groups? This is certainly no “effect”. Why are polyunsaturated FA concentrations lower in the surfactant groups?

Page 14, 2nd paragraph: why is SP-B/PL not highest in the mon SP-B group, but indeed lowest? It would be probably better to report absolute concentrations for both substances.

Page 15, 1st paragraph: same problem with table 4 and figure 5 data presentation as in table3/figure 4 data presentation. Table 4 data look as if mon SP-B group piglets had the least amount of lung injury. Why is the SP-B/A ratio highest, but the SP-B/PL ratio lowest in mon SP-B group piglets?

Discussion

Page 16, 1st paragraph definitely is part of an introduction but does not belong to the discussion of study results.

Page 17, 2nd paragraph: decrease of PaO2 levels in the natural surfactant group: this is not confirmed for its significance by any statistical test. You could
portion the 6 time points and do ANOVA for T=0 until 2h and then 3h until 5h to detect a statistical difference.

Page 17, 2nd paragraph: “reduction of shear stress”, the authors should also discuss that they used an injurious kind of ventilation, at least in the two surfactant groups by the use of VT of appr. 20 ml/kg.

Page 17, last paragraph: the superior effect of mon SP-B on lung histology seems to be speculative, as the issue of a minor degree of initial lung injury has not been ruled out.

Page 18, 2nd paragraph: the discussion on surfactant composition does not include many of the questions risen in the review of pages 14/15.

Page 18, last paragraph: “combination of both treatment strategies”, why didn’t the authors do it?

Page 19, 1st paragraph: pointing out the higher degree of shear stress of the lungs in the surfactant treated groups is in line with the finding of a lower SP-B/PL and SP-C/PL ratio, but not with the inverse findings of LSA percentage.

Page 20, 1st paragraph: As a limitation, high tidal volumes on the OLC group compared to previous OLC ventilation regimes are mentioned. Why should that be a limitation?

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.