**Reviewer's report**

**Title:** Increased permeability-oedema versus atelectasis in pulmonary dysfunction after trauma and surgery: a prospective cohort study

**Version: Date:** 19 April 2007

**Reviewer:** Andreas Reske

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**Reviewer's report:**

**General:**
Dr. Groeneveld submitted an interesting study aiming to evaluate the mechanisms of pulmonary dysfunction (ALI/ARDS) after trauma and major surgery, respectively. Although the focus of this study is most interesting, the results are unfortunately compromised by several methodological flaws. The manuscript could be strengthened in several areas, the text is often confusing and makes it difficult for the reader to follow. Many sentences are too long. Although I am not a native speaker of English, I encourage the authors to enlist the assistance of an English editor in order to improve the clarity of the manuscript. The manuscript could be shortened significantly.

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**Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached):**

**Abstract:**
1. No information is given regarding the degree of pulmonary dysfunction in the patients studied. How was “evidence” for atelectasis obtained? May be “evidence” is a bit too strong considering the unspecific information chest x-rays provide on the nature of the infiltrates, how was pleural effusion excluded? This comment also applies to the Methods section.
2. The facts provided in the Results paragraph need to be brought into a logical order. Why is, for example, a higher LIS attributable to a higher cardiac output? Please clarify.
3. The conclusion is not adequately supported the results.
4. Clearly, atelectasis significantly contributes to postoperative or postraumatic pulmonary dysfunction, however, this “major” contribution cannot be established based on the data presented here.

**Introduction:**
5. The introduction is lengthy and needs to be restructured and focused significantly.
6. Many statements in the first paragraph remain unclear such as the role of atelectasis in the pathophysiology of ALI/ARDS, and the ability of CT to differentiate between edema and atelectasis.
7. It is mentioned that a contribution of atelectasis to hypoxemia and radiographic abnormalities was “contrary” to the definition of ALI/ARDS. First of all, the paper describing the definition which the authors quote should be cited. I guess the authors refer to the AECC report published in both AJRCCM and ICM in 1994. In that paper, however, it was reported that the authors “felt” that the infiltrates should be consistent with pulmonary edema, however, atelectasis was not excluded. Moreover, atelectasis has been an intrinsic part of other descriptions of ALI/ARDS (cf. Ashbaugh et al. Lancet 1967, Ware & Matthay NEJM 2000).
8. Why does only atelectasis warrant the application of recruitment maneuvers? An edematous lung may be even better recruitable as seen, for example, in patients with cardiogenic pulmonary edema under CPAP?
9. The second paragraph could be shortened significantly. I do not think it’s necessary to mention every type of surgery together with the fact that it may be complicated by postoperative pulmonary problems, this fact is well established. Move methodological specifications (last paragraph) to the Methods section and present a clear and concise hypothesis here.

**Patients and method:**
10. The methodology is inadequately explained and some methodological aspects appear illogical. The methods section needs to be restructured and made more concise. The somewhat confuse order of methodological details makes the reading difficult. The end-points are not adequately defined. Did the authors perform a power analysis?
11. Was this really a prospective study? If so, what made the authors choose 77 years as the age cut-off for inclusion?
12. How was pulmonary dysfunction defined, prolonged postoperative ventilation doesn’t necessarily imply that there is pulmonary dysfunction! Please clarify.
13. How did the authors obtain “evidence for atelectasis” without performing CT scans? How could the radiologist examine the retrocardiac space on anteroposterior chest X-rays? Although CT scanning can
admittedly not distinguish between collapsed and fluid-filled lung units at the alveolar level, it provides most helpful information in this regard.

14. What was the rationale for defining overhydration by CVP >11/>13, why was PEEP=11 chosen as cut-off? Please explain or provide pertinent references. Were clinical and radiological findings indicating edema considered as well? Was the amount of intravenous fluids documented for both trauma and surgical patients? If so, this information should be specified, may be instead of data with marginal importance such as temperature (table 2).

15. You stated, that “patients were otherwise treated according to our guidelines for hemodynamic optimization and vasopressor/inotropic support with norepinephrine or dopamine”, please specify this guideline, otherwise this information remains meaningless and this sentence should be removed.

16. Were co-morbidities such as preexisting cardiac or pulmonary diseases documented? If so, please provide this data. Such co-morbidities are frequent in patients requiring esophageal surgery and may theoretically have interacted with your results.

17. Was weaning and extubation postponed in surgical patients for the purpose of this study? What was the indication for continuing mechanical ventilation postoperatively in surgical patients?

18. You stated, that “patients were otherwise treated according to our guidelines for hemodynamic optimization and vasopressor/inotropic support with norepinephrine or dopamine”, please specify this guideline, otherwise this information remains meaningless and this sentence should be removed.

19. Page 5, first sentence of Patients and methods: This sentence is too long and the order of its contents chaotic.

20. Page 5, line 10 of Patients and methods: You write: “after tracheal intubation ...” – which patients were intubated? When and why? I suppose, surgical patients were transferred from the OR being still intubated and ventilated. Trauma patients were likely intubated in the ED ... so mentioning the intubation here may confuse the reader. I suggest to delete this detail and to describe the mechanical ventilation only.

21. Page 6, line 10: Here you write that the scintillation detectors were positioned over the lung apices. Does this approach enable the study of the entire lung field, or were only the apical regions of the lung studied? Please explain. If only the apical lung regions were studied, discuss this limitation and its consequences.

22. Page 6, line 24: isn’t that technique (i.e. the COLD system) for measuring EVLW usually called “double-indicator technique”?

23. Page 6, line 24: You state that “a 4 F introducer was inserted into the femoral artery, for use in the study protocol, ...”. If this intervention was specifically performed for the purpose of the study, were the patients or their relatives informed about such “additional” interventions? Moreover, you wrote earlier in this section that the presence of a central venous line was an inclusion criterion, but you did not mention an arterial line as such. You later describe that you used radial artery catheters for hemodynamic measurements and femoral artery catheters for the COLD system. Did you insert two arterial catheters in patients who did not have any arterial line at admission to ICU? Please clarify.

Results:

24. The results section contains material also presented in the tables. Please remove redundant data.

25. The authors performed a large number of tests which may give rise to the problem of multiple testing considering the small number of patients in each group. To avoid further loss of power by correcting for multiple testing, we strongly encourage focusing the statistical analysis on the central hypotheses of the manuscript.

26. Page 8, line 1: When they authors expected limited comparability of groups a priori, why didn’t they simply include more patients? I am aware that this question is sort of provocative given the sophisticated method to measure the PLI ...! However, that point should be adequately discussed.

27. Page 8, line 8: It is mentioned that table 2 shows hemodynamic AND pulmonary data but it doesn’t! Table 2 shows hemodynamic data only. Respiratory variables are given in table 3 which, in turn, is not at all mentioned in the text.

28. Page 8 line 9, and page 9 line 1: Please move interpretation of data to the Discussion.

29. Page 9, line 9: How many patients had ALI/ARDS according to the AECC?

30. Page 9, line 12: It is surprising that you mention that compliances did not differ? What about the results given in table 3? The same applies to radiographic evidence for atelectasis (next paragraph).

31. Page 9, line 18 and 21. What do you mean by “rs” – r or r2?

32. Page 9, line 18 and 19: Figure 1 and 2 are mixed up.

Tables:

33. Please give p-values even if statistical significance was not reached.

34. Table 1: How long was the duration of mechanical ventilation?

35. Table 3 is not mentioned at all in the text!

36. Table 3: Please report tidal volume in ml/kg bodyweight here, this information could then be deleted in the results section.
Figures:
37. Figure 1 and 2 are mixed up, at least when compared to the figure legends and the order they are cited in the text.

Discussion:
38. The discussion is not focused on the hypotheses and the results of the manuscript. Many sentences are too long and difficult to understand.
39. Several points are overstated and not adequately supported by the results and the power of this study seems limited due to the small groups studied. This should be acknowledged and thus the authors should discuss and interpret their interesting findings more cautiously. Moreover, the authors should avoid making too many assumptions and should instead focus on their results.
40. The discussion should start with the major results of the study and not with what it may suggest.
41. It should also be discussed that only two patients with ARDS were analyzed, all other patients had mild (if at all) to moderate ALI. The authors should again point out what patients they studied.
42. The authors seem to confuse the role of edema and atelectasis in the pathophysiology of acute lung injury (ALI/ARDS). Not only in my opinion is atelectasis not a complication of ALI/ARDS but rather an intrinsic part of its pathophysiology. I agree that in many patients with ALI/ARDS, there is a co-existence of edema and atelectasis. However, the latter should surely not be considered a complication of the former (cf. Ware LB and Matthay MA NEJM 2000). Accordingly, the question should rather be which mechanism (i.e. edema or atelectasis) predominates. As correctly pointed out by the authors, knowledge of the predominating cause of alveolar de-aeration can have strong implications for the therapy.
43. Also, the authors need to check the points they made about the recruitability of atelectasis vs. edema as the response rate to recruitment maneuvers in patients with edema will be very high as well. This is illustrated by the usefulness of CPAP in cardiogenic pulmonary edema. In this context, I also refer to the work of Hubmayr and colleagues (cf. Hubmayr R AJRCCM 2002, Wilson TA JAP 2001).
44. In the paragraph dealing with the limitations of the study, the discussion of limitations is mixed with other aspects, please revise and complete this paragraph. What about statistical limitations, limited power, small sample size etc.? Limitations of the PLI method, problems due to regional sampling, sampling error etc.?
45. Page 10, line 10 and 11: How does your study confirm that “ventilatory criteria may better predict duration of ventilatory support” – please explain!
46. Page 10, line 13: should be “... an elevated PLI”, please delete “in”
47. Page 10, line 19: “We cannot exclude ...” This sentence is obscure, please clarify!
48. Page 11, line 23: Dependent atelectasis developing soon after induction of general anesthesia ARE (not only “may be”) a major cause of peri- and postoperative hypoxemia (cf. work from Göran Hedenstierna’s group). Conversely the role of high permeability edema is less clear and differentiation between high-permeability edema and edema due to fluid overload may be difficult.
49. Page 11, line 25 and 26: I doubt that your statement regarding the interaction of atelectasis and edema can be made based on your result. Especially when considering that your surgical patients had a median length of stay in the ICU of 1 day, this period may have been too short for complications of atelectasis to develop.
50. Page 12, line 9. You mention that central venous were used instead of mixed venous blood gases for calculation of venous admixture. The authors discuss some of the implications of this modus operandi but should be more consistent. What are the consequences of blood-sampling in the superior vena cava where the tip of the central venous line is usually positioned (and not in the right atrium, as the authors discuss).
51. Page 12, line 17: I do not agree with your generalization that the interpretation of CT scans is hard in terms of identification of atelectasis. Sure, differentiation of edema from atelectasis may be difficult in some patients but definitively not in general.
52. The conclusion is clearly overstated and not fully supported by the data, how can the authors establish a “major” contribution of atelectasis to ALI/ARDS based on their data?

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct):

Patients and methods:
1. Page 5, line 8 of Patients and methods: The abbreviation “PEEP” is used without previously defining it. Later (page 6, line 1) the authors use the full term “positive end expiratory pressure” instead of the abbreviation.
2. Page 6, line 16: is “CPM g-1” correct? Shouldn’t it be “CPM.g-1” or “CPM*g-1”? 
3. Page 7, line 9: LIS – the full term, although well-known, should be first written in full with the abbreviation in parentheses immediately after it.

4. Page 8, line 7: Wherever the authors mention mortality in the text, they always specify that it’s ICU mortality, even in table 1. Therefore, the sentence “Mortality refers to mortality in the ICU” appears unnecessary.

5. Page 7, line 1: what means “D5W”?

6. Page 7, line 3: “Muenchen” should be Munich.

7. Page 7, line 22: “Only leukocyte-depleted red blood cell concentrates ...” – Why was this statement placed here, within the description of the study protocol?

8. Page 8, line 4: Please insert Germany after “...(Osmomat, Gonotex, Berlin, ...”

Figures:

9. Figure 1 – radiographic densities vs. venous admixture: Labeling of the x-axis doesn’t require decimal places, which would be illogical. Could you show the regression line together with the 95% confidence band?

10. Figure 2 – number of packed red cell transfusions vs. PLI: Please graph the regression line together with its 95% confidence band. Could you indicate the normal range for the PLI?

Tables:

11. Table 2: I suggest to remove unnecessary data (e.g. temperature).

References:

12. Reference #4: Page numbers should be 983-988.


Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

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.