Reviewer's report

Title: Maximization of oscillatory frequencies during arteriovenous extracorporeal lung assist: a large-animal model of respiratory distress

Version: 1 Date: 22 July 2008

Reviewer: Gil Allen

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The authors demonstrate that during HFOV in a porcine saline-lavage model of lung injury, the employment of av-ECLA is required to supplement CO2 removal during higher frequencies of ventilation in order to keep CO2 closer to normal physiologic range, particularly at frequencies of 9Hz and above. The authors conclude that because higher frequencies facilitate lower tidal volumes during HFOV, and hence limit the risk of overdistention injury, the concurrent use of av-ECLA with HFOV may help promote the true potential of HFOV in preventing. The authors appropriately point out that such markedly lower tidal volumes may be of less benefit when delivered with more conventional means of ventilation due to the potential for progressive derecruitment of lung, but they did not compare HFOV and CMV, nor did they directly measure the effects of frequency on tidal volume in their model. The authors also appropriately concede that the clinical relevance of this is called into question when one considers the potential therapeutic implications of permissive hypercapnea during HFOV without av-ECLA, but then also point out that clinical conditions still arise in which hypercapnea is contraindicated.

Overall, the question could be better defined in the introduction. The methods are sound and well described, as are the data. The discussion is well balanced but a bit brief at times, with limited references. The authors do clearly acknowledge previous work in the field. The title and abstract do not really convey the key points made by the paper. I suggest modifying both. The writing is acceptable, but punctuation is shaky, and sentence structure is weak at times. Suggest another proofread before resubmission.

Major Points

1.) Although the hypothesis is clearly stated in the last sentence of the introduction, I had difficulty quickly discerning the purpose of the study until late in the discussion. The point that higher frequency HFOV facilitates lower tidal volumes at the expense of ventilation, and that av-ECLA facilitate higher frequency HFOV by "supplementing" CO2 removal needs to be more clearly stated in the introduction and reintroduced early in the discussion.

2.) The abstract is obtuse, particularly in the results and conclusions. I would rephrase last sentence of the results to “Normocapnea during HFOV was only maintained with the addition of av-ECLA during frequencies of 9Hz and above.” Conclusions should really focus on what can be directly concluded from the study
and if the authors wish to speculate on minimization of tidal volume, this should be clearly identified as speculation.

3.) Since the main purpose of the study was to demonstrate that av-ECLA facilitates higher frequency HFOV and hence lower tidal volumes, I do not understand why tidal volumes weren’t measured. Surely a high sampling rate pneumotach could have been used to acquire what seems a critical measurement to the objective of the study. Without this, some initial measurement of impedance (post-RM) could have at least helped estimate the delivered tidal volumes from the oscillatory pressure amplitudes and inverse frequency. Why was this not done?

4.) When comparing measurements before and after recruitment, the authors should refer to them as pre-RM and post-RM, as opposed to ARDS and post-RM. I understand that the reason for doing this is probably because of the differences in P:F ratios, but the RM does not reverse the lung injury. This makes the first sentence in 3rd para of results page (under heading “Hemodynamics and Oxygen Delivery”) and Table 1 confusing and difficult to follow.

5.) On last page of discussion before conclusions, 1st through 3rd line, authors need to provide reference for statement, “In adults, not surfactant deficiency, but rather alveolar flooding……lungs responding better to lung recruitment.”

6.) Table 1 is cramped and difficult to follow. I recommend moving columns to the left to permit widening of columns for PRM and 3, 9, and 12 Hz so that standard errors don’t have to wrap under the mean values.

7.) The authors describe many findings in their results section and even outline them in figures, but then never really elaborate within the discussion. In fact, I believe the 3rd sentence of the last page of results is erroneous when I read the table. For instance, “CO was significantly decreased and SVR and DO2 increased during HFOV/av-ECLA compared with HFOV…” Since PaO2 was relatively unchanged, the relative decrease in CO with HFOV/av-ECLA seems discordant with a relative increase in DO2. Could the authors please explain? Also, SvO2% is higher in the av-ECLA group at all frequencies. Was this predominantly due to the lower hemoglobin displacement imposed by the lower CO2 in the av-ECLA group? If anything, one would expect a lower CO to correspond with a lower SvO2%.

Minor Points

1.) Second page of discussion, line 9 of 2nd para: I believe the authors should rephrase as, “Nevertheless, mere VT-reduction during conventional ventilation leads to low peak pressure ventilation favoring further lung derecruitment.” I would also elaborate this in the following sentence describing the study by Dembinski and colleagues.

2.) Would rephrase sentence in lines 7-8 of last page of discussion (before conclusions), “ Therefore, on might argue that without (eliminate “need for”) avECLA,
3.) Last line of first concluding paragraph, “Thereby” is misspelled, and next sentence ends with two periods.

4.) Need to update reference # 26.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests