Reviewer's report

Title: Rationale and study design of PROVAR - A randomized controlled trial on the effects of variable versus conventional lung protective mechanical ventilation during open abdominal surgery

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Reviewer: Bela Suki

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Variable ventilation (VV) has been shown to improve both on the physiological state and the biology of the lung in multiple independent animal studies. Therefore, VV has the potential to improve ventilation outcome in human subjects. However, to date, no proper clinical trial with documented and detailed protocol has been carried out to test its effectiveness during surgery. This manuscript describes the background, rationale and methods for the first such trial for using VV during abdominal surgery. The initiation of this clinical project is important and timely.

Major compulsory Revisions

1) Generally, the protocol is well described, although lacks some small details. While it seems plausible that an independent group could repeat the studies, the actual technical details do depend on the particular ventilator used and whether the ventilator company has a built-in VV. The writing and inclusion of proper references are excellent. These are more like comments rather than criticisms.

2) In my opinion, the first part of the hypothesis - that VV improves lung function - will be successfully tested. However, the second part of the hypothesis – that VV will reduce lung inflammation - is to some extent less clear primarily because there is no animal data. Nevertheless, there is another confusing issue too. While abdominal surgery itself can produce post-operative inflammation, it is not clear how any existing inflammation before surgery will influence the data and it is not discussed how this situation would be handled. Should an existing inflammation be an exclusion criterion? That would certainly make the experiments cleaner. However, since the surgery can worsen an existing inflammation, which mechanical ventilation may further augment if it allows more atelectasis to develop, one could argue that in fact VV has the potential to reduce the worsening effect of mechanical ventilation on an existing inflammation. Therefore, I would certainly examine and take into account any pre-existing inflammatory and infectious condition in the final analysis.

3) The primary end point is FVC taken on the 1st postoperative day. It is unclear when this will happen. According to the methods, there will be blood gas and EIT measurements obtained immediately after wound closure, but no mentioning of FVC here. The Background refers to a paper (Ref. 3) that suggest that FVC can be changed up to 3 hours after surgery, but it seems FVC will be taken a day
later. Therefore, unless I missed something, I feel the primary end point is not well chosen. If the most important issue – provided safety has been proven – is to avoid any inflammation and/or bacterial infection possibly due to severe atelectasis, then other and more direct measures during and immediately after wound closure might be better primary end points. For example, at a fixed PEEP of 5 cmH2O, if the lung is generally more open during VV than CV, then peak airway pressures will also be lower during VV. Blood gases might also reflect the short time scale performance of VV and EIT immediately after surgery can detect gross lung collapse if it happens. Another possibility is to monitor respiratory elastance which will be very close to lung elastance due to the open abdomen. Elastance is perhaps the best measure of lung collapse and if the respirator allows, you can get a tracing basically breath by breath. Thus, I would reconsider the primary end point of the study especially because the primary end point does not say much about inflammation, the second part of the hypothesis.

Minor Essential Revisions

1) It would be useful to document whether VV remains safe during surgery. Any adverse event should be monitored and documented and it is indeed described in the manuscript. What is not described is that if any complication arises, how the team or the anesthesiologist will decide whether VV can be continued or it needs to be halted.

2) Will patients get any additional medications that can alter or obscure the effects and performance of ventilation patterns? For example, would some patients receive any medication to increase oxygenation such as inhaled or intravenous prostacyclin? If so, should it be an exclusion criterion?

3) Page 6, line 10 of first paragraph: Here, it is mentioned that spirometry is obtained hourly from the ventilator. It would be useful to be more specific here as to what will be obtained since likely, you will not disrupt VV hourly to obtain full spirometry. As far as I can tell, full spirometry is done only on visit 1 and visits 3 through 6.

4) Can you describe the statistical reasoning to establish the population size? Is the expectation that FVC will be better following VV than CV? Is this based on previous animal studies? What is the % improvement in FVC that you base your population size calculation?

Discretionary Revisions

1) Page 3, end of second paragraph: There is also evidence suggesting that once a patient has ALI or ARDS, recruitment maneuvers do not improve physiological outcomes and can even be harmful (see for example Meade et al. (2008) A study of the physiologic responses to a lung recruitment maneuver in acute lung injury and acute respiratory distress syndrome. Respir Care 53: 1441–1449.). This could strengthen your argument here.

2) Page 6, last paragraph: The text says the investigator can also decide to terminate a patient’s participation in the trial. But my understanding is that the investigators are blind to the ongoing ventilation type during surgery. Perhaps by investigator you mean the anesthesiologist? Also, does this imply that the
investigator can drop a subject from the population after surgery and after obtaining all data? If so, by what criterion?

3) There is a very recent paper by Kowalski et al (Can J Anesth/J Can Anesth (2013) 60:502–503) that reports VV in human subjects albeit not during abdominal surgery. The authors might want to check this out and cite if appropriate.

Level of interest: An article of outstanding merit and interest 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:

No

No

I do hold a patent in the US regarding a particular implementation of variable ventilation and its effect on surfactant. But I have not received any reimbursements, fees, funding, or salary related to the content of the manuscript?

No

I am an investigator in a small pre-clinical trial using variable ventilation in patients with acute lung injury.