Reviewer’s report

Title: Effect of low tidal volume ventilation on lung function and inflammation in mice

Version: 1 Date: 23 November 2009

Reviewer: Torsten Meier

Reviewer’s report:

General comment

Low tidal volume ventilation in combination with the application of a PEEP/FiO2 titration table is the only ventilation therapy in ARDS/ALI patients with a positive effect on mortality. This proceeding, which accepts a development of atelectasis to a certain degree, aims to preserve healthy lung areas against mechanical forces. Without sufficient elevation of PEEP, ARDS patients and also patients with healthy lungs, develop regional lung collapse with an increasing pulmonary shunt during low tidal volume ventilation. Because FRC is reduced and dead space ventilation is increased even with very low tidal volumes, pulmonary stress and strain can be increased. In a clinical study Terragani et al. could show that, despite the use of the NIH ARDS Clinical Trials Network protocol, overdistension of healthy lung areas occurs which shows that 6 ml/kg in some cases are not protective enough (Am J Respir Crit Care Med. 2007;175(2) 160-6).

In the present study the authors aimed to investigate the functional and structural effect of low tidal volume ventilation during 30 minutes in a mouse model. One group of spontaneously breathing mice and eight groups of anaesthetised animals with different tidal volumes (5ml/kg; 7 ml/kg, 10 ml/kg and 30 ml/kg) and with (2 cm H2O) or without PEEP were compared. To verify their hypothesis that tidal volumes lower than 10 ml/kg are less injurious the authors measured oxygenation, pulse rate, resistance, compliance, infiltration of PMN in lung parenchyma and expression of MIP-2 and TNF-alpha mRNA in mice lungs. Partly contrary to the initial hypothesis ventilation settings without PEEP and lower tidal volumes, less than 10 ml/kg, worsened the lung function and showed an increase in MIP-2 and TNF-alpha mRNA. Like many other studies the present data showed that ventilation without PEEP leads to an increase of ventilator induced lung injury (VILI). However, the authors conclusions go too far in respect that low tidal volume ventilation generally leads to enhanced inflammation and worsen lung function.

Major compulsory revisions:

There are some points that have to be better discussed by the authors. First of all it has to be explained why the presented data are partly in contrast to recently published clinical studies which investigated the application of low tidal volume ventilation (for example Terragani et al (Anesthesiology. 2009 Sep 7. [Epub ahead of print])). Especially it has to be clarified how low tidal volume ventilation...
in mice decreases the endexpiratory lung volume which has a major influence on
the development of VILI. Also it is not sufficiently explained how low tidal volume
ventilation causes PMN infiltration and why this infiltration is not influenced by
PEEP. Generally atelectatic areas per se are not an inflammatory factor which
can cause infiltration of PMNs or elevation of cytokines in healthy lungs.

Abstract: The Conclusion has to concentrate more on the major results in respect
to VILI. Formation of atelectasis is an important factor but there were no data
presented in the study. Also the oxygenation data are important. Most of the
animals were hypoxic in a different degree but how hypoxia influenced VILI was
not the hypothesis of the study.

Methods: Why was hypoxia tolerated during the study and how did this influence
the hemodynamic stability of the animals? How were tidal volumes measured
during the study and how were they kept constant? Why were TLC manoeuvres
performed at the end of the mechanical ventilation?

Results: The time course of the airway pressures should be presented. Can the
increased or decreased pulse rates be interpreted as a sign of hemodynamic
instability? May the rapid increase of PMNs in the lung be a result of an event of
systemic low perfusion or hypoxemia? Why did the application of PEEP show no
influence on the decrease of the measured compliance?

Discussion: The authors postulated that inflammation is aggravated due to the
increase of atelectatic areas. This is not the case; as inflammation may be
coursed by shear forces or overdistension even in very low tidal volume
ventilation if endexpiratory lung volume decreases. Only if lung volume can be
preserved by the sufficient application of PEEP, low tidal volume ventilation can
be postulated as being protective. In general, the formation of atelectasis in
healthy lungs causes no additional inflammation.

The data did not indicate that 10 ml/kg with 2 cm H2O of PEEP in mice are
comparable to protective ventilation in humans because no lung injury model was
used or any outcome variables in mice were studied.

Minor essential comments:
Abstract: Pulse rate results were presented in the abstract but not discussed
further.

Introduction: 6ml/kg is considered to be protective only in patients with ALI/ARDS
or patients who are at risk for ALI/ARDS.

Discussion: "The respiratory (delete: "minute") tidal volumes that were used in
the present study...."

Figure 1 and 2: To better distinguish between the study groups the presentation
of the figures has to be improved, especially the icons have to be changed as
well as the lettering.

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests