Lung-protective ventilation in intensive care unit and operation room

Tidal volume size, level of positive end-expiratory pressure and driving pressure

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Chapter 16

Summary & General Discussion

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Introduction

Several investigations have shown independent associations between three ventilator settings – tidal volume size, positive end–expiratory pressure (PEEP) and driving pressure – and outcomes in patients with the acute respiratory distress syndrome (ARDS). There is an increasing notion that similar associations may exist between these potentially modifiable ventilation parameters and outcomes in intensive care unit (ICU) patients without ARDS. Even in surgery patients, who usually receive mechanical ventilation for much shorter periods of time than ICU patients, outcomes could depend on these three settings.

Aims and general hypotheses

The overarching aim of research described in this thesis was to investigate associations between tidal volume size, PEEP and driving pressures, and outcomes in (a) ICU patients without ARDS, (b) patients receiving intraoperative ventilation, and (c) patients receiving extracorporeal support as a rescue therapy for ARDS. Four 'broad' hypotheses were tested in various investigations:

The first two hypothesis were:

1. Tidal volume, PEEP and driving pressure are independently associated with outcomes in ICU patients not suffering from ARDS; and
2. Tidal volume, PEEP, and driving pressure are independently associated with outcomes in surgery patients receiving intraoperative ventilation

Thereafter the focus of the thesis moved to current practice of ventilation in ICU patients without ARDS, where the following hypothesis was tested:

3. A considerable proportion of ICU patients is at risk of ARDS, and tidal volume, PEEP, and driving pressure in this group of patients differ from those in patients not at risk of ARDS

Finally, we tested the hypothesis that:

4. Tidal volumes, PEEP and driving pressure are independently associated with outcomes in ARDS patients under various forms of extracorporeal support

The first hypothesis was tested using two conventional metaanalysis (**chapter 2** and **8**), two individual patients data metaanalysis (**chapter 9 and 10**) and one substudy of a conveniently–sized international observational study (**chapter 12**). The second hypothesis was tested using one conventional metaanalysis (**chapter 2**), two individual patient data metaanalysis (**chapters 4** and **6**), one substudy of a large randomized controlled trial (**chapter 7**), followed by a discussion in an editorial (**chapter 5**). The third hypothesis was tested in a large worldwide observational study (**chapter 11**). Finally, the fourth hypothesis was assessed in two individual patient data metaanalyses (**chapters 14** and **15**) and was discussed in an editorial on this topic (**chapter 13**). This chapter summarizes the findings and discusses future steps in research. A Dutch translation is provided in **chapter 17**.

Main results of investigations described in this thesis

Chapter 2 discusses the results of one conventional metaanalysis of 20 studies covering 850 ICU patients and 1,972 surgical patients. The hypothesis was that a 'lung–protective' ventilation strategy using low tidal volumes is associated with better outcomes of patients under mechanical ventilation but with uninjured lungs. The results of this metaanalysis suggest that a 'lung–protective' ventilation strategy results in a lower mortality (ICU patients), prevents development of lung injury and pulmonary infections, and shortens hospital length of stay (in ICU and in surgical patients). Differences between the metaanalyzed studies, in particular durations of ventilation, could have blurred the associations, though. Also, the majority of studies used in this metaanalysis were observational in their designs, which may have caused bias.

Chapter 3 provides an extensive review of the literature on the physiology behind the potential importance of driving pressures as one of the components of 'lung–protective' ventilation strategies. A new concept, 'energytrauma', was coined – a concept in which the energy transferred from the ventilator to the lung may be the mainstream or central component in the pathophysiology of lung injury caused by mechanical ventilation: ventilation with higher driving pressures results in transfer of more energy to the lungs.

Chapter 4 describes the results of an individual patient data metaanalysis in 3,365 patients from 12 studies that tested the hypothesis that occurrence of postoperative lung injury is associated with worse outcome, and that the postoperative outcome depends on intraoperative ventilation settings. The results of this metaanalysis suggest that occurrence of postoperative lung injury increases the risk of dying and lengthens stay in ICU and in hospital. The impact of postoperative lung injury on outcome was bigger in patients who underwent thoracic surgery than those who underwent abdominal surgery. The results also suggest that use of 'lung–protective' ventilation strategies lowers the incidence of postoperative lung injury, but not mortality.

Chapter 5 is an editorial on a randomized controlled trial that suggests that an intensive recruitment strategy using high PEEP in patients who develop hypoxemia after cardiac surgery improves outcomes. Of note, patients in that trial were probably not having 'uninjured' lungs. This means that the beneficial effects of high PEEP after surgery may not necessarily translate into benefit in patients who did not develop lung injury during the surgical procedure.

Chapter 6 presents the results of an individual patient data metaanalysis in 2,250 patients from 17 investigations. The hypothesis was that the intraoperative driving pressure, and changes in the driving pressure as a result of changes in PEEP are associated with development of postoperative pulmonary complications. The results of this investigation suggest that high driving pressure as well as changes in the level of PEEP that result in higher driving pressures are associated with the occurrence of postoperative pulmonary complications. This finding, however, needs to be confirmed in randomized controlled trials.

Chapter 7 describes the results of a study in 242 surgery patients in whom plasma biomarkers of inflammation and lung injury were measured before and after surgery. This study tested the hypothesis that the kinetics of these biomarkers would differ between patients who do and patients who do not develop postoperative pulmonary complications, and also that these biomarkers could be used to discriminate these two groups of patients.

The kinetics of plasma levels of biomarkers were different between the two groups, but none of them, either alone or in combination showed sufficient prognostic capacity.

Chapter 8 presents the results of a systematic translational review and metaanalysis using 25 preclinical studies and six human trials, with a focus on tidal volume size. Ventilation with low tidal volumes was associated with less pulmonary complications, but well–powered randomized controlled trials are needed to determine whether this ventilation strategy truly benefits ventilated ICU patients without ARDS.

Chapter 9 describes the results of an individual patient data metaanalysis in 2,184 patients from seven investigations. In this investigation we tested the hypothesis whether the occurrence of pulmonary complications depends on tidal volume size in ICU patients without ARDS at the onset of ventilation, and whether development of ARDS worsens outcomes. The results of this metaanalysis show that ventilation with low tidal volumes reduces the risk of development of pulmonary complications in patients without ARDS at onset of ventilation. Occurrence of pulmonary complications was associated with a lower number of ICU-free days and a lower number of hospital-free days and increased hospital mortality.

Chapter 10 expands on the metaanalysis presented in the previous chapter. Here we tested whether use of lower tidal volumes is associated with a shorter duration of ventilation and whether use of lower tidal volumes affects sedation needs. The results suggest that use of lower tidal volumes in patients without ARDS at the onset of mechanical ventilation reduces duration of ventilation, while not affecting sedation or analgesia needs.

In **Chapters 11** the main results of an international prospective observational study in 935 patients without ARDS are presented. One of the hypotheses of the '*PRactice of VENTilation in critically ill patients without ARDS study*' (PRoVENT) was that ventilation practice differed between patients at risk of ARDS and patients not at risk of ARDS. Patients at risk of ARDS were ventilated with higher peak, plateau and driving pressures, higher PEEP, and higher respiratory rate and FiO_2. Pulmonary complications occurred frequently in patients at risk of ARDS, and their clinical outcomes were worse compared to patients not at risk of ARDS.

In **Chapter 12** the results of a preplanned sub–study of PRoVENT are presented. Here we hypothesized that potentially modifiable factors are associated with outcomes. Compared to patients who survived, patients who died had a higher risk of ARDS, received ventilation with higher maximum airway pressures, higher driving pressures, higher PEEP, higher FiO_2 levels, but similar tidal volumes. The only potentially modifiable ventilation factor associated with in-hospital mortality in multivariable analyses was the maximum airway pressure.

Chapter 13 is an editorial on extracorporeal life support for acute respiratory failure. It discussed the potential benefits of the extracorporeal life support and the best ventilatory management of patients undergoing extracorporeal support.

Chapter 14 presents the results of an individual patient data metaanalysis in 545 ARDS patients from nine studies. It was hypothesized that certain ventilator settings during extracorporeal membrane oxygenation, like tidal volume size, levels of PEEP and driving pressure are associated with outcome. This analysis suggest that the driving pressure during ECMO is the only ventilator setting that showed an independent association with in-hospital mortality in ARDS patients receiving extracorporeal membrane oxygenation for refractory hypoxemia.

Chapter 15 describes the results of an individual patient data metaanalysis of four studies and 129 ARDS patients undergoing extracorporeal carbon dioxide removal. The hypothesis was similar to the one in the previous chapter. In this analysis a shorter time interval between start of ventilation and start of extracorporeal carbon dioxide removal, as well as low driving pressures during extracorporeal support were associated with an higher number of ventilator–free days.

General discussion and future perspectives

The main findings of research described in this thesis are that three potentially modifiable ventilator settings – tidal volume, PEEP and driving pressure – have independent associations with diverse outcomes in ICU patients without ARDS, in surgery patients

receiving intraoperative ventilation, and in ARDS patients under extracorporeal support. All these findings strongly support the idea that strategies aiming at optimization of these three settings could improve outcomes of patients receiving mechanical ventilatory support.

Tidal volume

For many years ventilation strategies with high tidal volumes were preferred over strategies with low tidal volumes, as ventilation with high tidal volumes can prevent or at least reduce the amount of atelectasis. This was considered beneficial as the resulting decrease in ventilation–perfusion mismatches could reduce the need for high FiO_2 and PEEP. Ventilation strategies with high tidal volumes, however, were found to harm ICU patients with ARDS. The results of investigations in ICU patients without ARDS, and in patients undergoing intraoperative ventilation, abridged in this thesis in a series of individual patient data metaanalysis, contain several arguments against ventilation with high tidal volumes in patients with uninjured lungs.

Paradoxically, in contrast to the results in several metaanalyses showing associations between ventilation with high tidal volumes and outcomes, PRoVENT, the international prospective study on ventilation practices in ICU patients without ARDS described in **chapter 11**, found no association between tidal volume size and diverse outcomes. There are several reasons for this. First, in PRoVENT tidal volumes were noticeable lower in comparison to almost all preceding investigations, and also the range of tidal volumes was much smaller. Similar findings came from the '*Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE*' (LUNG SAFE), an international prospective study in ICU patients with ARDS,[1] and also the recently published '*Local Assessment of Ventilatory Management During General Anesthesia for Surgery and effects on Postoperative Pulmonary Complications study*' (LAS VEGAS), an international prospective study on ventilation practices during surgery.[2] LUNG SAFE and LAS VEGAS, alike PRoVENT (**chapter 11**), also failed to show independent associations between tidal volume size and outcomes. Second, interpretation of results from individual patient data metaanalysis always need to be looked at with some caution, as these analyses are sometimes little more than

so–called ‘per protocol’ analyses in which patients who actually received the intervention of interest are compared to patients who did not receive that intervention. Intentional as well unintentional reasons could be responsible for not receiving the intervention of interest, and some of these reasons, recognized or unrecognized, could have an association with outcome, and independent of the intervention itself. For example, in ICU patients with severe acidosis, who often need ventilation with higher tidal volumes to achieve an acceptable arterial pH, the (reason for) severe acidosis could have a much stronger association with outcome than tidal volume.

The results of PRoVENT (**chapter 11**), LUNG SAFE[1] and LAS VEGAS[2] clearly shows that tidal volume size has decreased in all patients who need mechanical ventilatory support, which could be seen as an improvement in care. Interestingly, tidal volume sizes were remarkable similar in these three studies. One could also conclude from PRoVENT (**chapter 11**), LUNG SAFE[1] and LAS VEGAS[2] that currently still half of the patients receive mechanical ventilation with tidal volumes higher than what we now consider safe. Alike in patients with severe ARDS,[3] an additional reduction in tidal volume size could further improve outcomes in patients with uninjured lungs.

Whether or not ICU patients without ARDS truly benefit from a further reduction in tidal volume size is currently uncertain. Two ongoing randomized controlled trials could help to answer this question: the ‘*PRotective VENTilation in patients without ARDS at start of ventilation)*’ (PReVENT) trial,[4] a Dutch national multicenter randomized controlled trial that compares ventilation with a tidal volume between 4 and 6 ml/kg PBW with ventilation with a tidal volume between 8 and 10 ml/kg PBW in 952 invasively ventilated ICU patients without ARDS, and the ‘*Preventive Strategies in Acute Respiratory Distress Syndrome (ARDS)’* (EPALI) trial,[5] a Spanish national multicenter randomized controlled trial comparing ventilation with a tidal volume between 4 and 6 ml/kg PBW with ventilation with a tidal volume between 8 and 10 ml/kg PBW in 400 invasively ventilated ICU patients at risk of ARDS. The results of these two trials are expected soon (personal communications with the principal investigators of the PREVENT trial and the EPALI trial).

Positive end–expiratory pressure

Ventilation with low tidal volumes has been suggested to induce alveolar instability, resulting in cyclic opening and closing of alveoli within each breath cycle. PEEP may open lung regions that collapse at the end of expiration, and thus prevent so–called 'tidal recruitment'. Benefit of ventilation with high PEEP was found in patients with ARDS, albeit only in those classified as having moderate or severe ARDS. Use of (high) PEEP, however, could come 'at a prize', as (high) PEEP could cause regional overdistension, in particular of the nondependent lung parts, and (high) PEEP could negatively impact the systemic circulation. The balance between benefit and harm of (high) PEEP may very well differ between ICU patients with ARDS, ICU patients without ARDS, and surgery patients under intraoperative ventilation. The results of several randomized controlled trials in ICU patients and in surgery patients, abridged in this thesis in a series of individual patient data metaanalysis, contain arguments against unselected use of (high) PEEP in patients without ARDS.

PRoVENT (**Chapter 11**) showed that higher levels of PEEP were used in ICU patients at risk for ARDS, compared to ICU patients not at risk of ARDS. Differences, though, were small. One important finding in one of the preplanned secondary analyses of PRoVENT, described in **chapter 12**, yet, was the absence of an independent association between PEEP and mortality. This is opposite to findings of a preplanned secondary analysis of LUNG SAFE[6] that showed that high PEEP was actually one of the factors associated with improved survival from ARDS, but in line with results of the '*PROtective Ventilation using HIgh versus LOw positive end-expiratory pressure trial*' (PROVHILO),[7] an international randomized controlled trial compared high PEEP versus low PEEP during intraoperative ventilation, that showed high PEEP not to prevent against postoperative pulmonary complications.

Interestingly, one yet unpublished secondary analysis of LUNG SAFE[1] found high PEEP to be one of the factors associated with worse survival from mild ARDS,[8] and also LAS VEGAS shows that high PEEP is associated with worse outcome in surgical patients.[2]

Recently, we tried to summarize the findings of all previous investigations of PEEP in ICU patients without ARDS.[9] The results of this conventional metaanalysis suggest that although ventilation with (high) PEEP is associated with a lower incidence of hypoxemia, it does neither reduce mortality nor shorter duration of ventilation. The findings of this metaanalysis should be interpreted with great caution, though, as heterogeneity was substantial and the quality of evidence was insufficiently low. Actually, it could be better to conclude that there is absence of evidence for benefit of PEEP in ICU patients without ARDS, due to the lack of well–powered randomized controlled trials.

Thus, whether or not PEEP benefits ICU patients without ARDS is a matter of debate. The '*REstricted versus Liberal positive end–expiratory pressure in patients without Acute respiratory distress syndrome*' (RELAx) trial, a soon to start Dutch national multicenter randomized controlled trial comparing a ventilation strategy with 'restricted use of PEEP' with ventilation with standard 8 cmH_2O PEEP in 980 invasively ventilated ICU patients without ARDS (personal communication with the principal investigator of the RELAx trial), may help addressing the role of PEEP in these patients.

Driving pressure

In several studies in patients with ARDS an association was found between driving pressure and outcome, and one large individual patient data metaanalysis of randomized controlled trials in ARDS patients showed that driving pressure was the ventilation parameter that was strongest associated with mortality.[10] In this thesis, we investigated the potential impact of driving pressure on outcome of ICU patients without ARDS, surgery patients receiving intaroperative ventilation, as well as patients receiving extracorporeal support as a resue therapy for ARDS.

As discussed above, several studies described in this thesis failed to show benefit of (high) PEEP in patients with uninjured lungs. However, we did find an independent association between (changes in) driving pressure (in response to PEEP increases), and diverse outcomes in surgical patients. Theoretically, recruitment of lung tissue by the use of (high) PEEP could lead to a decrease in driving pressure, as an increase in aerated lung

tissue results in a lower driving pressure when tidal volumes are not changed. However, independent of recruitment of some parts of the lung, other lung parts could get overdistended with (high) PEEP (**chapter 6**). This could actually increase the driving pressure, and we speculate that this could have been one of the reasons for why PROVHILO did not find benefit of high PEEP during intraoperative ventilation.[7]

The results of the preplanned secondary analysis of PRoVENT, described in **chapter 12**, suggest driving pressure to be associated with mortality in ICU patients without ARDS. This is in line with the findings from LUNG SAFE,[1,6] ,where driving pressure was associated with hospital mortality in patients with ARDS. In line with these findings, LAS VEGAS showed that patients who developed postoperative pulmonary complications had received intraoperative ventilation with a higher driving pressure than patients who did not develop these complications.[2] Finally, also the results of the two investigations describe in **chapter 14 and 15** are in line with these findings.

The role of the driving pressure could be explained by the fact that driving pressure itself is an important driver of the energy delivered by the ventilator to lung in each breath. With every artificial breath, the lung conserves some energy, as the elastic recoil returns less energy during exhalation than that absorbed during inspiration. In other words, there is considerable dissipation of energy, probably resulting in heat and lung tissue damage during each breath. This phenomenon is known as ‘lung hysteresis’, and the ‘hysteresis area’ may represent the energy dissipated across the parenchyma. Interestingly, driving pressure is closely related to the ‘hysteresis area’. This may mean that the total amount of energy transferred from the ventilator to the lung is, at least in part, a function of the driving pressure.

It could be very difficult to precisely measure the driving pressure in current clinical settings, especially when spontaneous modes of ventilator support are used. First, the driving pressure, as nowadays calculated from the upper airway pressure and PEEP, may not at all be a good surrogate of the true driving pressure, which is the transpulmonary driving pressure. This is often overlooked. It is certainly better to use an oesophagus balloon

for monitoring of transpulmonary driving pressure, but this approach is impractical and also expensive. Also, as driving pressure is closely related to the compliance of the respiratory system, this alone could explain why it is so predictive of survival. In these patients it could be impossible to modify driving pressure so that harm is reduced.

Whether or not modifications of the driving pressure can alter outcomes of ICU patients with ARDS, ICU patients without ARDS, or surgery patients who need mechanical ventilatory support is largely unknown. One planned randomized controlled trial in planned open abdominal surgery patients, the '*Driving prEsSure durIng GeNeral AnesThesIa for abdOmiNal surgery'* (DESIGNATION) trial, will compare a standard level of PEEP to PEEP titration aiming to the lowest driving pressure during intraoperative ventilation (personal communication with the principal investigator of the DESIGNATION trial). There are no planned randomized controlled trials in ICU patients yet.

Conclusions

The findings of investigations described in this thesis support the notion that the lungs of ICU patients without ARDS and surgery patients undergoing intraoperative ventilation should also be considered vulnerable to the damaging effects of ventilation – it is not the ventilator that is causing harm, but the way the operator sets tidal volume, PEEP and driving pressure.

One way to monitor the risk of damage caused by mechanical ventilation is to monitor the amount of energy transferred during mechanical ventilation. Future studies are needed to confirm this is feasible and effective – we need to define what amount of energy can be called 'safe' in patients who needs mechanical ventilatory support.

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