Lung-protective perioperative mechanical ventilation

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Chapter 12

Summary and general discussion
Introduction

As an introduction to this chapter, we briefly summarize findings published before the writing of the thesis titled: ‘lung-protective perioperative mechanical ventilation’. A more extensive overview of this literature is provided in chapter 1.

Postoperative pulmonary complications
Similar to mechanical ventilation in critically ill patients, intraoperative ventilation has a strong potential to cause lung injury.1 Certain intraoperative ventilation settings are associated with the development of pulmonary complications after surgery.2 Occurrence of so-called postoperative pulmonary complications is strongly associated with clinical outcome.3

Ventilation–associated lung injury
It is generally believed that overdistension and repetitive opening and closing of lung tissue are the two main mechanical causes of so-called ‘ventilation–associated lung injury’ (VALI).4 Use of too large tidal volumes could cause overdistension of lung tissue that remains aerated at the end of expiration, which could be aggravated by too high levels of positive end–expiratory pressure (PEEP). Too low levels of PEEP, though, could result in repetitive opening and closing of lung tissue that collapses at the end of expiration. Next to ‘mechanical stress’, ventilation could also cause ‘chemical stress’, as too high levels of fractional inspired oxygen (FiO2) can increase the production of reactive oxygen species (ROS),5 which have a direct toxic effect on lung cells. Too high levels of FiO2 could also increase the risk of resorption atelectasis.6 Lung-protective mechanical ventilation aims at low tidal volume ventilation to prevent overdistention, and higher levels of PEEP with recruitment manoeuvres to prevent repetitive collapse. Additionally, restrictive levels of FiO2 could protect against hyperoxia-induced lung injury.

Prevention of lung injury in critically ill patients
Two large metaanalyses convincingly confirmed the results from randomized controlled trials in critically ill patients with the acute respiratory distress syndrome (ARDS) that showed ventilation with low tidal volumes to improve morbidity and mortality.7,8 While three randomized controlled trials in patients with ARDS individually showed no benefit of higher levels of PEEP,9–11 one individual patient data metaanalyses strongly suggest higher levels of PEEP to improve outcome of patients with moderate or severe ARDS.7

The evidence for benefit of using low tidal volumes in critical care patients without ARDS is less convincing, with only one randomized controlled trial in these patients showing a lower incidence of VALI during low tidal volume ventilation.12 One conventional metaanalysis13 and two individual patient data metaanalyses14,15 confirm these findings, but the quality of the included studies was sometimes low, hampering firm conclusions. Whether patients without ARDS benefit from higher levels of PEEP, is even more uncertain, with one trial suggesting benefit,16 one trial showing no effect,17 and one trial even suggesting harm.12

Clinical trials investigating the effect of hyperoxia on lung injury in critical care patients with or without ARDS are lacking, but high levels of FiO2 seem to have the potential to be harmful in other organs than the lung critically ill patients.18,21
Prevention of lung injury in surgery patients

One metaanalysis\(^1\) of patients without ARDS undergoing mechanical ventilation on the ICU or for surgery confirmed the findings of several clinical trials, suggesting that ventilation with lower tidal volumes decreases the occurrence of pulmonary complications and improves clinical outcomes. One problem with all these trials is that the investigators often combined the use of low tidal volumes with higher levels of PEEP,\(^2\)\(^-\)\(^3\)\(^0\) which makes it difficult if not impossible to determine the precise role of each single intervention on the beneficial effect. Some investigations suggest hyperoxia during intraoperative ventilation to have harmful effects,\(^3\)\(^1\),\(^3\)\(^2\) but no clinical evidence on lung injury is available yet.

Summary of this thesis

The main aim of this thesis was to investigate the effect of intraoperative use of higher levels of PEEP, i.e., higher than the typical 0–2 cm H\(_2\)O as applied by many anaesthesiologists, and recruitment manoeuvres on occurrence of postoperative pulmonary complications. We hypothesized that the use of higher levels of PEEP and recruitment manoeuvres would protect against development of postoperative pulmonary complications during low tidal volume ventilation. We further investigated several other aspects of perioperative ventilation, focussing on ventilation practice and the associations between ventilator settings and postoperative pulmonary complications and outcome. In this chapter we summarize the results of the studies presented in this thesis, describes how these results can be placed in context of previous research findings, and speculates on future perspectives.

In Chapter 2 we describe a metaanalysis examining the effects of intraoperative ventilator settings on postoperative outcome of non–cardiac surgery patients.\(^3\)\(^3\) In this analysis we tried to separate the effects of tidal volume reduction and of higher levels of PEEP on postoperative complications. We hypothesized that low tidal volumes and higher levels of PEEP with or without recruitment manoeuvres could both prevent postoperative pulmonary complications. In the analysis of eight clinical trials comprising of 1669 patients, ventilation with lower tidal volumes was associated with a lower incidence of postoperative lung injury, pulmonary infections and atelectasis compared to ventilation with conventional tidal volumes. For the examination of settings for PEEP, only five of eight trials (1323 patients) were suited for the analysis, comparing ventilation without or with lower levels of PEEP with higher levels of PEEP during surgery. Patients ventilated with higher levels of PEEP developed less postoperative lung injury and atelectasis. A beneficial effect of high levels of PEEP on postoperative pulmonary infection was also found, but in this analysis there was moderate heterogeneity. We did not find trials investigating exclusively the effects of intraoperative recruitment manoeuvres. It should be taken into account that the five trials assessing the effect of ventilation with higher levels of PEEP and recruitment manoeuvres were also part of the metaanalysis on the effect of ventilation with lower tidal volumes. In this analysis it remained uncertain whether the use of high PEEP, with or without recruitment manoeuvres, added to the beneficial effects of intraoperative use of lower tidal volumes.
In **Chapter 3** we more extensively review the literature on intraoperative protective ventilatory strategies to prevent postoperative pulmonary complications. We describe six studies on predictive models of postoperative pulmonary complications, eleven trials on protective ventilation during general anaesthesia for surgery with a nonclinical primary outcome, and eight trials with a clinical primary outcome. We determined that increasing evidence shows that intraoperative lung-protective mechanical ventilation decreases the risk of postoperative pulmonary complications. However, the precise role of each single intervention remains uncertain. We conclude this review with a recommendation on intraoperative lung-protective ventilation and propose a new, alternative ventilation strategy during general anaesthesia: “permissive atelectasis”. In this new approach patients are ventilated with relatively low levels of PEEP and without recruitment manoeuvres, which reduces static stress in the lungs. Permissive atelectasis, however, could cause perioperative hypoxia, which can be counteracted by increasing in the inspired oxygen fraction.

**Chapters 4 and 5** present an international prospective observational study aiming to describe current ventilator practice regarding intraoperative ventilation, and to determine any association between ventilator settings and incidence of postoperative pulmonary complications. We hypothesised that low tidal volumes and high levels of PEEP were commonly used, and that both are associated with a reduced incidence of postoperative pulmonary complications. During a seven–day period, data of 8,327 consecutive adult patients requiring invasive ventilation during general anaesthesia for surgery from 146 centres worldwide was collected. Intraoperative ventilation settings and postoperative data on pulmonary complications up to day 5 were collected. Our results show that patients are generally ventilated with relatively low tidal volumes (median of 500.0 [454.2 – 550.5] mL or 8.1 [7.2 – 9.1] mL/kg PBW), PEEP levels of 4.0 [0.0 – 5.0] cmH2O, and that recruitment manoeuvres are rarely performed (9.5%). The chosen level of tidal volume represents the default settings on many anaesthesia ventilators, suggesting a lack of individualisation. Postoperative pulmonary complications occurred frequently after surgery (10.4%), and were associated with longer length of hospital stay and mortality. In two different multivariate models we found that the use of higher levels of PEEP, but not size of tidal volume was independently associated with increased development of postoperative pulmonary complications.

In **Chapter 6** we describe the results of an individual patient data metaanalysis using data from 15 randomized controlled trials of intraoperative ventilation. We tested the hypothesis that intraoperative ventilation with lower tidal volumes protects against postoperative pulmonary complications and improves clinical outcome, and that use of higher levels of PEEP adds to the beneficial effects of lower tidal volumes. The results from 2,127 patients show that intraoperative protective ventilation strategies have beneficial influence on incidence of postoperative pulmonary complications, but they did not have an effect on length of stay or mortality. Patients that developed a pulmonary complication postoperatively did have longer lengths of ICU and hospital stay and increased mortality rates. In the analysis of the individual effect of intraoperative low tidal volumes, we found decreased incidence of postoperative pulmonary complications. If higher levels of PEEP were added to low tidal volume ventilation, this did not attribute to additional benefit. The analysis on the individual effect of PEEP did not show significant influence on development of postoperative pulmonary complications.
Summary and general discussion

In Chapters 7, 8 and 9 we present an international trial comparing PEEP levels of 12 cmH$_2$O combined with recruitment manoeuvres to PEEP levels of 2 cmH$_2$O without recruitment manoeuvres in non-obese patients at high risk for postoperative pulmonary complications planned for open abdominal surgery with ventilation at tidal volumes of 8 mL/kg. In this trial we tested the hypothesis that a ventilation strategy with high levels of PEEP and recruitment manoeuvres protects against development of postoperative pulmonary complications. We randomized 900 patients from 30 centres throughout Europe and the Americas. The incidence of postoperative pulmonary complications in the first 5 days after surgery did not differ between patients receiving protective ventilation or non-protective ventilation. Patients receiving higher levels of PEEP more frequently developed intraoperative hypotension and needed more vasoactive drugs. In the lower PEEP group, the incidence of intraoperative desaturations was higher. The results of this trial indicate that protective ventilation with low tidal volumes does not gain from higher levels of PEEP with recruitment manoeuvres and may even impair hemodynamics.

In Chapter 10 we investigated whether development of postoperative lung injury attributes to incidence of morbidity and mortality, by performing a second metaanalysis using individual patient data from 12 investigations of intraoperative ventilation. We hypothesized that the occurrence of postoperative lung injury would be associated with worse outcome, and that postoperative outcome depends on intraoperative ventilation settings. In 3365 patients development of postoperative lung injury increased the risk of mortality, especially in patients submitted to thoracic procedures compared to abdominal procedures. The incidence of lung injury was similar between thoracic and abdominal surgery. Development of lung injury was associated with longer ICU and hospital lengths of stay. When examining the intraoperative ventilation strategies, protective ventilation was associated with lower incidence of postoperative lung injury, but not with reduced mortality rates. Also in the event of postoperative lung injury, the previously applied protective strategy of ventilation was not associated with reduced attributable mortality. This suggests that the benefits of intraoperative protective ventilation are restricted to the reduction of development of postoperative lung injury.

In Chapter 11 we extend our research from the operation room to patients ventilated in the intensive care unit after surgery. In a secondary analysis of two previous trials in patients undergoing elective and uncomplicated coronary artery bypass grafting (CABG), we investigated the effects of PEEP on pulmonary compliance and gas exchange in the first hours of weaning from mechanical ventilation and total time on the ventilator. We hypothesized that higher levels of PEEP improves pulmonary function, but does not shorten duration of postoperative ventilation. We found in 121 patients that ventilation with higher levels of PEEP resulted in better compliance and oxygenation. The beneficial effect on pulmonary compliance during ventilation was only sustained when PEEP levels were kept above 5 cmH$_2$O. After tracheal extubation the positive effect on both compliance and arterial oxygenation was not maintained. Nonetheless, patients ventilated with higher levels of PEEP required less supplemental oxygen on the ward, which could indicate that these patients had less atelectasis. Time on the ventilator was longer in patients ventilated with higher levels of PEEP. One partial explanation could be that these patients received infusion of hypnotics during a longer period of time.
General discussion

The main finding of this thesis is that intraoperative ventilation with higher levels of PEEP does not seem to reduce development of postoperative pulmonary complications during low tidal volume ventilation (chapter 6 and 8), in non-obese patients undergoing major surgery (cardiac, thoracic, abdominal, or spine surgery). High levels of PEEP may even be detrimental by causing hemodynamic compromise (chapter 8) and maybe even by increasing the risk of postoperative pulmonary complications (chapter 5).

In this thesis, we further show that lung-protective strategies using low tidal volumes combined with higher levels of PEEP reduce the incidence of postoperative pulmonary complications (chapters 2, 3, 6 and 10), but do not shorten hospital length of stay, or improve survival (chapters 6 and 10). In the event of a pulmonary complication, patients do have longer lengths of ICU and hospital stay, and have a higher incidence of mortality (chapter 5, 6 and 10). Finally, use of higher levels of PEEP during postoperative ventilation resulted in better compliance and oxygenation in patients undergoing elective and uncomplicated coronary artery bypass grafting, but this was not sustained after extubation and time to extubation was increased (chapter 11).

PEEP may not be beneficial

Contrary to general belief, this thesis shows that ventilation with higher levels of PEEP may not attribute to the protective effect of low tidal volumes on the development of postoperative pulmonary complications. Individual patient data analysis found no increased benefit of higher levels of PEEP in patients ventilated with low tidal volumes on development of pulmonary complications (chapter 6). Additionally, the analysis of dose–response relationship in this study suggests that there is neither a positive, nor a negative association between a higher level of PEEP and the development of postoperative pulmonary complications. In postoperative cardiac surgery patients, ventilation with higher levels of PEEP did not have a sustained effect on pulmonary compliance or arterial oxygenation (chapter 11). The PROVHILO trial showed that levels of 12 cmH2O PEEP did not protect against development of postoperative complications during low tidal volume ventilation (chapter 8). The chosen level of PEEP in this trial was criticized, because it is higher than normally applied in clinical practice. The resulting high end-inspiratory pressures might have caused overinflation of normally aerated alveoli. This could have diminished the clinical benefits of ventilation with higher PEEP levels. However, the level of PEEP was based on previous investigations, recommending a minimal level of 10 cmH2O PEEP to prevent cyclic opening and closing of alveoli during intraoperative ventilation. Indeed, as mentioned in our Author’s reply (chapter 9), the higher PEEP group showed increasing dynamic compliance during intraoperative mechanical ventilation. This suggests that effective lung recruitment was achieved, without overt overdistention. On the other hand, peak airway pressures were increased in the higher PEEP group, suggesting increased alveolar pressures that could have contributed to hyperinflation.

Experimental and clinical studies have previously questioned the beneficial effects of PEEP. As far back as the ’70s, studies in dogs with injured lungs found that application of a level of 10 cmH2O PEEP compared to no PEEP did not counteract formation of oedema fluid, when inspiratory pressure levels were kept equal. In pigs with non-injured lungs no difference in inflammatory
response was seen between high and low levels of PEEP during low tidal ventilation. When examining the alveoli up-close with in vivo microscopy in pigs with surfactant deactivated lungs, alveolar stability did not differ when PEEP was set a different levels.

In critical care patients with ARDS, no additional protective effect of higher PEEP levels was seen in mild ARDS. In critical care patients without ARDS, high PEEP had very limited beneficial effect on the lungs. During intraoperative ventilation no significant beneficial effect of PEEP level above 5 cmH₂O was seen on development of postoperative pulmonary complications in a retrospective study.

**PEEP may cause harm**

Use of higher levels of PEEP may even cause harm. High levels of PEEP can compromise intraoperative hemodynamics (chapter 8). Furthermore, use of PEEP may be associated with increased risk of postoperative pulmonary complications (chapter 5). In patients mechanically ventilated after CABG, high levels of PEEP prolonged weaning from the ventilator (chapter 11).

The undesirable effect of high levels of PEEP on hemodynamics has been identified in previous investigations. The negative effects of high levels of PEEP on development of pulmonary complications seem to be in contrast to recent clinical trials. A possible explanation could be that compared to these studies, the tidal volume size reported in chapter 5 was much smaller. Notably, the LAS VEGAS study found no association between tidal volume size and development of pulmonary complications. In the event of low tidal volume ventilation, higher levels of PEEP could attribute to hyperinflation of normally aerated lung areas and possibly augment intra-tidal shear stress of collapsed lung areas.

Earlier animal and human studies have described the potential harm of ventilation with high levels of PEEP. In healthy rats receiving low tidal volume ventilation, high levels of PEEP (15 cmH₂O) caused more pulmonary oedema than levels of 0 or 10 cmH₂O PEEP. In a surgical model of pigs without lung injury, high levels of PEEP were associated with increase of pulmonary inflammation. When examining different areas of rat-lung after surfactant depletion and injurious ventilation, alveolar injury was higher in the alveoli that remain open during the complete breath cycle, compared to the alveoli that collapse at end-expiration.

In mechanically ventilated patients with acute lung injury PET-CT scans showed maximum metabolic activity in the normally aerated lung regions, and no increase in metabolic activity in regions undergoing cyclic opening and closing.

The degree of metabolic activity in the aerated regions was associated with higher plateau pressures. This was also seen in a recent retrospective study in surgical patients, showing a strong association between reduction in plateau pressure and a decrease in postoperative pulmonary complications. These results suggest that even though higher levels of PEEP may lessen atelectasis formation, due to the consequential high plateau pressures normally aerated alveoli may become overdistended.
Driving pressure
Experimental studies confirm that ventilation with higher plateau pressures can be injurious (so-called stress), but suggest that repetitive deformation during the respiratory cycle can cause more injury to the lung (so-called strain).\(^{61-64}\) The maximal deformation of the lung during mechanical ventilation is best expressed by calculating the driving pressure: plateau pressure minus positive end-expiratory pressure. In mechanically ventilated rats, driving pressure appeared to be one of the most important ventilation factors for lung injury.\(^{57}\) In studies in patients with ARDS a possible association between driving pressure and poorer outcome was identified.\(^{65-67}\) In a large individual patient data metaanalysis on patients with ARDS receiving protective ventilation, driving pressure was the ventilation parameter that was strongest associated with mortality.\(^{68}\)

Functional lung size
Driving pressure is intrinsically connected to respiratory system compliance. To inflate the lung up to tidal volume (\(V_T\)), a certain pressure increase is required: the driving pressure (\(\Delta P\)). The amount of pressure necessary to inflate the lung depends on the compliance of the respiratory system (\(C = V_T/\Delta P\)). Lung compliance is strongly related to the volume of the remaining aerated lung, when functional lung volume is reduced (termed functional lung size). Normalization of tidal volume to functional lung size results in driving pressure (\(\Delta P=V_T/C\)). This is different to the generally used normalization to predicted body weight (mL/kg). The former adjusts for a possible decrease in lung aeration, while the latter corresponds with lung size of healthy, spontaneously breathing persons.

Functional lung size is decreased in patients with ARDS and in patients with healthy lungs undergoing mechanical ventilation. In ARDS, the diseased lung causes a decrease in compliance, while in patients with healthy lungs induction of anaesthesia or sedation causes large portions of the lung to collapse.\(^{69}\) In mechanically ventilated patients driving pressure may therefore better represent lung size, than lung size corrected for predicted body weight.

PEEP and driving pressure
The effects of the level of PEEP on compliance and driving pressure are complex. In patients with decreased compliance two different phenomena may simultaneously occur when levels of PEEP are increased. First, increased levels of PEEP prevent the lung from collapsing, thereby reducing the amount of lung tissue undergoing repeated/cyclic opening and closing. This increases functional lung size and compliance, and decreases driving pressure. Second, if the higher levels of PEEP do not effectively prevent atelectasis formation, end-inspiratory pressures and transpulmonary pressures will increase and result in hyperinflation of the aerated portion of the lung.\(^{62, 69, 70}\) The optimum of this delicate balance in prevention of alveolar stress and strain remains unsure and quite possibly differs considerably per patient. Further investigations are warranted, to provide individually tailored mechanical ventilation guidelines for each patient.
Future perspectives

*Individual PEEP titration*

The findings of this thesis suggest that setting one fixed level of PEEP may not be beneficial for all surgical patients in general. An improvement could be to focus more on individualized patient care, and titrate levels of PEEP on patient-specific parameters to minimize ventilator-associated lung injury. Previous studies have titrated “best PEEP” per individual patient by searching for the highest level of PEEP that optimizes aeration and avoids cyclic opening and closing of alveoli. This thesis suggests that high levels of PEEP may be harmful to the lung. Titration of levels of PEEP should therefore focus on “lowest PEEP”, to prevent hyperinflation of patent alveoli, while avoiding severe desaturation.

Several methods have been described to titrate levels of PEEP on patient-specific physiologic parameters. Many were based on oxygenation parameters, but these correlate poorly with the amount of lung recruitment and cannot indicate hyperinflation.

One method to titrate PEEP, is by oesophageal pressure measurement. By determining the oesophageal pressure, transpulmonary pressures can be calculated and used to titrate PEEP. Nonetheless, this method was primarily tested in critical care patients with ARDS. The technique is not easily transferred to the surgical population, where pneumoperitoneum and extreme positioning frequently occur and could severely alter the oesophageal pressure measurements. Furthermore, even though they seem to be strongly related, oesophageal pressures do not equal pleural pressures.

Another method is electric impedance tomography (EIT), which can image and evaluate regional distribution of alveolar aeration. With EIT the lowest levels of PEEP could be titrated by examining the aerated regions of the lung for signs of hyperinflation. Even though EIT seems to be a monitoring system with potential in experimental and clinical studies, it is not applied in clinical routine yet.

As mentioned previously, increased driving pressures seem to be strongest correlated with increased lung injury and mortality. Driving pressures may therefore be the most suitable global ventilation parameter to guide individual PEEP titration. However, the studies investigating driving pressure are all of retrospective design and performed post hoc analyses. Whether driving pressure can be manipulated at the bedside, and whether it is indeed associated with lung injury, needs to be tested in clinical trials.

*Permissive atelectasis*

In surgical patients with healthy lungs titration to the lowest levels of PEEP may not be necessary. Level of PEEP can be set at zero or low levels, as long as inspiratory volumes and pressures are kept within range. In chapter 3 we proposed a new ventilation strategy termed “intraoperative permissive atelectasis”. This approach combines intraoperative low tidal volume ventilation with relatively low levels of PEEP without recruitment manoeuvres. If hypoxemia (SpO₂ ≤ 92%) develops the FiO₂ should be increased first, followed by increase of levels of PEEP, and recruitment manoeuvres based on stepwise increase of tidal volume during regular mechanical ventilation.
Experimental and clinical studies have shown that during ventilation with levels of low or zero PEEP inflammation is less in lung regions with atelectasis than in the normally aerated portions of the lung,\(^5\), supporting the theory of permissive atelectasis. Permissive atelectasis could be a simple, acceptable method to reduce global strain in the lung and reduce alveolar hyperinflation during intraoperative low tidal volume ventilation in surgical patients with healthy lungs.

**In conclusion**

The main finding of this thesis is that intraoperative ventilation with higher levels of PEEP does not seem to reduce development of postoperative pulmonary complications during low tidal volume ventilation. Use of higher levels of PEEP may even cause harm. High levels of PEEP can compromise intraoperative hemodynamics. Furthermore, use of PEEP may be associated with increased risk of postoperative pulmonary complication.
Summary and general discussion

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