Lung-protective perioperative mechanical ventilation

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Chapter 1

General introduction and outline of the thesis

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Prevention of postoperative pulmonary complications

Mechanical ventilation is frequently considered a simple but foremost harmless intervention in patients under general anaesthesia for surgery. Recent investigations, however, suggest that intraoperative ventilation has a strong potential to cause so-called ventilator-associated lung injury. Of all patients undergoing ventilation during general anaesthesia for surgery, 5% will develop one or more postoperative pulmonary complications, that are associated with high morbidity and mortality. There are several mechanisms through which intraoperative ventilation could cause ventilator-associated lung injury, as such contributing to development of postoperative pulmonary complications (fig. 1). First, positive pressure ventilation can overstretch patent alveoli causing damage in those parts of the lung that are aerated during the whole breath cycle (fig. 1A & 1C). Second, repeated opening and closing of alveoli that collapse at the end of expiration is associated with increased shear stress, known to cause epithelial destruction (fig. 1B & 1D). Third, hyperoxia can result in absorption atelectasis, and cause injury of cellular structures through increased production of reactive oxygen species (ROS) (fig. 1E). All these harmful effects are suggested to be preventable through the use of lung-protective ventilator settings, using low tidal volumes for prevention of overdistension, use of positive end-expiratory pressure (PEEP) with or without so-called recruitment manoeuvres to prevent repeated opening and closing, and low oxygen fractions (FiO₂) preventing atelectasis and ROS production. These insights have led to a paradigm shift from supranormal intraoperative ventilation, with large tidal volumes to prevent atelectasis and high levels of FiO₂ to maximize oxygenation, to safer ventilation, using lower levels of tidal volumes, higher levels of PEEP and lower arterial oxygen thresholds.

Tidal volumes

Low tidal volumes in animal studies
The harmful effects of high tidal volumes were first recognized in animal studies of ventilation. In these preclinical studies lungs of animals were either challenged with injurious ventilation strategies using different tidal volumes alone, or in combination with other challenges such as intratracheal instillation of lipopolysaccharide or live bacteria. More or less they all showed that the extent of alveolar damage and pulmonary oedema depends on the size of tidal volumes used.

Low tidal volumes in patients with ARDS
Traditionally patients were ventilated with large tidal volumes of 10 to 15 mL/kg predicted body weight (PBW). These volumes far exceeded the range of normal tidal volumes in healthy subjects in rest (7 to 8 mL/kg PBW). The rationale was to prevent atelectasis, as such optimizing oxygenation and ventilation. Randomized controlled clinical trials in critically ill patients with the acute respiratory distress syndrome (ARDS), however, showed large tidal volumes to be harmful. Two metaanalyses convincingly confirmed that ventilation with low tidal volumes in patients with ARDS is associated with improved survival. Consequently, nowadays ventilation with low tidal volumes is standard of care in these patients.
Low tidal volumes in critically ill patients without ARDS

The finding that ventilation with low tidal volumes benefits patients with ARDS evoked interest in lung-protective ventilation in critically ill patients who need ventilation for other reasons than ARDS, for example comatose patients with neurologic damage and patients after major cardiac surgery. One randomized controlled trial comparing ventilation with low tidal volumes (6 mL/kg PBW) to ventilation with high tidal volumes (10 mL/kg PBW) indeed suggested benefit from low tidal volumes, as it seemed to reduce the incidence of ARDS.29 These findings were confirmed in a series of metaanalyses.18, 30, 31 In addition, these analyses revealed that ventilation with low tidal volumes was associated with earlier liberation from the ventilator. Even though a substantial reduction in tidal volume size is seen in recent years,27, 28 lung-protective ventilation using low tidal volumes is not yet considered standard of care for critically ill patients who need ventilatory support for reasons other than ARDS.

Low tidal volumes during intraoperative ventilation

Several small clinical trials of intraoperative ventilation suggested that tidal volume reduction could reduce local production of inflammatory mediators and possibly improve pulmonary mechanics.32-34 A large retrospective trial showed that pressure- and volume–limited ventilation during general surgery decreases the development of postoperative respiratory complications.35 Recently, three randomized controlled trials provided more robust evidence for benefit from this ventilation strategy.36-38 An Italian single–centre trial showed that a ventilation strategy using tidal volumes of 7 mL/kg PBW compared to ventilation with tidal volumes of 9 mL/kg PBW during abdominal surgery was associated with superior postoperative pulmonary function.36 A French multicentre trial found that in patients undergoing abdominal surgery a ventilation strategy with reduced tidal volumes of 6 mL/kg PBW compared to tidal volumes of 12 mL/kg PBW was associated with a decreased incidence of postoperative complications by almost 65%.37 One Chinese trial in patients undergoing spinal fusion reported an even more impressive benefit of tidal volume reduction from 12 to 6 mL/kg PBW on postoperative pulmonary complications.38 Contrasting to these results, one retrospective study showed that use of low tidal volume ventilation (6 to 8 mL/kg PBW) is associated with increased postoperative mortality, though the authors claim this to be caused by insufficient levels of PEEP.39 Despite the suggestion that low tidal volume ventilation in surgery patients is increasingly accepted,40, 41 recent studies show imperfect implementation of this strategy in the operation room.42-45

Positive end–expiratory pressure

Positive end–expiratory pressure in animal studies

Several studies in animals with lung injury have shown that ventilation with PEEP compared to ventilation without PEEP improves oxygenation and lung mechanics, and prevents formation of lung edema.5, 17, 46 Similar results came from studies in animals without lung injury. Ventilation with PEEP in combination with low tidal volumes attenuated local production of inflammatory mediators,47-52 lung edema,48, 51 and cell injury.47-52 One important shortcoming of PEEP, however, is that it could cause overdistension of the lung parts that remain aerated during the complete breath cycle.51 In addition, use of higher levels of PEEP could compromise the circulation.54
Figure 1. Mechanisms through which intraoperative ventilation could cause ventilator–associated lung injury

A) Ventilation at high lung volumes result in overdistention of the lung and hyperinflation may cause gross barotrauma (air leaks), but can also cause an increase in pulmonary oedema; B) ventilation at low lung volumes causes repeated opening and closing of alveoli that collapse at the end of expiration, resulting in increased shear stress and lung injury (atelectrauma). Collapse of large regions of the lung during ventilation at low lung volumes cause lung inhomogeneity; C) ventilation at too high levels of PEEP can aggravate overdistention of lung tissue at end-expiration; D) ventilation at low levels of PEEP increases formation of atelectasis and lung inhomogeneity; E) high levels of fractional inspired oxygen (FiO₂) can increase the production of reactive oxygen species (ROS), which have a direct toxic effect on lung cells. Too high levels of FiO₂ also increases the risk of resorption atelectasis; F) these mechanical and chemical stressors cause structural and biological changes in the alveoli. Inflammatory mediators are released in the lung and recruit neutrophils. They also cause changes that promote pulmonary fibrosis. The increase in alveolar-capillary permeability causes an increase in pulmonary oedema, but also facilitate translocation of mediators and bacteria to the systemic circulation; G) these structural and biological changes result in lung injury, which can cause an increase in postoperative pulmonary complications and worse clinical outcome with increased length of hospital stay and higher incidence of mortality (H)

Positive end–expiratory pressure in patients with ARDS

Three randomized controlled trials in patients with ARDS failed to show an effect of higher levels of PEEP on survival.55-57 One metaanalysis using the individual patient data of these three trials, however, showed survival benefit in patients with more severe ARDS.58 Consequently, nowadays most clinicians use higher levels of PEEP (10 cm H₂O and higher) in patients with moderate or severe ARDS.27
Positive end–expiratory pressure in critically ill patients without ARDS

In critical care patients without ARDS, there is limited evidence for benefit of PEEP.\textsuperscript{59, 60} One randomized controlled trial in patients at risk for ARDS showed no difference between a strategy using PEEP (5 to 8 cm H\textsubscript{2}O) and a strategy using a minimal levels of PEEP for adequate oxygenation with regard to later development of ARDS or mortality.\textsuperscript{59} This was confirmed in another trial in patients without ARDS, but in this trial use of higher levels of PEEP was associated with a lower incidence of ventilator–associated pneumonia.\textsuperscript{60} In the randomized controlled trial comparing low and high tidal volumes (6 ml/kg PBW versus 10 ml/kg PBW) in patients without ARDS mentioned above,\textsuperscript{29} an independent association between higher levels of PEEP and development of ARDS was found. In the postoperative phase there is also no clear evidence for benefit from PEEP. Indeed, while PEEP improves pulmonary compliance and arterial oxygenation, these effects only last in the first hours after surgery.\textsuperscript{61} This is also true for the prevention of atelectasis.\textsuperscript{62} In one trial in patients after cardiac surgery in which PEEP was titrated on the best achievable PaO\textsubscript{2} level no sustained benefit was found.\textsuperscript{63} In general, intensive care unit clinicians now use PEEP levels between 4 and 7 cm H\textsubscript{2}O in critically ill patients who need ventilation for other reasons than ARDS,\textsuperscript{28} though the best level of PEEP for these patients remains unclear.

Positive end–expiratory pressure during intraoperative ventilation

Induction of anaesthesia induces atelectasis,\textsuperscript{64} increasing ventilation–perfusion mismatch and suboptimal oxygenation.\textsuperscript{65} Intraoperative use of PEEP, with or without recruitment manoeuvres, is suggested to prevent atelectasis and repeated opening and closing of lung tissue.\textsuperscript{65} Indeed, use of higher levels of PEEP seems to improve oxygenation and respiratory mechanics in a wide range of patient populations and surgical settings.\textsuperscript{15, 66–74} However, in most trials of intraoperative PEEP, recruitment of lung tissue was not maintained in the postoperative period at the post anaesthesia care unit (PACU).\textsuperscript{72, 73}

Benefit of higher levels of PEEP on postoperative outcome was suggested in the three randomized controlled trials of lung–protective intraoperative ventilation mentioned above, where use of low tidal volumes was actually combined with higher levels of PEEP with recruitment maneuvers.\textsuperscript{36–38} It is difficult, if not impossible to conclude what prevented postoperative complications: the use of low tidal volumes or the high levels of PEEP, or recruitment manoeuvres, or altogether. Despite this, both low tidal volumes and high levels of PEEP with recruitment manoeuvres are suggested to be beneficial.\textsuperscript{75} A recent large retrospective study confirms this suggestion, showing that both low tidal volumes (< 10 mL/kg) and higher PEEP levels (≥ 5 cmH\textsubscript{2}O) are independently associated with a decreased risk of postoperative respiratory complications.\textsuperscript{35}

The lack of sufficient evidence for benefit of higher levels of PEEP during surgery is mirrored in the remarkable variation in use of intraoperative PEEP varying from 17% to as high as 82% of recently reported series.\textsuperscript{40–42, 44, 45}
Oxygen fractions

**Oxygen fractions in animal studies**
The potentially toxic effects of high fractions of inspired oxygen (FiO₂) have long been known from animal studies. Mice exposed to hyperoxia develop a condition similar to ARDS, which is at least in part dependent on an increased production of reactive oxygen species (ROS) by mitochondria.⁷⁶, ⁷⁷ Hyperoxia could further cause atelectasis, tracheobronchitis, interstitial fibrosis, protein leakage and neutrophil infiltration.⁷⁸-⁸⁰ In spontaneous breathing rodents with pneumonia, hyperoxia has been shown to contribute to bacterial spread beyond the lungs,⁸¹ lung injury and even lethality.⁸² More cytokine production and increased lung injury was found in experiments in ventilated rodents with hyperoxia during injurious ventilation (tidal volume > 20 mL/kg).⁸³-⁸⁵

**Oxygen fractions in patients with ARDS**
In human lungs high FiO₂ can also accelerate the production of ROS, which overwhelms natural anti-oxidant defences and injures cellular structures in the lung.⁹,¹⁶,⁸⁶,⁸⁷ Furthermore, hyperoxia can cause derecruitment of lung tissue by resorption atelectasis.⁸⁸ Critically ill patients with lung injury are possibly more prone to the harmful pulmonary effects of oxygen toxicity, which can coincide with the primary pulmonary injury (e.g., ARDS, pneumonia) and ventilator-associated lung injury.⁷⁷,⁸⁹,⁹⁰ One small trial found that 100% compared to 60% FiO₂ increased development of atelectasis in patients with ARDS, which was prevented by application of higher levels of PEEP.⁹¹ However, clinical trials examining the effect of hyperoxia on the development of lung injury in patients with ARDS are lacking.

**Oxygen fractions in critically ill patients without ARDS**
In critical care patients who need ventilatory support for reasons other than ARDS, an association between hyperoxia and mortality was found in ventilated patients,⁹⁵ patients after cardiac arrest,⁹² and patients with traumatic brain injury,⁹³ or stroke.⁹⁴ However, other studies did not reveal such associations.⁹⁰, ⁹⁵-⁹⁷ For example, two recent metaanalyses investigating the effect of high FiO₂ in critical care patients on survival showed mixed results.⁹⁸, ⁹⁹ One metaanalysis did not find a significant association in the general ICU,⁹⁸ while another metaanalysis of pooled data from all critically ill patients suggested arterial hyperoxia to increase the risk of mortality.⁹⁹ In subset analyses, hyperoxia was associated with decreased survival in patients after cardiac arrest, traumatic brain injury, and stroke.⁹⁸ In patients after cardiac arrest a dose-dependent association between hyperoxia and patient outcome was found.⁹⁹, ¹⁰⁰ Notably, arterial hyperoxia decreases coronary blood flow and cardiac output, increases systemic vascular resistance, and contributes to reperfusion injury in patients with myocardial infarction.¹⁰¹-¹⁰⁴ A recent randomized controlled trial in patients with myocardial infarction indeed clearly showed that supplemental oxygen increased myocardial injury.¹⁰⁵ Research on the effect of FiO₂ on the development of lung injury in patients ventilated for other reasons than ARDS, however, is currently unavailable. Despite the lack of evidence, current guidelines in critically ill patients aim at PaO₂ levels around 55–80 mm Hg.⁵⁵,¹⁰⁶

**Oxygen fractions during intraoperative ventilation**
Anaesthesiologists use high FiO₂ during pre-oxygenation and denitrogenation to prolong the apnoea tolerance time¹⁰⁷ and during intraoperative ventilation to correct for arterial hypoxemia
induced by ventilation–perfusion mismatches caused by alveolar collapse.\(^6^4\) High FiO\(_2\) (> 80%) increases the incidence of resorption atelectasis, which not only augments atelectasis formation after induction,\(^{107,108}\) but also directly before emergence from anaesthesia in the post–oxygenation phase, annulling the open lung created during intraoperative ventilation.\(^{109}\) At the same time, there is a risk of hyperoxia–induced injury to the lungs. The available trials and metaanalyses on perioperative hyperoxia focused on the beneficial effect of high FiO\(_2\) on postoperative nausea and vomiting\(^{110-112}\) and postoperative wound infections.\(^{113-118}\) A large trial on postoperative wound infections investigated the effect of 80% compared to 30% oxygen during surgery on development of postoperative pulmonary complications as secondary endpoint and found no difference in incidence of atelectasis, pneumonia, and respiratory failure.\(^{117}\) A clinical trial in obese patients showed worse postoperative lung function in patients receiving FiO\(_2\) during ventilation.\(^{119}\) One metaanalysis found no difference in presence or absence of atelectasis or postoperative gas exchange during intraoperative ventilation with either high or low FiO\(_2\).\(^{120}\) A large recent metaanalysis, however, suggested that hyperoxia was not associated with increased 30–day mortality.\(^{121}\) Sufficiently powered clinical trials on lung injury and postoperative pulmonary complications due to high FiO\(_2\) are lacking.

**Aims of this thesis**

This thesis is a collection of investigations that focused on several aspects of perioperative ventilation, specifically ventilation practice and the associations between ventilator settings and the effects on postoperative pulmonary complications and outcome. The main interest was on PEEP. We hypothesized that the use of higher PEEP and recruitment manoeuvres would protect against development of postoperative pulmonary complications during intraoperative ventilation.

The specific aims of this thesis were:

1. To investigate the effect of intraoperative use of PEEP and recruitment manoeuvres on occurrence of postoperative pulmonary complications during low tidal volume ventilation during open abdominal surgery.

2. To determine the association between intraoperative use of high tidal volumes, PEEP and recruitment manoeuvres, and the occurrence of postoperative pulmonary complications.

3. To investigate the effects of development of postoperative lung injury on postoperative clinical course and mortality.

4. To examine the effects of different levels of PEEP during postoperative ventilation after coronary artery bypass grafting on the duration to extubation.
Outline of this thesis

The following chapters in this thesis report on observational studies, clinical trials and metaanalyses that reported on several aspects of lung–protective perioperative ventilation, including effects of tidal volume size and level of PEEP.

Chapter 2 provides the results of a metaanalysis of eight clinical trials examining the effects of intraoperative ventilator settings on postoperative outcome of non–cardiac surgery patients. We hypothesized that use of low tidal volumes and/or PEEP with or without recruitment manoeuvres could prevent postoperative pulmonary complications, and as such improving postoperative outcome. In this metaanalysis we tried to separate the effects of tidal volume and PEEP manipulations.

Chapter 3 constitutes a comprehensive review of the literature on predictive models of postoperative pulmonary complications, the pathophysiology of ventilation–induced lung injury, and protective ventilation strategies, including the respective roles of tidal volume size, the level of PEEP and the use of recruitment manoeuvres. In this review we propose an algorithm for protective intraoperative mechanical ventilation.

In Chapter 4 and chapter 5 we describe the design and the results, respectively, of the ‘Local Assessment of Ventilatory Management during General Anaesthesia for Surgery’–study (LAS VEGAS), a prospective observational cohort study designed to assess intraoperative ventilation practice in Europe and the America’s, and to test the hypothesis that certain ventilator settings, especially high tidal volumes and low PEEP levels, are associated with the occurrence of postoperative pulmonary complications.

In Chapter 6 we show the results of a metaanalysis using individual patient data from 15 randomized controlled trials of intraoperative ventilation. We hypothesized that intraoperative ventilation with lower tidal volumes protects against postoperative pulmonary complications, and that use of higher levels of PEEP adds to the beneficial effects of lower tidal volumes.

Chapter 7 and chapter 8 constitute the design and results of the PROVHILO trial (High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery), a randomized controlled trial of intraoperative ventilation for open abdominal surgery. In chapter 9 entails letters with comments on PROVHILO written by peers, as well as our Author’s reply. In this trial patients were randomized to ventilation with high levels of PEEP (12 cm H\textsubscript{2}O) with recruitment manoeuvres or low levels of PEEP (0 to 2 cm H\textsubscript{2}O) without recruitment manoeuvres. We hypothesized that a ventilation strategy with high levels of PEEP and recruitment manoeuvres would protect against development of postoperative pulmonary complications.

In Chapter 10 we describe the results of another metaanalysis, using individual patient data from 12 clinical investigations of intraoperative ventilation. We hypothesized that the occurrence of postoperative lung injury was associated with a worse outcome, and that postoperative outcome would depend on intraoperative ventilation settings.
In Chapter 11 we present the results of a secondary analysis of two randomized controlled trials of postoperative ventilation in patients undergoing cardiac surgery, in which we determined the effects of PEEP manipulations on pulmonary compliance and gas exchange in the first hours of weaning from mechanical ventilation and time on the ventilator.\textsuperscript{122, 123} We hypothesized that higher levels of PEEP would improve pulmonary function, but not to be associated with a shorter duration of postoperative ventilation.

This thesis ends with a summary of the abovementioned studies and a general discussion in chapter 12, with Dutch translation in chapter 13.
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