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Lung-protective ventilation in intensive care unit and operation room

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Chapter 1

General introduction and outline of the thesis

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Ventilation–induced lung injury

Mechanical ventilation is one of the cornerstones of ventilatory support in patients with respiratory failure, and has always been one of the defining interventions for intensive care medicine as a medical specialty. Ventilation is also frequently required in surgical patients, especially when they receive general anesthesia for the procedure. In fact, ventilation is one of the most commonly applied interventions in intensive care units (ICUs) and operation rooms (ORs) worldwide.

Convincing and cumulating evidence from preclinical investigations using ventilation models in animals and clinical studies in ventilated ICU and OR patients revealed that ventilation is a far from safe intervention.[1] Indeed, ventilation is increasingly recognized as a harmful intrusion with a strong potential to damage the lung. This phenomenon is frequently referred to as '*ventilator–induced lung injury*' (VILI), although it could be better to name it '*ventilation–induced lung injury*' as it is not solely the ventilator that causes harm, but also, and maybe in particular the way the ventilator is set.

Pathophysiology of VILI

The pathophysiology of VILI consists of at least four interrelated mechanisms, though recently a fifth mechanism has been proposed (Figure 1).

Inflation of the lungs using positive pressure potentially can damage lung tissue so that air leaks develop, which is especially the case with use of high pressures. This phenomenon was called '*barotrauma*', and for a long time this complication was believed to be the one and only relevant factor in '*ventilation–induced lung injury*'.[2,3]

Better understanding of how ventilation could damage lung tissue came from preclinical investigations in which animals were subjected to ventilation with different tidal volumes but at similar airway pressures, showing that the extend of '*ventilation–induced lung injury*' was more related to the size of tidal volumes than the level of airway pressures used.[4,5] This phenomenon was termed '*volutrauma*' and from then restricting the size of tidal volumes was considered more important than limiting the level of airway pressures.

Then preclinical investigations in animals showed that the end–expiratory lung volume could be one important determinant of the degree and site of '*ventilation–induced lung injury*',[6,7] a concept frequently named '*atelectrauma*'. As ventilation with (higher levels of) positive end–expiratory pressure (PEEP) could prevent this type of harm, the use of PEEP became more widespread, and higher levels of PEEP were favored in patients with already injured lungs, e.g., acute respiratory distress syndrome (ARDS).

'*Volutrauma*' and '*atelectrauma*' may increase, or even induce local production and release of inflammatory mediators, not only resulting in additional inflammation within the lung itself,[8-10] but even distal organ injury when these inflammatory mediators leak to the circulation.[8,11-13] Thus, both the restriction in size of tidal volume restriction and use of adequate PEEP levels were considered key in the prevention of increased local inflammation and loss of compartmentalization, frequently termed '*biotrauma*'.[14]

Most recent insights into the pathophysiology of '*ventilation–induced lung injury*' came from the perspective that with every breath provided by the ventilator energy is transfered from the ventilator to the lung.[15,16] Indeed, some of the energy delivered by the ventilator dissipates to lung tissue, causing 'heat' and consequently lung inflammation.[15,16] The amount of energy transferred with each breath is suggested to be closely related to the difference between the maximum airway pressure and the level of PEEP, the so–called '*driving pressure*'. The *driving pressure* level depends on the ratio between the size of a delivered breath and the amount of aerated lung tissue.[15,16] This recently descibed factor maybe should be termed '*energytrauma*'.[15-18]

Prevention of VILI in patients with injured lungs

In patients with ARDS, the harmful effects of ventilation are suggested to be preventable through the use of so–called lung–protective ventilation strategies, in which the tidal volumes are restricted in size to prevent '*volutrauma*', as shown in pivotal randomized controlled trials,[19,20] and confirmed in a subsequent metaanalysis.[21] Also, recent studies suggests that a further restriction in the size of tidal volumes with use of extracorporeal removal of carbon

dioxide, could benefit ARDS patients even more.[22,23] Strategies using (higher) PEEP levels to prevent '*atelectrauma*' were tested without success in three randomized controlled trials.[24-26] However, one metaanalysis using individual patient data from these three trials suggested that patients with moderate or severe ARDS could benefit from higher levels of PEEP.[27] Based on these findings, recent guidelines strongly recommend using low tidal volumes and higher levels of PEEP in ARDS patients.[28]

VILI in uninjured lungs

Preclinical studies not only showed VILI to be an entity in models in which animals with lung injury were subjected to ventilation, but also that animals with healthy, i.e., having uninjured lungs could develop VILI. Indeed, VILI could be induced simply by applying mechanical ventilation using high tidal volumes in some preclinical investigations.[29,30]

Up till now, evidence for VILI in the clinical setting of uninjured lungs is less convincing. Epidemiological data, however, suggest that ARDS is rarely present at start of ventilation, but instead develops over a period of hours to days, and maybe only in subsets of patients.[31-33] One randomized controlled trial in critically ill patients without ARDS at onset of ventilation suggested that tidal volume reduction benefits patients without ARDS.[34] In that preliminary terminated trial, ventilation with high tidal volume contributed to the development of lung injury in patients without ARDS at the onset of mechanical ventilation. Indeed, some argued that ARDS could be seen as a 'man-made' syndrome, as a consequence of the aggressive regimens adopted to treat acutely ill patients.[35]

One recent review of intraoperative ventilation suggest that surgical patients may also suffer from '*ventilation–induced lung injury*', independent of an underlying pulmonary disease, if at all present.[36] Indeed, some small–sized clinical trials in patients undergoing intraoperative ventilation showed that, compared with ventilation strategies that could be seen as less protective, use of lung–protective ventilation was associated with less production of inflammatory biomarkers, and even reduced incidence of postoperative pulmonary complications (PPC) and health care utilization.[37-39]

Present uncertainties

Is 'ventilation–induced lung injury' an existing entity in patients with uninjured lungs?

As discussed above, '*ventilation–induced lung injury'* could be an important complication in patients without ARDS. Studies are needed to assess the importance of '*ventilation–induced lung injury'*, both in ICU and OR patients.

Is 'ventilation–induced lung injury' preventable in patients without ARDS?

It is uncertain how to set the ventilator so that it is least injurious, both in both in ICU and OR patients with uninjured lungs, and whether the proposed ventilation strategies are feasible in these patients.

Aim of this thesis

This thesis is a collection of a series of investigations focusing on several aspects of mechanical ventilation in ICU and OR patients, specifically ventilation practice and the association between ventilator settings and clinical outcomes. The investigations focus on tidal volume sizes, PEEP levels, and driving pressure levels.

We hypothesized that the use of low tidal volumes, high levels of PEEP and low driving pressure may benefit patients with uninjured lungs, reducing the incidence VILI (like occurrence of ARDS in ICU patients and PPC in OR patients), and improving clinical outcomes, like duration of mechanical ventilation in ICU patients and length of stay in hospital in OR patients.

The specific aims of this thesis therefore were:

1. To investigate associations between tidal volume size, level of PEEP and driving pressure on outcomes of critically ill patients without ARDS at onset of mechanical ventilation;
2. To investigate associations between intraoperative tidal volume size, level of PEEP and driving pressure on occurrence of PPC in patients undergoing general anesthesia for surgery;

3. To investigate the incidence of critically ill patients at high risk of ARDS and the differences of ventilation practice compared to patients not at risk of ARDS;
4. And finally, to examine the effect of tidal volume size, level of PEEP and driving pressure on outcomes of critically ill patients with ARDS submitted to extracorporeal life support.

Outline of this thesis

Chapter 2 provides the results of a conventional metaanalysis of studies examining associations between use of lung–protective ventilation with low tidal volume and clinical outcomes, including development of lung injury, pulmonary infection, and atelectasis, and mortality in ventilated patients without ARDS. In total, 20 studies were found, including 850 ICU patients and 1,972 OR patients. We here hypothesized that use of low tidal volumes to be associated with better outcomes, both in ICU patients and in OR patients.

Chapter 3 constitutes a comprehensive review of the literature on the physiology behind the importance of the driving pressure as a component of the lung–protective ventilation strategy. This review focuses on the interaction between energy dissipated in the lung during positive pressure ventilation as a rationale for aiming for the lowest driving pressure by manipulating tidal volume size and the level of PEEP in individual patients.

Chapter 4 describes the results of an individual patient data metaanalysis using data from 12 clinical investigations of intraoperative ventilation. The aim of this analysis was to determine and compare the crude and attributable mortality of development of PPCs in 3,365 patients after abdominal and thoracic surgery. 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 5** it is presented an editorial describing the impact and the importance of PEEP during postoperative ventilation of patients submitted to cardiac surgery.

Chapter 6 provides the results of an individual patient data meta-analysis from 17 studies investigating the association of tidal volume size, the level of PEEP, and driving pressure during intraoperative ventilation with the development of PPC. The aim of this paper

is to test if driving pressure is associated with PPC after mechanical ventilation for surgery in 2,250 patients. We hypothesized that intraoperative driving pressure, and changes in driving pressure according to changes in PEEP level would be associated with development of PPC.

In **Chapter 7** it is present the results of a sub-study of the 'High versus low positive end-expiratory pressure during general anesthesia for open abdominal surgery'–trial (PROVHILO), a randomized controlled trial comparing different levels of PEEP in patients receiving low tidal volume ventilation and submitted to open abdominal surgery. The aim of the present study is to test whether the kinetics of plasma biomarkers are capable of identifying patients who develop PPC, and whether their kinetics depend on the intraoperative level of PEEP in 242 patients. We hypothesized that kinetics of biomarkers of inflammation and lung injury differs between patients who do and do not develop PPCs, and that they discriminate those patients who develop one or more PPCs from patients who do not. We further hypothesized that the kinetics of the biomarkers are dependent from the intraoperative level of PEEP and driving pressure.

Chapter 8 presents a systematic translational review and metaanalysis of 25 animal studies and six human studies. We summarize present knowledge on the effects of ventilation with low tidal volumes in preclinical studies of ventilation in animals without lung injury and clinical trials of ventilation in ICU patients without ARDS. Furthermore, the clinical trials were meta-analyzed with regard to the effects of ventilation with lower tidal volumes on development of ARDS, mortality, development of pulmonary infections and duration of ventilation.

In **Chapter 9** it is described the results of an individual patient data metanalysis using data from seven studies. The aim was to determine the association between tidal volume and the occurrence of pulmonary complications in ICU patients without ARDS and the association between occurrence of pulmonary complications and outcome in these patients. We hypothesized that the occurrence of pulmonary complications depends on tidal volume size in ICU patients without ARDS at the onset of ventilation and that its' development worse the outcome of this group of patients.

Chapter 10 presents the results of an individual patient data metaanalysis from seven investigations. The aim of this study was to compare duration of ventilation and sedation needs in patients without ARDS. We hypothesized that use of lower tidal volumes is associated with a shorter duration of ventilation and that use of lower tidal volumes does not affect sedation needs.

In **Chapter 11** it is described the results of the 'Epidemiology, practice of ventilation and outcome for patients at risk of ARDS in Intensive Care Units in 16 countries'–study (PRoVENT), a prospective observational cohort study designed to assess ventilation practice in 935 patients around the world. The aim of this study is to determine the epidemiology for patients at risk of ARDS, describe ventilation management, and outcomes compared to patients at no risk. The hypothesis was that ventilation practice was different between patients at risk and not at risk of ARDS.

In **Chapter 12** we present the results of a sub-study of the 'Epidemiology, practice of ventilation and outcome for patients at risk of ARDS in Intensive Care Units in 16 countries'–study (PRoVENT), a prospective observational cohort study designed to assess ventilation practice in 935 patients around the world. The aim of the present study is to identify potentially modifiable factors for outcome in 935 critically ill patients without ARDS under invasive mechanical ventilatory support. We hypothesized that modifiable factors could lead to worse outcomes in this groups of patients, as higher mortality and longer ICU and hospital length of stay.

Chapter 13 presents an editorial describing the potential benefits of the extracorporeal life support a suggestion of the best ventilatory management of patients undergoing this kind of support.

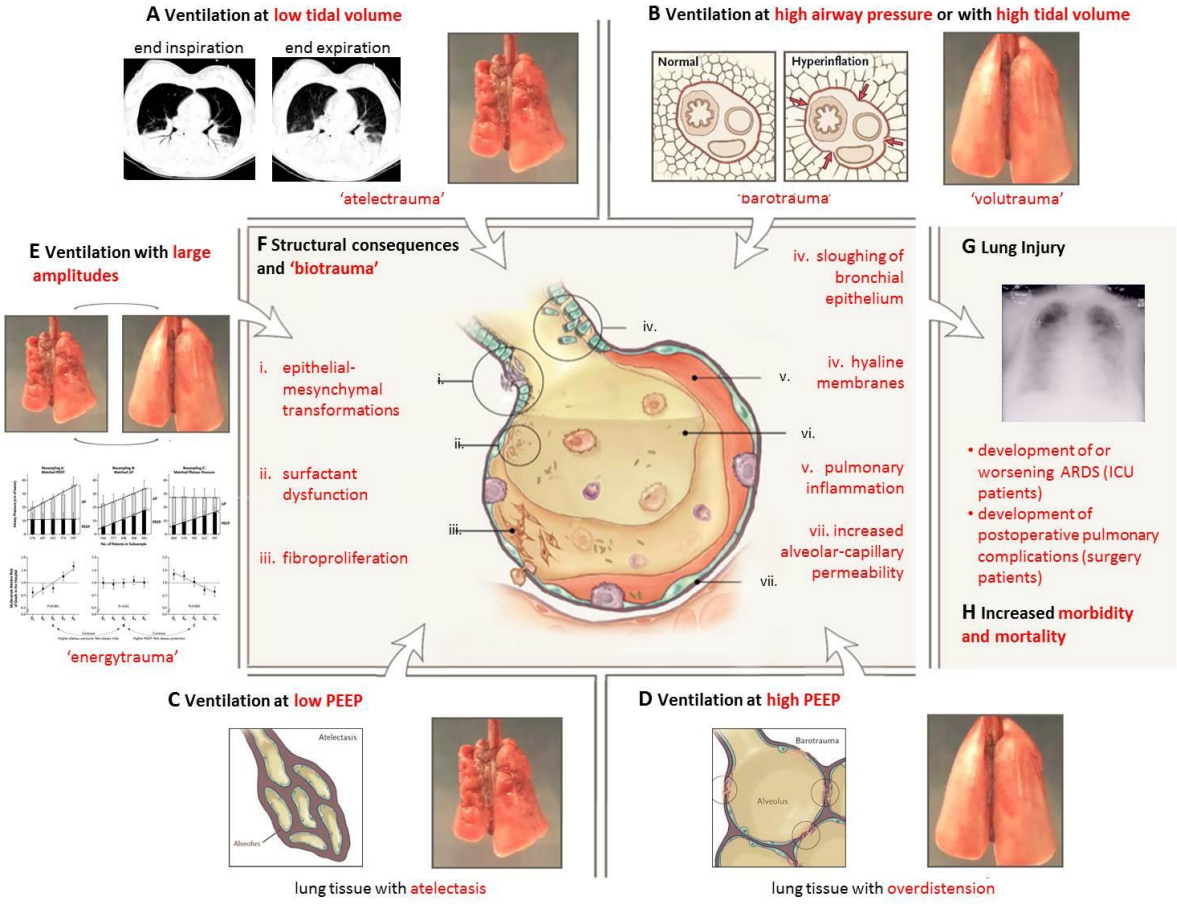
Chapter 14 constitutes an individual patient data meta-analysis of nine studies investigating associations between ventilatory settings during extracorporeal membrane oxygenation (ECMO) for refractory hypoxemia, and outcome in ARDS patients. The aim of this study was to evaluate associations between ventilatory settings during ECMO for refractory hypoxemia and outcome in 545 ARDS patients. We hypothesized that certain

ventilator settings during ECMO, like tidal volume size, levels of PEEP and driving pressure are associated with outcome.

In **Chapter 15** we describe again an individual patient data meta-analysis of four studies investigating associations between ventilatory settings during extracorporeal carbon dioxide removal ($ECCO_2R$), and outcome in ARDS patients. The aim of this study was to evaluate associations between ventilatory settings during $ECCO_2R$ and outcome in 129 ARDS patients. We hypothesized that certain ventilator settings during $ECCO_2R$, like tidal volume size, levels of PEEP and driving pressure are associated with outcome.

This thesis ends with a summary of the abovementioned studies and a general discussion in **Chapter 16**, with Dutch translation in **Chapter 17**.

Figure 1 – Mechanisms through which intraoperative ventilation could cause ventilator–associated lung injury



A) 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; B) 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; C) Ventilation at low levels of PEEP increases formation of atelectasis and lung inhomogeneity; D) Ventilation at too high levels of PEEP can aggravate overdistention of lung tissue at end-expiration; E) Ventilation with large amplitudes and higher driving pressure results in cell stretch and lung injury (energytrauma); 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).

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