Potential therapeutic strategies aimed at reducing the intensity of mechanical ventilation in ARDS
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General introduction and outline of the thesis

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The problem: Ventilator Induced Lung Injury

Approximately 35% of the patients admitted to the intensive care unit (ICU) are mechanically ventilated during their stay [1]. Although mechanical ventilation is necessary to prevent the patient from dying, there are also drawbacks resulting from mechanical ventilation. In some patients, mechanical ventilation can even worsen the outcome by inducing ventilator-induced lung injury (VILI). VILI is thought to result from three types of trauma; barotrauma, atelectotrauma and biotrauma [2, 3]. Barotrauma is caused by overstretched of the alveoli, during mechanical ventilation with large tidal volumes or the use of high driving pressures. Atelectotrauma results from repetitive opening and closing of the airways. Biotrauma is the result of pulmonary inflammatory responses. In particular, lungs that are ‘primed’ by an inflammatory insult, such as in acute respiratory distress syndrome (ARDS), are susceptible to additional injury inflicted by the ventilator.

Approximately a decade ago, it became clear that restricting tidal volumes to 6 ml/kg reduced mortality in patients suffering from ARDS [4]. Also, high driving pressures are increasingly recognized to contribute to VILI [5-7]. Thereby, guidelines advocate to ‘do no harm’ and to practice protective ventilation, including application of low tidal volumes and low inspiratory pressures. In some patients however, it is not feasible to maintain normocapnia using this approach. Tolerating an increase in carbon dioxide (CO₂) levels is called permissive hypercapnia. Permissive hypercapnia was shown to ameliorate lung injury. However, severe hypercapnia with acidosis may be detrimental, with severe consequences, including decreased host response to infection [8], impaired right ventricular function [9] and decreased diaphragm contractility [10].

Even in the era of protective ventilation and permissive hypercapnia, mortality rates of patients suffering from lung injury remain high [2, 3]. In a patient with ARDS, the demand of the ventilatory support intensifies and tidal volumes and pressures are increased to maintain an adequate gas exchange. However, this results in a vicious circle of increased baro- and atelectotrauma with a subsequent higher demand for potential injurious ventilation settings.

Therefore new therapies are warranted to limit VILI. We investigated both induced hypothermia and heliox ventilation as potential therapeutic strategies to reduce the intensity of mechanical ventilation.
A possible new strategy to limit VILI: Induced hypothermia

Induced hypothermia (32-34°C) is applied as a therapeutic intervention in the operating room and at the ICU. Induced hypothermia is associated with reduced ischemia-reperfusion injury during operative procedures [11] and improved neurological outcome following cardiac arrest [12, 13]. In cardiopulmonary surgery, hypothermia is associated with a reduced risk of stroke [14, 15]. The underlying mechanism of mitigating harmful effects of ischemia-reperfusion by controlling body temperature is proposed to be inhibition of an exaggerated inflammatory response. In line, in a pig model of cardiac arrest, hypothermia reduced expression of pro-inflammatory cytokines within the brain [16]. Also in various models of (sterile) ARDS, hypothermia is associated with a reduction in lung injury by a decrease of the inflammatory response [17-23]. This suggests hypothermia may mitigate harm, caused by an ‘overshoot’ of the systemic inflammatory reaction in response to ventilation. However, the animal ARDS models often used ex vivo settings and non-physiological acid-base balances, which hamper extrapolation to the clinical situation.

Besides lowering inflammation, induced hypothermia also lowers metabolism with a concomitant decrease in CO₂ production. Thereby, hypothermia may allow for reducing the intensity of mechanical ventilation, with a reduction in applied driving pressures or tidal volumes needed for adequate ventilation. In line with this, retrospective data in our ICU patients suggest that induced hypothermia has a favourable effect on gas exchange, with a decline of the partial CO₂ tension (PaCO₂), at unchanged minute ventilation [24]. Thereby, in lung injury, hypothermia may be beneficial via two distinct mechanisms.

Reducing the inflammatory response may, however, also have a drawback. An adequate adaptive host immune response to pathogens and infection is crucial [25] and fever is considered an important factor for optimal antimicrobial host defence [26]. Hypothermia inhibits immune responses [27], with delayed generation of pro-inflammatory cytokines by monocytes [28] and reduction of neutrophil and monocyte migration [29, 30]. The consequence of inhibiting host response by induced hypothermia may be a higher infection risk. Clinical data on the risk of infection following hypothermia show conflicting results. Trials in cardiac arrest patients reported no increased overall infection rates associated with hypothermia [12, 31]. In addition, prolonged hypothermia (>48 hours) did not increase risk of infection in patients with brain injury, annotated all patients received
selective decontamination of the digestive tract [32]. However, a recent systematic review showed an association of hypothermia with increased prevalence of pneumonia and sepsis in patients enrolled in randomized controlled clinical trials of therapeutic hypothermia for any indication, although overall infection rate was not affected [33].

In this thesis, we explore the effects of induced hypothermia on VILI. We hypothesized that induced hypothermia may limit VILI in two ways. First, hypothermia may reduce metabolism, thereby reducing CO₂ production. This might enable lower minute ventilation with maintaining adequate gas exchange and lower respiratory rates and/or lower tidal volumes, thereby limiting barotrauma and VILI. Secondly, hypothermia may reduce the inflammatory response, resulting in reduction of biotrauma and VILI. Furthermore, we also investigated whether hypothermia affects the innate immune response to bacterial infection.

**A possible new strategy to limit VILI: Heliox ventilation**

Helium is an inert gas with a lower density than air and thus flow of helium through an airway is less turbulent, leading to lower resistance [34]. In patients, ventilated with helium in a mixture with oxygen (heliox), lower driving pressures are necessary to distribute oxygen to the distal alveoli and improve oxygenation [34]. Therefore heliox ventilation may have therapeutic potential in patients suffering from VILI, by improving ventilation and allowing for reduction in driving airway pressures.

At the ICU, heliox has been safely used to reduce the work of breathing in both paediatric and adult patients, in whom airflow was obstructed due to increased airway resistance during exacerbations of asthma and COPD [35-38]. In ARDS, data are generally limited to paediatric patient populations and paediatric animal models of acute lung injury. Here, heliox persistently was found to improve gas exchange during ventilation modes, such as high frequency oscillation ventilation, that are more frequently used in infants instead of adults [39-44]. Data on the use of heliox during conventional mechanical ventilation in adult models are scarce.

We hypothesized that the use of heliox could be a new strategy to reduce VILI, by allowing lower minute ventilation and lower driving pressures, as a result of improved compliance and improved CO₂ removal, thereby decreasing lung injury.
Outline of this thesis

The general aim of this thesis was to investigate induced hypothermia and heliox ventilation as potential therapeutic strategies to reduce the intensity of mechanical ventilation with the aim to avoid or limit VILI. This dissertation is divided in two parts, with part I describing induced hypothermia and part II discussing heliox ventilation, both as as a potential therapeutic strategies. In both parts a translational approach was chosen, using preclinical and clinical studies.

Part I focuses on the effect of induced hypothermia on VILI. In chapter 2, we reviewed the literature on energy expenditure in several critically ill patient populations. Since body temperature may influence energy expenditure, we not only compared the metabolic state and caloric need in the critically ill patient groups, but also summarized the effect of body temperature, use of sedation and severity of illness on energy expenditure.

In chapter 3, effects of induced hypothermia were investigated in a clinically relevant animal model of VILI. Adult rats were mechanically ventilated with injurious mechanical ventilation settings, combined with hypothermia (32°C) or normothermia (37°C). We hypothesized that induced hypothermia would protect from VILI and investigated whether reducing respiratory rates would enhance lung protection, since repetitive opening and closing of airways can attribute to atelectotrauma and thus VILI.

The effect of induced hypothermia was also studied in an infectious model of Streptococcus pneumoniae pneumosepsis in chapter 4. Hypothermia (32°C) was induced for 4 hours, during mechanical ventilation. Bacterial dissemination and mitochondrial function were investigated to substantiate the beneficial effects of hypothermia.

Having established that hypothermia reduces lung injury in both sterile and infectious experimental models of VILI and ARDS, we expanded our investigations to clinical studies.

In chapter 5 body temperature of patients, admitted to the ICU after a cardiac arrest, was targeted to either 33°C (hypothermia) or 36°C (normothermia) [31]. In this population, we prospectively studied the levels of circulating mitochondrial DNA, since mitochondrial DNA is a marker of tissue damage and associated with adverse outcome [45].

In chapter 6 we focused on the effect of hypothermia on lung mechanics. Patients received a treatment with induced hypothermia for 24 hours and respiratory parameters were collected longitudinally. Patients served as their own control; hence no control group was required. In this study we hypothesized hypothermia could lower the intensity of mechanical ventilation.
Chapter 7 describes the results of induced hypothermia on immune response to several bacterial antigens. In cardiac arrest patients with a target temperature of 33°C or 36°C (identical design as in chapter 5), the effect of body temperature was investigated and compared within the groups and with healthy controls. We hypothesized that this study could be important to explore if the fear for higher infection risk, when using induced hypothermia, was legitimate.

In part II heliox ventilation was studied as a strategy to limit VILI. In chapter 8, we resumed available data on the effects of heliox ventilation in animal ARDS models and critically ill patients with ARDS or respiratory failure due to ARDS-like syndromes.

In chapter 9 an animal model of VILI, induced by barotrauma with tidal volumes of 15 ml/kg was executed. Rats were ventilated for 4 hours with either heliox or a standard gas mixture of oxygen-in-air. During mechanical ventilation respiratory data and blood gases were collected hourly, since we hypothesized that the use of heliox could facilitate CO₂ elimination, allowing for lower minute volume ventilation.

Chapter 10 describes a more severe animal model of ARDS. Lung injury was induced by intratracheal instilling 1 mg/kg lipopolysaccharide. Rats were mechanically ventilated with lung protective settings of 6 ml/kg tidal volumes and randomized to ventilation with heliox or oxygen-in-air. We expected more lung injury within this model and therefore hypothesized a more profound effect of heliox ventilation on the respiratory data.

In chapter 11 and 12, we evaluated in a clinical setting whether reduced intensity of mechanical ventilation could also be achieved by heliox administration during conventional mechanical ventilation in ICU patients. First, in chapter 11, safety and feasibility of heliox ventilation was tested in critically ill patients admitted to the ICU after a cardiac arrest. Secondly, the same patient population was studied in chapter 12, although the focus was shifted to the specific effect of heliox ventilation on gas exchange during the 3 hours the patients received heliox ventilation. We hypothesized heliox would allow a reduction in the intensity of mechanical ventilation. With that, this study could provide a proof of principle and thereby open doors for future research on heliox ventilation as therapeutic possibility in patients in whom protective mechanical ventilation is hampered by the development of respiratory acidosis.

The results of both the effects of induced hypothermia and heliox ventilation on VILI are summarized and discussed in chapter 13.
Reference List


