Potential therapeutic strategies aimed at reducing the intensity of mechanical ventilation in ARDS

Beurskens, Charlotte

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Summary and general discussion

*Charlotte J.P. Beurskens and Nicole P. Juffermans*
Mechanical ventilation is applied on a daily basis in the intensive care unit and thus ventilator-induced lung injury (VILI) is a well-known problem in critically ill patients. Although a protective ventilation strategy, using low tidal volumes is adopted worldwide [1], VILI still is an important issue [2, 3], with a staggering mortality rate of 60% in patients suffering from acute respiratory distress syndrome (ARDS) [4, 5]. Therefore, new therapies are warranted to target VILI. We investigated induced hypothermia and heliox ventilation as potential therapeutic strategies to reduce the intensity of mechanical ventilation. The rationale behind the application of induced hypothermia and heliox ventilation is extensively discussed in chapter 1.

**Induced hypothermia**

**Part I** of this thesis explores the possibility of induced hypothermia as a strategy to reduce VILI.

First, we investigated the actual metabolic state in critically ill patients, by reviewing the literature on energy expenditure in specific patients population in chapter 2. We learned that energy expenditure differs greatly among critically ill patient populations, as well within patient groups. In general, higher disease severity scores were associated with a higher metabolic state and the use of induced hypothermia seemed to decrease energy expenditure. Thereby, results seem to confirm the concept that metabolism during severe critical illness is high and is responsive to induced hypothermia. Another important finding in chapter 2 was that the use of a ‘one size fits all’ formula to estimate caloric need in the critically ill might not be appropriate because of the large variation within the patient groups. Therefore, given the variety of energy expenditure, it is advisable to measure metabolic demands by calorimetry for each patient individually.

In chapter 3, a clinically relevant model of VILI was used, with normal acid base balances, to study effects of induced hypothermia. Hypothermia reduced lung injury, which was independent from an adjustment on ventilator settings. This suggested that hypothermia does not ameliorate atelectotrauma, but has a direct anti-inflammatory effect in VILI. The hypothesized results on the reduction on lung injury by adjusting ventilator settings were not confirmed. Therefore our second hypothesis that hypothermia may reduce the inflammatory response was endorsed. Whether a reduction in tidal volume reduces barotrauma remains to be established.

The effect of induced hypothermia on ventilator settings was further explored in a clinical trial in hypothermic patients in chapter 6. Induced hypothermia improved ventilation
and allowed for lower driving pressures and PEEP levels during mechanical ventilation, while maintaining lung protective ventilation settings. It could not be determined in this study whether hypothermia also reduced lung injury, as these patients did not have lung injury. However, with these results we show that hypothermia is an effective intervention to lower the intensity of mechanical ventilation and underline our rationale of applying induced hypothermia to reduce VILI.

In chapter 4 we studied the effect of induced hypothermia on mitochondrial function. During sepsis, mitochondrial function is severely impaired, which is thought to be due to inflammatory damage to the respiratory chain subunits. We found improvement of the mitochondrial function, reflected by high ATP availability and increased oxidative phosphorylation of ADP to ATP. The efficiency of the mitochondrial function was unaffected by induced hypothermia. All this suggests that mitochondrial damage inflicted by inflammation is mitigated by the application of induced hypothermia.

The hypothesis that mitochondria may be better preserved due to hypothermia is underlined by findings in chapter 5. In cardiac arrest patients, induced hypothermia decreased levels of circulating mitochondrial DNA in the hypothermic patients. Within this small study population (N=10 vs. N=6), no effects on outcome could be measured. However, given that mitochondrial DNA is a marker of tissue damage [43], reduction of circulating mitochondrial DNA may reflect less damage to the mitochondria due to a inhibition of the inflammatory response.

Taken together, these clinical results, combined with the experimental data, suggest induced hypothermia reduces the inflammatory response and therefore the mitochondrial damage. As ATP availability and ATP turnover increase, this undermines the theory of an adaptive response of mitochondrial ‘shutdown’, with reduced ATP demand and less oxygen consumption.

Concerns remain about the risk of infection, when using induced hypothermia. In the infectious model of Streptococcus pneumoniae pneumosepsis in chapter 4, hypothermia (32°C) reduced markers of lung injury, while ventilation settings were unaltered. Interestingly, hypothermia also decreased bacterial dissemination. These results point towards a preserved endothelial-epithelial barrier function by reduction of injury. It could, however, not be determined whether this beneficial effect remains after rewarming and ultimately affects outcome. Thereby, the safety of inducing hypothermia during fulminant infection remains a concern.
Chapter 7 describes the results of induced hypothermia on immune response to bacterial antigens. We found that patients after cardiac arrest have a systemic inflammatory response compared to healthy controls, associated with an attenuated immune response to bacterial antigens. These findings resemble what is termed ‘immune paralysis’ in sepsis patients. Apparently, the same phenomenon is present in patients who have survived a cardiac arrest and suffered a sterile inflammatory response. These findings may have relevance, as they suggest that cardiac arrest patients are prone to develop nosocomial infection. Another important finding of this study is that hypothermia did not alter immune response to bacterial antigens compared to normothermia. As host response to bacterial antigens is critical in combatting infections, we believe that induced hypothermia itself does not increase risk of infection.

Conclusion

We believe to have established that hypothermia reduces lung injury in both sterile (chapter 3) and infectious (chapter 4) experimental models of VILI and ARDS. The reduced lung injury is in line with extensive research in animal models of several hyper-inflammatory conditions [6-13]. In these models hypothermia showed a reduction in organ failure that was associated with a decrease of the pro-inflammatory cytokines levels [6-13]. We ascribed these findings to a protective effect on mitochondrial function. This finding warrants further exploration of mitochondria as a therapeutic target.

In our clinical studies, induced hypothermia also showed a reduction of the systemic inflammatory response (chapter 7), but without compromising the immune response to bacterial antigens. These results are in contrast with clinical data in cardiac arrest patients that show induced hypothermia was an independent risk factor for infection [14]. Also a recent systematic review of patients, treated with therapeutic hypothermia for any indication, showed an association of hypothermia with increased prevalence of pneumonia and sepsis, although the overall infection rate was not affected [15]. However, these studies were performed without a normothermic control group, as was done in our studies (chapter 5; 7). Taken together, our results suggest that although a critically ill patient is more prone to infection by a decreased immune response, this risk of infection is not further increased by induced hypothermia. As induced hypothermia has shown to improve ventilation (chapter 6), hypothermia could be a potential strategy to lower intensity of mechanical ventilation in patients in whom protective ventilation is not feasible.
Recently it was shown that induced hypothermia (33°C) did not further improve neurological outcome after cardiac arrest, compared to a target temperature of 36°C [16]. Therefore, it might be only thermoregulation and maintaining normothermia that is sufficient to avoid the ‘overshoot’ of the systemic inflammatory response.

With regards to VILI, induced hypothermia can reduce the baro- and biotrauma, but whether induced hypothermia or just maintaining normothermia is protective, needs to be determined in future research.

**Heliox ventilation**

Part II of this thesis describes the possibility of heliox ventilation as a strategy to reduce VILI.

In chapter 8, available data on the effect of application of helium ventilation in animal ARDS models and clinical studies of critically ill patients with ARDS or respiratory failure due to ARDS-like syndromes were reviewed. In both animal models and clinical studies, heliox improved gas exchange, while allowing for less invasive ventilator settings. Studies predominantly focussed on neonatal and paediatric patient populations. Also outcome parameters were usually short-termed and concentrate on lung mechanics. Therefore, although potentially promising in ARDS, the effect of heliox on clinically relevant outcomes is not unequivocally proven.

Until now, heliox is often applied in patients with respiratory failure due to severe asthma or COPD to avoid endotracheal intubation and mechanical ventilation. In these patient populations work of breathing and elevated airway resistance are of more importance, compared to the ARDS patient population. Therefore, we believe the effect of heliox is more outspoken in these patient populations. Nevertheless, ARDS patients do have increased airway resistance with inadequate gas exchange, resulting in the need of mechanical ventilation with larger tidal volumes and higher inspiratory pressures to prevent the development of respiratory acidosis.

Data on the effect of heliox in ARDS are limited to paediatric models. To determine whether heliox ventilation exerts effects in a specific cause of lung injury, two models of lung injury were used in this dissertation. In chapter 9 in a clinically relevant VILI model, heliox ventilation allowed for a reduction in minute volume ventilation, while maintaining normal acid-base balance. Heliox did not allow for a decrease in driving pressures, possibly because this model was too mild. In a more severe ARDS animal
model, induced by intratracheal instillation of lipopolysaccharide (chapter 10), heliox ventilation allowed for a decrease in driving pressures needed to achieve the pre-set tidal volumes. Taken together, these experimental data suggest that heliox can reduce the intensity of mechanical ventilation and maintain protective ventilation in ARDS.

In chapter 11 and 12, clinical data was gathered on the effect of heliox on patients during conventional mechanical ventilation. Heliox ventilation in critically ill patients did not result in negative side effects or desaturation (chapter 11). Also, the delivery of tidal volumes was done accurately as the used ventilator was adjusted and calibrated. This is relevant, as the reduced gas density of heliox, compared to oxygen-in-air, results in an underestimated flow and tidal volumes, when the ventilator is not calibrated. When taking this into account, helium ventilation can be safe and is feasible in patients on conventional mechanical ventilation.

In chapter 12, we looked in more detail to the effect of heliox on ventilation in cardiac arrest patients during conventional mechanical ventilation. Heliox ventilation improved CO₂ elimination and allowed for decreased minute volume ventilation and peak pressures. Although this patient population is not our patient group of interest, this study provides proof that heliox allows for a reduction in ventilator settings. Therefore, heliox ventilation may be a therapeutic possibility in patients in whom protective mechanical ventilation is hampered by the development of respiratory acidosis.

**Conclusion**

The results of heliox ventilation on VILI and ARDS are modest, suggesting the models used were not representative for ARDS. However, in both animal models, parameters described as clinical relevant for animal models of ARDS were present [17]. Since lung injury is caused by a variety of insults and patients with acute lung injury constitute of a very heterogeneous patient population [18, 19], we chose two different animal models. The model of VILI (chapter 9) induced by barotrauma is clinically relevant, because all patients who are mechanically ventilated are at risk of developing ventilator-associated lung injury [20]. The ARDS animal model (chapter 10) is a frequently used method to mimic indirect lung injury, resulting from a systemic inflammatory response syndrome after for example trauma or major surgery. Although in our clinical studies, patients did not have pre-existing lung injury (chapter 12), heliox ventilation still resulted in less invasive mechanical ventilation by reducing the minute volume ventilation and used
pressures. These results are of relevance, since most data on the use of heliox ventilation is done in paediatric animal models or patient populations (chapter 8).

Taken together, in both preclinical and clinical studies, heliox allows for a reduced intensity of mechanical ventilation. However, our effects of heliox ventilation are small compared to the effects of heliox in asthma and COPD. We believe this can be ascribed to the fact that in ARDS, airway resistance plays a less important role than in exacerbations of asthma or COPD. Also therefore, we feel that our data do not point towards large studies in the future to investigate heliox as a therapy in patients with severe ARDS. Such studies would require too large numbers of patients to yield an effect of heliox ventilation. However, since heliox ventilation is proven to be safe and feasible, we believe heliox could be applied as a rescue therapy in individual patients who are suffering from respiratory failure. In these patients, usually ventilated with injurious large tidal volumes and pressures to maintain an adequate gas exchange, heliox ventilation could reduce the intensity of mechanical ventilation.
Reference list

1. Petrucci N, De Feo C: Lung protective ventilation strategy for the acute respiratory distress syndrome. The Cochrane database of systematic reviews 2013, 2:CD003844.


