Explorations of the therapeutic potential of influencing metabolism during critical illness

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General outline of this thesis

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Multiple organ failure is a common complication which can occur in the course of sepsis or systemic inflammatory response syndrome (SIRS) (1). The host response to invading micro–organisms or to a sterile inflammation can cause endothelial damage, microvascular dysfunction and vasodilatation, ultimately resulting in impaired tissue oxygenation and organ injury (2). Although an adequate host response may be needed to combat infection, it is thought that the hyper–inflammatory response seen during sepsis (and SIRS) may also contribute to ‘collateral damage’. The lungs and kidneys are the first failing organs, resulting in acute respiratory distress syndrome (ARDS) (3) and acute kidney injury respectively (4), significantly contributing to adverse outcome in these patients (5–7).

Increased inflammation and coagulation play a role in the pathogenesis of multiple organ failure, obstructing microcirculation and hampering organ perfusion (8). However, the pathogenesis of organ failure is not entirely understood. Even during adequate organ perfusion, there is a failure of mitochondria to live up to increased ATP demand, thereby causing bio–energetic failure, eventually leading to organ failure (9). Mitochondrial dysfunction is thought to occur as a result of damage inflicted by proinflammatory mediators. Most studies in sepsis have shown a decrease in mitochondrial respiration and ATP generation. Alternatively, it has been hypothesized that reduced cellular metabolism may potentially be a functional, protective mechanism. A metabolic shut–down may thereby increase the chances of survival of cells, and thus organs, during overwhelming inflammation. Regardless the cause, mitochondrial dysfunction is increasingly recognized as an important key player in the occurrence of organ failure in the critically ill.

Treatment of organ failure traditionally consists of goal–directed supportive care (10), ensuring adequate tissue perfusion and oxygenation to meet the high metabolic demands of severe inflammation. Although mechanical ventilation is a life–saving treatment, it can also cause additional lung injury, termed ventilator–induced lung injury (VILI) (11;12). Mechanisms of VILI include repetitive opening and closing as well as overstretching of alveoli, resulting in a pro–inflammatory response with enhanced pulmonary coagulation and complement activation (13–15). Mechanical ventilation not only contributes to lung injury, but can also affect distant organs (11). Thereby, the management of ARDS is a double edged sword. In the past decade, much knowledge has been gained about how we should ventilate our critically ill patients. Application of low tidal volumes has proven to be an effective therapy to reduce mortality in the critically ill (16). However, even in the era of protective ventilation, mortality in ARDS patients remains high (17). Taken together, physicians treat the underlying cause, they try to inflict ‘no further harm’ by their supportive care and wait for the disease to abate. Specific treatment options for these critically ill patients are not available. This has led us to hypothesize about a new perspective.
Instead of enhancing oxygen delivery, an alternative approach may be to reduce energy consumption. The regulated induction of a hypo–metabolic state, analogous to hibernation, may be beneficial in the imbalance between oxygen delivery and demand, thereby protecting the cells from severe bio–energetic failure and a critical fall in ATP. In naturally hibernating animals, a stepwise decrease in metabolism is followed by a reduction in body temperature when temperatures reach far below zero (18). It might be argued that humans do not hibernate and that we have only limited tolerance to hypoxia. Nevertheless, the human myocardium for example is able to adapt to chronic hypoxia in patients with ischemic heart disease, termed myocardial hibernation. Regulated down–regulation of myocardial contractions may thereby be an adaptation to reduced energy supply in the myocardium (19). Also, survivors of prolonged deep accidental hypothermia suggest that humans have an ability to reduce metabolism when oxygen delivery is compromised (20). We hypothesize that regulated induction of a hypo–metabolic state may reduce organ injury in critically ill patients by restoring the imbalance between oxygen delivery and demand, thereby protecting the cells from severe bio–energetic failure and a critical fall in ATP supply.

Introduction

In chapter 2 and 3, we discuss the mechanisms advancing organ failure. Special emphasis is put on the inability of mitochondria to use oxygen due to dysfunction, leading to a bio–energetic failure. Interventions aimed at decreasing metabolic rate are discussed, including hypothermia and hydrogen sulfide (H₂S) induced suspended animation, as novel strategies to reduce organ failure in the critically ill. The effects of H₂S on various regulatory systems including metabolism, circulation and inflammation, are described in detail in chapter 4. We further discuss potential therapeutic possibilities of a H₂S–induced suspended animation–like state.

Induced hypothermia

Induced hypothermia is applied in patients admitted to the intensive care unit following cardiac arrest because it improves neurological outcome (21). The beneficial effect of hypothermia is thought to occur from reducing excessive inflammation and by reducing cerebral energy demands (22). In this thesis, we investigated whether induced hypothermia was also beneficial in reducing lung injury in animal models of ARDS. In chapter 5, we studied the effect of hypothermia on lung injury inflicted by mechanical ventilation. We hypothesized that hypothermia would allow for lower respiratory rates required for adequate gas exchange, thereby reducing the ‘repetitive strain injury’ from repeated opening and closing of alveoli. We found that in a physiological rat VILI model, mild hypothermia (32°C) not only
reduced lung injury markers, but also allowed for lower respiratory rates while maintaining normal acid–base balance compared to animals kept at 37°C body temperature. In chapter 6, we induced hypothermia in mechanically ventilated rats with established *S. pneumoniae* pneumosepsis. Hypothermia was associated with diminished bacterial dissemination to the spleen and reduced levels of lung injury markers, as well as with improved mitochondrial function, as reflected by a high ATP availability and mitochondrial respiration in the liver and muscle. Next we studied the effect of hypothermia on respiratory parameters in patients following an out of hospital cardiac arrest. In these patients, applied hypothermia reduced arterial CO₂ at unchanged alveolar dead space ventilation, minute volume ventilation and static compliance, thereby improving ventilation (chapter 7). As a prospective sub–analysis of a randomized controlled trial on the effect of hypothermia after cardiac arrest, we were able to dissect the effect of hypothermia on levels of circulating mtDNA. These parts of mitochondria reflect the amount of tissue damage and are thought to act as ‘alarmins’, which can strongly drive the host inflammatory response and is associated with adverse outcome in SIRS (23). We found that applied hypothermia reduced circulating mtDNA levels in cardiac arrest patients (chapter 8).

**Hydrogen sulfide**

Inhalation of H₂S causes a reversible hypo–metabolic state, termed suspended animation like state in mice, (24). Besides a rapid reduction in metabolism, H₂S also has anti–inflammatory effects and improves mitochondrial function and integrity (25). In a rat VILI model, infusion of NaHS, which is a H₂S donor, reduced body temperature, heart rate and exhaled CO₂ levels, thereby resembling a suspended animation like state (chapter 9). NaHS protected against lung injury, an effect which was independent of ensuing hypothermia. NaHS infusion also improved cardiac performance by increasing stroke volume at unchanged cardiac output. Of note, after cessation of NaHS infusion, rats showed no behavioural or neurological damage. Next, we hypothesized that H₂S–induced hypo–metabolism is associated with reduced lung injury and maintenance of mitochondrial function in rats with established pneumosepsis (chapter 10). We again observed a significant reduction in lung and kidney injury markers, associated with improved mitochondrial respiration with increased ATP availability and less oxidative damage. Improved mitochondrial function was associated with upregulation of regulators of VDAC, such as α–tubulin and phophorylated PKC–ε. VDAC is a voltage dependent porin involved in ATP and ADP exchange between mitochondria and the cytosol. Not only was mitochondrial function better preserved, H₂S also improved mitochondrial biogenesis. As prolonged hypo–metabolism may be more beneficial, we observed surprising results in animals with LPS induced SIRS with ARDS, during short and prolonged course of NaHS infusion (chapter 11).
While short course of NaHS infusion offered organ protection, prolonged infusion did not enhance protection in a rat endotoxemia model. In this model, intravenous NaHS caused both a pro-inflammatory as well as an anti-inflammatory response, with increased TNF–α and IL–10 levels. In LPS stimulated whole blood co-incubated with NaHS and neutralizing IL–10 antibody, NaHS abrogated inflammation. These results suggest that NaHS offers protection possibly via IL–10 production.

3–iodothyronamine (T1am)
Pharmacological induction of a hypometabolic state may have less side effects then hypothermia and H₂S. In chapter 12 we hypothesized that T1am, a thyroid hormone derivate known to rapidly reduce metabolism, would protect against lung injury caused by LPS in spontaneously breathing mice. After T1am injection the animals stopped moving and their O₂ consumption and CO₂ production decreased. Reduced metabolism was however not associated with a reduction in lung injury. Reversely, inflammation was even enhanced, associated with elevated plasma T3 levels.

This thesis closes with a summary and general discussion, followed by a summary in Dutch (appendix A) and acknowledgements (appendix B).
References


