REVIEW

Induction of a hypometabolic state during critical illness – a new concept in the ICU?

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ABSTRACT

Induced hypothermia after cardiopulmonary resuscitation provides organ protection and is currently considered standard of care in clinical practice. An increasing number of reports indicate that induced hypothermia is also beneficial in other conditions of hypoxia-induced organ injury, including brain injury, intestinal ischaemia-reperfusion injury and acute lung injury. The mechanism of the protective effect is thought to be caused by a reduction in metabolism. A hibernation-like state, characterised by hypothermia, bradypnoea and a reduction in metabolic rate, was induced in animals that normally do not hibernate, after inhalation of hydrogen sulphide. This state was termed a 'suspended animation-like state'.

In critically ill patients, an exaggerated systemic inflammatory response is common, which often results in multiple organ injury. Inducing a hypometabolic state during critical illness may limit organ injury by reducing oxygen consumption, constituting a fascinating new therapeutic perspective for the treatment of critically ill patients. In this manuscript, we describe mitochondrial dysfunction during critical illness and preclinical data that suggest a potential therapeutic possibility of lowering metabolism. In addition, we discuss issues that warrant further research before clinical applicability.

KEYWORDS

Critical illness, hydrogen sulphide, hypothermia, metabolism, suspended animation-like state

INTRODUCTION

Sepsis is the exaggerated systemic inflammatory response to infection, characterised by endothelial damage, microvascular dysfunction and vasodilatation, ultimately resulting in impaired tissue oxygenation and organ injury.[1] Systemic inflammatory response syndrome (SIRS) can also result in vasodilatory shock, with the same features as sepsis. SIRS can occur as a reaction to a variety of noninfectious insults, including severe trauma, cardiothoracic surgery and ischaemia-reperfusion injury. When untreated, the dysregulated host inflammatory response in sepsis and SIRS results in multiple organ failure (MOF). The development of MOF, including acute lung injury and acute kidney injury, contributes strongly to morbidity and mortality in the critically ill.[2]

The inflammatory response seen in MOF requires an acceleration of glycolytic adenosine triphosphate (ATP) supply by the mitochondria to maintain the heightened level of activity and to prevent ATP levels from falling below threshold level, the latter of which would compromise normal cell metabolism and trigger apoptotic cell death. Treatment of MOF traditionally consists of supportive care, ensuring adequate tissue perfusion and oxygenation to meet the high metabolic demands of severe inflammation, an approach that ignores oxygen consumption.

In this manuscript, the potential beneficial effects of reducing metabolism in critically ill patients are discussed. Inducing a hypometabolic state may limit organ injury by restoring the dysbalance between oxygen demand and consumption, which holds the promise of a novel therapeutic approach in critically ill patients.

CHANGES IN MITOCHONDRIAL FUNCTION IN SHOCK STATES

Mitochondrial function
Under aerobic conditions, cellular energy production depends on glycolysis in the cytoplasm, the Krebs cycle and the electron transport chain embedded in the inner mitochondrial membrane.[3] By glycolysis, highly energetic

molecules such as NADH and FADH2 are produced, which can enter the mitochondria together with fatty acids and amino acids. After oxidisation in the Krebs cycle, these products transfer electrons through the mitochondrial complexes, generating an electron current for the production of ATP by oxidative phosphorylation.[4] During ATP production, oxygen is reduced to water by cytochrome c oxidase, the terminal enzyme of the respiratory chain complex. During shock states, the aetiology of multiple organ failure in critical illness is thought to include a deficiency in tissue oxygen delivery, due to shunting in the microcirculation and to a failing cardiac output in relation to oxygen demand, causing inadequate oxygen supply to cells resulting in hypoxia, which affects cellular energy metabolism.[5] However, this view does not support several observations. Despite apparently sufficient oxygen delivery, signs of hypoxia and/or metabolic dysfunction have been found to persist. Rather then caused by microcirculatory hypoxia, the tissue distress seen in MOF may be caused by disturbances in cellular metabolic pathways. The finding of an increased tissue oxygen tension in the presence of metabolic acidosis in sepsis patients suggests that oxygen is available at the cellular level and that the predominant defect may be a decreased use of oxygen in the mitochondria.[6,7] This condition is termed 'cytopathic hypoxia' and is thought to play a role in cellular dysfunction and organ failure.

Mitochondrial dysfunction in MOF
Mitochondrial abnormalities have been found in models of sepsis, reporting loss of structural integrity of mitochondrial membranes and swelling.[8,9] Studies on mitochondrial function in models of sepsis have yielded variable results. Both an increase and a decrease in mitochondrial respiration have been reported (reviewed by Singer[10]). These conflicting results have been contributed to the use of different species or organs between models, as well differences in the degree of resuscitation. However, in long-term sepsis models, a decrease in mitochondrial function is a consistent finding. Preclinical findings of mitochondrial dysfunction include the cytotoxicity of proinflammatory mediators. Tumour necrosis factor alpha (TNF) and nitric oxide (NO), both produced in excess during sepsis, affect oxidative phosphorylation by inhibiting several respiratory enzymes in the electron transport chain, thereby inducing direct functional damage to the mitochondria.[11] In accordance, most laboratory models of sepsis have shown a decrease in mitochondrial activity and ATP generation,[12-14] and respiratory activity.[15-18] The clinical relevance of mitochondrial dysfunction was shown in patients with septic shock. Skeletal muscle ATP concentration, a marker of mitochondrial oxidative phosphorylation, is depleted in septic shock, together with structural changes in the mitochondria, which was associated with worse outcome.[17]

Thus, bioenergetic failure (i.e. an inability to utilise oxygen) may be a mechanism underlying MOF in the critically ill.

Hypothesis of mitochondrial 'shutdown' during critical illness.
It has been proposed that mitochondrial energy alterations are part of the strategic defence.[19] The perceived failure of organs might instead be a potentially protective mechanism. Reduced cellular metabolism could increase the chances of survival of cells, and thus organs, in the face of an overwhelming insult. In this view, the modifications induced by sepsis should not be regarded solely as a failure of energy cell status, but as an integrated response. The decline in organ function may be triggered by a decrease in mitochondrial activity and oxidative phosphorylation, leading to reduced cellular metabolism, the process of which may be triggered by acute changes in levels of hormones and inflammatory mediators. The fact that organ dysfunction is reversible in survivors of MOF[19] suggests a window of opportunity in which strategies to improve mitochondrial function may be possible.

REGULATING CELLULAR SUBSTRATE DURING CRITICAL ILLNESS INFLUENCES OUTCOME

In recent years, some evidence has emerged that efforts to improve bioenergetic failure by regulating cellular substrate supply are beneficial in the critically ill. Hyperglycaemia is a common finding in critically ill patients, as a result of stress-induced insulin resistance and accelerated glucose production. Intensive insulin treatment aimed at maintaining normoglycaemia was shown to reduce mortality in patients on a surgical intensive care unit, as well as reduce inflammation and the occurrence of MOF.[20,21] The protective effect of normoglycaemia may occur via maintenance of mitochondrial integrity. In a post-mortem study, liver mitochondria from patients who were assigned intensive insulin therapy showed less morphological abnormalities when compared with patients assigned conventional therapy, which correlated with a higher activity of respiratory chain complexes I and IV.[22] In an experimental model of critical illness, it was found that mitochondrial dysfunction and organ damage was due to hyperglycaemic-induced cellular glucose overload and not to the actions of insulin.[23]

Another cellular substrate which has been studied to improve mitochondrial function in sepsis is succinate. Unlike complex I, complex II is relatively preserved during sepsis. Succinate is a component of the citric acid cycle and specifically donates electrons to complex II of the electron transfer chain, bypassing complex I. In an *ex vivo* rat model of sepsis, the addition of succinate was found to increase mitochondrial oxygen consumption.[24] The clinical significance of this strategy remains to be explored.

Aslami, et al. Induction of a hypometabolic state during critical illness.

MAY 2010, VOL. 68, NO 5

191

The effects of supplementing several amino acids have been studied in the critically ill too. Arginin, an NO donor, increases protein synthesis and improves immunological host defence during sepsis. Arginin-enriched enteral feeding formulae have been found to decrease the occurrence of multiple organ failure in critically ill trauma patients,[25] and to reduce mortality of septic patients.[26] Glutamine is a precursor of the antioxidant gluthathione. Improving the balance between overproduction of reactive oxygen species and depletion of antioxidants during sepsis may prevent the generation of peroxynitrite within the mitochondria, thereby restoring mitochondrial function. In accordance, in a model of sepsis, glutamine increased mitochondrial oxygen consumption, as exemplified by an increase in ATP synthesis.[27] In septic patients, a supplement containing glutamine dipeptides, antioxidative vitamins and trace elements resulted in faster recovery from organ dysfunction compared with control patients,[28] possibly by restoring low plasma levels of glutathione.[29]

HYPOTHERMIA AS A STRATEGY TO REDUCE ORGAN FAILURE

Induction of a hypometabolic state

Instead of enhancing oxygen delivery to meet enhanced demands, or regulating mitochondrial substrate, an alternative approach may be to reduce energy consumption. The regulated induction of a hypometabolic state, analogous to hibernation, may be beneficial in the imbalance between oxygen delivery and demand, thereby protecting the cells from severe bioenergetic failure and a critical fall in ATP.

Application of hypothermia in hypoxia-induced organ damage

Induced hypothermia by external cooling is a well-known beneficial preventive strategy in conditions causing tissue injury, such as cardiothoracic surgery and organ transplantation.[30] In addition, cooling the body to 32 to 34°C ameliorates neurological outcome when applied in patients who have suffered a cardiac arrest.[31] Other causes of hypoxic brain damage may also benefit from hypothermia, including stroke, traumatic brain injury and spinal cord injury.[32] Studies in experimental settings indicate that hypothermia may be protective in other organs suffering from of hypoxia-induced injury.[33-35] The beneficial effect is thought to occur via preservation of energy metabolism and reduction of the inflammatory response (*table 1*). Hypothermia reduces metabolism by 7% per grade, with reduction of ATP formation and reduction of cellular oxygen and cerebral glucose requirements. NO, which is produced in excess during sepsis, competes with oxygen in binding to cytochrome c oxidase in the mitochondrial membrane, thereby blocking the electron transport chain and resulting

Table 1. *Effects of H_2S-induced suspended animation and hypothermia on cardiovascular function, metabolism, inflammation and coagulation*

	H_2S-induced suspended animation	Induced mild hypothermia	References
Vascular system	Vasodilatation	Vasoconstriction	30, 55, 80, 88
Cardiac function	Decrease in heart rate Increase in stroke volume, No effect on contractility, Decrease or no effect on cardiac output	Decrease in heart rate Increase or no effect on contractility, Impaired or no effect on diastolic relaxation, Decrease or no effect on cardiac output	66, 74, 80, 89
Metabolism	Decrease in CO_2 production and O_2 consumption Inhibition mitochondrial respiration, no change in lactate production, increased rate of glucose oxidation Preservation of mitochondrial function	Decrease in brain CO_2 production and O_2 consumption Decrease in ATP production Increase in lactate production Increase or decrease in extraction ratio Breakdown of free fatty acids Decrease insulin secretion, insulin resistance	43, 56, 66, 90-92
Inflammation	Reduction MPO activity Decrease in chemokine levels Reduction lipid peroxidase	Decrease in production of free radicals Decrease in white cell count and neutrophil influx Decrease in chemokine levels Differential effect on levels of cytokines; decrease or increase in TNF and IL-6, no effect on IL-2, increase in IL-10 and IL-1 Decrease apoptosis	30, 67, 68, 86, 93-95
Coagulation	Not known	Increased generation of prostaglandins Decrease in platelet count Decrease in platelet adhesion Decrease in levels of thrombin-antithrombin complexes	96-98

Aslami, et al. Induction of a hypometabolic state during critical illness.

MAY 2010, VOL. 68, NO 5

192

in overproduction of free oxygen radicals. Mild to moderate hypothermia prevents the production of superoxide and subsequent formation of reactive oxygen and nitrogen species during ischaemia (*table 1*).[36] Another protective mechanism may include the prevention of apoptosis, which may also be linked to mitochondrial function.[32] The recovery of multiple organ failure has been found to be associated with improvement in mitochondrial respiration in survivors of septic shock.[17] As discussed above, both a lack of oxygen as well as an inability to utilise oxygen is likely to contribute to organ failure during critical illness. We hypothesise that hypoxic-induced organ damage in critically ill patients may benefit from induced hypothermia, by preservation of residual mitochondrial function or faster mitochondrial recovery after inflammation has resolved.

Induced hypothermia in acute lung injury

In 30 to 60% of critically ill patients, acute lung injury occurs in the course of an exaggerated inflammatory host response during MOF.[37] The mechanisms that contribute to acute lung injury involve inflammatory processes as well as mechanical processes due to overstretching of alveoli. Reducing mechanical stress is a very beneficial strategy in these patients: the use of lower tidal volumes during mechanical ventilation has been found to reduce pulmonary damage in critically ill patients.[38] Besides too large tidal volumes, too frequent repetitive strain of respiratory cycles also may cause lung injury, as lowering of respiratory frequency attenuated lung damage in experimental models.[39] However, the use of low tidal volumes and lower respiratory rates is limited by the fact that the resulting low minute ventilation results in high levels of arterial pCO_2 and concomitant severe respiratory acidosis.

In animal models, induced hypothermia has been found to attenuate lung injury via reduction of neutrophil-mediated inflammation (*table 1*).[40,41] Hypothermia may also exert protective effects by its effect on metabolism. Reduced CO_2 production and O_2 demand may allow lower minute ventilation. Indeed, it was found that hypothermia enabled mechanical ventilation using a low respiratory rate, thereby attenuating lung injury in a rat model, a strategy which was termed 'lung rest'.[42]

The clinical significance of hypothermia during acute lung injury has been shown in an earlier study. In moribund patients with severe acute lung injury, hypothermia applied as a last resort was found to reduce mortality.[43] However, progress has been made since this trial, and treatment of the critically ill has changed considerably. Whether the beneficial effects of hypothermia can be reproduced in less severely ill patients with acute lung injury awaits exploration.

Hypothermia in acute kidney injury

Acute kidney injury shows a striking similarity to the inflammatory reaction observed in acute lung injury.

An exaggerated inflammatory response, including the induction of cytokines and the initiation of coagulation, contributes to acute kidney injury.[44] Another defining feature is the damage to the microvascular endothelium and epithelium leading to altered blood flow and oxygen extraction, as well as an increased permeability to proteins and solutes. Notably, acute lung injury may induce acute kidney injury. Deterioration of kidney function in the course of acute lung injury carries a poor prognosis.[45] Data on the effect of hypothermia on hypoxia-induced kidney injury are limited to ischaemia-induced kidney injury associated with the use of cardiopulmonary bypass. In series of patients, hypothermia applied during cardiopulmonary bypass for aortic surgery has been reported to protect against renal failure.[46,47] It can be hypothesised that the protective effect of hypothermia found in models of acute lung injury also applies to acute kidney injury.

Hypothermia in gut ischaemia

In sepsis-induced multiple organ failure microcirculatory abnormalities may depress gut barrier function and contribute to bacterial translocation.[48] In critically ill patients, increased intestinal permeability was found to be predictive of the development of MOF.[49] In a model of intestinal ischaemia-reperfusion injury, hypothermia reduced the amount of injury, which was related to both a reduction in neutrophil infiltration as well as to a complete recovery of hepatic ATP synthesis.[35] The mechanism of this protective effect may have been inhibition of NO-mediated oxidative stress, as hypothermia attenuated NO production and prevented depletion of gut glutathione.[50] Interestingly, hypothermia applied during gut ischaemia shifted cardiac substrate utilisation from fatty acid oxidation to carbohydrate, as shown by an inhibition of carnitine palmitoyl transferase I activity.[51] The importance of mitochondrial dysfunction in this model was exemplified by the correlation between preservation of hepatic ATP levels and mortality.[52]

SUSPENDED ANIMATION AS A NOVEL STRATEGY TO REDUCE MULTIPLE ORGAN FAILURE

The concept of suspended animation

As induced hypothermia is not without complications, a more physiological approach to limit organ injury during critical illness could be the reduction of cellular energy expenditure, like hibernating animals when confronted with an environmental hypoxic insult. Hibernating mammals are thought to be tolerant to hypoxic conditions by a regulated suppression of ATP demand and ATP supply to a new hypometabolic steady state.[53]

Aslami, et al. Induction of a hypometabolic state during critical illness.

MAY 2010, VOL. 68, NO 5

193

A hibernation-like state has been induced in animals that normally do not hibernate, with the use of hydrogen sulphide (H_2S).[54] H_2S is commonly referred to as an environmental hazard. However, H_2S is endogenously produced from L-cysteine within the vasculature.[55] By competing with oxygen in binding to cytochrome c oxidase, H_2S can inhibit mitochondrial respiration, thereby reducing cellular oxygen consumption. Mice exposed to H_2S had a drop in core body temperature and a concomitant drop in metabolic rate, as measured by decreased O_2 consumption and CO_2 production.[56] After cessation of H_2S exposure, the mice awoke, without displaying neurological or behavioural deficits. Besides H_2S, nitric oxide and carbon monoxide are important gaseous signalling molecules, which act as an oxygen reducer and inhibit cytochrome c oxidase, similar to H_2S.[57] Carbon monoxide has also been used to induce suspended animation in nematodes.[58]

Suspended animation during severe hypoxia

H_2S has been found to protect against myocardial ischaemia-reperfusion injury in nonhibernating doses,[59-61] as well as in a dose that preserved mitochondrial structure and function compared with controls,[62] via a vasorelaxant effect,[59] attenuation of inflammation[62] and reduction of apoptosis (*table 1*).[60,62] In a model of trauma-induced acute lung injury, H_2S at high doses attenuated lung injury, by decreasing proinflammatory cytokines and upregulating anti-inflammatory cytokines.[63] In addition, an antioxidant effect of H_2S was observed.

A possible protective effect of H_2S on oxygen deprivation is of particular interest in critically ill patients suffering from severe lung injury, in which potentially damaging high pressure mechanical ventilation is used to maintain oxygenation. Of interest in this respect are experiments with carbon monoxide. Inhibition of cytochrome c oxidase by carbon monoxide can protect nematodes against severe hypoxia by inducing suspended animation.[58] This has led to the suggestion that suppressing oxygen demand before oxygen supply falls short may protect the generation of reactive oxygen species and subsequent cell damage. In support of this hypothesis, it was shown that prior exposure of mice to H_2S increased survival during lethal hypoxia by a reduced oxygen demand.[64]

Suspended animation during anaesthesia and mechanical ventilation.

If the approach of lowering energy expenditure is to be applied in critically ill patients, these patients will be sedated and mechanically ventilated. Anaesthetic agents also suppress metabolic rate and can result in hypothermia. Studies exploring the effects of H_2S on metabolism in anaesthetised and mechanically ventilated animals found that both hypothermia and H_2S reduced oxygen consumption and CO_2 production (*table 1*),[65,66] but that mitochondrial integrity was preserved during H_2S exposure only and not in hypothermic controls, as measured by a reduction of cytochrome c-stimulated mitochondrial oxygen influx.[67] Also, H_2S resulted in a shift of substrate utilisation towards increased carbohydrate oxidation, an effect that was not observed in hypothermic subjects. This suggests that H_2S has distinct effects on metabolism, which are not induced by a mere fall in body temperature.

Figure 1. *Physiological changes during a suspended animation-like state in rats induced by infusion of 2 mg/kg/hr of an H_2S donor*
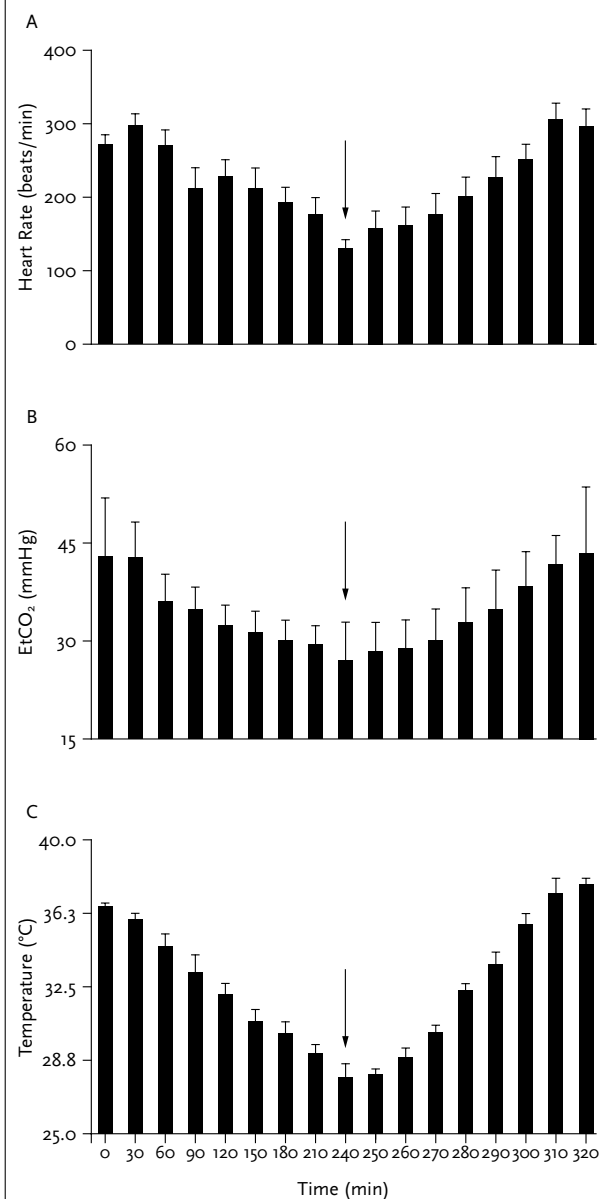
Arrow: cessation of the H_2S infusion. EtCO$_2$: end tidal CO_2. Data represented as mean ± SD of 8 animals.

Aslami, et al. Induction of a hypometabolic state during critical illness.

MAY 2010, VOL. 68, NO 5
194

Studies on the effect of suspended animation during disease states are still limited. Of interest, high doses of H_2S gas that reduced metabolism, exemplified by lower oxygen consumption, was found to be protective against stress-induced ulceration.[68] Also, preliminary data suggest that 'hibernating' doses of the H_2S donor NaHS reduced lung injury inflicted by mechanical ventilation, thereby providing evidence for protection of a hypometabolic state in a model that is relevant in the intensive care.[69] Importantly, all physiological changes induced by H_2S disappear after cessation (*figure 1*). The finding that the effects of H_2S are transient is an important finding with regard to suitability of clinical application. However, major issues remain that warrant exploration before clinical application.

HURDLES TO THE INDUCTION OF A HYPOMETABOLIC STATE

Risks of induced hypothermia during critical illness

Adverse events of induced hypothermia, in particular infections and bleeding, are not increased during hypothermia when compared with normothermia in patients after a cardiac arrest.[31] Therefore, in experienced hands, hypothermia is a safe treatment in these patients. However, hypothermia has not been applied before in multiple organ failure. It can be hypothesised that hypothermia hampers adequate immune response during bacterial infections, possibly leading to diminished clearance of bacteria. Indeed, a role for mediators that are produced during fever has been suggested for adequate host defence against bacteria.[70] In line with this, septic patients who develop hypothermia have a worse outcome compared with those who maintain a normal body temperature. Also, perioperative hypothermia is associated with increased surgical wound infections.[71] Several experimental studies, however, have reported favourable effects of mild hypothermia, increasing survival during sepsis[72] and after haemorrhagic shock.[73] The effect of controlled hypothermia in patients with sepsis has not been studied.

Hypothermia results in a prolonged bleeding time and diminished platelet aggregation. Although pulmonary bleeding is not a major feature of acute lung injury, hypothermia may increase the risk of bleeding from inflamed lung tissue with an altered morphology or may result in other types of bleeding. In addition, hypothermia reduces cardiac output, probably by reducing heart rate.[74] During sepsis or SIRS, relative myocardial dysfunction, in which oxygen delivering capacity is insufficient to meet oxygen demand, is a common finding. It remains to be determined whether the reduction of energy expenditure during hypothermia is sufficient to counteract an H_2S-induced decrease in cardiac output.

Feasibility of suspended animation in humans

Humans do not hibernate naturally and have a limited tolerance to inadequate oxygenation. In former times, when oxygen supply on earth was limited, life forms using sulphur as energetic substrate were abundant. The fact that humans produce H_2S within the vessel wall may suggest that the ability to switch to an alternative substrate, or go into a hypometabolic state with lowered oxygen consumption, may latently be present.[75] Several anecdotal reports on survival of deep and prolonged circulatory arrest, with good neurological recovery, may support this thought.[76-78]

An important issue is the clinical relevance of rodent models. Studies on H_2S-induced suspended animation in several larger animal models, including sheep and pigs[65,79] have yielded conflicting results, which may have resulted from differences in experimental set up, including the use of different H_2S donor compounds as well as the use of anaesthetic agents that may have influenced oxygen consumption. Conceivably, a difference in body mass may also contribute to these differences. Due to a large surface-to-mass ratio, rodents can rapidly reduce core body temperature, which may be difficult to induce in larger mammals and humans. However, in several experiments, the metabolic effect of H_2S occurred before core body temperature had dropped, suggesting that the suppressive effects of hibernation on metabolism are independent of the effects on body temperature.[79,80] Also, thermal inertia of large mammals did not prevent the induction of profound hypothermia in former experiments.[81] Therefore, although the induction of a suspended animation-like state is still far from clinical application, it may be feasible in large mammals and humans.

The dual role of H_2S in mediating inflammation.

The role of H_2S during systemic inflammation is a matter of debate, as H_2S in nonhibernating doses exerts both proinflammatory and anti-inflammatory effects. Inhibition of endogenous H_2S synthesis by DL-propargylglycine (PAG) demonstrated marked proinflammatory effects in various murine models; PAG inhibited production of cytokines and chemokines as well as leucocyte trafficking in sepsis models, thereby mediating or aggravating organ inflammation.[82-84] *In vitro*, H_2S has been found to promote apoptotic cell death.[85] In contrast, also anti-inflammatory effects have been found. H_2S donors reduced leucocyte-mediated oedema formation in a hindpaw oedema model.[63,86] More relevant to the intensive care is the finding that an H_2S donor improved survival in a murine model of smoke and burn-induced lung injury.[63] These differential effects of H_2S may be the result of variable doses and timing. Of note, anti-inflammatory effects of the H_2S donor NaHS in experimental pancreatitis were found to be dose-dependent.[87]

Aslami, et al. Induction of a hypometabolic state during critical illness.

MAY 2010, VOL. 68, NO 5

195

Practical hurdles

Although H_2S gas is highly flammable, this objection has been overcome with other flammable gases such as oxygen, as well as other 'toxic' gases, such as NO. In addition, H_2S has the smell of rotten eggs. In a closed system of mechanical ventilation, exposure of patients and personnel to the odour may be limited. Lastly, corrosion of tubes and metal parts may shorten durability of the mechanical ventilator.

CONCLUSION

Mitochondrial dysfunction plays a role in critically ill patients with MOF. Preclinical evidence suggests that inducing a hypometabolic state limits organ injury by inhibition of the inflammatory response and by preservation of mitochondrial function. Restoring the imbalance between oxygen demand and consumption may provide a fascinating novel therapeutic approach towards critically ill patients.

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Aslami, et al. Induction of a hypometabolic state during critical illness.

MAY 2010, VOL. 68, NO 5

196

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Aslami, et al. Induction of a hypometabolic state during critical illness.