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EDITORIAL

Keep it cool on the ICU

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Reduction of the proinflammatory response in cases of systemic and/or regional hypoperfusion and reperfusion, and sepsis has long been considered a promising method to preserve organ function. However, it only remains promising since so far studies intervening at a specific pathway have been disappointing in terms of patient outcome and survival.[1] Although our understanding of the proinflammatory and anti-inflammatory response in severe illness is growing, it is still very limited and the models on which the trials were designed too simplified. The systemic inflammatory response ultimately results in impaired tissue oxygenation and multiple organ failure. The current management of such patients with critical illness is primarily aimed at supportive care, providing adequate tissue perfusion and oxygenation in order to meet the high metabolic demands and correction of the cause.

As pointed out by Aslami and Juffermans, since mild therapeutic hypothermia (MTH) favourably interferes at many pathways for the pro-inflammatory response and apoptosis, it seems attractive to put forward MTH as a therapeutic intervention to reduce organ failure.[2] Additionally, MTH reduces tissue oxygen demands. Indeed, MTH has proven beneficial effects in patients after cardiopulmonary resuscitation in terms of neurological outcome. Lower levels of evidence exist for the beneficial effects of MTH in other forms of organ failure related to hypoperfusion and reperfusion, such as myocardial infarction (smaller infarct size), traumatic brain injury (decrease of intracranial pressure and improved neurological outcome), and major thoracic cardiovascular surgery (prevention of brain and spinal injury). Case series have demonstrated favourable effects of MTH in patients with severe pulmonary inflammation, ARDS.[3]

Recently, more attention has been given to the importance of mitochondrial dysfunction and bioenergetic failure during sepsis and shock. There is evidence that sepsis-induced mitochondrial dysfunction is associated with a loss or failed synthesis of mitochondrial DNA and mitochondrial recovery, as indicated by blood mitochondrial DNA levels. The latter has been shown to be associated with survival.[4] Preservation of mitochondrial dysfunction might, therefore, present a target for therapy. Baumgart *et al.* showed that, in a mice model, inhaled hydrogen sulphide (H_2S) adds to the preservation of mitochondrial function during hypothermia.[5] All this makes MTH a potential therapeutic intervention to reduce organ failure.

The practice of MTH is currently well feasible and established. However, 'dose-finding studies' on how low the temperature should be, and for how long, and at which rate the temperature should decrease and at a later stage increase to normotemperature, are all lacking. Randomised studies in intensive care medicine are very difficult to perform and to interpret, related to the diversity of the population and the obligatory multiple interventions.[6] MTH has not been studied in patients with sepsis. Known and unknown side effects of MTH may be anticipated when applied in sepsis. Since, especially in survivors, fever is present in patients with severe infection and sepsis, MTH is teleologically unattractive. Aslami and Juffermans adequately discuss the pros and cons of the use of MTH during critical illness. Inducing a hypometabolic state in order to inhibit the inflammatory response and preserve mitochondrial function is an appealing idea in view of the existing evidence. In this respect, hypothermia is the most attractive option. But, as in all therapies, the final outcome depends on the balance between favourable effects and negative side effects. The challenge is not only to investigate the effect of MTH, with or without H_2S, but also to investigate 'the dose' of MTH, as outlined above. That means that if MTH is ineffective if applied according to a specific protocol, e.g. starting MTH within two hours after diagnosing sepsis to 35°C for 48 hours with rewarming at a rate of 0.2°C/h, it will also be ineffective using another protocol, with other endpoints of temperature. Understanding of the mechanism will probably help to – finally – design the best possible studies. Until then, there is still a long way to Tipperary.

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