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Can we treat post cardiac arrest shock by removing cytokines from circulation with high cut-off veno-venous hemodialysis?

Editorial

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Circulatory failure with clinical features resembling septic shock, is a common complication in patients resuscitated after an out-of-hospital cardiac arrest (OHCA) ¹. A well-known feature in these critically ill patients, is an inflammatory response the magnitude of which is associated with organ failure, which appears to contribute to their long-term outcome ². Plasma levels of inflammatory biomarkers correlate with the severity of refractory shock and vasopressor requirements during post-resuscitation care, and appear associated with poor neurological outcomes ³⁻⁵.

A variety of treatment modalities have been tried in an attempt to modify the inflammatory response in the past. Targeted temperature management (TTM) is one such therapeutic intervention that is commonly applied in post cardiac arrest patients. However, despite of the proven effects of this treatment modality, the post-hoc analysis of the TTM trial, that compared a target temperature of 33°C versus 36°C showed no statistical difference in the inflammatory response between these two temperature goals ^{6,7}.

Another interesting treatment option is the use of corticosteroids. In patients with sepsis, the use of corticosteroids may not improve outcome, but does appear to shorten the time patients require vasopressor therapy ⁸. This is in contrast to patients with traumatic brain injury, where the use of corticosteroids worsens neurologic outcome. ⁹. In victims of cardiac arrest with return of spontaneous circulation, a small randomized, controlled pilot trial, showed that the use of corticosteroids

significantly reduced the levels of plasma IL-6, but failed to reduce the need for vasopressors⁴.

In this issue of *Resuscitation*, Geri and colleagues present the results of the elegant HYPERDIA trial, a small proof-of-concept study, aiming at using high cut-off veno-venous hemodialysis (HCO-CVVHD) in an attempt to remove pro-inflammatory cytokines and thereby, alleviating the need for vasopressors¹⁰. In sepsis, this method has been demonstrated to lower plasma cytokine concentrations and reduce vasopressors need¹¹. In the HYPERDIA trial, 35 patients were randomized to receive two sessions of HCO-CVVH with CVVH in between if needed during the first 48 hours in the interventional group CVVH as deemed necessary by the treating clinician in the control group. Despite the intuitive appeal of this hypothesis, the study did not show any difference in time to weaning vasopressors, or the levels over time of multiple important cytokines.

There are several possible explanations for these interesting findings. One thing that is difficult to control for, is the fact that any form of continuous renal replacement therapy in of by itself, may lower blood pressure and increase the need for vasopressors. Indeed, prolonged vasopressor need is not that common in OHCA patients. Moreover, the use of higher doses of vasopressors in order to improve blood pressure in OHCA patients, does not appear to be associated with harm¹².

It is important to note that the plasma levels of proinflammatory cytokines recorded by the authors were much lower, compared to those reported in septic shock patients and as the investigators point out, the low concentration gradient may have decreased the efficacy of the method^{11,13}. Furthermore, renal replacement treatment such as hemodialysis (HD) is not an immunologically neutral treatment. It can induce inflammation due to activation of complement and other immune mechanisms on the surface of the tubing systems and membranes of the HD-apparatus¹⁴. The possible beneficial impact of cytokine removal on the systemic inflammatory balance may be countered by the activation of other proinflammatory mechanisms.

What is more important is that even though the circulatory failure following cardiac arrest resembles septic shock, the underlying pathophysiology is largely different¹⁵. In sepsis, the cytokines are produced in response to invading microorganisms, whose antigens remain in the body for a long time, driving continuous systemic inflammation and adaptive immune response. In cardiac arrest, the cytokines reflect a non-specific inflammatory reaction to transient whole body ischaemia. It is possible that for an intervention like this to work, it would need to be started very early, and this is not possible in the clinical setting. Future research should explore in more detail the inflammatory mechanisms triggered in the tissues by whole body ischaemia, in order to identify potential targets for inhibiting the inflammatory response on the tissue level. A translational approach combining the expertise of researchers of basic immunology and clinical intensive care might prove worthy. We recognize that conducting randomized, controlled trials in post resuscitation care patients is very difficult. Even more so with a very advanced and labor-intensive intervention such as CVVH. The HYPERDIA investigators are to be congratulated for conducting this very important proof-of-concept study.

Conflict of interest:

Markus B Skrifvars has received speakers fees and travel reimbursement from BARD Medical.

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