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How to explain and exploit the beneficial effects of high-volume hemofiltration on hemodynamics and strong ion gap

Received: 23 December 2012

Accepted: 6 January 2013

Published online: 30 January 2013

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This editorial refers to the article available at:
doi:[10.1007/s00134-012-2800-0](https://doi.org/10.1007/s00134-012-2800-0).

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Early high-volume hemofiltration has been suggested as adjuvant treatment for critically ill patients with severe septic shock to stabilize the circulation [1]. Several non-randomized clinical and animal studies have shown a benefit [2]. The rationale for this treatment is that within the setting of an overwhelming inflammatory response, pro- and antiinflammatory mediators can be removed [3] and homeostasis restored [4]. Grootendorst et al. [5] had already found that substance removal by hemofiltration likely plays a role, because the infusion of ultrafiltrate from endotoxemic pigs depresses myocardial performance in normal pigs, while the infusion of ultrafiltrate from healthy pigs does not. However, a recent meta-analysis including randomized controlled trials and subgroups from randomized controlled trials was not able to show any benefit of continuous renal replacement therapy (CRRT) versus no CRRT or a higher dose of CRRT in patients with severe sepsis or septic shock in terms of survival, hemodynamics, pulmonary gas exchange, organ failure and length of stay [6]. The effect of CRRT on survival was not modified by CRRT dose. This was recently confirmed by a large randomized controlled trial [7].

Bellomo et al. [8] now specifically report on data from this trial from a nested cohort of 115 patients from two of the participating ICUs. Patients were treated with venovenous hemodiafiltration of either low intensity (with effluent flow at 25 ml/kg/h) or high intensity (at 40 ml/kg/h). They focused on the control of metabolic acidosis, mean arterial blood pressure and noradrenaline dose and their relationship during the first 24 h of treatment. They found that pH and traditional markers of the metabolic component of acid base balance, i.e. bicarbonate and base excess similarly improved in both groups. However, in the high-intensity arm, lactate and in particular the strong ion gap (SIG) decreased significantly, concomitantly with an increase in mean arterial blood pressure and a decreased noradrenaline dose. These improvements were not observed in the low-intensity arm.

These results may be of clinical importance. But how do we explain and more importantly how do we exploit them?

Substance removal and reversal of hypotension

High-intensity CRRT likely removes more inflammatory mediators than the low-intensity modality. However, the removal of cytokines is often not sufficient to decrease plasma concentrations [9]. The reasons may be the high size and low free fraction of the cytokines, and the higher rate of production compared to removal. In contrast, free-circulating mediators in the middle molecular range, such as complement factors [1], prostaglandins and leukotrienes [10], and myocardial depressant factors [11] are removed [12, 13].

In the present study, SIG significantly decreased in the high-intensity group, which was not the case in the low-intensity group. This may indicate that substance removal contributed to improved hemodynamics. In this setting, SIG likely represents unmeasured strong anions. They

accumulate in sepsis, renal failure and organ dysfunction, but their origin and chemical nature is only partially understood [14, 15]. Increased glycolysis, protein catabolism, mitochondrial dysfunction and decreased clearance likely contribute to their accumulation. Potential candidates include sulfate, urate, hydroxybutyrate, succinate, pyroglutamate, D-lactate and Krebs cycle intermediates, but also components of drugs, nutrients or synthetic colloids [15–18]. However, despite using elaborate techniques to determine the components of SIG, the majority of its determinants are not yet identified [15].

The decrease in SIG paralleled the decrease in L-lactate [8]. Lactate removal by CRRT corresponds to lactate concentration in plasma times milliliters filtrate per minute, and is only a fraction of lactate production, being about 14 mmol/kg/min [19]. Thus, the decrease in lactate more likely reflects improved circulation.

The decrease in SIG was much more pronounced in the high-intensity group. As we do not know normal levels of SIG ‘production’ in health and disease, we can only speculate on whether this decrease was caused by improved circulation or alternatively if it was contributing to improved hemodynamics, or at least its surrogate measurement mean arterial pressure. If so, this would be a possible therapeutic target. If not, the removal of ‘something else’ may have contributed to the improved homeostasis [13, 20].

Survival

Although high-intensity CRRT induced an earlier stabilization of the circulation, it was not associated with improved survival. This seems a controversial finding because early goal-directed treatment of the circulation can improve patient outcome [21]. Furthermore, early lactate clearance is significantly associated with decreased levels of biomarkers, improvement in organ dysfunction and outcome in severe sepsis and septic shock [22]. We can only speculate why. In addition to its positive effects, high-intensity CRRT may have negative effects as well. First, high-intensity CRRT removes more beneficial substances, counteracting the beneficial removal of harmful compounds. Beneficial substances include micronutrients such as water-soluble vitamins, trace elements, amino acids and circulating beneficial mediators of whatever kind [23, 24]. In particular, hypophosphatemia may play a role as its incidence was increased by high-intensity CRRT in the original trial from which the current nested cohort was taken [7]. A second issue deserving attention is that higher intensity CRRT requires a different antibiotic dosing schedule, and may therefore be associated with antibiotic under-dosing [25]. These possible harmful effects of high-intensity CRRT may explain why the favorable effects of early stabilization of the circulation do not translate into better survival.

Cooling and reversal of hypotension

This ‘something else’ could theoretically be heat. The authors mention that in all cases fluids were warmed to 37 °C or more. However, warming to 39 °C is required to prevent the loss of heat in high-intensity CRRT. Thus if levels of warming were similar in the low- and high-intensity modalities, heat loss would likely have been higher in the high-intensity arm. On the other hand, fever is ultimately mediated by prostaglandin E₂ (PGE₂), a 352-kDa protein which freely passes the filter membrane [10]. Interestingly, PGE₂ is not only the final mediator of fever but also causes hypotension. PGE₂ is a direct vasodilator and inhibits the release of noradrenaline from the nerve endings. Thus, a higher rate of removal of PGE₂ may have contributed to both cooling and a higher blood pressure in the high-intensity arm.

Conclusion

High-intensity hemofiltration seems to contribute to early stabilization of the circulation in critically ill patients with acute kidney injury. This effect might be due to increased removal of components of SIG, other unknown mediators or loss of heat. However, this early beneficial effect does not translate into improved survival. This may be because we insufficiently compensate for its possible associated harm, such as increased loss of beneficial substances and inadequate antibiotic dosing. Avoiding harm of CRRT should be a clinical priority, but in selected patients, high-volume CRRT should not be overlooked.

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