Commentary

Pro/con clinical debate: Is high-volume hemofiltration beneficial in the treatment of septic shock?

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Abstract

Although there have been exciting advances in the management of sepsis and septic shock, mortality still remains high. Recent data suggest that high-volume hemofiltration (HVHF) may play a role in these patients. In contrast to the usual rate of hemofiltration, HVHF is felt to be better able to remove the inflammatory mediators associated with sepsis and septic shock. Such an approach is currently incapable of selectively removing specific mediators. This may be a problem when one considers that several mediators may in fact be beneficial. When determining whether HVHF should be instituted in a patient with septic shock, one need remember that its role is far from clear and its usefulness remains the subject of much debate. Although early data is encouraging, it is clear that additional data is required before HVHF becomes standard management. The authors of this pro/con debate, which is based on a clinical scenario, first describe their own position and then respond to their opponent's position.

Keywords hemofiltration, sepsis, septic shock

The scenario

You have a 40-year-old male in your intensive care unit who has septic shock as a result of bacterial pneumonia. He is on moderate dose levophed to maintain a systolic pressure of 90 mmHg. Apart from respiratory and cardiovascular failure, he has not developed any other end-organ failure. You feel confident you are giving him the best supportive care possible; however, his septic shock still bothers you. You remember hearing once that HVHF may have a role in this type of patient to rid them of the mediators that cause septic shock and to possibly improve patient outcome, but you are unsure whether you should try it.

Pro: HVHF is beneficial

Karl Reiter, Rinaldo Bellomo and Claudio Ronco

The sepsis syndrome is associated with an overwhelming systemic overflow of pro-inflammatory and anti-inflammatory mediators, leading to generalized endothelial damage, multiple organ failure, and altered cellular immunological responsiveness.

The inflammatory network is exaggerated, synergistic, and acts like a cascade. It includes mediators with autocrine and paracrine actions, as well as cellular and intracellular components [1]. Some substances have a pronounced role in the cascade. For instance, there is tumor necrosis factor-α,

ARF = acute renal failure; CVVH = continuous venovenous hemofiltration; HVHF = high-volume hemofiltration; IL = interleukin; Q_{UF} = maximum ultrafiltration flow rate.

IL-1β and IL-6 proximally, and there is reactive oxygen species, nitric oxide, and nuclear factor-κB distally, to name but a few. Antagonizing a single mediator has not, however, reduced sepsis mortality in human trials [2].

Almost paralleling the surge of pro-inflammatory mediators, there is a rise in anti-inflammatory substances by which a state of immunoparalysis (i.e. 'monocyte hyporesponsiveness') can be induced [3]. As both the pro-inflammatory and anti-inflammatory sides become upregulated and interact together, any intervention favoring one side or the other is hazardous because, without 'on-line' measurements of the inflammatory status, the intervention appears to be blind.

Continuous hemofiltration has been used successfully for the treatment of acute renal failure (ARF) for years. Additional advantages advocated in the treatment of sepsis comprise a distinctly different concept, since a wider spectrum of substances is targeted for removal. Uremic toxins are targeted in ARF, whereas in sepsis pro-inflammatory and anti-inflammatory mediators are sought to be removed as well as uremic toxins.

Early animal studies delivered sound evidence that whatever is removed by continuous venovenous hemofiltration (CVVH) should be significant in terms of sepsis pathophysiology. This is because re-infusion of the ultrafiltrate produced high mortality in healthy animals with symptoms indistinguishable from sepsis [4,5].

Numerous *in vitro* studies as well as animal and human studies [6] have shown that synthetic filters used in hemofiltration can extract nearly every substance involved in sepsis to a certain degree. This occurs by convection and by adsorption to the filter membrane, a process that is saturable within a few hours. An augmentation can be reached by increasing the membrane surface and the rate of ultrafiltration, which probably extends the surface used for adsorption more distally into the membrane pores [7].

In most studies, the decrease in the plasma levels of the mediators is either absent or of a minor degree. Nevertheless, early clinical studies in septic patients demonstrated clinical improvement, albeit slight (for instance, in their norepinephrine requirements). Increasing the effectiveness of the treatment may be possible using either a higher ultrafiltration rate with the filters currently available and/or altering the chemicophysical properties of the membrane.

A randomized, controlled clinical trial in 425 critically ill patients with ARF showed that the ultrafiltration dose (rate per body weight) correlated significantly with survival [8]. With an ultrafiltration dose of 20 ml/kg/hour, the mortality was 59%. This compares with 43% mortality with a 35 ml/kg/hour dose and 42% mortality with a 45 ml/kg/hour dose. This amounts, on average, to ultrafiltration of more than 2 l/hour, which should be designated HVHF. In each randomized group in this trial, 11–14% of the patients had sepsis; and in this subgroup there was direct correlation between treatment dose and survival, even above 35 ml/kg/hour, in contrast to the whole group where a survival plateau was reached with that dose.

This observation lends support to the concept of a 'sepsis dose' of hemofiltration in septic patients, rather than a 'renal dose' in critically ill patients without systemic inflammation; the former probably being distinctly higher (without a proven upper limit) than the latter. In sepsis, ultrafiltration at the rate of 2 l/hour, even if applied very early, does not seem to be sufficient [9].

Further recent human studies tested 'sepsis doses' of ultrafiltration in the range 3.8–6 l/hour, demonstrating increased survival and decreased vasopressor requirements [10,11]. In a cohort of 20 patients with refractory circulatory shock, short-term HVHF (35 l/4 hour) lead to an impressive improvement in hemodynamic parameters and survival [12]. Patients with higher body weight showed less improvement, possibly because they received a smaller ultrafiltration dose per body weight.

Supporting evidence is provided by recent animal studies that demonstrate significant hemodynamic benefit [13–15], improvement in immune cell responsiveness [15], and reduced mortality [14,15] with HVHF of about 80–100 ml/kg/hour.

How far have we come with these new data?

We believe there is a sound basis to recommend an ultrafiltration dose of at least 30 ml/kg/hour in ARF in critically ill patients. In patients with sepsis there is accumulating evidence that hemofiltration, especially in the high ultrafiltration range above 2 or 3 l/hour, may confer benefit. This is in favor of the concept of removing as broad a range of mediators (pro-inflammatory and anti-inflammatory) as possible because there is clinical benefit, even if there are no measurable decreases in selected plasma cytokine levels. The probable theory behind this concept is that, with continuous blood purification treatment, unmeasured (and unknown) mediators (and probably existing but unmeasured peaks in the plasma concentrations of known mediators) are cut (the 'peak concentration hypothesis').

There are already encouraging results from refining the technique by including higher molecular weight molecules for removal. A new exciting avenue has been opened in plasma filtration/adsorption techniques: biocompatible high-gain adsorbing columns [16]. These enable more effective removal of mediators in the borderline zone of filtration by hemofilters (40–60 kDa).

Is it time for a trial?

Should we carry out a prospective, randomized, controlled trial of HVHF in sepsis with survival as the major endpoint? HVHF is still considered experimental. We do not know the optimal treatment dose. Problems inherent to the technique include a significant increase in the patient's need for re-infusion fluid and a lack of monitoring devices with adequate precision for the high volumes involved. Certainly, the risk of discrepancy between what is prescribed and what is delivered is increased, potentially leading to dosing errors. Furthermore, the metabolic consequences of HVHF, including intermediate metabolism, are far from clear. HVHF could conceivably exert important beneficial effects on metabolism in multi-organ dysfunction syndrome, but may encompass significant hazards. Nevertheless, it appears that a treatment schedule of HVHF over a few hours per day is safe and feasible.

HVHF has gained much supportive evidence as a treatment modality in sepsis syndrome. It has been safely performed even in the most unstable, critically ill patients with promising results. A prospective, controlled, randomized trial is justified to allow recommendations for clinical practice.

Con: HVHF is not beneficial

John A Kellum

In considering whether high-volume continuous renal replacement therapy is likely to be beneficial, one must first define 'high-volume' and then define 'benefit' in the context of this particular patient. The definition of high-volume continuous renal replacement therapy has not been standardized. Traditionally, CVVH has been limited by available technology to a maximum ultrafiltration flow rate (Q_{UF}) of 2 l/hour. Recently, Ronco *et al*. demonstrated improved survival in critically ill patients with ARF when treated with CVVH at 35 ml/kg/hour Q_{UF} compared with 20 ml/kg/hour Q_{UF}, but no further improvement was observed when Q_{UF} was increased to 45 ml/kg/hour [8]. The response from industry has been to modify existing technology to permit $Q_{UF} > 2$ l/hour and, thus, $Q_{UF} = 3–4$ l/hour can no longer be considered 'high-volume'. In 2000, the nomenclature workgroup of the Acute Dialysis Quality Initiative defined high-volume CVVH as $Q_{UF} > 35$ ml/kg/hour [17].

What sort of benefit might we expect to achieve using CVVH at $Q_{UF} > 35$ ml/kg/hour? We know at the outset that there is no evidence that increasing Q_{UF} beyond 35 ml/kg/hour improves survival in critically ill patients with ARF, including those with sepsis [8]. However, care of the critically ill is not only guided by evidence of effectiveness for achieving clinical endpoints [18]. Importantly, intensivists must also manipulate physiologic variables (such as blood pressure, arterial oxygen content, fluids and electrolytes) in the hope of supporting patients through their critical illness. Efficacy data from carefully controlled clinical studies can often guide this therapy. For example, although prone positioning does not appear to improve survival in patients with moderate to severe acute lung injury, it does improve arterial oxygenation [19]. In a patient with life-threatening hypoxemia, refractory to other therapies, prone positioning may be life-saving.

So what physiologic endpoints are we trying to manipulate with high-volume CVVH? There is no data to suggest that fluid, electrolyte, and acid–base control will be any better with higher Q_{UF} levels. Indeed, control of these variables is usually excellent with $Q_{UF} < 35$ ml/kg/hour. Although uremic toxins are removed with greater efficiency at higher Q_{UF} levels, there is no reason to believe that 35 ml/kg/hour will not achieve excellent control of uremic toxins.

However, the patient in the present scenario is also septic. Might high-volume CVVH remove more inflammatory mediators and help modulate the inflammatory response? Unfortunately, there is no direct evidence that increasing the Q_{UF} increases cytokine removal with CVVH. Indeed, the available evidence suggests that adsorption to the dialysis membrane, rather than convective clearance, is the primary mechanism responsible for cytokine removal [20]. Moreover, there is no evidence that cytokine removal will be beneficial in the first place. Sepsis induces a complex immune response that is at times pro-inflammatory and at other times anti-inflammatory [21,22]. While CVVH can affect circulating cytokine concentrations, there is currently insufficient knowledge whether this will help or harm this particular patient.

Finally, this patient is in shock. There is emerging evidence that high-volume CVVH can improve hemodynamics, both from animal studies [13] (improved blood pressure) and from clinical trials [10] (reduced vasopressor requirements). If this patient was in refractory shock with evidence of end-organ injury, high-volume CVVH might be tried as 'salvage therapy'. However, such therapy cannot be provided by conventional machines and should only be attempted by experienced personnel.

Pro's response to Con's arguments

Karl Reiter, Rinaldo Bellomo and Claudio Ronco

The concerns raised by Dr Kellum are legitimate. At present, we have level IB evidence that CVVH at 35 ml/kg/hour is beneficial in patients with ARF, and a suggestion that CVVH >45 ml/kg/hour might be particularly helpful if sepsis is also present (although this effect did not reach statistical significance) [8]. We also have level IIB evidence that CVVH >70 ml/kg/hour improves blood pressure in established septic shock [10].

Whether this information constitutes sufficient evidence to apply such high-volume therapies to selected patients with septic shock must remain a matter of judgment for each clinician. Whatever the decision, adequate competence and knowledge of blood purification technology and its principles remain mandatory before high-volume therapy is applied.

Con's response to Pro's arguments

John A Kellum

Dr Reiter, Dr Bellomo and Dr Ronco believe there is sufficient evidence that high-volume CVVH improves outcome in patients with sepsis. I do not agree.

In their study [8], there was not a direct correlation between treatment dose and survival in the small subgroup with sepsis. In fact, there was no correlation at all: 25%, 18% and 47% of patients with sepsis in the three dose categories survived ($P = 0.23$, Cox proportional hazards). The additional evidence cited to support their view comes from three studies. The first used a physiologic outcome (vasopressor requirement) [10], and the other two were uncontrolled (phase I equivalent) series [11,12] comparing observed mortality with predicted mortality. These studies provide important safety and feasibility data but do not establish effectiveness.

Both sides agree that a randomized trial is needed. I contend that, currently, a randomized trial is the only place that high-volume CVVH should be used.

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