Review Article

Hemodynamic improvement after continuous renal replacement therapies: Not only immunomodulation

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ABSTRACT

Hemodynamically unstable patients under continuous renal replacement therapies (CRRT) frequently show an improvement in hemodynamic parameters and a reduction in vasopressor agents. Different mechanisms have been proposed to explain this effect. A high rate of fluid exchange between interstitial and intravascular compartments seems to contribute to the therapeutic effect of CRRT. Other mechanism that seems to play a role is cooling; a raise in BP and SVR will follow a moderate heat loss but this effect will be accompanied by a decrement in oxygen delivery that can be detrimental and, when the cooling is severe, a shock can theoretically be precipitated. Metabolic acidosis, usually present when RRT is started, is a proinflammatory stimulus and conditions vasopressor unresponsiveness; the efficient control provided by CRRT can explain in part a positive hemodynamic response. Ionized calcium may have a role based on a potential effect on cardiac function and has been used in some studies in high concentration but there are limited *in vivo* data supporting this effect. The role of sodium concentration as a factor influencing hemodynamic tolerance has been reported for IHD but for CRRT has not been studied so far. Clearance of cytokines is the central key factor proposed as a mechanism for hemodynamic improvement but we have conflicting data regarding elimination. The volume of fluid exchange involved is a critical factor in order to reach an effective clearance but at this point we lack a proven theory for the way CCRT works. In this review we aim to explore possible mechanisms involved in the hemodynamic effect of CRRT on critically ill unstable patients.

Key words: continuous renal replacement therapies, hemodynamics, immunomodulation

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Access this article online

Website: www.intern-med.com

DOI: 10.4103/2224-4018.129498

Quick Response Code:

INTRODUCTION

Acute kidney injury (AKI) is a frequent complication in the intensive care unit requiring over 40% of the cases renal replacement therapies (RRT).[1] Intermittent hemodialysis (IHD) is a challenge because it induces hypotensive episodes and cardiac dysrhythmias[2] and splanchnic perfusion may be compromised during IHD because of hypovolemia, inflammatory response, and blood flow redistribution even in normotensive patients.[3] IHD can be used in unstable patients[4] but still there are reports of frequent hypotensive episodes with this modality.[5]

Since 1977 Kramer's[6] description of continuous renal replacement therapies (CRRT), it was clear that these therapies provided improvement in hemodynamic parameters while reducing need for vasopressor agents in shock.[7] Different factors have been referred as possible explanation apart from a hypothetical role in immunomodulation, like a slow exchange of fluids providing a better elimination of interstitial fluid and a subsequent improvement in perfusion; a raise in vascular resistance[8] secondary to a decreased temperature[9] or an efficient normalization of acid-base status. In this review we aim to explore the possible mechanisms involved in the hemodynamic effect of CRRT on critically ill unstable patients.

Fluids exchange

A slow withdrawal allows the interstitial fluid to replace the intravascular fluid (refilling) at the same rate that it is extracted.[10] This loss of plasmatic water can increase the return rate of interstitial albumin to plasma contributing to the therapeutic effect of depletive treatments[11] and can also ameliorate neuro-hormonal responses to water retention while maintaining hemodynamics,[12] looking as a promising approach for patients with chronic heart failure and fluid overload.[13] In 1987, Simpson *et al.*[14] used slow continuous ultrafiltration (SCUF) on 13 patients resistant to diuretic therapy and observed a positive response in 12, with a median withdrawal of 12 l/day. Later, Rimondini *et al.*[15] treated 11 patients reporting a positive response in all. In 2005, Bart *et al.*[16] reported a positive response in 90% of cases. More recently, Constanzo *et al.*[17] studied reported a positive effect on the clinical picture and in the number of hospital readmissions for patients managed with SCUF.

These positive results present themselves as an attractive argument for the use of SCUF in critically ill patient, when a balanced in-out take[18,19] of fluids can be critical. In continuous veno-venous hemofiltration (CVVHF), even when reducing the interstitial volume, intracellular fluid volume does not change markedly.[20] The problem arises when considering the effect of isovolemic CRRT not explained then by a net negative fluid balance.[21] A high fluid exchange could be playing a leading role as well because under conditions of constant mean arterial pressure and venous pressure, saline infusion has been shown to induce transport of albumin coupled to water flux in the same manner as it would have occurred as a result of increased venous pressure.[22] These transport results in an increase in lymphatic flow[23] that, as discussed later, can mobilize inflammatory mediators enhancing their elimination.[24]

Effect on temperature changes

According to Schneditz,[25] almost all RRT provide heat removal and several factors (dialysate and patient temperatures playing the main role) control this loss. During cold HDI, vascular resistance and venous tone, as well as arterial blood pressure, are significantly higher[8] and a moderate cooling can help in the improvement of tolerance in some patients.[9,26] But this potentially beneficial effect has been challenged for the acutely ill patient and come to that for the ESRD patient as well. Also, in CRRT, we must add other factors as the prolonged time under treatment and the high amount of convective fluid exchange involved. The final effect of temperature on hemodynamics and oxygen delivery is still controversial with some reports pointing to a positive impact by moderate cooling that may even hypothetically facilitate resuscitation.[27] But these findings have been challenged by other investigators suggesting that lowering fever may indeed be harmful by worsening the tissue perfusion.[28]

Even in IHD the role of cooling has been challenged and as early as 1983 Schaefer *et al.* showed in 10 chronic patients that heart rate, systolic blood pressure or mean arterial pressure remained unchanged by changes in body temperature.[29] A recent study found that actively controlled body temperature has no significant impact on the incidence of intradialysis hypotension in the ICU setting.[30] Differences on vascular reactivity in response to cooling are not completely elucidated and when some relationship between heating loss and hemodynamic stability should be expected,[31] while different clinical studies do not present this as an advantage.[8,32] Even more, the effects of CRRT-induced cooling on regional perfusion and energy metabolism in critically ill patients have not been well defined,[33] and few studies have systematically investigated the temperature changes during CRRT, so, thus far, the optimal temperature target remains unknown, particularly in the septic patients. Rogiers *et al.* induced peritonitis in 20 sheep and 4 hours later treated them by continuous hemofiltration (CVVHF) with (n = 10) or without (n = 10) blood warming, observing that the group without warming experienced an important decrease in temperature (below 36ºC) followed by a significant decrease in blood pressure and cardiac output and showed a higher metabolic acidosis and serum lactate levels. None of the animals without warming survived, while all the animals with warming survived to 16 hours.[34] In human studies, as early as 1994, Matamis *et al.* demonstrated how the hypothermic patients showed a reduction in oxygen delivery.[9] More recently, Rokita *et al.* investigated nine septic mechanically ventilated patients during CVVHF (30-35 mL/kg per hour) measuring hepatic venous hemoglobin oxygen saturation, gastric mucosal PCO_2, blood gases, lactate and pyruvate and performing hemodynamic monitoring with pulmonary arterial catheters, reporting that neither hepatosplanchnic oxygen nor energy balance were influenced but significant changes occurred in hemodynamics; even when arterial pressure raised a significant decrease in cardiac output and systemic oxygen delivery developed.[35]

We must always count on temperature losses during CRRT (probably deeper with convective therapies) that will induce a raise in the blood pressure and vascular resistance but also a decrement in oxygen delivery and when this cooling triggers overt hypothermia, theoretically, a state of shock could be precipitated. Until new data arrive, the safest approach would be always to aim for the isothermal treatments. Hypothermia was frequent in the past (43) and should be less significant nowadays because of automatized heat control systems and even now this complication can be found in a significant percentage of cases.

Effect on acid-base and ionic equilibrium

Metabolic acidosis is usually encountered in RRT patients when the procedure is started and this is a well known factor underlying vasopressor unresponsiveness[36] and precipitating organ dysfunction.[37] A rapid and efficient control of the acid-base status can explain in part the initial positive response seen when these therapies are initiated. As a fact, failure to correct metabolic acidosis has been recognized as a good predictor of mortality in septic patients under RRT.[38] The buffer added to the solutions used in RRT could have an important impact in the control of acid-base status. Initially, acetate was the preferred buffer but shows deleterious effect on cardiac function that precludes its use in the critically ill setting.[39] Lactate is still frequently used because of the higher stability and lower cost compared to bicarbonate but is thought to have negative effects on metabolic and hemodynamic parameters as well. Bohm *et al.* investigated the hemodynamic effects of lactate and bicarbonate substitution fluid and did not found any differences.[40] Thomas *et al.* compared in a randomized trial the hemodynamic changes during lactate- or bicarbonate-based hemofiltration and found that these variables were not significantly affected.[41] Barembrock *et al.* published in 2000 the only experience showing clear differences in hemodynamics between lactate- and bicarbonate-buffered fluids. In an open, randomized, multicenter study, they investigated 117 patients randomized to CVVH either with bicarbonate or lactate and found that 15% patients treated with bicarbonate and 38% treated with lactate developed hypotensive crisis but in their analysis the occurrence of negative events was related to previous cardiovascular history and the better outcome was evident for patients with cardiac failure but not with septic shock.[42] Some authors also pointed to the possibility of lactate accumulation that may result in depression of cardiac function[42,43] but this effect has not been definitively proven. Regarding acid-base control, most of the published reports showed that bicarbonate fluids can lead to a more rapid fall in lactate and greater improvement in base excess during CRRT, but not better overall control of acidosis.[40,41,44] Based on these data, we can no longer make a strong recommendation for any of these buffers and there are no studies addressing this aspect for the use of citrate.

Changes in some electrolytes, specifically ionized calcium, could theoretically affect hemodynamic response to CRRT and its inclusion in fluids for resuscitation has been based in a potential effect on cardiac function[45] but there are limited *in vivo* data supporting its use.[46,47] In CRRT inclusion of calcium and magnesium is mandatory to avoid a negative balance of these molecules but up to now the role of high concentrations of these ions has not been elucidated, even when has been tested in some studies.[48] Sodium concentration as a factor influencing hemodynamic tolerance has been reported for IHD[49] while in CRRT has not been studied so far.

Clearance of inflammatory mediators and immunomodulation

Severe sepsis is the leading cause of MOF in the ICU and one main cause for mortality.[10,18] Different studies have demonstrated that an adequate and early approach to it management can alter its course and improve the prognosis.[18] In this approach, we can consider some innovative measures capable to immune-modulate the response of the patient that can be different extracorporeal therapies.[50] Sepsis can be seen as a balance between inflammatory and anti-inflammatory mechanisms[51] based in the production of different molecules (cytokines) that initiate the inflammatory process. An exaggerate response has been proposed to lead to an exhaustion (immunoparalysis) that facilitates secondary nosocomial infections or virus reactivations.[52] The GenIMS study,[53] measuring IL-6 and IL-10, put in evidence how higher levels of cytokines are related to higher mortality. In this context, the use of an extracorporeal device aiming for the clearance of these molecules seems attractive, and as early as 1989, Barzilay *et al.* reported in a retrospective study about benefit on hemodynamics over a group of patients with MOF managed with arterial-venous hemodiafiltration (CAVHF).[7]

In 1991, Stein *et al.*[54,55] reported the use of Coli lipopolysaccharide (LPS) and the posterior use of CAVH in pigs with a dose of 600 mL/h for 6 hours finding that the treatment was able to improve hemodynamics independent of intravascular volume and the effect was attributed to clearance of small and medium sized molecules. Shortly after, Grootendorst *et al.*[56] developed a model of shock in pigs with the use of LPS and CAVHF at 6 L/h. An improvement on cardiac performance and blood pressure was evident during the second hour of treatment. The most relevant aspect of this paper was its role as a promoter of a high-volume hemofiltration (HVHF) pulse therapy developed more recently.[50] These some investigators showed later[57] that the ultrafiltrate obtained in septic animals when injected to healthy ones reproduced the picture. This effect on cardiac function was demonstrated once again by Mink *et al.* and the effect attributed to the removal of circulating substances with a molecular weight of less than 30,000 Da.[58] These results have been repeatedly proven in subsequent studies[59] that confirmed the elimination of different molecules.[60-64] Yekebas *et al.*[64-66] in a series of experiments based in a model of pancreatitis in pigs allocated subjects to different levels of intensity of hemofiltration plus adsorption and were able to demonstrate an improvement in serum cytokine levels, sepsis-related down-regulation of major histocompatibility

complex II and CD14 expression on leukocytes, bacterial translocation, and endotoxemia related to the increasing intensity of the treatment provided. In this way, a definitive immunomodulation capability was demonstrated (in an experimental setting) for the use of hemofiltration plus adsorption.

Of course, any animal model will be different to the septic process in humans and we cannot assume data obtained in experimental studies as necessarily representative of the real process in humans.[67] As a fact, there is still a debate ongoing on the exact role of CRRT in the clearance of cytokines in clinical studies and whether this clearance is dependent or not on the intensity of the therapy.[52] Clearance has been reported with convection[4,68-71] but with conflicting results in some publications[5,6] and negative results as well, ranging from not clearance at all[72] to elimination that lacks real impact in cytokines serum levels.[68,73,74] Adsorption on the other side removes a substantial amount of IL-6, IL-8, IL-10 and TNF-α, trapping as much as 25-43% of the cytokine load presented in the first hour of treatment.[73] In a detailed review published in 1999 by De Vriese *et al.*, the authors concluded that inflammatory mediators can be removed (by convection or membrane adsorption) but in most studies this removal was not enough to result in a significant and sustained effect on plasma concentrations.[75] In fact, cytokines clearance seems to be related to the dose administered[76] as some experimental[64] and clinical studies suggested.[77] In a study by Ghani *et al.* on 33 septic patients with septic shock randomized to receive 6 hours of CVVH at 32 mL/kg per hour or HVHF at 100 mL/kg per hour, serum IL-6 levels at baseline were similarly elevated in both groups while the HVHF group showed a significant reduction after 6 hours of treatment with no results found in the CVVH group.[78]

Considering these conflicting results, it is difficult to ascertain any positive effect to cytokines clearance alone. Different theories have been proposed to explain the role of CRRT on immunomodulation. The first proposed theory by Ronco *et al.* was known as the "peak concentration" hypothesis[79] and stated that depuration could interrupt the inflammatory cascade through nonspecific removal of mediators lowering their peak plasmatic concentration even when a significant effect on plasma concentration would not be evident. The problem with this hypothesis is that while removal of excess cytokines from the circulation might have some systemic effects, it is unlikely to have much impact at the local level. The second theory proposed by Honore *et al.*[80] is called the "threshold modulation" hypothesis. In this, depletion of a particular mediator in plasma by hemofiltration would result in its redistribution from tissue into the circulation, making more material available for filtration and subsequent interruption of the inflammatory cascade. The problem with this theory is again the local effect of cytokines. Finally, Di Carlo *et al.* proposed the "mediator delivery" hypothesis,[24] postulating that a high fluid exchange induces some degree of exchange through the interstitium, resulting in an active flow through the lymphatic system that could mobilize pro-inflammatory mediators and other plasma proteins that would then be cleared by the filter but also delivered to organs capable of their clearance as the reticular-endothelial system, the liver or the kidney. Following Di Carlo, a peak concentration reduction may be responsible for the initial systemic changes produced by RRT, but persistent inter-compartmental fluid flux is probably responsible for the clearance of cytokines in a more delayed stage.

Regarding clinical effect, data are suggestive of a positive hemodynamic effect of RRT. Honore *et al.*[50] in a study on 20 patients with severe septic shock evaluated HVHF as a rescue therapy and analyzed the effect over the cardiac index and the vasopressor dosage. They found a positive response in a high percentage of patients and showed how those patients that improved (responders) had mortality significantly lower than the expected. Cole *et al.*[77] found hemodynamic improvement as well as a significant reduction in serum levels of C3a, C5a and IL-10, results confirmed by other groups.[21,78,81-83] Finally, in an interesting study conducted by Cornejo *et al.,* the authors included pulse HVHF in the management of refractory septic shock finding a high percentage of responders. In an interesting review, Bouman *et al.* evaluated the effect of RRT on hemodynamic parameters and found that most of the HVHF studies performed in animals and patients reported beneficial hemodynamic[76] but when we took into consideration the quality of the studies involved, this improvement cannot be definitely proven for high volume modalities.

That cytokines clearance is not the only explanation for the beneficial effect of CRRT in sepsis is stressed by the fact that a beneficial hemodynamic effect is also achieved (less consistently) when using more conventional-dose treatments (low dose hemofiltration or hemodiafiltration)[84] or how adding diffusion to convection or applying diffusion alone improves outcome in our patients.[85] Of course, there can be other molecules implicated in this process, not necessarily of medium molecular size[86] that could hypothetically be cleared by diffusion. But it is also possible that this effect could be explained by the side-effects already discussed (temperature, fluid transfer, internal milieu changes…) and shared by convective and diffusive therapies. In a recent experimental study by Herrera-Gutierrez *et al.,*[87] a positive effect on hemodynamic with no cytokines elimination was found with the use of high dose diffusion. But the authors found that the clinical positive effect was higher and cytokines clearance effective when a convective

technique was employed.[87] These authors concluded that, when prescribing an extracorporeal depuration in the early stages of severe sepsis, convective/adsorptive therapies would be given preference to isolated diffusion. Following Clark *et al.*,[88] future studies should focus on alternative extracorporeal therapies as adsorption as adjuvant therapies for septic shock.[89,90]

CONCLUSION

The influence of a high exchange of fluid between the interstitial and intravascular compartments beside an intrinsic capability of high dose CRRT to clear cytokines is an attractive theory that rests on sound experimental studies. Results of clinical studies are more conflicting and when taking into consideration the quality of the evidence involved, a sustained improvement in hemodynamic profile cannot be definitely proven for high volume CRRT. So, until more evidence is at our disposal, use of CRRT aiming to modulate the septic process must be considered an experimental procedure. In this scenario convective/adsorptive therapies would be given preference to isolated diffusion but alternative therapies as molecule-specific adsorption may bring more positive results.

A positive effect on hemodynamic stability can be in part related to the high interchange of fluid between interstitial and intravascular compartments but the main effect of this mechanism maybe rests in the possibility to reach a high negative balance with excellent tolerance even in unstable critically ill patients.

A mild hypothermia can raise blood pressure but this effect must not be necessarily positive because the fall in organs perfusion that follows and (when hypothermia ensues) even could precipitate shock.

Ionized calcium may have a role because a potential effect on cardiac function and has been used in some studies in high concentration in CRRT solutions but at this point there are limited *in vivo* data supporting this effect.

The role of sodium concentration as a factor influencing hemodynamic tolerance has been reported for IHD but for CRRT has not been studied so far.

Metabolic acidosis, usually present when RRT is started, is a proinflammatory stimulus and conditions vasopressor unresponsiveness; the efficient control provided by CRRT can explain in part a positive hemodynamic response.

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How to cite this article: Herrera-Gutiérrez ME, Seller-Pérez G, Arias-Verdu D, Delgado-Amaya M. Hemodynamic improvement after continuous renal replacement therapies: Not only immunomodulation. J Transl Intern Med 2014;2:11-7.
Source of Support: Nil, **Conflict of Interest:** None declared