High-flow Hemofiltration as an Adjunctive Therapy in Sepsis

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Introduction

Almost ten years ago, standard hemofiltration was often provided at 1 or 2 l/h of ultrafiltration and only in pre-dilution mode. However, practice began to change as results from new studies were published in the early 2000s demonstrating a beneficial effect on outcome of increasing the ultrafiltration rate to 35 ml/kg/h in patients with acute kidney injury (AKI). Two methods of high volume hemofiltration (HVHF), with different underlying concepts and results, became prevalent: Continuous high volume hemofiltration (CHVH) providing 50 to 70 ml/kg/h 24 hours a day, and intermittent high volume hemofiltration (IHVH) with brief, very high volume treatment at 100 to 120 ml/kg/h for 4 to 8 hours (previously called 'pulse' HVHF). Two recently published studies [1, 2] highlight the crucial role of adequate dosage of continuous venovenous hemofiltration (CVVH), demonstrating that, in critically ill patients with renal failure, a dose of 35 ml/kg/hour was associated with dramatic improvement in survival of nearly 20 %. The incorporation of the results from these studies into daily clinical practice can now be deemed to be urgent, although the results of other ongoing confirmatory (or not) studies are awaited. In a world increasingly guided by evidence based medicine, two level I studies lead to a Grade A recommendation, and this intervention should, therefore, be applied by every intensivist instigating continuous hemofiltration, while awaiting the results of the ongoing studies. Nevertheless, the implementation process is exposed to a number of potential difficulties. These encompass items such as blood flow requirements, vascular access problems, pre-and post-dilution policy, type of membranes used, as well as restitution fluid and the possible need for associated dialysis. Implementation of these findings will necessitate a collaborative network between medical staff members and the entire nursing staff.

Mechanism of Action: Hemofiltration as a New Shield against the 'Chaos Theory' and 'Complex Non-linear Systems' in Sepsis

Hemofiltration was first used in AKI, which is an independent factor for increased severity of illness and poor outcome in critically ill patients. Early studies had shown that the mortality rate of patients requiring renal replacement therapy (RRT) for AKI in the ICU was nearly twice as high compared to those without AKI (62.8 vs 38.5 %) [3, 4]. This suggests, therefore, that AKI is independently responsible for increased mortality, even if RRT is used. In fact, while standard RRT significantly reduced mortality in patients with AKI in comparison with mortality rates before

RRT was used, mortality rates were still not as low as in patients without AKI. The new concept of 'purification plasma challenge' was then developed to try to decrease mortality. Systemic inflammatory response syndrome (SIRS), sepsis and septic shock, and acute pancreatitis are known to be the leading causes of AKI in ICU patients, creating an immunologic disturbance with a cytokine storm. Sepsis and inflammatory pathologies disrupt homeostasis with a cellular and humoral response, generating secretion of cytokines such as interleukins and tumor necrosis factor (TNF)-α. Over the years, many attempts have been made to block some parts of the inflammatory cascade or to destroy specific components; some positive results were obtained in animal models but were not translated into clinical benefit [5]. It has been suggested that a large and non-specific reduction in cytokines in the blood compartment could in theory reduce mortality more than simply concentrating on removing or blocking one specific element [6]. However, this approach is complicated by the fact that neither the pharmacodynamics nor the pharmacokinetics of cytokines and other immune components are well known, not even their precise functions. Some of the leading theories in this field are provided by current experts in hemofiltration. First, the 'peak concentration hypothesis' of Ronco and Bellomo postulates that removing the peak cytokine concentration from the blood circulation during the early phase of sepsis could stop the inflammatory cascade and the accumulation of free cytokines, which are the leading cause of organ damage and homeostasis disruption [7, 8].

The second concept is called the 'threshold immunomodulation hypothesis', also called the 'Honore' concept [9, 10]. In this concept, the removal of cytokines does not only affect the cytokine concentration in the blood stream but also in the tissues. Indeed, when cytokine concentrations are reduced in the blood, blood and tissue concentrations may equilibrate to remove the immune components trapped in the organs. This could explain why no crucial reduction in cytokine concentration is observed in the blood stream during hemofiltration, because cytokines from the organs permanently replace those lost in the blood. The third theory, which has been proposed by Di Carlo, sheds new light on the mediator delivery hypothesis, in which the use of HVHF with a high volume of crystalloid fluids (3 to 5 l/hour) is able to increase the lymphatic flow by 20 to 40 fold [11, 12]. Indeed, this increase is correlated with the infusion of a high dose of fluids. Since cytokines and other immune components are transported by the lymphatic stream, this could explain their removal even though large amounts of cytokines were not found in ultrafiltration fluid [13]. Thus, the use of high volumes of exchange fluid might be the principal motor of cytokine removal.

To achieve a wider view of these theories, we need to explore the new paradigm of chaos and 'complex non-linear systems' in sepsis and SIRS [14]. The principal goal underlying these theories is not only removal of cytokines but also immunomodulation and control of the inflammatory response, which becomes deleterious when it surpasses its designed purpose. Indeed, the immune response of the host against septic aggression could be compared to a complex non-linear system which is defined by the infinite number of possible actions in response to a lone stimulus. In a complex non-linear system, e.g., the situation by which a flight of butterflies in China can change the weather in Boston three days later, a bacterial attack or cytokine secretion will have repercussions in the whole body. This explains why homeostasis is not a state of stability *per se* but rather the ability to stay stable while the status is permanently changing. Yet this incredible adaptability is halted when the system is drowned by an excess of information and when the 'endocrine effect' of

cytokines and other immune messages are lost in the storm [15, 16]. The resources of the body system become depleted, and the complex non-linear system becomes a linear system, with only one course of action. This heralds the onset of multiple organ dysfunction syndrome. It may be that hemofiltration could play a role at this point by decreasing the cytokine storm and by allowing the efficacy of the immune messages to be recovered. Thus, the system's own resources increase, allowing a return of the complex non-linear system and homeostasis

Recent Animal Trials and Clinical studies Highlighting the Crucial Roles of Dosing and Timing

Studies have shown benefits in terms of survival when 'early' and 'large' hemofiltration doses were applied in septic animals. Early use of hemofiltration has been thoroughly investigated in animal models [17, 18]. In most of the earlier studies, hemofiltration was used before or just after the injection of a bolus or even before the infusion of endotoxin. It was only in the late 1990s that investigators started to wait about 6 to 12 hours before using HVHF after a sepsis challenge, thereby 'allowing' the animals to become extremely ill, hemodynamically unstable, and to develop early multiple organ dysfunction before starting hemofiltration [19]. In this way, animal models were able to 'mimick' some aspects of the clinical situation. Only animal models in which HVHF was applied early proved to be very beneficial (some spectacularly), mainly due to the fact that in addition to early application, the investigators administered a much 'stronger' dose of HVHF. However, the differences between human and animal models do not allow these results to be extrapolated to humans. One of the greatest remaining problems with human studies (and especially the mechanistic studies) is the fact that the number of patients is very limited since the technique is so expensive. Moreover, clinical studies have fallen far short of the mean exchange obtained in animal models (only 40 ml/kg/h versus 100 ml/kg/h in animal studies) [20]. As a consequence, many effects seen in animal models can never be reproduced in human settings owing to the use of inadequate doses of HVHF. On the other hand, there is huge variability between clinical trials concerning the range of doses applied, ranging from 1 to 15 fold in the recent studies [20]. The foundations of the high volume technique were laid by Ronco and co-workers who showed that in their subgroup of sepsis patients, increasing the volume of treatment from 35 to 45 ml/kg/h could improve outcome [1]. That study effectively demonstrated that hemofiltration could be considered as a viable medication in the ICU. The volume of treatment not only has to be adapted to body weight but also to the severity of illness of ICU patients. If non-septic acute renal failure is being treated, then a lower dose may be optimal; however, a septic patient with AKI may need a higher dose close to 50 or 70 ml/kg/hour and perhaps even higher or with different modalities for catecholamine-resistant septic shock, refractory hypodynamic septic shock, or even acute severe pancreatitis. At the end of the 1990s, Journois et al. used HVHF (100 ml/kg/h) in 20 children during cardiac surgery and reported a reduction in postoperative blood loss, earlier extubation time, and reduced cytokine plasma levels [21]. The first large study using pulse HVHF, at about 100 ml/kg/hour for 4 consecutive hours (then 35 ml/kg/hour), was in 20 septic patients with refractory hypodynamic shock [22–24]. In this study, pulse HVHF-treated patients had a dramatically increased survival compared with classical treatment. The observed mortality (55 %) was significantly lower than that predicted by

two severity scores (79 %). However, some patients were hemodynamic non-responders (9/20) with disastrous mortality rates. At the same time, a monocenter study by Oudemans Van Straaten and colleagues, with a prospective cohort design of mainly cardiac surgery patients with oliguria (306 patients), showed an observed mortality that was statistically lower in the group treated by intermittent HVHF with a mean volume of 3.8 l/h (nearly 50 ml/kg/h for a 70 kg patient) than the predicted mortality evaluated by three validated severity scores [25].

Studies in the early twentieth century concentrated on effects on hemodynamic response and cytokine removal; for example, Cole et al. showed interesting hemodynamic improvement in septic patients treated by HVHF [26]. Recently, a South American team headed by Cornejo did a study similar to that by Honoré et al. [22] and obtained comparable results [27]. They created an algorithm based on the international recommendations for sepsis treatment and incorporated intermittent HVHF (100 ml/kg/h for a single 12 hour period) as a salvage therapy for patients in refractory septic shock [27]. However, as in the study by Honoré et al. [22], although the observed mortality (40 %) was lower than the expected one (60 %), there was also a responder and a non-responder group. In contrast, Joannes-Boyau and colleagues studied the effect of HVHF at 50 ml/kg/h maintained for 96 hours in patients with septic shock with multiple organ dysfunction syndrome [28], and found that, although results in terms of mortality were comparable to those in previous studies (45 % observed vs 70 % predicted), all the patients were hemodynamic responders. A retrospective study by Piccinni et al. recently reported the same results with HVHF maintained at 45 ml/kg/h in 40 septic patients, in comparison with a historical group who were treated by standard CVVH [29]. Finally, a prospective study by Ratanarat et al. confirmed the earlier results of Honoré [22] and Cornejo [27], with a similar protocol of pulse HVHF (85 ml/kg/h for 6–8 hours) in 15 septic patients with multiple organ dysfunction syndrome [30]. All these studies were only single center, non-randomized and uncontrolled, but they all showed the same results and proved that HVHF can be delivered safely. The sole difference in results among the studies is in the occurrence of hemodynamic responders and non-responders in studies using intermittent hemofiltration which was not reported in studies using the continuous method.

A single study comparing HVHF with standard CVVH was conducted by Bouman et al.; 106 patients were randomized into three groups – early HVHF (within the first 12 hours of AKI), early standard CVVH, and late standard CVVH [31]. There were no differences in terms of 28-day mortality or recovery of renal function, but no statistical conclusions could be drawn owing to the lack of power, with only 35 patients in each group. Indeed, the very specific patient population, most coming from cardiac surgery, perhaps explains the low mortality rate, making the possibility of finding any statistical differences among the groups even more remote. Several studies, in particular in Asia, have also explored the effects of HVHF in severe acute pancreatitis. Wang et al. in animals [32] and humans [33] and Jiang et al. in humans [34] demonstrated the clinical benefit of HVHF in this context. They studied the effects of HVHF alone, or in comparison with standard CVVH, on mortality and organ function recovery and showed a clear benefit in using high volumes with early initiation.

While all these studies were promising, it is now time for larger studies and randomized controlled trials. The results from one such study, the so-called VA/NIH study were published in 2008 [35]. This was a very large and well conducted randomized study comparing two different doses of CRRT (20 vs 35 ml/kg/h) and two

different intensities of intermittent RRT depending on the hemodynamic status of the patient; nevertheless several criticisms have been made [36, 37], including regarding the supposed 35 ml/kg dose of CVVH in the intensive treated group which was split into 18 ml/kg/h of dialysis (1500 ml/h) and 17 ml/kg/h of convection rate, giving an actual dose of roughly 15 ml/kg/h (when taking into account the pre-dilution modality instead of full post-dilution). Additionally, the patients were enrolled in the study after being a mean of roughly 7 days in the ICU and roughly 10 days in the hospital which represents a considerably longer delay in treatment than used in any other study. Of note also, more than 65 % of the patients received either intermittent hemodialysis or sustained low efficiency dialysis (SLED) treatment within 24 hours prior to the randomization. Needless to say, the results of the ANZICS clinical trials group renal study (clinicaltrials.gov number NCT00221013) comparing augmented with normal RRT in severe acute renal failure are eagerly awaited.

A recent animal study has also highlighted the direct action of hemofiltration on the cellular mitochondria of the septic myocardium [38]. Indeed, this study was able to demonstrate that hemofiltration could reverse the negative effects of sepsis on myocardial mitochondrial respiratory chain complex activity in porcine septic shock [38]. This study could be seen as the missing link between the hemodynamic effects of HVHF and its effects on outcome.

Practical Aspects for the Bedside Clinician

New treatment volumes imply changes in hemofiltration practice so as to guarantee the efficacy and safety of the technique. Indeed, to reach 60 or 100 ml/kg/h of treatment volume, important principles need to be respected. First, a high blood flow is necessary to maintain a filtration fraction below 25 %, a level above which 'protein cake' clogging in the membrane becomes a major concern. In our practice, in order to attain an exchange flow of 35 ml/kg/h even in very heavy patients (up to 120 kg), we have, for nearly 8 years, used a constant high blood flow of 300 ml/min which allows the clinician to run a hemofiltration device at 35 ml/kg/h with a filtration fraction below 25 % even in patients with a body weight of 120 kg as long as the blood flow is equal to 300 ml/min (**Table 1**). However, to attain such a blood flow, excellent vascular access is required, with a large catheter (13.5 or 14 French), using an adequate location (right jugular is the best followed by femoral approach, while the subclavian route should not to be used) [39] and good structure (coaxial with 360° arterial intake). Second, the best restitution fluid is probably buffered bicarbonate and should be administered 1/3 in pre-dilution and 2/3 in post-dilution, i.e., the best compromise between loss of treatment efficacy and optimization of blood rheology [40]; in patients with citrate anticoagulation, the proportions of pre-and post-dilution might be different [41]. The choice of membrane is also primordial and a highly biocompatible synthetic filter with a high exchange surface is recommended (1.7 to 2.1 m^2). Temperature control is not important with low fluid exchange volumes but becomes essential when the volume increases dramatically. Two systems are possible for temperature control: Heating the fluid before restitution or heating the blood directly. Empirically heating the replacement fluid seems preferable to heating the blood, owing to possible deleterious effects of high temperatures on the blood. However, to date no problems have been recorded and the two systems have demonstrated their safety and efficacy. The new machines specifically dedicated to high volumes have extremely sensitive and precise pressure control and volume bal-

Table 1. How to reach an exchange flow of 35 ml/kg/h with a fixed blood flow of 300 ml/min

Weight/kg	Therapeutic dose 35 ml/kg/h	Pre-Dilution 1/3 therapeutic dose	Post-Dilution 2/3 therapeutic dose	
50	1800	600	1200	
55	1900	600	1300	
60	2100	700	1400	
65	2300	800	1500	FF.13 %
70	2400	800	1600	
75	2600	900	1700	
80	2700	900	1800	
85	3000	1000	2000	
90	3200	1100	2100	FF.17 %
95	3300	1100	2200	
100	3500	1200	2300	
105	3700	1200	2500	
110	3900	1300	2600	
115	4000	1300	2700	
120	4200	1400	2800	FF.23 %

FF: filtration fraction

ance functions. Furthermore, it is important to stay in the normal pressure range for optimal use of high flow hemofiltration. Indeed, staying below -120 mmHg of arterial pressure is indicative of a catheter problem and likely early machine failure. The same is true with a venous line, where high pressure indicates catheter or bubble trap clotting. The transmembrane pressure reflects the state of clogging in the filter while a high pressure indicates that many fibers are clogged. To alleviate the pressure problem, it is recommended that treatment is stopped when the patient is being nursed or moved, especially with high volumes. HVHF also requires adequate management and control of fluid exchange and small solutes. In fact, small molecules are largely removed during hemofiltration and strict monitoring of sodium, glucose, and acid-base balance is mandatory. Detection of infection during hemofiltration may be difficult as this technique can blunt hyperthermia but recent studies have showed interesting new tools for early detection of infection in these conditions [42]. Adaptation of antimicrobials during HVHF is also crucial in order to avoid underdosing [43]. Finally, on-line techniques may be crucial in the future [44]. Widespread application of fluid substitution in hemofiltration at 35 ml/kg/h remains surprisingly lacking; despite the evidence, recent unpublished surveys have shown that less than 50 % of units are applying this scientifically sound regimen.

Future Directions Regarding the Use of Hemofiltration in Sepsis

In terms of recommendations for clinical practice, patients with septic AKI should receive a renal replacement dose of at least 35 ml/kg/hour (level II evidence and grade C recommendation) [45] and probably a higher dose if they have septic shock. As discussed earlier, the VA/NIH study did not have enough power to change this recommendation in view of its shortcomings [36, 37]. Catecholamine-resistant septic

shock, either hypo- or hyperdynamic, could be seen as an indication for HVHF (level V evidence and grade E recommendation) for clinicians experienced in HVHF therapies [23, 24, 45]. However, HVHF should be integrated into practice algorithms for use as a salvage therapy in ICUs as no other treatment has proved its efficacy in these patients with a very high risk of mortality [27]. HVHF should be reserved for patients with AKI; although the benefit of early treatment has been shown, initiating RRT before renal injury is not yet recommended. In fact, the best time to start hemofiltration may be the renal injury state (creatinine × 2 from baseline or oliguria < 0.5 ml/kg over the preceding 12 hours) from the RIFLE (Risk, Injury, Failure, Loss, and End-stage Kidney) classification which could represent the best compromise between early initiation and renal impairment [46]. To evaluate HVHF, more, larger prospective randomized studies are needed which must respect certain conditions. First, the safest technique must be used, but this requirement is the easiest to meet as new hemofiltration machines are much safer and more efficient. Second, we need to define the exact time to start hemofiltration in relation to the start of sepsis and AKI. The best policy is to use a common classification for AKI, such as RIFLE, and to start in the first 24 hours following the onset of sepsis. Third, it is of primordial importance to define the volume of treatment according to body size in ml/kg/h. Finally, we should develop a greater understanding of the mechanisms of sepsis and SIRS in order to identify the targets for HVHF. In future trials, it would be interesting to detect any potential interference or possible synergy between HVHF and drotrecogin alfa (activated), for example. The best design for the use of hemofiltration still remains to be defined and the sequences and the duration of high volume 'rushes' need to be established [47]. Although prolonged HVHF seems more able to stop the initial inflammatory storm and late immunoparalysis, the efficiency and practicability of pulse high volume should be explored. While several large randomized trials are currently in progress investigating hemofiltration doses in AKI patients, only one is comparing HVHF with standard CVVH (The IVOIRE (hIgh VOlume in Intensive Care) study, clinicaltrials.gov ID NCT00241228). This study will try to expand the findings of the initial study by Ronco and colleagues [1] to septic patients. Indeed, this large randomized study will include patients with septic shock plus AKI, as defined by the RIFLE classification. After computerized randomization, patients will receive HVHF at either 35 or 70 ml/kg/h. This study will try to demonstrate that 'higher' doses (i.e., 70 ml/kg/hour) will further improve the survival rate from septic AKI in ICU patients at 28, 60, and 90 days. The first interim analysis will be performed when 150 patients have been included and this is expected to happen sometime in 2009.

Conclusion

The use of hemofiltration has steadily increased in the last decade, from a simple treatment for AKI to adjunctive therapy for sepsis or other acute episodes of SIRS, such as acute pancreatitis. The story is continuing to evolve and we can be sure that with the development of further technology and better understanding of the pathology, hemofiltration doses and the efficacy of the machines will be better defined. For the moment, 35 ml/kg/h should be the standard hemofiltration dose in ICUs for all patients with AKI, while in some situations, like sepsis, the dose should be increased as a salvage therapy in view of the high mortality rates in these patients. However, more trials are needed before HVHF can be recommended as routine treatment in

ICUs, in order to determine the best scheme of use and to obtain some form of consensus. In recent years, a number of techniques have been studied and developed in the field of RRT in the septic patient. Manipulation of ultrafiltrate dose, membrane porosity, mode of clearance, and combinations of techniques have yielded promising findings. However, at present, conclusive evidence based on well designed, randomized controlled trials remains scarce, limiting the practical implementation of many techniques in daily practice outside the context of a study. From the few well designed and documented studies that we have so far, it is safe to say that optimalization of delivered dose in RRT has a proven positive effect. An ultrafiltration rate between 35 and 45 ml/kg/h, with adjustment for predilution and down time, can be recommended for the septic patient until other data are available. The results of further dose outcome studies with higher ultrafiltration rates will likely be the stepping stone to further improvements in daily clinical practice. Hybrid techniques will also likely have a role in the expanding field of RRT in the septic patient in the near future [48, 49].

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