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High-volume Hemofiltration in the Intensive Care Unit

A Blood Purification Therapy

Thomas Rimmelé, M.D., Ph.D.,* John A. Kellum, M.D., F.A.C.P., F.C.C.M.†

ABSTRACT

High-volume hemofiltration is an extracorporeal therapy that has been available in the intensive care unit for more than 10 yr. Recent improvements in technology have made its clinical application easier and safer. However, the definition, indications, and management of this technique are still unclear, and considerable controversy and confusion remain. The aim of this review is to analyze the available data while taking into account the distinction between two very different clinical situations: acute kidney injury requiring renal support, and severe inflammatory states where blood purification has been suggested as an adjuvant therapy. For patients with acute kidney injury requiring renal replacement therapy, the two largest multicenter studies performed to date established that high ultrafiltration flow rates are not necessary. Conversely, much experimental and some clinical evidence suggest that high-volume hemofiltration can be beneficial for the subset of critically ill patients with severe inflammatory states such as septic shock.

* Assistant Professor of Anesthesiology and Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Edouard Herriot Hospital, Hospices Civils de Lyon, University Claude Bernard Lyon1, Lyon, France. † Professor of Critical Care Medicine, the CRISMA (Clinical Research, Investigation, and Systems Modeling of Acute Illness) Center, Department of Critical Care Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania.

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Address correspondence to Dr. Rimmelé: Department of Anesthesiology and Critical Care Medicine, Edouard Herriot Hospital, Hospices Civils de Lyon, Place d'Arsonval, 69003 Lyon, France. th.rimmele@gmail.com. Anesthesiology 2012; 116:1377–87

FOUR to 6% of critically ill patients undergo renal replacement therapy (RRT) because of acute kidney injury (AKI).[1,2] Although the mortality rate for these patients can reach 60%,[1] many aspects of the prescription of RRT and related management are still not well defined. Modality, timing of initiation, duration, anticoagulation strategy, and modifications in drug prescription remain controversial. Recent trials have helped to clarify RRT dosing for AKI,[3,4] but concerns remain that some patients will not receive adequate intensity.[5] Therefore, treatment of patients with AKI is very "practitioner-dependent" and thus highly heterogeneous, both nationally and internationally.[6–8]

Intermittent hemodialysis was the main RRT modality until the end of the 1970s, when continuous RRT was introduced. The solute transport principle on which hemodialysis is based is named diffusion, corresponding to a passive transfer of solutes through a semipermeable membrane, from blood to a dialysate along each solute's concentration gradient. Solvent (plasma water) is not concerned with this phenomenon. The solute transport principle of hemofiltration is called convection, meaning that both plasma water and solutes are carried across the membrane by a hydrostatic pressure gradient. Plasma volume is then replaced by sterile electrolyte solutions, which are infused intravenously. Replacement fluid may be given before the hemofilter (predilution), after the hemofilter (postdilution), or a combination of both. This plasma water crossing the membrane is called ultrafiltrate, and it contains all the molecules from the plasma able to cross the membrane (molecular weight below the membrane cutoff). Figure 1 shows an illustration of what diffusion and convection are, along with a diagram of a hemodialysis circuit and a hemofiltration circuit. In 2012, although it has never been proven that continuous RRT provides better outcomes as compared with intermittent RRT,[9,10] it is safe to say that continuous veno-venous hemofiltration (CVVH) has become the therapy of choice for critically ill patients requiring RRT, especially for those with hemodynamic instability.[3,4,11] The recent large, prospective, European multicenter and observational DO-

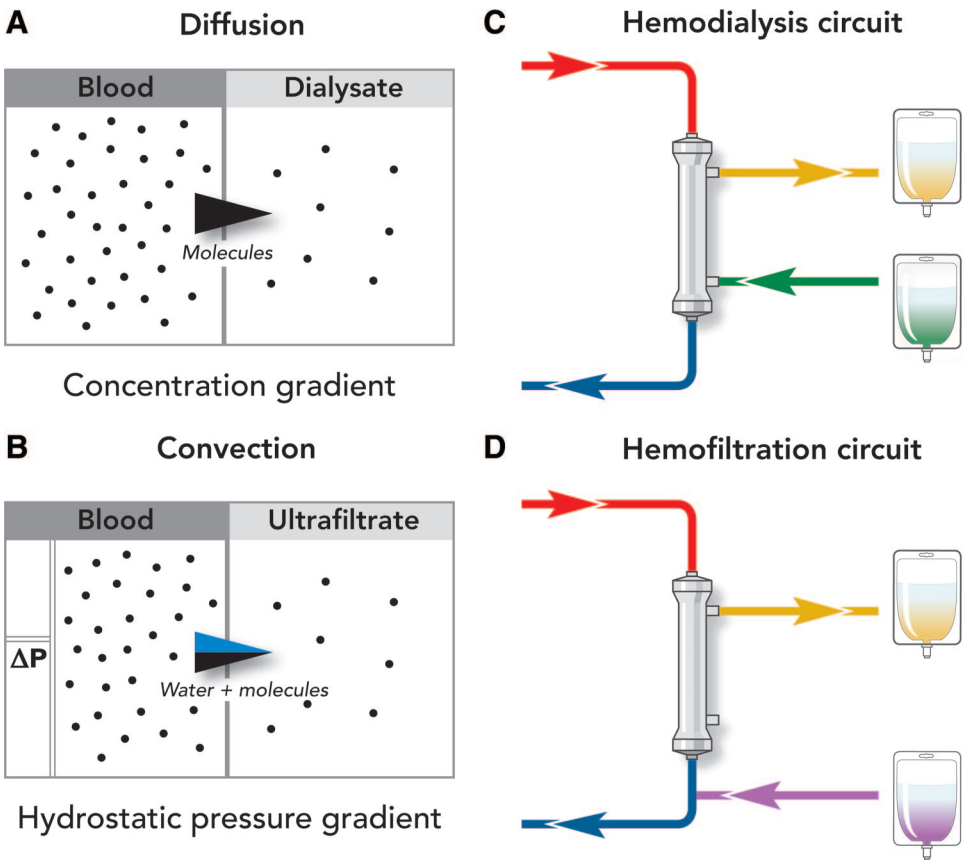

Fig. 1. Diffusion (*A*) and convection (*B*) solute transport principles. Hemodialysis (*C*) and hemofiltration (*D*) extracorporeal circuits. For the hemodialysis circuit, the *green bag* represents the dialysate and the *yellow bag* the used dialysate. For the hemofiltration circuit, the *yellow bag* represents the ultrafiltrate and the *purple bag* the postdilution replacement fluid.

RE-MI study reported that among patients treated with only one RRT modality (either continuous only or intermittent only), 82% received continuous RRT.[12] This percentage tends to be similar in the United States and in Australia, and it does not seem that the type of intensive care unit (closed *vs.* open) plays a major role in the choice of the RRT modality.[6,13]

However, there is less consensus as to the application of high-volume hemofiltration (HVHF). This can easily be explained by the lack of clear evidence to guide application of HVHF during the last 20 yr. Thus, the aim of this review is to help clarify the situation by analyzing the available studies, taking into account the distinction between two very different clinical situations: AKI requiring renal support and severe inflammatory status requiring blood purification, and to examine whether HVHF might be useful in these situations. To achieve this goal, we conducted a systematic review of the COCHRANE and MEDLINE databases using PubMed with the following search terms: high-volume hemofiltration, acute kidney injury, blood purification, renal replacement therapy, and septic shock. The search included experimental and clinical studies, and we separated renal support for AKI from blood purification for systemic inflammation.

Definition of High-volume Hemofiltration

HVHF is not well defined in medical literature. Terms such as "high-volume," "high intensity," or "high flow" are used in publications for a large range of ultrafiltration flow rates, including some that by contemporary standards are not "high." Additional confusion stems from the fact that the same given ultrafiltration flow rate can be evaluated both in the "high-volume" arm of one study and in the "low-volume" arm of another one. For example, in the Acute Renal Failure Trial Network study, 35 ml · kg^{-1} · h^{-1} is the ultrafiltration flow rate for the group receiving the intensive therapy strategy, and, in the Boussekey *et al.* study, this ultrafiltration flow rate was used in the "low-volume" hemofiltration group.[4,14]

In 2002, the Acute Dialysis Quality Initiative workgroup defined HVHF as more than 35 ml · kg^{-1} · h^{-1}.[15] In 2012, this threshold is not universally accepted anymore, especially because, from a practical standpoint, 35 ml · kg^{-1} · h^{-1} does not seem that high. Consequently, Honoré and other experts recently updated and clarified the definition of HVHF.[16] They agreed that HVHF includes continuous high-volume treatment of more than 50 ml · kg^{-1} · h^{-1} 24 h a day and intermittent high-volume hemofiltration with brief, very high-volume treatment at 100–120 ml · kg^{-1} · h^{-1} for a short period of 4–8 h, followed by conventional CVVH.[17]

This latter strategy is also called "pulse HVHF" and was initially developed by Ronco *et al.*[18] This definition is consistent with the 2001 Critical Care Nephrology conference held in Melbourne, Australia, where HVHF was defined as ultrafiltration flow rates greater than 50 ml · kg^{-1} · h^{-1} and very HVHF for ultrafiltration flow rates greater than 100 ml · kg^{-1} · h^{-1}.[19] At that time, it was also decided to universally use the "ml per kilogram per hour" as the unit to be used to express the ultrafiltration flow rate.

Renal Support

The question of the adequate dose for renal support in AKI patients requiring RRT was first illustrated in a landmark study by Ronco *et al.* in 2000.[20] In this single-center Italian study, an ultrafiltration flow rate of 35 ml · kg^{-1} · h^{-1} improved survival in AKI patients receiving postdilution CVVH, as compared with those who received 20 ml · kg^{-1} · h^{-1}. Nearly simultaneously, Schiffl *et al.* reported that intensive hemodialysis (performed daily) reduced mortality in patients with acute renal failure, as compared with conventional (alternate-day) intermittent hemodialysis.[21] Consequently, at that time, a relationship between the dose of renal support prescribed and patient outcomes, including mortality, was highly suspected.

However, subsequent randomized controlled studies did not confirm these results. Bouman *et al.* found that survival and recovery of renal function were not different in 106 critically ill patients randomized in three different strategies of RRT: early HVHF, early low-volume hemofiltration, and late low-volume hemofiltration.[22] Similarly, Tolwani *et al.* recently reported no difference in patient survival or renal recovery in 200 critically ill patients with AKI undergoing 35 ml · kg^{-1} · h^{-1} *versus* 20 ml · kg^{-1} · h^{-1} of continuous venovenous hemodiafiltration with prefilter replacement fluid.[23] On the contrary, Saudan *et al.* published in 2006 interesting data suggesting that increasing dialysis dose by adding a dialysis component to CVVH increased survival. Indeed, in this trial that randomized 206 patients, the 28-day survival was significantly increased from 39% in the CVVH group to 59% in the continuous hemodiafiltration group ($P = 0.03$), and the 90-day survivals were even more pronounced (34 *vs.* 59%, $P = 0.0005$).[24]

So why did all these randomized controlled studies not find the same results? First, they are all relatively small, single-center studies (two centers for the Bouman study), and consequently, their results have limited external validity. It is well known that interventions tested in single clinical environments are not necessarily generalizable to a broader population, especially in critical care.[25] Second, the trials were conducted by committed experts of RRT with a lack of blinding, increasing the risk of a possible Hawthorne effect (some patients belonging to one group consciously or unconsciously treated differently than the other).[26] Third, AKI patients studied in these trials were drastically different. For example, the percentage of septic patients was below 15% in the Ronco study, whereas it was 60% in the Saudan study. Mortality rates in these studies were also very different, demonstrating the patients' heterogeneity in terms of severity and consequently pointing out the difficulty in analyzing them collectively. In the Bouman study, survival at day 28 was indeed unusual, reaching 70%. Lastly, management of RRT was very different between these trials. Substitution fluid replacement was sometimes administered in postdilution (Bouman and Ronco studies) and sometimes in predilution (Saudan and Tolwani studies), therefore modifying the actual delivered dosage from the prescribed dosage. Furthermore, the percentage of patients achieving a delivered dosage greater than 80% of the prescribed dosage was not always provided. Whereas all patients reached values of ultrafiltration of at least 85% of the prescribed dose in the Ronco study, only 77% of patients achieved greater than 80% of the prescribed dosage in the Tolwani study.

Recently, the two large multicenter prospective randomized trials were published, producing nearly identical results. The Acute Renal Failure Trial Network study, from the Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network, enrolled 1,124 AKI patients from 27 tertiary-care Veterans Administration and university hospitals in the United States.[4] Patients were randomized to either an intensive or a conventional management strategy. Patients assigned to the intensive treatment strategy received intermittent hemodialysis six times per week or continuous venovenous hemodiafiltration at 35 ml · kg^{-1} · h^{-1}, depending on their hemodynamic stability. For patients receiving the less-intensive treatment strategy, intermittent hemodialysis was provided three times per week or continuous venovenous hemodiafiltration was prescribed to provide an effluent flow rate of 20 ml · kg^{-1} · h^{-1}. There was no significant difference between the two groups in terms of mortality rates from any cause at day 60, duration of RRT, AKI recovery, and recovery from nonrenal organ failure. The RENAL study enrolled 1,500 patients from 30 intensive care units in Australia and New Zealand. AKI patients were randomized to receive an "augmented" continuous RRT regimen of 40 ml · kg^{-1} · h^{-1} or a normal regimen at a dose of 25 ml · kg^{-1} · h^{-1}.[3] The dose of 25 ml · kg^{-1} · h^{-1} represents the average practice in Australia and New Zealand, which is also true in Europe and the United States.[6,12,27] Results of the RENAL study were similar to those of the Acute Renal Failure Trial Network study, with an odds ratio of 1.0 for the 90-day mortality. Finally, two recent meta-analyses including all of the above trials concluded that no benefit could be demonstrated by increasing RRT intensity beyond the currently recommended 20–25 ml · kg^{-1} · h^{-1}.[28,29] However, in order to achieve this dose in clinical practice, prescriptions of 25–30 ml · kg^{-1} · h^{-1} are generally required, and close monitoring of dose delivery is advised.[3–5,12,30]

In conclusion, if the physician's singular goal is renal support through a RRT prescription for a patient with AKI, the

best evidence currently available suggests that hemofiltration should be prescribed at 25 to 30 ml · kg^{-1} · h^{-1}.

Blood Purification for Systemic Inflammation

Pathophysiological Rationale

Systemic inflammatory states, such as severe sepsis and acute pancreatitis, are known to be major causes of AKI and other organ failures in critically ill patients.[31] But they are also responsible for an important immunologic disturbance with the release into the bloodstream of numerous inflammatory mediators.[32] Some aspects of this systemic inflammatory response may be beneficial to combat systemic infection, but when it is excessive, uncontrolled, or unbalanced, it has deleterious effects, including multiorgan failure and death. Indeed, inflammatory mediators such as cytokines have direct harmful effects on tissues (cytotoxic effects),[33] and the prolonged release of antiinflammatory mediators, interpreted as a protective mechanism to prevent an excessive effect of the pro-inflammatory phase, leads to impaired immunity;[34] this defect plays a major role in mortality.[35,36] The overall concept of blood purification is therefore to attenuate this overwhelming systemic overflow of pro- and antiinflammatory mediators released at the early phase of sepsis and to restore a broad-based humoral homeostasis in order to improve outcome. A variety of mediators are involved in this inflammatory response, such as cytokines, chemokines, complement components, platelet-activating factor, leukotrienes, thromboxanes, and kinins.[37] In the past, every attempt to modulate this inflammatory response by targeting one component has failed, at least at the clinical phase.[38] Thus, the concept of blood purification has evolved toward a nonspecific removal of a large spectrum of inflammatory mediators.

Different pathophysiological theories have been proposed to support the concept of blood purification. First, Ronco and Bellomo hypothesized that shaving the cytokine peak concentration by removing them from the blood compartment during the early phase of sepsis could stop the inflammatory cascade, limit organ damage, and consequently decrease the incidence of multiorgan failure syndrome. This hypothesis is called the "peak concentration hypothesis."[39,40] More recently, Honoré proposed the "threshold immunomodulation hypothesis," which takes a more dynamic view, postulating that the cytokine removal from the blood compartment leads to the removal of cytokines located at the tissue level because of an equilibration of their concentrations between these two compartments.[41,42] This theory is interesting because it affects cytokines at the tissue level, which is where cytokines are harmful, and it also explains why numerous studies assessing blood purification techniques found an improvement of outcomes with no modification of cytokine blood concentrations as cytokines from the tissues replace those removed from the blood.[43,44] Di Carlo and Alexander also proposed the "mediator delivery hypothesis," in which HVHF is responsible for an increase of the lymphatic flow by 20- to 40-fold because of the high amounts of crystalloid fluids used for replacement with this technique.[45–48] This leads to a significant drag and displacement of inflammatory mediators to the blood compartment, making them available for removal. In this theory, HVHF is therefore not only able to remove cytokines from the blood but also to insure that lymphatic transport from tissue and interstitium to the blood compartment occurs. Finally, Kellum has suggested that blood purification therapies act at the inflammatory cell level in order to restore the immune function through the regulation of monocytes and neutrophils.[49–51] A novel component of this hypothesis is that by removing mediators from the plasma in the situation of systemic inflammation, one can restore the concentration gradient from plasma to infected tissues (fig. 2). This gradient has large effects on leukocyte trafficking and bacterial clearance.[52] Thus the "cytokinetic model" may be more important than the cytotoxic models traditionally considered to explain the association between high cytokine levels and mortality. It needs to be acknowledged that neither of these different theories is based on robust data, and once discussed, they usually lead to subsequent questions. For example, do other extracorporeal blood purification techniques such as the use of endotoxin sorbents interfere with the inflammatory response in the same way as HVHF? It is wise to imagine that several different mechanisms may be responsible for the effects observed with these techniques. Moreover, because of the activation of leukocytes during the passage of blood through the artificial extracorporeal circuit, could HVHF interfere with the apoptotic or the leukocytic infiltration pathways of sepsis-induced AKI pathophysiology? Or, for the same reasons, could it be responsible for an aggravation of the tubular injury lesions observed in patients with septic induced-AKI, as recently hypothesized by Lerolle *et al.*?[53]

Regarding pathophysiology, HVHF is an attractive therapy in order to successfully remove a significant amount of a wide range of inflammatory molecules involved in the host inflammatory response. First, these circulating molecules are mostly water-soluble, and convection carries both plasma water and solutes across the membrane. Second, most inflammatory mediators are so-called "middle molecular weight molecules," with a wide range of mass from 5 kDa to 60 kDa. Convection is far more effective than diffusion in removing middle molecules,[54,55] at least with traditional membranes. Third, depending on their composition, most hemofiltration membranes also have some adsorptive properties. This associated principle corresponds to the saturable fixation of some molecules directly on the membrane along an affinity gradient depending on ionic, hydrophobic, and van der Waals interactions (fig. 3). The ultrafiltrate contains the molecules from the plasma that have a molecular weight below the membrane cutoff, and adsorption allows the removal of some molecules with a molecular weight higher than the membrane cutoff. Therefore, a very large panel of inflammatory mediators can be affected by hemofiltration. Finally, the use of HVHF is important because it has been

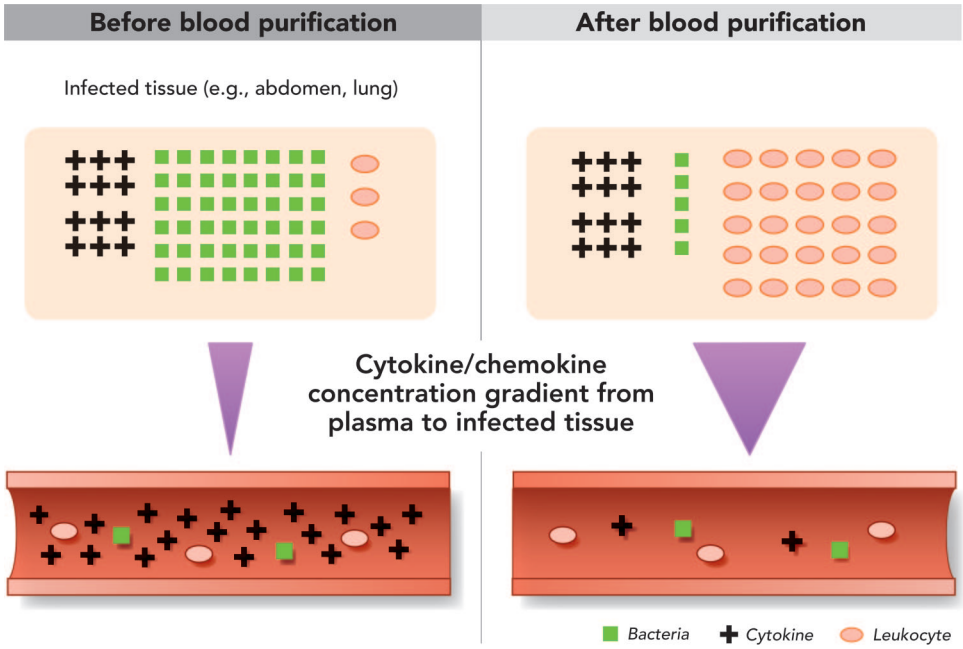

Fig. 2. The "cytokinetic" model. By removing inflammatory mediators from the blood compartment, blood purification therapies increase the cytokine/chemokine concentration gradient from plasma to infected tissue. Leukocyte trafficking is therefore driven toward the nidus of infection, increasing local bacterial clearance.

shown that conventional hemofiltration, with low ultrafiltration flow rates, is not effective for blood purification.[56,57] Increasing the ultrafiltration flow rate may also increase the adsorption properties of the hemofilter because of its effect on transmembrane pressure (greater membrane site recruitment) and exposure of more of the internal matrix of the filter, thus increasing the available adsorptive surface area.[58]

Animal Studies

Many animal studies have been performed to assess HVHF, especially in the 1990s, when HVHF was still very experimental in humans. Grootendorst *et al.* reported in 1992 an improvement in right ventricular function and the cardiac performance in 18 pigs with endotoxin-induced shock when zero balance HVHF (ultrafiltrate = 6,000 ml/h) was applied. He hypothesized that some vasoactive mediators, responsible for the myocardial depression, were removed with HVHF.[59] Two years later, he also found in a gut ischemia and reperfusion porcine model that HVHF not only improved short-term hemodynamics, but also reduced macroscopic bowel damage observed at autopsy and improved 24-h survival.[60] In an experimental pancreatitis model, HVHF improved hemodynamics, reversed sepsis–induced immunoparalysis, and increased 60-h survival.[61] In addition, in this pancreatitis study, Yekebas *et al.* showed that survival rates were best with a very high ultrafiltration flow rate (100 ml · kg^{-1} · h^{-1}) and frequent filter changes (every 12 h).[51] In septic dogs, Bellomo *et al.* found that 80 ml · kg^{-1} · h^{-1} HVHF improved hemodynamic parameters compared with a sham circuit with no hemofilter. This study also raised the likelihood of the beneficial effect of the adsorption properties of the polyacrylonitrile hemofilter used in the HVHF group.[62] Rogiers *et al.* found similar results in dogs with endotoxin-induced shock, showing an improved cardiac performance when HVHF was performed with polyacrylonitrile membranes compared with polysulfone membranes. However, these effects that are supposed to be related to the adsorption properties of the membrane are temporary because of saturation phenomenon.[63]

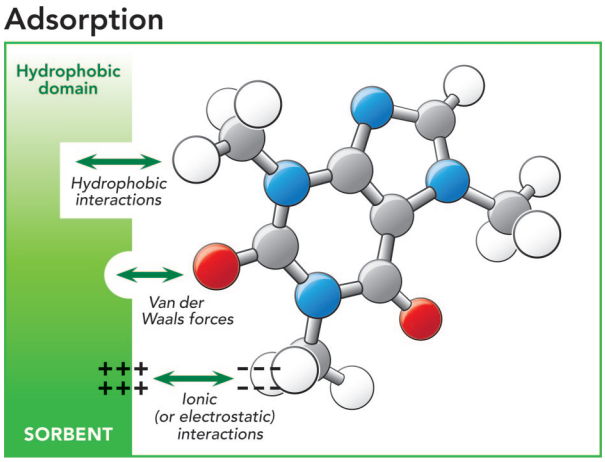

Fig. 3. Adsorption corresponds to the saturable fixation of some molecules directly on a sorbent or a membrane along an affinity gradient depending on ionic, hydrophobic, and van der Waals interactions.

Some animal studies assessed HVHF by looking at ultrafiltrate obtained from either healthy donor or septic donor animals and infused into a healthy acceptor animal. The ability for HVHF to remove toxic mediators is suggested

when ultrafiltrate obtained from septic animals leads to hemodynamic disturbances or even death in healthy animals.[64–66] In a prospective randomized controlled study including 65 septic pigs, Lee *et al.* reported an increase survival time in filtered animals compared with matched nonfiltered animals. Increments in survival time even increased directly with filtration fraction. Moreover, ultrafiltrate concentrate obtained from septic pigs produced death in healthy animals, whereas the infusion of clean ultrafiltrate concentrate produced no response, supporting the hypothesis that HVHF was able to remove harmful mediators.[65]

Although most of the well-conducted animal studies found benefits in terms of hemodynamics, respiratory function, and survival, they should be interpreted with caution. Septic animal models, especially endotoxemia, are indeed very difficult to extrapolate to clinical conditions. For example, most infection models do not include antibiotics, and the blood purification therapy is usually started at the very early phase after the bacterial insult, which is far different from clinical settings.

Human Studies

Like in animals, numerous human studies have shown beneficial hemodynamic effects of HVHF. Journois *et al.* were among the first to study HVHF as a blood purification technique in humans. They studied children undergoing cardiac surgery with cardiopulmonary bypass.[67,68] In 20 children, zero-balance, HVHF (100 ml · kg^{-1} · h^{-1}) showed a reduction in postoperative blood loss, time to extubation, and cytokine plasma levels.[67] In 2001, Cole *et al.* assessed the hemodynamic impact of HVHF in a small, randomized crossover clinical trial. In 11 patients with septic shock and multiorgan failure, an 8-h period of HVHF (6 l/h) was associated with a greater reduction in norepinephrine requirements than a similar period of CVVH (1 l/h).[58] Reduction of vasopressor requirements with HVHF was also found more recently in another pilot randomized study comparing CVVH at 65 ml · kg^{-1} · h^{-1} *versus* 35 ml · kg^{-1} · h^{-1} in 20 septic shock patients with AKI.[14]

Using mortality as the primary outcome, large randomized controlled studies of HVHF in septic shock are extremely difficult to conduct because the sample size requires several hundred subjects. Therefore, such studies have not yet been performed; however, one such study is currently ongoing in Europe, known as the IVOIRE study (hIgh VOlume in Intensive caRE), which compares 70 ml · kg^{-1} · h^{-1} *versus* 35 ml · kg^{-1} · h^{-1}. Although results from this study will be formally released within the next 6 months, we already know from the investigators that the enrollment process was very slow and therefore the study may be underpowered. Thus, the only available studies regarding mortality compared observed-mortality *versus* expected-mortality based on the patients' severity scores at admission. However, despite being uncontrolled and thus limited in their ability to draw strong conclusions, at least six studies have found significant (sometimes spectacular) reductions in mortality rates with HVHF compared with predicted mortality.[69–74] In 2000, Honore *et al.* reported a reduction of the mortality rate from 79% (expected mortality based on APACHE II and SAPS II scores) to 55%.[70] A few years later, Joannes-Boyau *et al.* obtained a similar result with a predicted 28-day mortality of 70% and an observed mortality of 46% in a study assessing the effect of 40–60 ml · kg^{-1} · h^{-1} maintained for 96 h in patients with septic shock and multiorgan dysfunction syndrome.[71] In addition, Ratanarat *et al.* reported a reduction of the 28-day mortality rate from 70% (predicted) to 47% (observed) when septic patients underwent daily pulse HVHF.[74]

In patients without sepsis but with systemic inflammation, the effect of HVHF on mortality was evaluated in two randomized controlled trials. The largest study assessing mortality with HVHF in randomized patients was performed on 61 resuscitated cardiac arrest patients.[75] This whole-body ischemia-reperfusion represents an interesting "sepsis-like" syndrome.[76] Although the primary analysis was negative, after adjusting for imbalances in baseline characteristics, very HVHF (200 ml · kg^{-1} · h^{-1} during 8 h) was associated with improved 6-month survival (logistic regression odds ratio, 4.4; 95% CI, 1.1–16.6) and a decreased risk of death from early intractable shock.[75] Similarly, in 37 patients with acute pancreatitis, hemodynamics and short-time survival rates were significantly better with HVHF (4 l/h) than in patients receiving low-volume hemofiltration (1 l/h).[77] The most important recent studies assessing mortality with HVHF as a blood purification therapy are summarized in table 1.

Unlike these promising results using HVHF, standard "renal dose" continuous RRT appears to be ineffective as an immune-modulating therapy. In 1998, Kellum *et al.* found modest effects of CVVH (2 l/h) compared with continuous hemodialysis on tumor necrosis factor and interleukin-6 in a small (n = 13) randomized crossover study.[55] When patients served as their own controls, median differences in the tumor necrosis factor level were only 16% and highly variable between patients. In 2002, Cole *et al.* studied the effects of early CVVH (2 l/h) on plasma concentrations of several inflammatory mediators and on organ dysfunctions in 24 septic patients without AKI. In this randomized controlled trial, CVVH was not associated with a reduction in any plasma cytokine concentrations and did not decrease organ dysfunctions, as compared with no hemofiltration.[56] Recently, Payen *et al.* found similar results (and even a trend toward worse outcomes) in septic shock patients without AKI who underwent CVVH (25 ml · kg^{-1} · h^{-1} for a 96-h period) at the early phase of sepsis compared with those who were managed conventionally. This study confirmed that low-volume hemofiltration (standard continuous RRT) is not a suitable technique for blood purification in sepsis but, as the authors stated in their conclusion, it did not rule out a beneficial effect of HVHF on the course of sepsis.[57]

Table 1. Most Important Recent Human Studies that Assessed the Effects of HVHF as a Blood Purification Technique on Hemodynamics and Survival

Design	First Author, Year	Number of Patients	Clinical Setting	Dose (ml · kg^{-1} · h^{-1})	Improved Hemodynamics with HVHF	Improved Survival with HVHF	*P* Value (Survival)
Randomized, controlled trials	Laurent, 2005[75]	61	Resuscitated cardiac arrest	200	Yes	Yes; 6-mo survival: 21–45%	0.026
	Jiang, 2005[77]	37	Severe acute pancreatitis	4,000 ml/h	Yes	Yes; 14-day survival: 68.4–94.4%	<0.01
	Boussekey, 2008[14]	20	Septic shock	65	Yes	No	0.65
	IVOIRE study, on going	≈150	Septic shock	70	—	—	—
Randomized, crossover trial	Cole, 2001[58]	11	Septic shock with multiorgan failure	6,000 ml/h	Yes	Not assessed	N/A
Prospective, cohort, uncontrolled trials	Honoré, 2000[70]	20	Refractory septic shock	115	Yes	Yes; 28-day survival: (Expected) 21–(Observed) 45%	<0.05
	Joannes-Boyau, 2004[71]	24	Septic shock	40–60	Yes	Yes; 28-day survival: (Expected) 30–(Observed) 54%	<0.075
	Ratanarat, 2005[74]	15	Severe sepsis	85 (pulse HVHF)	Yes	Yes; 28-day survival: (Expected) 30%–(Observed) 53%	N/A
	Cornejo, 2006[69]	20	Refractory septic shock	100	Yes	Yes; Hospital survival: (Expected) 37–(Observed) 60%	<0.03
Retrospective trials	Piccinni, 2006[73]	80	Septic shock	45	Yes	Yes; 28-day survival: 27.5–55%	0.005
	Zhu, 2009[88]	63	Severe acute pancreatitis	60–80	No	Yes; 28-day survival: 65.5–91.2%	0.014

HVHF = high-volume hemofiltration.

Alternatives to HVHF for Blood Purification

Other extracorporeal blood purification therapies are currently available besides HVHF. Indeed, coupled plasma filtration adsorption, polymyxin-B hemoperfusion, and the use of high cutoff membranes have also been proposed as adjuvant treatments for sepsis.[78–80] However, at this time, it is not possible to state which technique is most effective, because they have not been compared with each other so far. Nevertheless and interestingly, some additional hybrid techniques can synergistically combine HVHF and hemoadsorption in a technique named "high adsorptive hemofiltration." This therapy consists of optimizing the performances of the hemofilters regarding cytokine and/or endotoxin removal through hemoadsorption by manipulating their composition or structure. For example, positive hemodynamic effects of a polyacrylonitrile hemofiltration membrane having endotoxin adsorption properties were recently reported in septic pigs.[81] The membrane surface polarity was modified by the addition of a polyethyleneimine coating, a positively charged polymer, allowing the membrane to catch negatively charged endotoxins *via* surface adsorption (fig. 4). In the same line, other models where HVHF and high-permeability

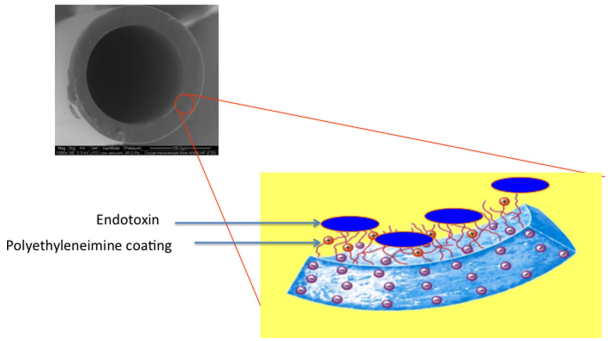

Fig. 4. High adsorptive hemofiltration. The membrane surface polarity is modified by the addition of a polyethyleneimine coating, a positively charged polymer, allowing endotoxins' surface adsorption.

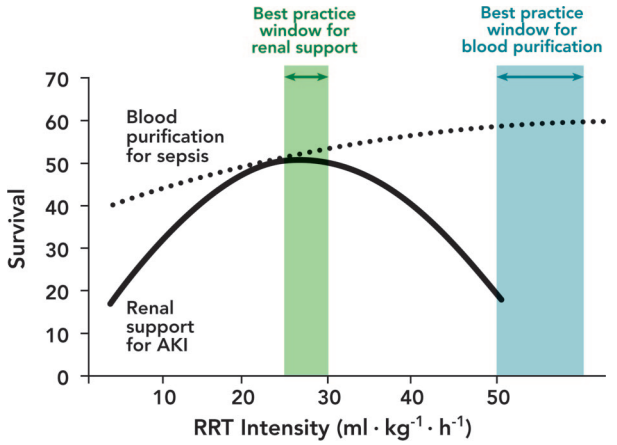

Fig. 5. For renal support, high-volume hemofiltration is not necessary, and ultrafiltration flow rates ranging from 25 to 30 $ml \cdot kg^{-1} \cdot h^{-1}$ seem adequate in order to reach the optimal delivered dose of 20–25 $ml \cdot kg^{-1} \cdot h^{-1}$. For blood purification in sepsis, the dose-response relationship may be very different and high-volume hemofiltration may be considered.

hemofiltration work synergistically have shown promising results.[82]

Clinical Use of HVHF

Although new machines dedicated for RRT or blood purification are more reliable with very sensitive and precise pressure control and volume balance functions, the use of HVHF still requires attention to several technical aspects. First, in order to keep filtration fraction below 25%, the blood flow rate has to be increased. This consequently requires the use of large dialysis catheters with diameters such as 13.5–15 French inserted in an adequate location, the right jugular site perhaps being the best.[83] Second, the optimal pre- and postdilution ratio for replacement fluid is suggested to be 1/3–2/3 by some experts.[17] Indeed, a good compromise between the loss of efficacy because of predilution and its benefit regarding blood rheology conditions is suitable, although data addressing this particular aspect are limited.[84] Third, to date, no recommendation about anticoagulation can be made because of the lack of evidence of any superiority of any one strategy. However, citrate is increasingly employed because of its advantages in terms of filter lifetime and coagulation. Fourth, highly biocompatible synthetic membranes with a high exchange surface of at least 2 m^2 are suitable.[17] Fifth, temperature monitoring must be performed very closely because of the greater heat loss observed with high convective exchanges and the subsequent risk of hypothermia. Sixth, HVHF may be responsible for an important loss of small beneficial molecules including nutrients, amino-acids, vitamins, trace elements, and antimicrobials in the ultrafiltrate.[85,86] Thus, nutritive supplementation (*e.g.*, glutamine) and adaptation of drug prescriptions must be taken into account.[87] Antibiotics levels in particular should be checked whenever possible. When using pulse HVHF, it is therefore advisable to dose around the procedure, much the same way drugs are managed in intermittent hemodialysis. For the same reason, strict monitoring of sodium, potassium, phosphorus, glucose, and acid-base balance is mandatory.[17]

Regarding safety, it is also important to recall that HVHF is usually performed in patients with a multiorgan failure syndrome, and therefore the adverse effects of the therapy are exacerbated by the severity of these patients. HVHF has the same risks as other extracorporeal therapies such as bleeding related to anticoagulation, infection, gas embolism, and hemodynamic intolerance, but the use of high fluid exchanges multiplies the risk of metabolic consequences if there is an error in the replacement fluid composition. In other words, physicians have to be aware that a small mistake in the therapy prescription can rapidly have major deleterious consequences. Finally, the difference between the prescribed and delivered dose can rapidly become important with HVHF if the therapy is interrupted for some reason (nursing activities, coagulation issues, transfer to the operating room, or radiology).

Conclusion

Physicians initiating RRT should first identify their goals. If the strategy is to support renal function, then HVHF is not necessary and ultrafiltration flow rates ranging from 25 to 30 $ml \cdot kg^{-1} \cdot h^{-1}$ will be adequate for the majority of patients. Conversely, if the strategy is to overtake renal support and modulate systemic inflammation, HVHF appears to be a promising, though still experimental, option (fig. 5). Although there are still no large multicenter randomized controlled trials showing beneficial effects on mortality with HVHF, preliminary studies in humans and preclinical animal data support continued research in this area.

In our opinion, during the next decade, considerable work needs to be done in order to find and optimize the best blood purification strategy for systemic inflammatory states. Convection, diffusion, and adsorption should probably not be seen as opposed or competitive mechanisms for blood purification but rather as complementary ones. Since the

mechanism by which blood purification therapies work on modulating the cytotoxic and cytokinetic effects of inflammatory mediators is still unclear, we believe that basic science studies are still warranted. In addition, more clinical trials conducted in both mono- and multicenters are suitable in order to evaluate the ability of HVHF to improve clinical outcomes (*i.e.*, mortality or organ failure) rather than to study surrogate markers (*i.e.*, inflammatory mediator clearance or physiologic variables such as oxygenation and hemodynamics).

References

1. Metnitz PG, Krenn CG, Steltzer H, Lang T, Ploder J, Lenz K, Le Gall JR, Druml W: Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. Crit Care Med 2002; 30:2051–8
2. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Ronco C, Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators: Acute renal failure in critically ill patients: A multinational, multicenter study. JAMA 2005; 294:813–8
3. RENAL Replacement Therapy Study Investigators, Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, Lo S, McArthur C, McGuinness S, Myburgh J, Norton R, Scheinkestel C, Su S: Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 2009; 361:1627–38
4. VA/NIH Acute Renal Failure Trial Network, Palevsky PM, Zhang JH, O'Connor TZ, Chertow GM, Crowley ST, Choudhury D, Finkel K, Kellum JA, Paganini E, Schein RM, Smith MW, Swanson KM, Thompson BT, Vijayan A, Watnick S, Star RA, Peduzzi P: Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med 2008; 359: 7–20
5. Kellum JA, Ronco C: Dialysis: Results of RENAL–what is the optimal CRRT target dose? Nat Rev Nephrol 2010; 6:191–2
6. Overberger P, Pesacreta M, Palevsky PM: VA/NIH Acute Renal Failure Trial Network: Management of renal replacement therapy in acute kidney injury: A survey of practitioner prescribing practices. Clin J Am Soc Nephrol 2007; 2:623–30
7. Palevsky PM: Indications and timing of renal replacement therapy in acute kidney injury. Crit Care Med 2008; 36: S224–8
8. Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Oudemans-van Straaten H, Ronco C, Kellum JA: Continuous renal replacement therapy: A worldwide practice survey. The beginning and ending supportive therapy for the kidney (B.E.S.T. kidney) investigators. Intensive Care Med 2007; 33:1563–70
9. Ghahramani N, Shadrou S, Hollenbeak C: A systematic review of continuous renal replacement therapy and intermittent haemodialysis in management of patients with acute renal failure. Nephrology 2008; 13:570–8
10. Pannu N, Klarenbach S, Wiebe N, Manns B, Tonelli M, Alberta Kidney Disease Network: Renal replacement therapy in patients with acute renal failure: A systematic review. JAMA 2008; 299:793–805
11. Rabindranath K, Adams J, Macleod AM, Muirhead N: Intermittent *versus* continuous renal replacement therapy for acute renal failure in adults. Cochrane Database Syst Rev 2007; 3:CD003773
12. Vesconi S, Cruz DN, Fumagalli R, Kindgen-Milles D, Monti G, Marinho A, Mariano F, Formica M, Marchesi M, René R, Livigni S, Ronco C, DOse REsponse Multicentre International Collaborative Initiative (DO-RE-MI Study Group): Delivered dose of renal replacement therapy and mortality in critically ill patients with acute kidney injury. Crit Care 2009; 13:R57
13. Cole L, Bellomo R, Silvester W, Reeves JH: A prospective, multicenter study of the epidemiology, management, and outcome of severe acute renal failure in a "closed" ICU system. Am J Respir Crit Care Med 2000; 162:191–6
14. Boussekey N, Chiche A, Faure K, Devos P, Guery B, d'Escrivan T, Georges H, Leroy O: A pilot randomized study comparing high and low volume hemofiltration on vasopressor use in septic shock. Intensive Care Med 2008; 34: 1646–53
15. Kellum JA, Mehta RL, Angus DC, Palevsky P, Ronco C, ADQI Workgroup: The first international consensus conference on continuous renal replacement therapy. Kidney Int 2002; 62:1855–63
16. Honore PM, Joannes-Boyau O, Kotulak T: Report of the working party on high volume hemofiltration including definitions and classification. Paper presented at: Proc 2nd Czech Conference on Critical Care Nephrology; 2007; Pardubice, Czech Republic, April 18–19, 2007
17. Honore PM, Joannes-Boyau O, Boer W, Collin V: High-volume hemofiltration in sepsis and SIRS: Current concepts and future prospects. Blood Purif 2009; 28:1–11
18. Brendolan A, D'Intini V, Ricci Z, Bonello M, Ratanarat R, Salvadori G, Bordoni V, De Cal M, Andrikos E, Ronco C: Pulse high volume hemofiltration. Int J Artif Organs 2004; 27:398–403
19. Honore PM, Jamez J, Wauthier M: Very high volume hemofiltration: A comprehensive review. Proceedings from the International Symposium on Critical Care Nephrology (ISCCN). Melbourne, Australia, November 1–3, 2001
20. Ronco C, Bellomo R, Homel P, Brendolan A, Dan M, Piccinni P, La Greca G: Effects of different doses in continuous venovenous haemofiltration on outcomes of acute renal failure: A prospective randomised trial. Lancet 2000; 356:26–30
21. Schiffl H, Lang SM, Fischer R: Daily hemodialysis and the outcome of acute renal failure. N Engl J Med 2002; 346: 305–10
22. Bouman CS, Oudemans-Van Straaten HM, Tijssen JG, Zandstra DF, Kesecioglu J: Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: A prospective, randomized trial. Crit Care Med 2002; 30: 2205–11
23. Tolwani AJ, Campbell RC, Stofan BS, Lai KR, Oster RA, Wille KM: Standard *versus* high-dose CVVHDF for ICU-related acute renal failure. J Am Soc Nephrol 2008; 19:1233–8
24. Saudan P, Niederberger M, De Seigneux S, Romand J, Pugin J, Perneger T, Martin PY: Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. Kidney Int 2006; 70:1312–7
25. Bellomo R, Warrillow SJ, Reade MC: Why we should be wary of single-center trials. Crit Care Med 2009; 37:3114–9
26. Eckmanns T, Bessert J, Behnke M, Gastmeier P, Ruden H: Compliance with antiseptic hand rub use in intensive care units: The Hawthorne effect. Infect Control Hosp Epidemiol 2006; 27:931–4
27. Bellomo R: Do we know the optimal dose for renal replacement therapy in the intensive care unit? Kidney Int 2006; 70:1202–4
28. Jun M, Heerspink HJ, Ninomiya T, Gallagher M, Bellomo R, Myburgh J, Finfer S, Palevsky PM, Kellum JA, Perkovic V, Cass A: Intensities of renal replacement therapy in acute kidney injury: A systematic review and meta-analysis. Clin J Am Soc Nephrol 2010; 5:956–63
29. Van Wert R, Friedrich JO, Scales DC, Wald R, Adhikari NK, University of Toronto Acute Kidney Injury Research Group: High-dose renal replacement therapy for acute kidney injury: Systematic review and meta-analysis. Crit Care Med 2010; 38:1360–9
30. Honoré PM, Jacobs R, Boer W, Joannes-Boyau O, De Regt J, De Waele E, Van Gorp V, Collin V, Spapen HD: New insights

regarding rationale, therapeutic target and dose of hemofiltration and hybrid therapies in septic acute kidney injury. Blood Purif 2011; 33:44–51

31. Hoste EA, Schurgers M: Epidemiology of acute kidney injury: How big is the problem? Crit Care Med 2008; 36:S146–51
32. Kellum JA, Kong L, Fink MP, Weissfeld LA, Yealy DM, Pinsky MR, Fine J, Krichevsky A, Delude RL, Angus DC, GenIMS Investigators: Understanding the inflammatory cytokine response in pneumonia and sepsis: Results of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Study. Arch Intern Med 2007; 167:1655–63
33. Suntharalingam G, Perry MR, Ward S, Brett SJ, Castello-Cortes A, Brunner MD, Panoskaltsis N: Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. N Engl J Med 2006; 355:1018–28
34. Hotchkiss RS, Coopersmith CM, McDunn JE, Ferguson TA: The sepsis seesaw: Tilting toward immunosuppression. Nat Med 2009; 15:496–7
35. Adib-Conquy M, Cavaillon JM: Compensatory anti-inflammatory response syndrome. Thromb Haemost 2009; 101:36–47
36. Turnbull IR, Clark AT, Stromberg PE, Dixon DJ, Woolsey CA, Davis CG, Hotchkiss RS, Buchman TG, Coopersmith CM: Effects of aging on the immunopathologic response to sepsis. Crit Care Med 2009; 37:1018–23
37. Tetta C, Bellomo R, Inguaggiato P, Wratten ML, Ronco C: Endotoxin and cytokine removal in sepsis. Ther Apher 2002; 6:109–15
38. Bone RC: Sir Isaac Newton, sepsis, SIRS, and CARS. Crit Care Med 1996; 24:1125–8
39. Ronco C, Ricci Z, Bellomo R: Importance of increased ultrafiltration volume and impact on mortality: Sepsis and cytokine story and the role for CVVH. Edtna Erca J 2002; Suppl 2:13–8
40. Ronco C, Tetta C, Mariano F, Wratten ML, Bonello M, Bordoni V, Cardona X, Inguaggiato P, Pilotto L, d'Intini V, Bellomo R: Interpreting the mechanisms of continuous renal replacement therapy in sepsis: The peak concentration hypothesis. Artif Organs 2003; 27:792–801
41. Honore PM, Joannes-Boyau O: High volume hemofiltration (HVHF) in sepsis: A comprehensive review of rationale, clinical applicability, potential indications and recommendations for future research. Int J Artif Organs 2004; 27:1077–82
42. Honoré PM, Matson JR: Extracorporeal removal for sepsis: Acting at the tissue level–the beginning of a new era for this treatment modality in septic shock. Crit Care Med 2004; 32:896–7
43. Honoré PM, Joannes-Boyau O, Gressens B: Blood and plasma treatments: The rationale of high-volume hemofiltration. Contrib Nephrol 2007; 156:387–95
44. Klouche K, Cavadore P, Portales P, Clot J, Canaud B, Béraud JJ: Continuous veno-venous hemofiltration improves hemodynamics in septic shock with acute renal failure without modifying TNFalpha and IL6 plasma concentrations. J Nephrol 2002; 15:150–7
45. Di Carlo JV, Alexander SR: Hemofiltration for cytokine-driven illnesses: The mediator delivery hypothesis. Int J Artif Organs 2005; 28:777–86
46. Olszewski WL: The lymphatic system in body homeostasis: Physiological conditions. Lymphat Res Biol 2003; 1:11–24
47. Onarheim H, Missavage AE, Gunther RA, Kramer GC, Reed RK, Laurent TC: Marked increase of plasma hyaluronan after major thermal injury and infusion therapy. J Surg Res 1991; 50:259–65
48. Wasserman K, Mayerson HS: Dynamics of lymph and plasma protein exchange. Cardiologia 1952; 21:296–307
49. Peng Z, Singbartl K, Simon P, Rimmelé T, Bishop J, Clermont G, Kellum JA: Blood purification in sepsis: A new paradigm. Contrib Nephrol 2010; 165:322–8
50. Ronco C, Brendolan A, Lonnemann G, Bellomo R, Piccinni P, Digito A, Dan M, Irone M, La Greca G, Inguaggiato P, Maggiore U, De Nitti C, Wratten ML, Ricci Z, Tetta C: A pilot study of coupled plasma filtration with adsorption in septic shock. Crit Care Med 2002; 30:1250–5
51. Yekebas EF, Eisenberger CF, Ohnesorge H, Saalmüller A, Elsner HA, Engelhardt M, Gillesen A, Meins J, The M, Strate T, Busch C, Knoefel WT, Bloechle C, Izbicki JR: Attenuation of sepsis-related immunoparalysis by continuous veno-venous hemofiltration in experimental porcine pancreatitis. Crit Care Med 2001; 29:1423–30
52. Call DR, Nemzek JA, Ebong SJ, Bolgos GL, Newcomb DE, Remick DG: Ratio of local to systemic chemokine concentrations regulates neutrophil recruitment. Am J Pathol 2001; 158:715–21
53. Lerolle N, Nochy D, Guérot E, Bruneval P, Fagon JY, Diehl JL, Hill G: Histopathology of septic shock induced acute kidney injury: Apoptosis and leukocytic infiltration. Intensive Care Med 2010; 36:471–8
54. De Vriese AS, Vanholder RC, Pascual M, Lameire NH, Colardyn FA: Can inflammatory cytokines be removed efficiently by continuous renal replacement therapies? Intensive Care Med 1999; 25:903–10
55. Kellum JA, Johnson JP, Kramer D, Palevsky P, Brady JJ, Pinsky MR: Diffusive *versus* convective therapy: Effects on mediators of inflammation in patient with severe systemic inflammatory response syndrome. Crit Care Med 1998; 26: 1995–2000
56. Cole L, Bellomo R, Hart G, Journois D, Davenport P, Tipping P, Ronco C: A phase II randomized, controlled trial of continuous hemofiltration in sepsis. Crit Care Med 2002; 30: 100–6
57. Payen D, Mateo J, Cavaillon JM, Fraisse F, Floriot C, Vicaut E, Hemofiltration and Sepsis Group of the Collège National de Réanimation et de Médecine d'Urgence des Hôpitaux extra-Universitaires: Impact of continuous venovenous hemofiltration on organ failure during the early phase of severe sepsis: A randomized controlled trial. Crit Care Med 2009; 37: 803–10
58. Cole L, Bellomo R, Journois D, Davenport P, Baldwin I, Tipping P: High-volume haemofiltration in human septic shock. Intensive Care Med 2001; 27:978–86
59. Grootendorst AF, van Bommel EF, van der Hoven B, van Leengoed LA, van Osta AL: High volume hemofiltration improves right ventricular function in endotoxin-induced shock in the pig. Intensive Care Med 1992; 18:235–40
60. Grootendorst AF, van Bommel EF, van Leengoed LA, Nabuurs M, Bouman CS, Groeneveld AB: High volume hemofiltration improves hemodynamics and survival of pigs exposed to gut ischemia and reperfusion. Shock 1994; 2:72–8
61. Wang H, Zhang ZH, Yan XW, Li WQ, Ji DX, Quan ZF, Gong DH, Li N, Li JS: Amelioration of hemodynamics and oxygen metabolism by continuous venovenous hemofiltration in experimental porcine pancreatitis. World J Gastroenterol 2005; 11:127–31
62. Bellomo R, Kellum JA, Gandhi CR, Pinsky MR, Ondulik B: The effect of intensive plasma water exchange by hemofiltration on hemodynamics and soluble mediators in canine endotoxemia. Am J Respir Crit Care Med 2000; 161:1429–36
63. Rogiers P, Zhang H, Pauwels D, Vincent JL: Comparison of polyacrylonitrile (AN69) and polysulphone membrane during hemofiltration in canine endotoxic shock. Crit Care Med 2003; 31:1219–25
64. Grootendorst AF, van Bommel EF, van Leengoed LA, van Zanten AR, Huipen HJ, Groeneveld AB: Infusion of ultrafiltrate from endotoxemic pigs depresses myocardial performance in normal pigs. J Crit Care 1993; 8:161–9
65. Lee PA, Matson JR, Pryor RW, Hinshaw LB: Continuous arteriovenous hemofiltration therapy for Staphylococcus aureus-induced septicemia in immature swine. Crit Care Med 1993; 21:914–24

66. Rogiers P, Zhang H, Smail N, Pauwels D, Vincent JL: Continuous venovenous hemofiltration improves cardiac performance by mechanisms other than tumor necrosis factor-alpha attenuation during endotoxic shock. Crit Care Med 1999; 27:1848–55
67. Journois D, Israel-Biet D, Pouard P, Rolland B, Silvester W, Vouhé P, Safran D: High-volume, zero-balanced hemofiltration to reduce delayed inflammatory response to cardiopulmonary bypass in children. ANESTHESIOLOGY 1996; 85:965–76
68. Journois D, Pouard P, Greeley WJ, Mauriat P, Vouhé P, Safran D: Hemofiltration during cardiopulmonary bypass in pediatric cardiac surgery. Effects on hemostasis, cytokines, and complement components. ANESTHESIOLOGY 1994; 81:1181–9, 26A–27A
69. Cornejo R, Downey P, Castro R, Romero C, Regueira T, Vega J, Castillo L, Andresen M, Dougnac A, Bugedo G, Hernandez G: High-volume hemofiltration as salvage therapy in severe hyperdynamic septic shock. Intensive Care Med 2006; 32: 713–22
70. Honore PM, Jamez J, Wauthier M, Lee PA, Dugernier T, Pirenne B, Hanique G, Matson JR: Prospective evaluation of short-term, high-volume isovolemic hemofiltration on the hemodynamic course and outcome in patients with intractable circulatory failure resulting from septic shock. Crit Care Med 2000; 28:3581–7
71. Joannes-Boyau O, Rapaport S, Bazin R, Fleureau C, Janvier G: Impact of high volume hemofiltration on hemodynamic disturbance and outcome during septic shock. Asaio J 2004; 50:102–9
72. Oudemans-van Straaten HM, Bosman RJ, van der Spoel JI, Zandstra DF: Outcome of critically ill patients treated with intermittent high-volume haemofiltration: A prospective cohort analysis. Intensive Care Med 1999; 25:814–21
73. Piccinni P, Dan M, Barbacini S, Carraro R, Lieta E, Marafon S, Zamperetti N, Brendolan A, D'Intini V, Tetta C, Bellomo R, Ronco C: Early isovolaemic haemofiltration in oliguric patients with septic shock. Intensive Care Med 2006; 32:80–6
74. Ratanarat R, Brendolan A, Piccinni P, Dan M, Salvatori G, Ricci Z, Ronco C: Pulse high-volume haemofiltration for treatment of severe sepsis: Effects on hemodynamics and survival. Crit Care 2005; 9:R294–302
75. Laurent I, Adrie C, Vinsonneau C, Cariou A, Chiche JD, Ohanessian A, Spaulding C, Carli P, Dhainaut JF, Monchi M: High-volume hemofiltration after out-of-hospital cardiac arrest: A randomized study. J Am Coll Cardiol 2005; 46:432–7
76. Adrie C, Adib-Conquy M, Laurent I, Monchi M, Vinsonneau C, Fitting C, Fraisse F, Dinh-Xuan AT, Carli P, Spaulding C, Dhainaut JF, Cavaillon JM: Successful cardiopulmonary resuscitation after cardiac arrest as a "sepsis-like" syndrome. Circulation 2002; 106:562–8
77. Jiang HL, Xue WJ, Li DQ, Yin AP, Xin X, Li CM, Gao JL: Influence of continuous veno-venous hemofiltration on the course of acute pancreatitis. World J Gastroenterol 2005; 11:4815–21
78. Bellomo R, Tetta C, Brendolan A, Ronco C: Coupled plasma filtration adsorption. Blood Purif 2002; 20:289–92
79. Cruz DN, Antonelli M, Fumagalli R, Foltran F, Brienza N, Donati A, Malcangi V, Petrini F, Volta G, Bobbio Pallavicini FM, Rottoli F, Giunta F, Ronco C: Early use of polymyxin B hemoperfusion in abdominal septic shock: The EUPHAS randomized controlled trial. JAMA 2009; 301:2445–52
80. Morgera S, Haase M, Kuss T, Vargas-Hein O, Zuckermann-Becker H, Melzer C, Krieg H, Wegner B, Bellomo R, Neumayer HH: Pilot study on the effects of high cutoff hemofiltration on the need for norepinephrine in septic patients with acute renal failure. Crit Care Med 2006; 34:2099–104
81. Rimmelé T, Assadi A, Cattenoz M, Desebbe O, Lambert C, Boselli E, Goudable J, Etienne J, Chassard D, Bricca G, Allaouchiche B: High-volume haemofiltration with a new haemofiltration membrane having enhanced adsorption properties in septic pigs. Nephrol Dial Transplant 2009; 24:421–7
82. Uchino S, Bellomo R, Goldsmith D, Davenport P, Cole L, Baldwin I, Panagiotopoulos S, Tipping P: Super high flux hemofiltration: A new technique for cytokine removal. Intensive Care Med 2002; 28:651–5
83. Mandolfo S, Galli F, Costa S, Ravani P, Gaggia P, Imbasciati E: Factors influencing permanent catheter performance. J Vasc Access 2001; 2:106–9
84. Ricci Z, Ronco C: Pre- *versus* post-dilution CVVH. Blood Purif 2005; 23:338
85. Bellomo R, Tan HK, Bhonagiri S, Gopal I, Seacombe J, Daskalakis M, Boyce N: High protein intake during continuous hemodiafiltration: Impact on amino acids and nitrogen balance. Int J Artif Organs 2002; 25:261–8
86. Maxvold NJ, Smoyer WE, Custer JR, Bunchman TE: Amino acid loss and nitrogen balance in critically ill children with acute renal failure: A prospective comparison between classic hemofiltration and hemofiltration with dialysis. Crit Care Med 2000; 28:1161–5
87. Singer P, Berger MM, Van den Berghe G, Biolo G, Calder P, Forbes A, Griffiths R, Kreyman G, Leverve X, Pichard C, ESPEN: ESPEN guidelines on parenteral nutrition: Intensive care. Clin Nutr 2009; 28:387–400
88. Zhu Y, Zhang P, Yuan J, He Q, Jiang H, Hu X, Chen J: Adjunctive continuous high-volume hemofiltration in acute severe pancreatitis patients: A retrospective study. Scand J Gastroenterol 2009; 44:1363–9