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High-Volume Hemofiltration in Sepsis

Theoretical Basis and Practical Application

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Introduction

Continuous renal replacement therapy (CRRT) in the ICU is a common treatment in acute renal failure (ARF). CRRT is mainly conceived as merely supportive and as a replacement of the lost kidney function. On the other hand, evidence accumulating over the last years demonstrates that many soluble mediators of the systemic inflammatory (and anti-inflammatory) response syndrome can be removed by CRRT. This has led to the suggestion that CRRT could play a major role in sepsis therapy as immunomodulatory treatment and not only as a blood purification technique. In this perspective, whereas animals studies yielded encouraging results, early clinical trials only showed minor clinical benefits, mainly dealing with hemodynamic improvements. The question of treatment dose has appropriately been raised which still has to be defined and it represents a matter of controversy. A large-scale clinical trial has clarified issues on treatment dose in ARF, but a sufficiently powered study on hemofiltration dose in sepsis is still lacking.

In this article we will review the rationale for application of CRRT in treatment of the septic syndrome with specific focus on the use of high ultrafiltration rates (i.e. high-volume hemofiltration: HVHF). We will integrate the discussion into the most recent hypothesis proposed to explain some of the clinical results obtained with high efficiency non-selective removal of mediators of sepsis.

Further, we will describe the necessary technical requirements for HVHF and the most recent machine development concurring with these.

The Rationale of CRRT in Sepsis

The sepsis syndrome has been described as a systemic malignant inflammation, where the circulation is invaded by enormous amounts of pro-inflammatory mediators produced by activated mononuclear cells. In fact, sepsis is associated with an overwhelming, systemic overflow of both pro- and anti-inflammatory mediators; this leads to altered immune cellular responsiveness, generalized endothelial damage and multiple organ failure derived from a complete disruption of the 'immunological homeostasis' [1, 2].

The characteristics of the mediator network are of fundamental relevance in order to allow selection of the most rational and effective treatment approach. The network is redundant and synergistic; it acts like a cascade modulated by multiple positive and negative feedback loops. A vast array of humoral mediators involved have been identified exerting pro-inflammatory effects; on the other hand, a seemingly equally broad spectrum of molecules with opposite function has been demonstrated to emerge in the time course of the septic syndrome. Both pro- and anti-inflammatory mediators, while designed to mainly
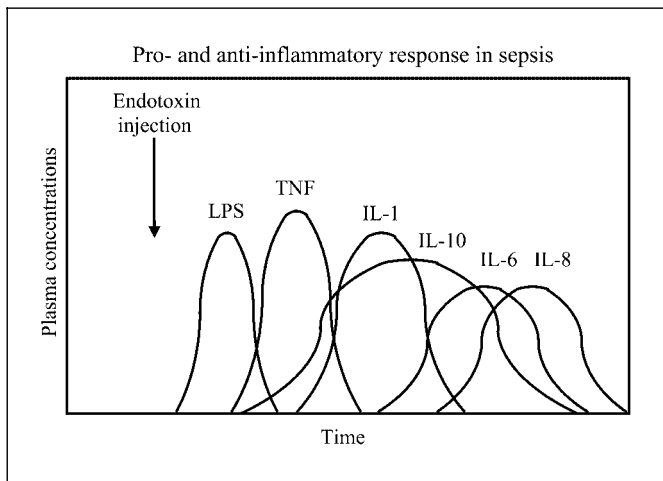
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Fig. 1. The sequential appearance of various cytokines in sepsis.

Fig. 2. The peak concentration hypothesis: the sequential appearance of various cytokines in sepsis is schematically depicted. By CRRT, peak plasma cytokine levels could be unselectively reduced bringing the organism at a less severe degree of immunological derangement. Lower levels of pro- and anti-inflammatory mediators could allow the restoration of immuno-homeostasis.

act in an autocrine and/or paracrine mode, are spilling over into the circulation during sepsis and display disastrous systemic effects. In some circumstances, depending on which additional stimuli are present, the same mediator can exert alternatively pro- or anti-inflammatory action. Apart from inciting substances (e.g. endotoxin, products of cell injury) and very early mediators of the septic process (e.g. complement factors, F XIIa) chemokines and cytokines have a central role in the propagation of the inflammatory process including regulatory effects on immune cells. In fact, mortality in sepsis is correlated with persistently elevated levels of pro-inflammatory cytokines [3, 4] and in a parallel way, persisting immune cellular hypo-responsiveness associated with high levels of anti-inflammatory cytokines [5, 6]. This has been similarly observed early in the sequence of effects induced by endotoxin injection in animal models (fig. 1) [7].

The Peak Concentration Hypothesis

The concept of blocking one mediator has not led to measurable outcome improvement in patients with sepsis [8]. Possibly more rigidly defined subgroups would gain profit by TNF-antagonizing treatments [9]. On the other hand, it has been shown that antagonizing a cytokine could lead to deleterious consequences encompassing substantially higher mortality [10]. A low-level TNF response seems to be necessary for the host defense to infection [11, 12] as well as high levels seemingly need to be modulated by an anti-inflammatory feedback; in sepsis, howev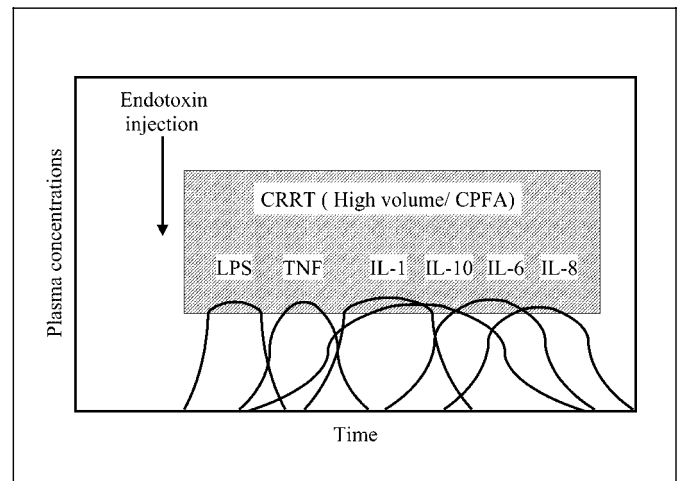er, failed regulation may cause an excess of anti-inflammatory response which generates monocyte downregulation and exposes to further infections. Both these processes (inflammation and anti-inflammation) are designed to act in response to specific stimuli in a well-balanced fashion defined as immuno-homeostasis. The excess of one over the other may produce a deleterious effect either leading to systemic inflammation or immune-cell hyporesponsiveness. In the septic syndrome, it seems that these processes are both exaggerated in the time course of the disease and may put the patient alternatively at risk for endothelial dysfunction and shock, or overwhelming infections.

Furthermore, the time point in the septic process of therapeutic intervention seems to be crucial. As the network acts like a cascade early intervention would seem most beneficial. On the other hand, sepsis does not fit a one-hit model but shows complex and varying time courses in mediator levels. Neither single-mediator-directed nor one-time interventions therefore seem appropriate.

One of the major criticisms attributed to continuous blood purification treatments in sepsis – its lack of specificity – could turn out to be a major strength. Unspecific removal of soluble mediators – be they pro- or anti-inflammatory – without completely eliminating their effect may be the most logical and adequate approach to a complex and long-running process like sepsis. The concept of cutting peaks of soluble mediators, e.g. through continuous hemofiltration (fig. 2), is a paradigm called by us 'the peak concentration hypothesis' [13].

Ultrafiltration Dose and Outcome

Numerous in vitro as well as animal and human studies [reviewed in 14] have shown that synthetic filters in common use in hemofiltration can extract nearly every substance involved in sepsis to a certain degree. Prominent examples are complement factors [15, 16], TNF, IL-1, IL-6 [17–19], IL-8 [20] and PAF [21].

Regarding plasma cytokine levels the decreases appeared nevertheless of minor degree. Other studies could not show any influence on cytokine plasma levels by CRRT [22, 23].

On the other hand significant clinical benefits in terms of hemodynamic improvement have been achieved even without measurable decreases in cytokine plasma levels [24].

Obviously the removal of substances different to the measured cytokines was responsible for the achieved effect. In alternative, bioactive substances including some of the measured cytokines were removed causing the observed beneficial effect. When the response to sepsis is viewed in a network perspective, absolute values would be less relevant than relative ones within an array of interdependent mediators as even small decreases could induce major balance changes. This makes measurement of cytokine plasma levels debatable whilst more local or tissue levels should be measured. These issues are extremely controversial and do not permit a definitive solution in favour or against the use of CRRT as a therapy of sepsis. In this context a further step in clarifying the immunological impact of CRRT has been taken by measuring a more downstream event integrating several cytokine influences: the monocyte responsiveness [25, 26].

In spite of some encouraging results as mentioned, the extent of achievable clinical benefit with conventional CRRT (using conventional filters and flow rates) in sepsis has generally been disappointing. Consequently it was sought to improve the efficiency of the methodology regarding removal of soluble mediators of sepsis by increasing the amount of plasma water exchange, i.e. increasing ultrafiltration rates.

Animal studies provided much support of this concept. Starting in the early nineties several studies using different septic animal models examined the effect of high ultrafiltration rates (up to 300 ml/kg/h) on physiological parameters and outcome.

In a landmark study, a porcine model of septic shock induced by endotoxin infusion was investigated [27]. The animals developed profound arterial hypotension and a decrease in cardiac output, stroke volume and right ventricular stroke work index. By HVHF at 6 liters/h right ventricular function, blood pressure and cardiac output showed a remarkable improvement compared to control and sham-filtered animals [27, 28]. The same group extended their findings in the same model by intravenously administering ultrafiltrate of endotoxin-infused animals into healthy animals. These developed a hemodynamic picture similar to septic shock whereas animals infused with ultrafiltrate of healthy animals showed a moderate blood pressure rise [29].

In a further study by the same group a bowel ischemia-reperfusion model in pigs was investigated. HVHF started before clamping of the superior mesenteric artery significantly diminished bowel damage and prevented hemodynamic deterioration [30].

These classic studies established that a convection-based treatment can remove substances with hemodynamic effects resembling septic shock, when sufficiently high ultrafiltration rates are applied.

Several studies confirmed and refined these results. In three of them [31–33] the correlation of survival with ultrafiltration rate was specifically examined. A direct correlation could be demonstrated. Significant improvements in cardiac function, systemic and pulmonary vascular resistance and hepatic perfusion [31] were found. Another study in lambs showed significant improvements in lung function [34]. Only a minority of studies identified reduced mediator plasma levels [33, 35].

A very recent study in pigs made septic by induced pancreatitis compared low-volume CVVH with HVHF of 100 ml/kg/h. In the same study the influence of frequent filter changes on survival, changes in TNF levels as well as monocyte and PMNL function was analyzed [33]. Early filter change allows to delineate the effect of cytokine removal by adsorption on the filter since membrane capacity saturates after a few hours. By changing filters, adsorption is continued to a certain extent.

In this model a hyperdynamic septic picture is induced through an intervention which approximates underlying conditions encountered in human sepsis. Additionally the intervention started late to simulate real clinical conditions. Hemofiltration was commenced when the animals developed the clinical picture of hyperdynamic septic shock. HVHF was superior in all mentioned endpoints and, importantly, increasing ultrafiltration had more effect than frequency of filter change [33].

Of major influence concerning human sepsis studies has been the finding that ultrafiltration dose is correlated to outcome in critically ill patients with ARF. In a large randomized, controlled study including 425 patients, an
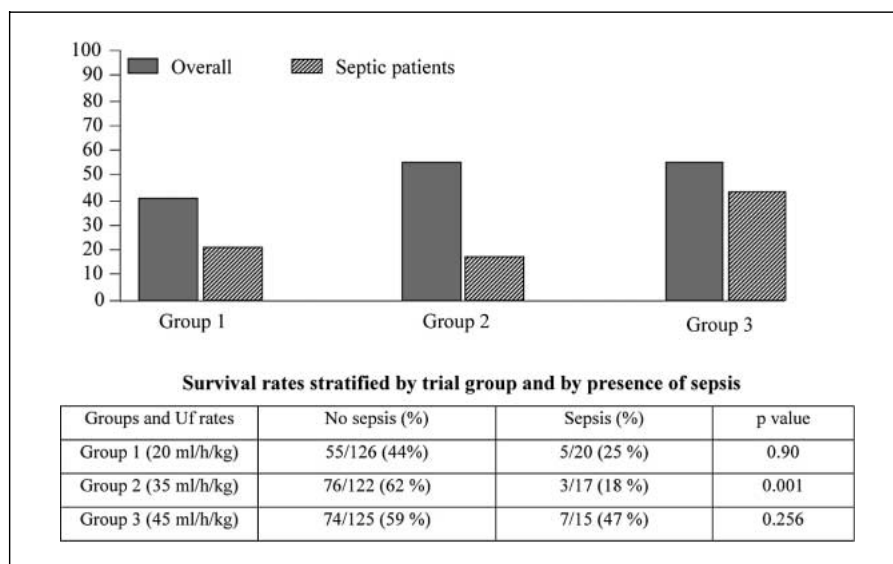
Survival rates stratified by trial group and by presence of sepsis

Groups and Uf rates	No sepsis (%)	Sepsis (%)	p value
Group 1 (20 ml/h/kg)	55/126 (44%)	5/20 (25 %)	0.90
Group 2 (35 ml/h/kg)	76/122 (62 %)	3/17 (18 %)	0.001
Group 3 (45 ml/h/kg)	74/125 (59 %)	7/15 (47 %)	0.256

Fig. 3. Survival rates observed in patients treated with different hemofiltration dose. While the effects is evident in the overall population from group 1 to group 2 and no further effect is observed on group 3, when patients are stratified for sepsis, a significant effect of higher doses of treatment is observed in group 3.

ultrafiltration dose of 35 ml/kg/h increased survival rate from 41 to 57% compared to a dose of 20 ml/kg/h [36].

Eleven to 14% (per randomization group) of the patients had sepsis. In these subgroups there was a trend of direct correlation of treatment dose with survival even above 35 ml/kg/h in contrast to the whole group where a survival plateau was reached (fig. 3).

This lends support to the concept of a 'sepsis dose' of hemofiltration in septic patients contrasting to a 'renal dose' in critically ill patients without systemic inflammation, the former being probably distinctly higher (without proven upper limit). Of note, there was no increase in adverse effects even with the highest ultrafiltration dose.

Over the last years several human studies examined the clinical effects of high-volume hemofiltration. In 20 children undergoing cardiac surgery, zero-balanced HVHF was administered with UF rates equivalent to 7–9 liters/h for a 70-kg adult [37]. Endpoints correlating to the cardiopulmonary-bypass-associated delayed inflammatory response were examined. There was a significant reduction in post-operative blood loss, time to extubation and improvement in the arterial-alveolar oxygen gradient.

In a prospective cohort analysis in 306 critically ill patients with varying underlying diseases a mean ultrafiltration rate of 3.8 liters/h was applied [38]. Observed survival rates were significantly higher in the treated population compared to predicted survival by three well-validated scores.

A study in 12 critically ill patients with ARF comparing low-volume CVVH (1,500 ml/h) with a high-volume technique was performed in a non-randomized, comparative fashion [39]. High-flux bicarbonate dialysis amounting to 4,200 ml/h was used and the effect on monocyte responsiveness (ex vivo endotoxin-stimulated TNF production) was studied. Both techniques resulted in early improvement but only in the high-volume technique displayed persistent effects. Ultrafiltrate contained monocyte suppressive activity only with high-flux dialysis.

In another trial in 11 septic patients with shock and MODS a randomized cross-over design of 6 vs. 1 liters/h ultrafiltration was applied [40]. The HVHF group displayed significantly greater reduction in vasopressor requirements (fig. 4). Both treatment groups showed a decrease in C3a and C5a plasma levels which was significantly greater in the HVHF group.

Impressive clinical results were obtained in an evaluation of short-term HVHF in 20 patients in catecholamine-refractory septic shock [41] comprising a patient cohort with very poor expected survival. A control group was not defined. Only one 4-hour session of HVHF removing 35 liters of ultrafiltrate replaced by bicarbonate-containing fluid was applied as soon as mean blood pressure could not be stabilized above 70 mm Hg with dopamine, norepinephrine and epinephrine after appropriate volume resuscitation. HVHF was followed by conventional CVVH. Endpoints were the increase in cardiac index, mixed venous oxygen saturation and arterial pH and decrease in epinephrine requirements. Eleven patients reached all predefined endpoints and showed impressively good survival (9 of 11) at 28 days. Nine patients did not reach all endpoints and had a 100% mortality rate. Apart
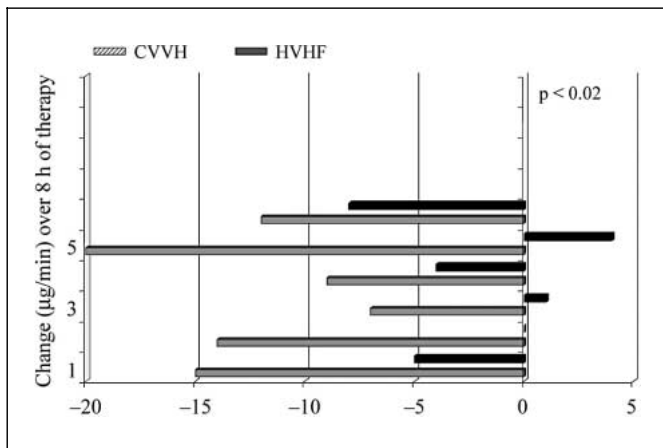
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Fig. 4. Significant reduction in norepinephrine requirement is observed in unstable septic patients treated with high-volume hemofiltration. Less evident is the effect of low-volume CVVH.

from responding to HVHF, only time from ICU admission to start of HVHF and body weight were survival-associated factors in the analysis. Patients with higher body weight did worse possibly because they received a smaller ultrafiltration dose per body weight as speculated by the authors.

These trials still need cautious interpretation with respect to their limited design, but they certainly deliver sound evidence of feasibility and efficacy to set the stage for a large-scale trial on HVHF in sepsis.

Unsolved Issues

Ultrafiltration is associated with loss of a vast array of water-soluble substances. Not all of these losses are desired and many have not been characterized quantitatively [42] or even qualitatively. HVHF constitutes a major intervention in acid-base balance as much strong ions and up to now poorly defined small to middle molecular acids (and bases) of intermediate metabolism are filtered.

Furthermore, lactate replacement fluid leads to hyperlactatemia which possibly can be tolerated well even in septic shock [43], but not in all patient groups [44, 45]. Bicarbonate replacement would appear physiologic but is very expensive and not available in many parts of the world.

Losses of hormones, vitamins, molecules of intermediate metabolism and amino acids in HVHF have not been studied up to now. As CRRT can be regarded as a powerful metabolic intervention (constituting a contin-

uous plasma water exchange), its intensification by using HVHF may encompass undefined dangers (by loss of specific substances, by high lactate loads). On the other hand, it possibly opens a therapeutic avenue to administer substances with specific metabolic activity without volume restriction (e.g. inosine [46], pyruvate [47]).

Another issue involved the modification of thermal energy balance especially when high volume of fluid is exchanged. Specific studies have not been carried out, but an increasing consensus exists on the need for a fluid warmer in the newly designed machines.

Methodological Aspects of HVHF

Major methodological details in using a technique which deserves a fluid exchange rate of 6 liters/h and more (possibly up to 10 liters/h what would equal about 140 ml/kg in a 70-kg adult) have to be considered. To avoid excessive hemoconcentration within the filter with consecutive clotting problems high blood flows in the range of 400–500 ml/min have to be applied. For the same reason at least part of the replacement fluid has to be administered in a predilution mode. This may reduce middle molecule clearance proportionally by the dilutional effect at filter entry [55].

Certainly high volumes increase risks of technical problems (catheter problems, disconnection, dosing errors). Catheters have to be large to tolerate blood flows at least above 300 ml/min. High blood flows must be maintained at all times and in variable patient positions with minimal recirculation.

Consequently, the technique needs a high level of supervision by experienced personnel exclusively devoted to the treated patient. Most practical in this respect seems to be an intermittent technique with HVHF over 4–8 h during daytime embedded in conventional CVVH for the rest of the day. Furthermore, high amounts of replacement fluids are needed which may reach financial limits. Systems designed for in-line preparation of fluids by cascade filtration may have to be considered.

Obviously the hemofiltration machine is vital for the safe performance of HVHF. First of all machines need to be capable of administering volumes in this range including warming capacity. Further safety regards are appropriate pressure monitoring, exactness in applying high volumes and calculating balances. Certainly a friendly user interface and the easiness of use is a must (fig. 5).

The Aquarius Haemofiltration machine (ELS, Germany) has been developed specifically to reach the above-mentioned goals and serves as a representative of the latest generation of machines in the field. In this machine, HVHF can be performed in addition to all other types of blood purification therapies considered for use in the ICU.

Blood flows required for effective HVHF in the range of 300–450 ml/min can be programmed. Ultrafiltration rate in the range of 6 liters/h (requiring replacement fluid infusion rates of about 100 ml/min) can be prescribed as well.

The Aquarius machine delivers pump flow rates up to 450 ml/min for blood, up to 10 liters/h for pre- or postdilution replacement and up to 2,000 ml/h for additional fluid removal.

Volume accuracy as well as sensitive, fast-response pressure monitoring is of utmost importance in these high ranges.
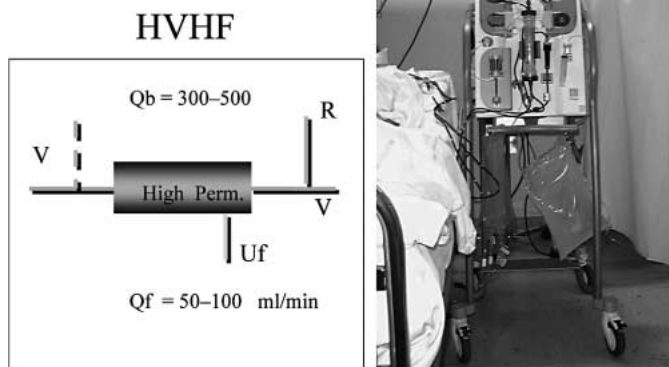
Fig. 5. High-volume hemofiltration performed either in pre or post-dilution modes (machine: Aquarius from Edwards Life Sciences GmbH, Unterschleissheim, Germany).

Fig. 6. Coupled plasma filtration with adsorption. Plasma filtered in a plasma filtration unit is circulated through an adsorbent cartridge and then returned to the main stream. Reconstituted blood is then dialyzed (machine: Multimat B from Bellco s.p.a., Mirandola, Italy).

This is properly realized with scales ensuring substitution and filtrate volume accuracy with 0.1% precision. Pump accuracy reaches 5%. Only a 50-gram deviation of the target value is permitted before alarming will be activated. Precision within this range is obligatory for HVHF.

Replacement fluid can be administered in a pre- and post-dilution mode and concurrently. Pressure monitoring is installed in the access and return line as well as in a prefilter position and in the ultrafiltrate compartment. Sensor accuracy amounts to ± 5 mm Hg. The pressure sensors operate without blood-air interface. Air embolism is prevented by an ultrasonic air detector which controls a line clamp. Effective heating capacity is essential when high volumes are processed. Otherwise major energy losses and possibly severe hypothermia could be induced in the patient. For this purpose the machine uses a coil-tubing design which ensures heating up to 39°C up to 6 liters/h fluid turnover. HVHF is a high-risk procedure regarding immediate consequences of technical or user errors. In order to minimize their probability of occurrence user-friendly properties are of high priority. This need is served by the concept of a one-button machine. A single selector knob guides all functions supported by a self-explanatory screen.

Other Approaches to High Efficiency Blood Purification in Sepsis

Cytokines and other immunomodulating substances have generally molecular weights in the range from 5 to 50 kD. They may be eliminated by diffusion, convection or adsorption depending on material and the rather variable cut-off of highly permeable membranes (from 30 to 40 kD) [17]. A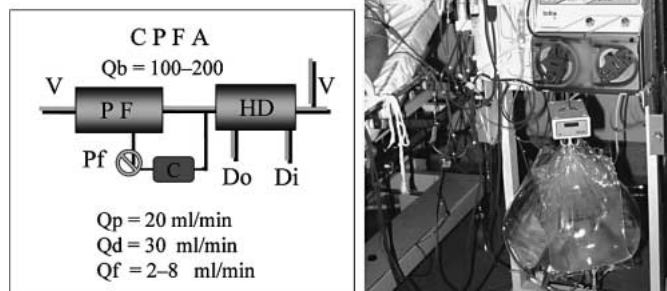s adsorptive processes easily saturate and are therefore transient, the effect of CRRT on sepsis could be limited because of a low convective clearance of many mediators.

Therefore other approaches to achieve higher mediator clearance in sepsis have been sought. Apart from increasing ultrafiltration rates, higher removal rates of middle molecular weight molecules could be achieved by enlarging pore size of membranes. Animal data [49, 50] as well as preliminary clinical data [51] demonstrate feasibility and probable superior removal rates of select cytokines using larger cut-off membranes.

A study in 30 patients with severe sepsis using continuous plasmafiltration for 34 h [52] found attenuation of the acute-phase response and a trend towards clinical benefit although not significant (fewer failing organs). A further refining has been achieved with plasma filtration coupled with adsorption and followed by dialysis or filtration (fig. 6) [53]. This would allow effective removal of mediators in the borderline zone of filtration by hemofilters (40–60 kD) without the need of exogenous plasma replacement. Furthermore higher plasma clearance rates could be achieved. An animal study [54] and a first clinical trial reported beneficial effects on hemodynamic and immune cell function [26, 55].

Conclusions on efficiency would be premature to draw. Taken the available data together more studies are required to see a major advantage in laboratory and clinical endpoints with plasma filtration compared to ultrafiltration techniques.

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Certainly larger pore size membranes and plasma filtration combined with sorbent techniques enlarge the therapeutic armamentarium significantly. They constitute a promising adjunctive modality easily to be used in combination with hemofiltration.

Concluding Remarks

A vast array of mostly water-soluble mediators play a strategic role in the septic syndrome. Compared to eliminating or completely antagonizing single mediators, therapeutic intervention by nonselective removal of pro- and anti-inflammatory mediators seems a rational and possibly superior concept. A further advantage seems to be constituted by a continuously acting therapy as in the case of continuous renal replacement therapies. Hereby, sequentially appearing peaks of systemic mediator overflow could be curbed as well as persistently high plasma levels reduced. This process is proposed as the underlying biological rationale for a series of innovative therapies in sepsis. The whole story of antagonizing pro- and anti-inflammatory processes by reducing the relative excess of active substances undergoes the term of 'peak concentration hypothesis'.

Recent animal and human trials have delivered much support to this concept. It has been conclusively shown that treatment dose in CRRT is a major factor concerning survival in ARF in the critically ill patient. There is accumulating evidence of increased efficacy of high-volume hemofiltration compared to conventional CVVH in terms of laboratory and clinical improvement including survival. Machines to perform HVHF safely are available on the market.

Yet the evidence still is not strong enough to recommend HVHF outside clinical studies taking into account possible adverse effects of the technique. A large-scale clinical trial is urgently needed to resolve the issue.

Other blood purification techniques using large pore membranes or plasma filtration with sorbent perfusion are in the early stages of clinical testing. They are conceptually promising and possibly constitute an important refinement.

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