High volume haemofiltration and hybrid techniques in sepsis: new insights into the rationale

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Introduction
For more than a decade it has been advocated (1, 2) that the reduction of cytokines in the blood compartment could, in theory, lead to a reduction in mortality in the septic patient. However, in the knowledge that the pharmacodynamics and pharmacokinetics of cytokines can best be described as complex, it is fair to say that this is an oversimplification of the situation.

In recent years, three separate theories have been put forward as possible explanations for the clinical findings in septic patients undergoing a number of different blood purification techniques. The high volume haemofiltration (HVHF) and the hybrid techniques presently available to the clinician are diverse in nature and deserve further description. It is the inherent nature of these techniques that determines their suitability for one or more of the three theories described.

There is still no consensus on the definition of high volume but we report on the final proposals made by a recent working party report. (3) These are: continuous high volume consisting of a dose higher than 35 ml/kg/h. Pulse high volume consisting of a dose higher than 45 ml/kg/h (the post hoc analysis in Ronco’s study suggests that this method is beneficial in septic acute renal failure(4)) carried out for a run of 4, 6 or 8 hours on condition that pulse therapy be directly followed by a continuous dose of continuous renal replacement therapy (CRRT) at 35 ml/kg/h (3).

Three theories
In the peak concentration hypothesis (5, 6, 7) described by Ronco and Bellomo [Figure I] efforts are concentrated on removing mediators and cytokines from the blood compartment in the pro-inflammatory phase of sepsis. It is hoped that by reducing the amount of free cytokines, remote organ and associated damage can be limited, thereby attenuating associated mortality. Changes in mediators and cytokines at interstitial and tissue level are not taken into account in this theory, except that they are of clinical importance. In this setting, techniques that facilitate rapid and substantial removal of mediators are preferred.

After an extensive literature review, a model was developed that coupled mediator removal from the blood compartment to changes in interstitium and the blood compartment.

This second concept, the Threshold Immunomodulation hypothesis [Figure II], sometimes referred to as the Honore concept (8,9), takes a far more dynamic view of the system. Pro-mediators as well as mediators are removed at interstitial and tissue levels, following removal from the blood compartment, until the threshold point is reached, at which time some pathways and cascades are brought to a complete standstill. At this level, the cascade is subsequently lost and no further harm can be done to the tissue of the organism. However, in clinical practice when applying high volume haemofiltration, determining this point is fraught with difficulty as there might be significant changes at interstitial and tissue level, while no changes in the blood compartment can be determined. A number of studies using haemofiltration, although observational only, have demonstrated improved haemodynamics and survival in some patients without a significant drop of mediators inside the blood compartment itself (10,11,12). It may therefore be concluded that the substantial biological effects of HVHF are obtained without any dramatic fall in plasma cytokine level because cytokine or mediator levels fall at tissue level where they do harm. Although, the study done by Klouche et al (12) was not performed using HVHF, but lower volumes the results of this study support the theory. This model has not yet shown how HVHF promotes mediator and cytokine flow from tissue and interstitium to the blood compartment.

The Mediator Delivery hypothesis [Figure III] (13), otherwise known as the Alexander concept, emphasizes the use of high volume haemofiltration and high replacement volumes (3 to 5 litres/hour) in particular. Several papers have demonstrated a 20 to 40-fold increase in lymphatic flow (14,15,16) with concomitant substantial drag and displacement of mediators and cytokines to the blood compartment, making them available for removal. Thus, the use of high volumes of replacement fluid might be of great importance, not only for extraction but also to propagate lymphatic transport between the interstitium and tissue on the one hand and the blood compartment on the other.

Blood purification techniques
A number of blood purification techniques are currently available to the clinician treating sepsis in the ICU. Despite this myriad of different techniques, solute transport is effectuated either by diffusion or convection, ad-or absorption or a combination of these modalities. In classic intermittent haemodialysis (IHD) and derived techniques utilized in the ICU, diffusion (a concentration gradient across a semi-permeable membrane causes solute transport) is the driving force behind solute removal. In haemofiltration and derived techniques, solute removal is perpetuated by convection (a pressure gradient causes fluid movement across a semi-permeable membrane with so-called solute drag), favouring removal of middle molecules. Convection is more effective than diffusion in removing middle molecules.
Despite this, there is no firm evidence favouring one form of solute clearance over the other in the septic patient, nor is there evidence favouring a continuous technique above intermittent haemodialysis. However, there is evidence to suggest that if a continuous technique is available, clinicians are more inclined to choose it for the unstable patient.(27). It stands to reason that the delivered dose, as in conventional intermittent haemodialysis outside the ICU setting, could influence morbidity and therefore mortality. Consequently, positive results have been described in a number of randomized controlled studies both for intermittent haemodialysis (18), for continuous veno-venous haemofiltration (4), and for a combination of both (19).

However, a smaller randomized controlled trial (RCT), found no association between survival and ultrafiltration dose.(20) It should be pointed out that in this study 28-day survival in all groups was relatively high as compared to other studies, suggesting that the study population differed from that of other studies. However, severity of illness scores do not support this suggestion. In addition, hospital survival in the Bouman study (63, 49 and 61 respectively) was comparable to 90-day survival in the Saudan study (59% and 34% respectively and 63 and 38% respectively, if untreated and moribund patients were excluded). (19,20). As mentioned above, a number of observational studies (10,11,12), with higher fluid replacement in continuous veno-venous haemofiltration CVVH, seem to demonstrate an additional effect, though methodological restrictions surely apply.

A position paper published by an ADQI (Acute Dialysis Quality Initiative) group, has underlined that HVHF could be used by clinicians in catecholamine resistant septic shock (CRSS) (Level V Evidence and Grade E Recommendation) (22,23). The same position paper supported extended use of fluid replacement at the 35 ml/kg/h in CVVH (D) Level II Evidence and a Grade C Recommendation (22). A recent guideline, based on an updated literature review, published in the Netherlands Journal of Critical Care elevates this to a Grade A recommendation (24).

Nevertheless, it is difficult at this point to differentiate a recommended dose for septic versus non-septic ARF, as in nearly all reported randomized studies, the population studied was a mixture of both types of patient and therefore, we have to await the results of ongoing trials regarding strictly septic ICU-ARF (acute renal failure) populations.

The knowledge that many mediators have molecular weights exceeding the cut-off points of conventional haemofilters has led to the development of techniques whereby filter porosity is increased (25-30). High permeability haemofiltration (HPHF)(31), super-high flux haemofiltration (SHHF)(32), and haemo-adsorption (27) are examples of these. Indeed, in a pilot study, Morgera et al. demonstrated a decreased dose of norepinephrine in the HPHF group, coupled with a lower plasma levels, with a demonstrable clearance increase in mediators (IL-6, IL-1ra) (31). However, this study, though promising, was not designed to study patient survival, nor was ultrafiltrate replacement rate fully optimized.

The use of haemofilters with increased filter porosity is burdened by the potential risk of loss of larger beneficial molecules (drugs, hormones, nutrients, anti-inflammatory components). Because of this, a number of hybrid techniques were developed such as coupled plasma filtration and adsorption (CPFA) (33) and cascade haemofiltration (CHHF) (34), whereby the type of substances removed can be targeted more precisely.

In theory, removal of relatively large molecules within a narrow band of molecular weight is then possible in these hybrid techniques. It should be pointed out that, strictly speaking, in some techniques, adsorption is not the appropriate term as blood is flowing through a semi-permeable membrane. Therefore, the latter is not the net effect of convective plus oncotic forces that result into the passage of mediators through this kind of device. It is then more appropriate to use the term absorption as chemical and physical forces come into play in this setting (22).
Which technique for which theory? A discussion

In the setting of the peak concentration hypothesis, techniques removing cytokines or mediators from the blood compartment more rapidly and substantially are privileged. Intrinsically, both convective and diffusion techniques are able to clear the blood compartment of mediators. However, in both the threshold immunomodulation hypothesis and the mediator delivery hypothesis, effects are brought to bear outside the blood compartment in the interstitium and at tissue level, whilst in the latter, a high fluid replacement rate is obligatory. Preference is then given to high volume (and possibly very high volume) haemofiltration techniques as well as a number of hybrid techniques using high fluid replacement, though as yet these conclusions remain speculative (35,36).

Very high volume is defined by pulse-HVHF over 100 ml/kg/h on the condition that pulse is followed by CRRT at 35 ml/kg/h according to the latest proposals from a working party report (3). In clinical practice dose most definitely plays an important role, despite the fact that no mode of renal replacement therapy has been proved superior. Both in the paper published by the ADQI group and in the recent guideline presented in this journal, an effluent rate of at a rate of at least 35 ml/kg/h was recommended in CRRT. In IHD a similar dose corresponds to a single pool Kt/V of 1.4 per day, thereby implying the need for daily IHD in case this mode is chosen.(37) It stands to reason that up to now, the dose recommendations apply to every critically ill patient with ARF whether it is secondary to sepsis or not. In classic hyperdynamic septic shock on the ICU, particularly if accompanied by acute septic renal injury or acute septic renal failure (based on the RIFLE classification), the results of a number of dose outcome studies (the ATN study in the US, the Renal study in Australia and New Zealand and the IVOIRE study in Europe) are awaited with interest. (38,39). RIFLE is an acronym of Risk, Injury, Failure, Loss and End Stage in relation to kidney function (40). Two of these dose outcome studies are not restricted to acute septic injury as both the ATN and RENAL studies did not restrict their inclusion criteria to only septic renal injury but also included non-septic injury. The IVOIRE study is ongoing and has the potential to give us important insights for the future, hopefully giving us further tools for optimal dosing in subgroups of septic patients with acute renal injury. More than 480 ICU patients with septic shock plus acute renal injury defined by the RIFLE classification will be included.

After computer randomization into two groups, one group receives 35 ml/kg/h and the other group 70 ml/kg/h. In the light of the findings of the Ronco study (4), in which septic patients in the 45 ml/kg/h group tended to have better survival, this study was designated to demonstrate increased overall survival in the higher dose group (70 ml/kg/h). This study is now fast approaching the first interim analysis (38,39). Finally, we summarized the positive and negative studies regarding specifically HVHF in Sepsis or SIRS (systemic inflammation response syndrome) plus ARF (Table 1) and ranking those studies with their level of evidence. We chose the studies which had the most scientific merit in terms of design and number of patients included (39,40).

Conclusions

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 led to promising findings. However, for the present conclusive evidence on the basis of well designed randomized controlled trials remains scarce, limiting the practical implementation of many techniques in daily practice outside the context of a study. The three theories described undoubtedly have a role to play in the further development and study of techniques and go some way in explaining findings to date.

On the basis of the few well designed and documented studies it is safe to say we have shown that optimization 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 with confidence. The results of further dose outcome studies with higher ultrafiltration rates will likely be the stepping stone to further improvements in daily clinical practice. Surely hybrid techniques will have a role in the expanding field of renal replacement therapy in the septic patient. For now, the jury is out.

Keywords

Hemofiltration, high volume, sepsis, rationale, review, acute kidney injury.
References


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