Role of adsorption for Renal Replacement and Support in Sepsis and Multiple Organ Failure

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INTRODUCTION

Sepsis is the leading cause of acute renal failure and mortality in intensive care units. It generally develops as a result of the host response to infection. The pathogenesis of sepsis, represents a complex mosaic of inter-connected events in respect to which therapeutic strategies remain elusive. Sepsis may be considered a form of severe systemic inflammation due to local and systemic effects of circulating pro-inflammatory mediators. Although several therapeutic attempts have targeted specific components in the pro-inflammatory septic cascade, no improvement in survival has been obtained in large-scale clinical trials focusing on specific molecules. Components of Gram-negative bacteria cell wall, such as the lipid-A containing lipopolysaccharide (LPS), trigger a global response that involves both cellular and humoral pathways with the generation of pro- and anti-inflammatory mediators. These include a major group of middle molecular size (5-30 kilodaltons) peptides, collectively called as cytokines, phospholipase A2-dependent products such as platelet-activating factor (PAF), leukotrienes and thromboxanes, complement-derived activated products such as C3a, C5a and their desarginated products. Other agents play a role in the pathophysiology of sepsis such as surface- expressed and soluble adhesion molecules, kinins, thrombin, myocardial depressant substance (s), b-endorphin and heat shock proteins. In normal conditions, the biological activity of these mediators is under the control of specific inhibitors that may act at different levels. In sepsis or SIRS (systemic inflammatory response syndrome) the homeostatic balance is altered and a profound disturbance of relative production of different mediators may be observed. The pathogenesis of sepsis might therefore be described by a sudden and severe imbalance of pro- and anti- inflammatory factors in the host. The concept of sepsis as a simply pro-inflammatory event has been consequently challenged. Recent studies on knockout mice have shown that deficiency of the gene encoding for ICAM-1 renders mice resistant to the lethal outcome of high-dose endotoxin shock. In these conditions, cell-associated cytokines in peripheral blood mononuclear cells (PBMCs) is decreased and the capacity of these cells to produce TNF-α and IL-1β in vitro, in response to LPS is significantly reduced. Hyporesponsiveness is not only present in monocytes but it occurs in whole blood and it is associated with increased plasma levels of IL-10 and prostaglandin E2 which are known to inhibit the production of proinflammatory cytokines. Terms such as monocyte deactivation, immunoparalysis or more simply cell hyporesponsiveness have been introduced in order to illustrate the incapacity of cells to respond to LPS stimuli due to overproduction of anti-inflammatory cytokines. All therapies specifically devoted to sepsis have so far obtained frustrating results. Liano et al prospectively observed that acute renal failure in ICU occurs predominantly as part of a multiple organ failure, while isolated acute renal failure is the usual presentation in non-ICU patients. This studied implied a higher mortality in critically patients who developed ARF supporting the concept of a direct effect of the ARF itself on the mortality. Nevertheless, not only therapeutic strategies should be applied to treat acute renal failure itself, but any available technique should be involved in the possible prevention of such derangement. This global approach may probably help in modifying the course of the septic syndrome and it may have an impact on mortality of the critically ill patients.

CONTINUOUS RENAL REPLACEMENT THERAPIES (CRRT)

Critically ill patients with ARF are preferably treated with CRRT. Conventional CRRT such as hemofiltration (CVVH) or hemodiafiltration (CVVHDF) have allowed to treat patients who could not be treated otherwise, due to the remarkable hemodynamic instability and the severe catabolic status. Due to slow and gentle ultrafiltration, CRRT make possible to control fluid and electrolyte balance maintaining the patient in steady hemodynamic conditions. Continuous fluid removal allows to infuse large amounts of fluids and to ensure adequate caloric intake. The advantages reported for CRRT involve a series of clinical aspects.

Solute removal appears to be very efficient in continuous therapies because of the steady concentration of toxins maintained in the circulation. Due to the low clearance, major imbalances between intravascular and extravascular compartments are not observed and solute removal occurs with a single pool kinetics. This is in contrast to what is observed in short highly efficient hemodialysis treatments where a remarkable reduction in serum concentration is observed during treatment, but a significant concentration rebound takes place after the session demonstrating the presence of a series of sequestrated solute pools. This remarkably reduced the efficiency of intermittent treatments and limits the dose of blood purification delivered under such circumstances.

Fluid removal is achieved in presence of a remarkable hemodynamic stability. This is the result of a slow continuous ultrafiltration in CRRT which never exceeds the capacity for intravascular refilling from the interstitium. In this way, blood volume is maintained during treatment and organ perfusion is not impaired. Considering that fresh ischemic renal lesions have been found in autopsies after 30 days or more from the oncet of acute renal failure, this may considered a mayor advantage of CRRT. Aggressive ultrafiltration during intermittent hemodialysis may in fact contribute to a decrease in circulating blood volume and impaired renal perfusion especially in the presence of loss of renal autoregulation. In this sense, CRRT may result as a protective therapy leading to the best possible clinical course of the syndrome and to the early recovery of renal function. Other aspects are important when considering a renal replacement therapy in sepsis and multiple organ dysfunction. Electrolyte and acid-base disorders may frequently occur. Due to the possibility of infusing customized replacement solutions, virtually any disorder can be corrected. Not only correction is possible, but also a subsequent maintenance of steady physiologic conditions is facilitated by the use of CRRT.

Thanks to all these advantages, CRRT are today considered a first choice treatment in the patient suffering from renal dysfunction during sepsis.

In spite of these definite advantages, the role of CRRT in the framework of blood purification has been challenged and it is sometimes considered of minimal or no clinical relevance. Nevertheless, the use of CRRT is expanding and new potential advantages have been proposed.

The use of high permeability membranes in CRRT allows the removal of measurable quantities of cytokines although pla sma levels seems not to be affected. The mechanism of cytokine removal from the circulation seems to rely on filtration and membrane adsorption. Transport of sepsis-associated mediators across highly permeable membranes may be largely unpredictable because of variable effects of filtration rates, molecular interactions, presence of electric charges, hydrophilic or hydrophobic sites on the membrane, and finally binding to plasma proteins and/or acute phase reactants, as well as to cell receptors. The possible elimination of cytokine-inducing compounds rather than the cytokines should also be emphasized considered when dealing with highly permeable membranes.

Hoffman et al reported that hemofiltration may remove cardiotoxic compounds and TNFa-, but not IL-6- or IL-1b-inducing compounds. A large part of these mediators have molecular weights above the cut-off of highly permeable synthetic membranes used in CRRT. Therefore, considering all above mentioned factors, it seems that highly permeable membranes may have a limited capacity of removal for molecules involved in the pathogenesis of sepsis. Because of the limited capacity of filtration and the possible early saturation of the sites for adsorption, it is very unlikely to obtain significant variations in plasma circulating levels of the substances involved in the systemic inflammatory syndrome.

NEW CRRT TECHNIQUES

Conventional CRRT have gained increased popularity for their ability to remove the excess of fluid and sodium in septic patients. The efficiency in terms of urea and other toxin removal is not questioned today. Limitations seem to become evident for protein bound compounds or for solutes in the molecular range beyond the membrane cut-off. In order to enhance the removal of septic associated mediators, two approaches have been taken under consideration. In their original proposal, Grootendorst et al. suggested that high volume (100 L/day) hemofiltration could remove myocarcardial depressant factors and other sepsis mediators. Some of these mediators could be found in the ultrafiltrate extracted from a pig model of septic shock. In a subsequent clinical study, Bellomo et al confirmed this possibility as evidenced by a significant reduction in norepinephrine administration in animals with septic shock.

A different approach has been to use membranes with larger pores and permeability characteristics superior to those currently used in hemofiltration. Lee et al suggested an increased survival in a porcine model of septic shock and related it to a general effect of enhanced blood purification. Other Authors have reported either in animal or in human studies improved survival when using plasmapheresis. In vitro studies show that plasmafiltration allow the removal of higher amounts of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-β (IL-1β), and interleukin-8 (IL-8)). Clearance and sieving coefficients of these cytokines are significantly increased with “open” plasmafiltration membranes in comparison to high flux hemofiltration membranes. Based on these considerations, it would appear of great interest to expand the use of plasmapheresis in septic patient and to study its impact on survival on a larger scale. However, plasmapheresis is hardly considerable as a CRRT. Large amounts of plasma substitutes and the evident cost implications may in fact limit the application of these techniques in the clinical stage. Furthermore, plasmafiltration techniques may lead to unwanted losses of plasma constituents that cannot be adequately replaced by substitution fluids.

The combined requirements of a continuous renal replacement therapy with high sieving capacity and possible selective removal of sepsis-associated mediators, seem to find an answer in the application of sorbents.

The use of sorbents in extracorporeal therapies has been applied to different treatment strategies that in the past were mostly designed for acute intoxication. Classically, hemoperfusion has been described as a technique in which the sorbent was placed in direct contact with blood in an extracorporeal circulation. More recently this technique and other techniques like apheresis have witnessed intensive research. Sorbents may be of natural origin such as charcoal (mineral or vegetal) or synthetic (different resins with covalently bound groups reactive with specific ligands). Sorbents have been applied in different treatment modalities such as hemoperfusion (HP), hemoperfusion coupled with hemodialysis (HPHD), or coupled plasma filtration-adsorption (CPFA). Hemoperfusion has the advantage of a much simpler circuit, but it requires a very biocompatible the sorbent because of the direct contact with blood and with blood cells in particularly. Charcoal has a high adsorbing capacity especially for low molecular weight waste products that accumulate during kidney or liver failure. Its use in hemoperfusion however requires a coating of the sorbent surface to make it biocompatible. Coated charcoal, although biocompatible, has a remarkably reduced adsorptive capacity due to the cut-off of the coating material. More recently, synthetic polymers have been introduced with remarkable capacity for adsorption. The size selectivity is only offered by the size of the pores on the surface of the granular elements and not by the material itself. Another approach consists on the use of sorbents in "uncoated" form. These however cannot be placed in direct contact with whole blood and they are used for the treatment on-line of the ultrafiltrate or the plasmafiltrate. In these systems, plasma or plasma water is separated from whole blood and, after passing through the sorbent, they are reinfused into the blood circuit reconstituting whole blood structure.

In another technique using uncoated sorbents (Detoxification plasma filtration, DTPF HemoCleanse, Inc., West Lafayette, IN), a hemodiabsorption mechanism is associated with a push-pull plasmafiltration system (a suspension of powdered sorbents surrounding 0.5 micros plasma filter membranes). Bidirectional plasma flow (at 80-100 ml/min) across the plasmafiltration membrane provides direct contact between plasma proteins and powdered sorbents, as well as clearance of cytokines (tumor necrosis factor-α, interleukin-1β, and interleukin-6).

There has been a widespread tendency to remove "bad factors" rather than to attempt to bring about a restoration of balance of physiological factors. Often, too much emphasis has been placed on individual markers. We rather suggest that treatments should focus more carefully on a "balancing hypothesis" trying to restore a correct equilibrium between immunological suppression and activation.

This comes to be particularly true when the converging concepts of plasmafiltration coupled with adsorption are to be applied to the very complex scenario of severe sepsis evolving in septic shock.

CONTINUOUS PLASMA FILTRATION ADSORPTION (CPFA)

Continuous plasmafiltration adsorption is a modality of blood purification in which plasma is separated from whole blood and circulated in a sorbent cartridge. After the sorbent unit, plasma is returned to the blood circuit and the whole blood undergoes hemofiltration or hemodialysis.

The rationale consists in the attempt to achieve adequate removal of molecules that are not removed by other hemofiltration or hemodialysis techniques. The rationale for exposing the plasma to the sorbent in a plasma-filtration system is to exclude the blood cells from the contact with the sorbent and to reinfuse endogenous plasma after non-selective simultaneous removal of different sepsis-associated mediators without the need of donor plasma. The main issue is concerning the sparing effect on endogenous plasma as compared to potential unwanted losses of autologous plasma compounds.

The interesting rationale for such application has stimulated a series of studies in vitro and in animal specifically on a model of rabbit endotoxic shock. These studies also aimed at assessing safety. Various types of sorbents have been tested for this application .

In vitro studies demonstrated that removal rates for different molecules may be very different according to the structure and nature of the used sorbent. More importantly, when tested at different linear velocity of the cross flow, the efficiency in removing cytokines is maintained in a wide range of flow rates. Increased cross flow velocity may reduce the efficiency of the sorbent. In spite of that, the amount of cytokine removed in one passage is far above the overall amount of cytokine carried into the sorbent cartridge (calculated on the basis of the highest levels detected in the plasma and the blood flows utilized in CRRT) by the blood from septic patients. These studies also showed that for hydrophodic resins of a given particle and pore size the binding of cytokines (TNF-α) occurs after prior adsorption of α_2-macroglobulin, the carrier of cytokines in plasma.

A major criticism may be risen concerning the removal of beneficial substances or drugs by the mechanism of adsorption. In several experimental conditions, except for Vancomycin, where a modest removal could be observed, the levels of other antibiotics such as Tobramycin or Amikacin remained stable over time.

Animal studies were performed in a rabbit model of septic shock. The model consisted on a single i.v. injection of lipopolysaccharide. The dose was experimentally adjusted to determine a mortality of 80% of the control animals at 72 hr. Coupled plasmafiltration-adsorption resulted in a significant (p=.0041) survival (85%) at 72 hr with respect to untreated control rabbits injected with the same amount of lipopolysaccharide.

In the pathogenesis of Gram-negative infections, the complex and dynamic host interaction involves the inflammatory cascade, complement activation, the coagulation cascade, hemodynamic derangements. In the animal model, improved survival was negatively correlated with the severity score which included plasma lipopolysaccharide concentration, bioactive TNF as well as MAP, BE and WBC. However, cumulative survival was not correlated with the levels of circulating TNF. It must be emphasized that the overall net effect on survival could be due to the removal not only of the measured mediators, but also to many other mediators not monitored in our study. The possibility that simultaneous removal of different mediators could be linked in a cause-effect relationship with improved survival in our experimental model was suggested. Furthermore, the study provided the rationale for the application of this new method of blood purification in septic patients undergoing CRRT.

A prospective randomized cross-over trial aimed at comparing clinical and biological effects of CPFA versus continuous veno-venous hemofiltration (CVVH) in critically ill septic patients has recently been concluded. Preliminary results were presented in abstract form. The major findings can be summarized as follows: restoration of cell responsiveness to exogenous LPS after 5 hr treatment in all patients; increased systemic vascular resistances and significant reduction of the dose of norepinephrine required to maintain a stable hemodynamics in the patients (mean 30%). These data suggest the possibility that CPFA, as opposed to CVVH, may ensure an improved hemodynamic response in highly unstable patients. Since CPFA may be modular to conventional CVVH, the two modalities can be carried out in series. The system may ensure a fluid and salt balance together with enhanced blood purification for various molecules.

According to all these observations the possible approach to renal support and protection during sepsis and multiple organ failure cannot be seen as a "magic bullet" against a single molecule or agent. The complete spectrum of molecules involved in the syndrome is upregulated and the peaks of both pro-and antiinflammatory mediators should probably be eliminated by a continuous surveillance on circulating blood levels. This can only be achieved through a non specific, continuous system for blood purification in which the imbalance of molecules involved in the inflammatory response is modulated and possible down regulated. The new therapies, although still in an experimental phase, will probably make a great deal of difference in the coming future in terms of possibility of renal protection and renal support.

CONCLUSIONS

Efficiency and adequacy of treatment, known milestones in the extracorporeal treatment for chronic renal failure, are now reconsidered in critical care nephrology. The complex scenario of sepsis must not be underestimated. Notwithstanding, twenty years or so after the first descriptions, we all face a disease with an ever increasing incidence and unacceptably high mortality.

Innovative techniques address the importance of dedicated extracorporeal systems for sespis where acute renal failure is just one of the pathologic complications.

This wider approach to the concept of blood purification opens new perspectives in a revisited strategy for the application of extracorporeal treatments.