CHAPTER 173

High Cutoff Membranes for Mediators Removal

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OBJECTIVES

This chapter will:
1. Illustrate the engineering characteristics of high cutoff membranes.
2. Review the recent literature dealing the clearance effects of high cutoff membranes on large molecules.
3. Provide some practical suggestions on bedside management of septic patients treated with high cutoff membranes.

Cytokines are middle molecular weight molecules having autocrine, paracrine, and/or endocrine effects. These molecules regulate the hormonal, metabolic, and immunologic responses to external (e.g., infection, trauma) or internal (e.g., ischemia, cancer) aggressions.[1] After an insult, patients produce and release a vast amount of these mediators and, in some cases, may overexpress them in relation to the etiologic stimulus. This impairment in regulation of cytokines is recognized as a main pathophysiologic mechanism in the systemic inflammatory syndromes (i.e., sepsis or severe acute pancreatitis), common among critically ill patients.[1–3] A number of attempts have been made in the past to attenuate the clinical expression of the dysregulation through the suppression of specific mediators implicated in either inflammatory or antiinflammatory pathways.[4] However, those efforts failed to produce required clinical improvement because of the redundant and pleiotropic effects of the cytokines. Instead, the nonselective contemporary removal of various mediators has been recognized as the effective alternative.[3] The latter is actually able to modify inflammatory and antiinflammatory effects in different metabolic pathways. During the last decade, the extracorporeal removal of cytokines has been proposed as one of the therapeutic options to reduce these overexpressed molecules. Numerous theories have been offered to explain the role of this in modulating the inflammatory pathways. The "peak concentration hypothesis" states that by preventing the early peak of circulating molecules, these techniques are capable of preventing and modulating the clinical effects of inflammatory and antiinflammatory responses.[3] This extracorporeal removal reduces the serum concentration of different cytokines in the same pathways preventing its clinical manifestation ("threshold immunomodulation hypothesis").[5] The reduction in serum concentration achieved by high-volume fluid exchange treatments, which is accompanied by an increased lymphatic flow, leads to a proportional reduction in tissue cytokine concentration as mentioned in the "mediator delivery hypothesis."[6] Furthermore, the reduction in the circulating level of molecules could restore the concentration gradient necessary to guide the reticuloendothelial system to the main production site (i.e., the source of infection), improving the efficiency of the immune system (cytokinetic model).[7] Finally, a direct immune-homeostatic role has been demonstrated for some extracorporeal blood purification therapies that modulate the *HLA-DR* expression, correlating with cell activation and interaction with some cell reproductive systems.[8]

Numerous types of blood purification therapies have been described in last few years for the mediator removal in the hyperinflamed patients in the intensive care unit (ICU),[8] but none is recognized as superior over others. The use of high cutoff membranes (HCO) in the extracorporeal circuit for renal replacement therapy has been proposed as a valuable therapeutic choice for hyperinflamed patients with acute kidney injury (AKI) in the ICU.[7]

The effects of HCO for the mediator removal in hyperinflamed patients with AKI have been tested previously, with conflicting results seen in the literature.[9] The lack of a standardized definition of HCO and the different settings and treatment modalities in studies undertaken are possible explanations for these nonhomogeneous clinical results.[10] Indeed, many terms have been used to categorize these membranes (e.g., high permeability, super high-flux), causing major confusion to compare results. In fact, although several randomized clinical trials and observational studies claim to have used an HCO, they failed to actually express all the membrane characteristics including pore size or cutoff value. Moreover, studies often miss specifying the treatment settings as blood flow or effluent dose rendering them useless for comparative purposes. On a systematic review recently published, Villa et al. have showed these pitfalls[10]; in particular, these authors have performed a systematic review using all possible terminology related to HCO (e.g., high cutoff, high permeability, super high flux, large pore). With this search strategy, the authors obtained 98 studies; nevertheless, most of them were excluded for the lack of specific information about the treatment setting or because, although the authors declared to have used an HCO, the actual membrane cutoff was lower than 60 kDa. Interestingly, at the end of the screening process, only three case reports,[11–13] three studies on animals,[14–16] 11 in vitro/ex vivo studies,[17–27] and six randomized clinical trials/observational studies[28–33] fulfilled the optimum criteria.

Most international scientific societies agree that a univocal definition of the membrane cutoff and HCO should be adopted.[34]

ENGINEERING CHARACTERISTICS OF HIGH CUT-OFF MEMBRANE

The development of HCO represents one of the most recent advances in membrane technology for renal replacement therapy.[35] Their indications encompass all clinical conditions in which an effective removal of substances in the range of 20 kDa to 50 kDa is desired. The sieving coefficient (SC) profile slightly differs from that observed in the physiologic glomerular filtration barrier, and a comparable clearance may be obtained for molecules such as myoglobin, free light chain immunoglobulins, or cytokines.[35]
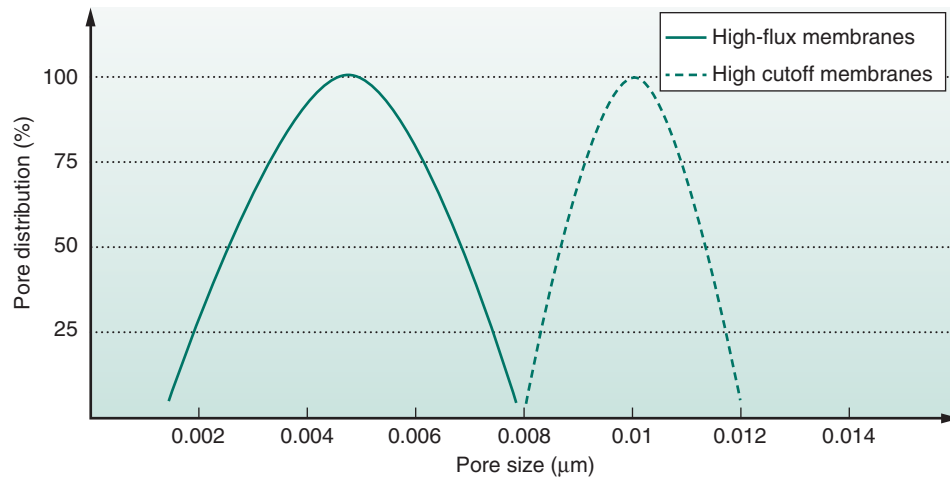
FIGURE 173.1 Pore size distribution for high-flux and high cutoff membranes.

The high transmembrane clearance for middle molecular weight molecules achievable with a HCO is due mainly to the increase in the pore size (>0.01 μm, around double that of a standard high-flux membrane, Fig. 173.1) and thus to the increased membrane porosity for middle molecular weight molecules.[36] As a consequence, an increased cutoff usually is perceived.

The cutoff value for a membrane is identified with the range of molecular weights of the smallest solutes cleared by the membrane. Otherwise stated, considering the normal distribution of membranes' pore size, the statistical cutoff value is identified as the molecular weight of the solute with an SC of 0.1. Currently, HCO are identified clinically as membranes with a cutoff value that approximates the molecular weight of albumin (i.e., 60 KDa).[34] This feature is important to achieve clinically relevant clearance of "filterable" toxins such as multiple myeloma light chains, myoglobin, or inflammatory mediators.[10]

On the other hand, HCO showed an increased retention onset, defined as the mean value of the molecular weight of those molecules with an SC equal to 0.9. Retention onset is clinically represented by the molecular weight of the smallest molecules that are subjected to transmembrane retention. The higher retention onset allows the clinician to increase and maintain clearance of molecules with a lower molecular weight for longer periods of time (i.e., myoglobin [18KDa],[37] β2-microglobulin [12KDa],[23] interleukin-8 [8 KDa]).[28] The adhesion of proteins to the membrane surface commonly occurs during the treatment, and this new layer ("protein cake") acts as a barrier that further affects the transmembrane clearance by means of pore occlusion. This phenomenon leads to the so-called membrane fouling. The increase in the retention onset by increasing pore size diminishes the membrane fouling effect, allowing a prolonged clearance for molecules with lower (up to 20KDa) molecular weight.[35]

CLINICAL EVIDENCE

Effects of High Cutoff Treatment on Cytokines

A reduction in serum inflammatory and antiinflammatory cytokines is reported in most of the studies performed with HCO on hyperinflamed patients in the ICU.[10] Increasing the membrane pore size significantly broadens the extent of molecules cleared by the extracorporeal treatment[38]; higher clearance usually is reported for HCO if compared with standard high-flux membrane used in the ICU. In a double-blind, crossover, controlled trial by Haase et al.,[28] a difference in clearance properties was observed between HCO and standard high-flux membranes. These authors randomized 10 septic patients with AKI to HCO or high-flux intermittent hemodialysis, and they found a significant and stable decrease in serum IL-6 concentration after 4 hours with HCO-hemodialysis. A significant difference was also observed in IL-6 concentration at the end of treatment between HCO and high-flux treated patients. Moreover, for IL-6, IL-8, and IL-10, a greater reduction in prefilter to postfilter plasma cytokine levels was observed during HCO compared with high-flux treatments.[28] In line with these results, Morgera et al.[32] reported a high SC for IL-6 in a prospective single-center pilot trial on 16 patients with multiple organ failure induced by septic shock treated with HCO-hemofiltration for 12 hours per day for 5 days. In particular, they reported that the SC for IL-6 resulted at 0.87 (0.76–1.00) 30 minutes after initiation of hemofiltration, and it remained stable throughout the treatment. Mean IL-6 clearance was 12 to 17 mL/min during the entire treatment. A significant reduction in the total amount of circulating IL-6, estimated by the plasma IL-6 area under the curve, was observed. They also found a correlation between IL-6 concentrations in plasma and effluent.[32]

Several factors may affect the amount of mediators' removal during renal replacement therapy with HCO. Previous studies have compared diffusive versus convective HCO renal replacement therapy in terms of cytokine clearance rates and effects on plasma protein levels.[30] In a prospective controlled trial, Morgera et al.[30] randomized 24 septic patients with AKI to receive diffusive versus convective HCO renal replacement therapy. Convective technique was shown more efficient than diffusive in reducing circulating cytokine (IL-6 and IL-1ra). In the same study, an increase in effluent rate also was recognized to increase solute clearance. Regrettably, with the use of convective technique and increasing the effluent rate, a higher clearance for albumin also was detected.

The transmembrane removal of cytokine is characteristically unselective in nature; in particular, proinflammatory and antiinflammatory mediators are removed during the treatment. According to "peak concentration hypothesis,"[39] the contemporary reduction of inflammatory and

antiinflammatory mediators may attenuate the immunologic impairment in septic patients, potentially reducing bacterial, virus, and/or fungal superinfections and achieving immunomodulation. Beyond sepsis, this effect may be particularly important for all critically ill patients with immunologic dysregulation. Villa et al. have reported a clinical reduction of antiinflammatory mediators, such as IL-10 (40 KDa), during HCO in a hematologic immune-depressed patient with differentiation syndrome treated with high-dose corticosteroids, who developed an opportunistic infection.[40]

In these terms, the use of HCO in particular clinical conditions, other than sepsis, has been described. In particular, Kade et al. reported a reduction in IL-4, IL-6, IL-10, and IL-12 in a patient with multiple organ dysfunction after cardiac arrest.[12] Chelazzi et al. reported the use of continuous hemodialysis with HCO for severe acute pancreatitis (SAP), recording a net reduction of hematic cytokine concentration, especially of IL-6, which is recognized as one of the most important molecules in SAP pathophysiology.[2]

Effects of High Cutoff Treatment on Albumin

It is well established that HCO hemofilters have a risk of albumin loss. In the study conducted by Morgera et al.[32] albumin loss was particularly high in the initial phase of the treatment. However, this phenomenon rapidly declined over time probably because of clotting and clogging of the membrane. An SC equal to 0.04, 0.02, and 0.01 was observed at 0.5, 2, and 12 hours of treatment, respectively. The authors reported a protein loss of nearly 8 g/day with a convective dose of 1 L/hr. A mean value of 140 mL of substitution plasma (either fresh frozen plasma or human albumin) was administered to maintain stable plasma albumin levels. The same group in a prospective controlled trial,[30] randomized 24 septic patients with AKI to receive diffusive versus convective HCO renal replacement therapy. Convective technique was demonstrated to be more efficient than diffusive to reduce circulating IL-6 and IL-1ra but was associated with a higher albumin loss in the effluent (100–830 vs. 40–410 mg/hr with 1 L/hr in effluent for CVVH and CVVHD, respectively).

In the above-mentioned randomized trial, Haase et al.[28] prescribed blood and dialysate flows of 200 and 300 mL/min, respectively. A significant reduction in serum albumin was observed among patients treated with HCO with respect to high-flux membranes and higher levels of albumin loss in the effluent (7.7 g vs. 1 g, respectively, $p < .01$). However, the HCO albumin clearance fell from 1.9 to 0.9 mL/min after 4 hours of treatment.[28]

In a pure convective technique, the increase in effluent rate significantly raises the albumin loss. In a randomized controlled study, albumin clearance significantly increased from 0.27 mL/min with an effluent rate of 1 L/hr to 1.7 with 2.5 L/hr[30] after 30 minutes of treatment. Similar finding was observed in diffusive techniques. An increase in clearance from 0.36 to 0.81 was observed increasing the dialysate rate from 1 L/hr to 2.5 L/hr.[30] At this moment, after interpreting these results, an increase in the effluent flow in a pure dialytic treatment is the best suited option of therapy to increase the cytokine clearance preventing excessive albumin loss.

In 2005 Mariano et al. observed an increase in albumin clearance comparing HCO to high-flux membrane in an in vitro study comparing albumin clearance in hemofiltration for 6 hours.[27] Similarly, in an ex vivo study, Morgera et al. treated blood from healthy volunteers incubated with endotoxin with HCO (cutoff 100 KDa, area 1.2 m²).[22] Convective and dialytic treatments were interchanged during the procedure as well as the effluent rate. The author suggested that by increasing the ultrafiltration rate from 1 to 3 L/hr, a higher clearance for IL-1 receptor antagonist (IL-1ra), IL-6, and TNF-α was obtained with significant concomitant increase in albumin loss. Similar findings were observed with pure dialytic treatment. Comparing hemofiltration with hemodialysis in the 1 L/hr mode revealed a higher clearance for TNF-α and albumin. The advantages of hemofiltration lost their statistical significance when the procedures were switched to the 3 L/hr mode. Only albumin clearance still remained statistically higher in the hemofiltration group.[22]

Last, similarly to that observed for serum albumin, the transmembrane clearance also may affect potential clinically useful solutes, such as the biomarkers or coagulation factors. Indeed, a significant reduction in procalcitonin (PCT; molecular weight 13 KDa) serum concentration was observed during the treatment with HCO. Although this effect could be related to the antiinflammatory effect of the treatment, a direct transmembrane clearance was also observed (SC of 0.45), decreasing the clinical accuracy of PCT as biomarker of sepsis.[41] However, considering the role of PCT as a mediator of tissue transmigration and activation of monocytes,[42] its active extracorporeal removal also could retain a therapeutic effect. Furthermore, taking into account the molecular weight of protein C (62 kDa), protein S (69 kDa), and antithrombin III (AT III, 60 kDa), a reduction in these molecules during a treatment with HCO may be expected. Nevertheless, Morgera et al. have reported that these solutes are not affected in septic patients treated by intermittent HCO hemofiltration. In particular, stable values were found for plasma AT III, factor II (69 kDa), protein C, protein S, and factor VIII (265 kDa) from baseline to 12 hours and after 72 hours of HCO hemofiltration, and there was no need for the substitution during the entire study.[32]

Effects on Organ Function

Clinical studies in literature have shown that the application of HCO may improve the organ function in septic patients with AKI. In particular, an improvement in the hemodynamic parameters and oxygenation indices usually is reported in sepsis-related and non–sepsis-related multiple organ dysfunction.[2,29,30] Nevertheless, none of these studies has demonstrated clearly a reduction in patients' mortality rate.[7,10]

A prospective clinical trial showed a significant reduction in APACHE II and multi-organ dysfunction score (MODS) during the treatment with HCO. These facts were not significantly different between patients treated with convective or diffusive techniques.[30] In a randomized controlled trial on 30 septic patients with AKI, HCO hemofiltration was associated with reduced SAPS II score at 48 hours of treatment with respect to baseline. Moreover, SAPS II scores of HCO patients were statistically lower when compared with high-flux hemofiltration-treated patients.[29] The reduction in the scores of organ dysfunction was related mainly to an improvement in hemodynamic parameters, with a stable decrease of vasopressor requirement in treated patients.[29] The authors showed a significant reduction in norepinephrine dose in HCO with respect to patients treated by high-flux hemofiltration. Similar results were obtained by Haase et al. with an increase in mean arterial pressure and a stable decrease in norepinephrine requirement in patients treated with intermittent hemodialysis with HCO.[28] Morgera et al. observed a significant improvement

in patients' cardiovascular condition during intermittent hemofiltration with HCO. An increase in cardiac output (from 5.9 to 8.4 L/min) and mean arterial pressure (77.5 to 80 mm Hg) was observed at 12 hours of treatment, with a concomitant reduction in norepinephrine requirement (0.26 to 0.19 µg/kg/min).[32] Comparable findings have been shown in nonseptic patients treated with HCO, with an improvement in hemodynamic parameters and in indices of oxygenation.[2]

All these results were not replicated in 2009 by the High Cut-Off Continuous Veno-venous Hemodialysis in Sepsis (HICOSS) study, which aimed to randomize 120 patients to CRRT with either the HCO or the conventional membrane.[9,43] Here, vasopressor use and 28-day mortality were the same in both groups, as were the requirement for mechanical ventilation and ICU length of stay. However, several factors may affect these results. First, the authors have not provided the actual delivered dose obtained during the treatments; because sepsis and septic shock are dynamic processes, the effect of HCO-CRRT may be linked to the total delivered dose rather than the prescribed dose. Second, according the same authors of the study, the negative results of HICOSS may be related to the use of a pure dialytic modality (continuous veno-venous hemodialysis [CVVHD]) instead of a continuous veno-venous hemodiafiltration (CVVHDF) or continuous veno-venous hemofiltration (CVVH) with high-volume hemofiltration (whose association with HCO may have synergic effects).[44] Third, patients in the HICOSS study had sepsis of various causes, potentially jeopardizing the effectiveness of the treatment and the affordability of results. In a retrospective study recently published, Chelazzi et al. have compared the effectiveness of HCO in a specific well-selected group of patients with monomicrobial gram-negative sepsis and AKI treated with HCO or high-flux membranes.[45] These authors have observed that patients treated with HCO-CVVHD spent less cumulative days on vasopressors and mechanical ventilation as a ratio to their total ICU-LOS and had reduced rates of ICU mortality. In this study, HCO-CVVHD was associated with better hemodynamics and reduced ventilation requirements as shown by a reduced ratio of days spent on vasopressors and mechanical ventilation to the total ICU-LOS for patients in the HCO group. Furthermore, a significant progressive reduction of norepinephrine doses in the first 24 hours of treatment was statistically evident in the HCO-CVVHD group, but not in the HF-CVVHDF group.[45] According to the authors' conclusions, all these effects of HCO-CVVHD may have indirectly affected the outcomes by giving the appropriate antibiotic treatment the "right amount of time" to act, provided any surgical source of infection had been removed.[45,46] Indeed, appropriate and timely antibiotic treatment stands as the only measure clearly associated to survival in septic patients. Adequacy and dose adjustment of antibiotic therapy during CRRT are important issues and several reports in literature warn that the risk of underdosing is real.[47]

Effects on Antibiotics

It is well established that, because of extracorporeal removal, the dosage of several administered drugs frequently requires adjusting during CRRT.[48] This is particularly important for antimicrobial therapy, whose clinical efficacy is related to the tight equilibrium established among patients, pathogens, and drug concentrations at the infection site.[49]

Serum and tissue antibiotic concentrations are affected strongly by the alterations typically observed in critically ill patients, such as changes in volume of distribution (Vd), hepatic or renal clearance, or protein binding.[49] Indeed, the clearance of antimicrobial agents may be increased by CRRT, mainly during dialysis because of their relatively low molecular weight. Usually, the smaller the extent of protein binding and the Vd, the higher the extracorporeal clearance induced by CRRT.[48] The subsequent alterations in antimicrobial concentrations may prevent reaching specific pharmacokinetic/pharmacodynamic (PK-PD) targets required for pathogen eradication.[50] Despite the increasing availability of data about adjustments in drug dosing during the main CRRT techniques,[51,52] few data have been reported for blood purification therapies and in particular for HCO.

The first report on the extracorporeal clearance and PK-PD parameters of antibiotics in three critically ill septic patients treated with HCO-CVVHD has been published recently.[47]

In this study, the saturation coefficient (SA) and the extracorporeal clearance (CL_{HCO}) were calculated to assess the transmembrane removal of linezolid during HCO-CVVHD. A mean SA of 0.75 was found and compared with values reported in other studies in which AKI patients were treated with hemodiafiltration or hemofiltration with standard high-flux membranes. In particular, Kraft et al. calculated an SA ranging from 0.77 to 0.81 during CVVHDF,[53] and similar results have been reported by several authors for the SC obtained during CVVH.[48,54–56] These data are not surprising, considering that SC and SA are usually close to the free fraction of drug, unbound to serum protein.[57] Linezolid has a very low molecular weight (337 Da) even if compared with the pore radius of the standard high-flux membranes. For this reason, according to the authors' discussion, transmembrane drug removal is not increased because of the larger pore of the HCO, irrespective of the particular type of filter used. However, an increase in transmembrane loss should be expected with HCO if a convective clearance is applied during the treatment. In particular, although not routinely performed, hemofiltration with HCO increases the protein loss and thus allows major removal of a protein-binding drug in the hemofilter. In this context, an increase in antibiotics SC may be observed.

CL_{HCO} of linezolid calculated by these authors ranged from 2.1 to 2.53 L/hr. Although the extracorporeal antibiotic removal was similar, the antibiotic pharmacokinetic/pharmacodynamic parameters widely ranged across the considered patients, and these seem to be related mainly to the specific patients' clinical conditions during critical illness.

In line with these results, the use of HCO in continuous venovenous hemodialysis seems to behave in a similar manner to standard high-flux membranes; furthermore, the high variability in antibiotic PK-PD found is more likely to be related to the patient's critical condition and/or organ dysfunction than to the capability of the filters themselves in removing the drug.

CONCLUSION

The lack of a standardized definition of dialysis membranes has led to contrasting results on the clinical effect of HCO. An SC for albumin over zero should be used to define a membrane as HCO (cutoff value of at least of 60 KDa).

A reduction in serum inflammatory and antiinflammatory cytokines is common in HCO treatment. Convective technique and increase in effluent rates have shown to be more efficient in reducing circulating cytokines in relation to higher clearance of albumin. An increase in the effluent

flow in a pure diffusive treatment is the best-suited option of a therapy to increase the cytokine removal and to reduce excessive albumin loss.

Improvement in the hemodynamic parameters and indices of oxygenation have been shown in septic and nonseptic patients treated with HCO. The use of HCO in specific clinical conditions, other than sepsis (as severe acute pancreatitis or retinoic acid syndrome), should be considered and explored.

The use of HCO in continuous venovenous hemodialysis has a similar result as standard high-flux membranes in terms of antibiotic removal.

Key Points

1. Renal replacement therapy (RRT) with high cutoff membranes (HCO) has been proposed as a valuable therapeutic choice for hyperinflamed patients with acute kidney injury (AKI) in the intensive care unit.
2. A reduction in serum inflammatory and antiinflammatory cytokines is reported in most of studies on septic patients treated with HCO-RRT.
3. Clinical studies in literature have shown that the application of HCO may improve the organ function in septic patients with AKI.
4. The albumin and coagulation factors removal is a potential harmful effect of HCO-RRT.

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