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CRRT efficiency and efficacy in relation to solute size

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CRRT efficiency and efficacy in relation to solute size. Removal of blood solutes in patients with decreased or absent glomerular filtration is the prime objective of continuous renal replacement therapies (CRRTs). However, because these blood solutes are of different molecular weights, factors such as the porosity and hydrophobicity of the filter membranes and the extracorporeal flow rates determine the CRRT that is the most effective filtration system. This article discusses both small and large solute removal, the interaction of convection and diffusion, and the potential for CRRTs to remove particular inflammatory mediators of acute renal failure.

One of the foremost objectives of renal replacement therapy in patients with acute renal failure (ARF) is the removal of blood solutes that are retained as a consequence of decreased or absent glomerular filtration. Solute removal can occur by several different mechanisms in continuous renal replacement therapy (CRRT). The ability of a specific CRRT to remove a certain solute or class of solutes is determined by numerous treatment parameters. Important among these parameters are filter membrane characteristics, such as porosity and hydrophobicity, and the extracorporeal flow rates (blood, dialysate, and ultrafiltration) used.

The purpose of this article is to provide an overview of the factors determining the removal of solutes by CRRT over a broad molecular weight range. For relatively small solutes, the effect of increasing dialysate flow rate on continuous venovenous hemodialysis (CVVHD) efficiency is discussed. The potential interaction between diffusion and convection for small solutes in CRRT is also discussed. For solutes of larger molecular weight, the importance of convection and adsorption is emphasized. Finally, the issue of inflammatory mediator removal by convective CRRT is presented. For some of these issues, information learned in the chronic hemodialysis setting will provide a reference base.

Key words: solute, clearance, diffusion, convection, membrane, hemofiltration.

SMALL SOLUTE REMOVAL IN CRRT

Interaction between diffusion and convection: Intermittent hemodialysis versus CRRT

In both intermittent hemodialysis (IHD) and some continuous therapies, solute removal by diffusion and convection occurs simultaneously. In IHD, the use of high blood and dialysate flow rates results in relatively high small solute clearances. These clearances are primarily diffusive in nature but there is also a convective component related to plasma water ultrafiltration. In IHD, diffusion and convection interact in such a manner that total solute removal is significantly less than what is expected if the individual components are simply added together, a phenomenon explained in the following way. Diffusive solute removal results in a decrease in solute concentration in the blood compartment along the axial length (that is, from blood inlet to blood outlet) of the hemodialyzer. As convective removal is directly proportional to the blood compartment concentration of the solute, convective removal decreases as a function of this axial concentration gradient. On the other hand, hemoconcentration resulting from ultrafiltration of plasma water causes a progressive increase in plasma protein concentration and hematocrit along the axial length of the filter. This hemoconcentration and associated hyperviscosity cause an increase in diffusive mass transfer resistance and a decrease in solute transport by this mechanism. Numerous investigators have analyzed the effect of this interaction on overall solute removal in IHD [1, 2]. The most useful analysis has been performed by Jaffrin [2]:

$$K_T = K_D + (Q_F \cdot Tr)$$

In this equation, K_T is total solute clearance, K_D is diffusive clearance under conditions of no ultrafiltration, and the final term is the convective component of clearance. The latter term is a function of the ultrafiltration rate (Q_F) and an experimentally derived transmittance coefficient (Tr):

$$Tr = S\ (1 - K_D/Q_B)$$

where S is the solute sieving coefficient. Thus, Tr for a particular solute is dependent on the efficiency of diffusive

removal. At very low values of K_D/Q_B, diffusion has a very small impact on blood compartment concentrations and the convective component of clearance closely approximates the quantity $S \cdot Q_F$. However, with increasing efficiency of diffusive removal (that is, increasing K_D/Q_B), blood compartment concentrations are significantly influenced. The result is a decrease in Tr and, consequently, in the convective contribution to total clearance.

Due to the markedly lower flow rates used in CRRT, the effect of simultaneous diffusion and convection on overall solute removal is quite different. Based on a comparison of urea, the diffusive clearance in continuous arteriovenous hemodialysis (CAVHD), CVVHD, and continuous venovenous hemodiafiltration (CVVHDF; typically 17 to 34 ml/min) [3–7] is only approximately 5 to 15% of that achieved in IHD. Therefore, the small solute concentration gradient along the axial length of the filter (that is, extraction) is minimal compared to that which is seen in an IHD setting, in which extraction ratios of 50% or more are the norm.

In a classic clinical study published over a decade ago, Sigler and Teehan specifically assessed the potential interaction between diffusion and convection in CAVHD [4]. A 0.4 m^2 hemofilter was used in conjunction with a constant dialysate flow rate of 1 liter/hr (providing approximately 17 ml/min of diffusive clearance) and ultrafiltration rates ranging from 4 to 13 ml/min. The convective clearance associated with a specific ultrafiltration rate was determined by subtracting diffusive clearance from the (measured) total clearance. Figure 1 provides several lines of evidence indicating no interaction between diffusion and convection under the specific conditions of this study. First, the relationship between total clearance and ultrafiltration rate is linear and the separate curves for total clearance and convective clearance are parallel. Second, providing an internal check of consistency of the data set, extrapolation of the total clearance curve to the case of pure diffusion ($Q_F = 0$) results in the expected y-intercept value of approximately 17 ml/min. Although these data pertain to CAVHD, they are also applicable to CVVHD performed under similar treatment conditions.

Whereas a dialysate flow rate of 1 liter/hr was fairly typical for CAVHD/CAVHDF and CVVHD/CVVHDF for several years, flow rates of 1.5 to 2 liter/hr are now commonly used. Because this use of higher flow rates has increased the efficiency of diffusive small solute removal, diffusion and convection may interact. Brunet et al have recently assessed this possibility [7]. These investigators measured the clearance of urea, creatinine, uric acid, phosphate, and β_2-microglobulin (β_2m) over a wide range of dialysate flow rates (0 to 2.5 liter/hr) and ultrafiltration rates (0 to 2 liter/hr) in pre-dilution CVVHDF employing either a 0.6 or 0.9 m^2 hemofilter. These measured clearances were compared to those predicted by adding the separate diffusive and convective components (based on the dialysate flow and ultrafiltration rates, respectively). Even at the combination of dialysate flow and ultrafiltration rates of 2.5 and 2.0 liter/hr, respectively, the differences between the actual and predicted solute clearances for urea, creatinine, uric acid, and phosphate were minimal (<5%). These data suggest the prescription of relatively high flow rates still results in no significant interaction between diffusion and convection in CVVHDF, at least when a large surface area hemofilter is used.

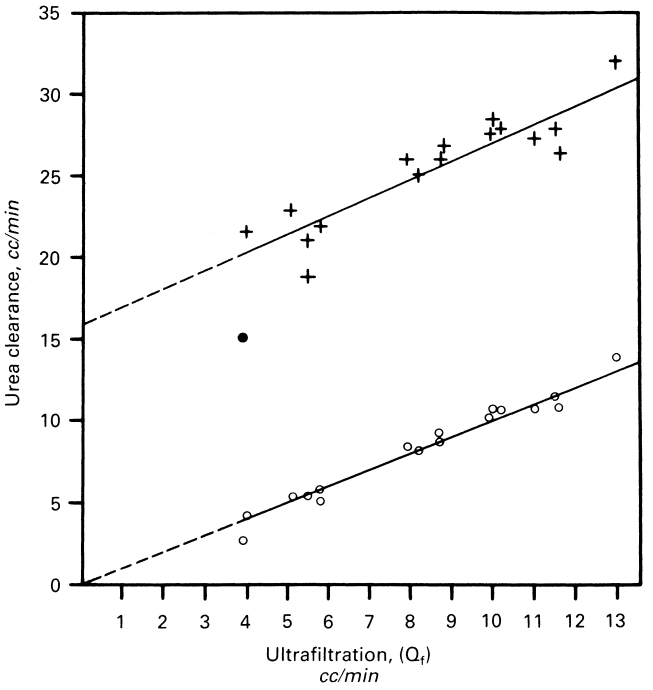

Fig. 1. Components of urea clearance in continuous arteriovenous hemodialysis. Each total clearance point (+) has its corresponding convective component (○) plotted directly below it; one point (●) was not included in the regression because of a very low blood flow and lack of membrane equilibrium. Reprinted with permission from the International Society of Nephrology [4].

Effect of high dialysate flow rates on small solute removal efficiency in CVVHD

In the Sigler and Teehan study, a dialysate flow rate of 1 liter/hr resulted in an effluent dialysate/plasma concentration ratio (D/P) of approximately 1 such that effective "saturation" of the effluent dialysate was achieved [4]. This saturation phenomenon appears to be dependent on both dialysate flow rate and filter surface area. Using a 0.6 m^2 AN69 filter, Bonnardeaux et al measured clearance and D/P for urea and creatinine over a dialysate flow rate (Q_D) range of 0 to 4 liter/hr [8]. For both solutes, the relationship between clearance and Q_D was linear for the Q_D range of 0 to 2 liter/hr, after which there was a plateau effect for both solutes. Although D/P was approximately 1 for both solutes at a Q_D 1 liter/hr, it

progressively fell as Q_D increased, reaching a value of approximately 0.87 and 0.79 at Q_D 2 liter/hr and 0.65 and 0.55 at Q_D 4 liter/hr for urea and creatinine, respectively. Using the same filter, Relton, Greenberg and Palevsky reported mean urea D/P values of 0.99 and 0.87 at Q_D 1 and 2 liter/hr, respectively, while the same values for creatinine were 0.84 and 0.66 [5].

In a more recent study, Brunet et al assessed the role of filter surface area on solute clearances in CVVHD [7]. These investigators measured clearances of urea, creatinine, urate, and phosphate over a Q_D range of 0 to 2.5 liter/hr for AN69 filters of surface area 0.6 and 0.9 m^2. At Q_D 1 liter/hr, membrane surface area had no significant effect on the clearance of any solute. However, at Q_D 2.5 liter/hr, the clearances of urea, creatinine, urate, and phosphate were 6%, 15%, 18%, and 16% higher, respectively, with the larger surface area filter. These data indicate that the efficiency of small solute removal during high-flow rate CVVHD is enhanced by the use of relatively large surface area filters.

Pre-dilution versus post-dilution CVVH: Effect on small solute removal

In CVVH, the method by which replacement fluids are administered influences small solute removal efficiency. In post-dilution CVVH, small solute mass removal per unit volume of ultrafiltrate is relatively high because solute concentrations within the filter are the same as in the plasma water. However, the volumetric rate of ultrafiltrate production is limited by the operating characteristics of the system, mainly the hematocrit (viscosity) and blood flow (shear) rate that exist in the filter. In general, the maximum achievable ultrafiltration rate in a post-dilution system is limited to approximately 25% of the plasma flow rate through the filter [9]. Because ultrafiltration rate and clearance are essentially equivalent in a post-dilution system for small solutes, the maximum clearance achievable in a patient with a hematocrit of 0.30 and treated with a blood flow rate of 150 ml/min is approximately 26 ml/min.

In pre-dilution CVVH, small solute removal per unit volume of ultrafiltrate is less because solute concentrations in the filter are lower than those in the plasma water. For urea, the degree to which this "dilution" reduces the filter solute concentrations is proportional to the ratio of the dilution fluid administration rate divided by the total blood water flow rate through the filter. Under most circumstances of contemporary CVVH, this dilution factor and the associated reduction in efficiency is approximately 10 to 15%. However, the ultrafiltration rate in a pre-dilution system is not constrained by viscosity and shear rate, and the modest decrease in efficiency related to the dilution of filter small solute concentrations can easily be overcome by the use of a relatively high ultrafiltration rate. These principles explain the ability of pre-dilution CVVH to deliver therapy doses that far exceed those achieved with post-dilution systems.

REMOVAL OF MIDDLE- AND LARGE-SIZED MOLECULES IN CRRT

Middle molecule removal in CRRT

For the characterization of dialyzer performance, vitamin B_{12} (molecular weight, 1355 daltons) is widely used as an *in vitro* middle molecule surrogate. However, this solute has little relevance in *in vivo* dialyzer evaluations due to its extensive plasma protein binding. A more relevant middle molecule is vancomycin (molecular weight, 1448 daltons) for several reasons. First, the drug is commonly used in patients with ARF and assays for serum concentration are widely available. Second, vancomycin is minimally protein-bound in patients with renal failure [10] and available to be removed by extracorporeal techniques. Finally, the drug's volume of distribution is well characterized [11] and, although it has a slightly larger range, it approximates that of urea.

In IHD, although vancomycin removal by low-flux dialyzers is negligible, substantial diffusive elimination is achieved with high permeability membranes [12–17]. During high-flux HD, vancomycin mass transfer between well perfused compartments of the body (for example, extracellular space) and poorly perfused compartments (intracellular space) is slow relative to the rate of mass transfer across the dialyzer. The clinical manifestation of this phenomenon is a significant rebound in the plasma vancomycin concentration during the immediate post-HD period [18]. Due to the much slower rate of extracorporeal removal of vancomycin during CRRT, the disequilibrium between body compartments described above for high-flux IHD is predicted to be an insignificant factor.

The diffusivity of a solute, whether in solution or in an extracorporeal membrane, is inversely proportional to its molecular weight. Consequently, as solute molecular weight increases, diffusion becomes a relatively inefficient dialytic removal mechanism and the relative importance of convection increases. Jeffrey et al have recently shown that convection is quantitatively more important than diffusion in vancomycin removal when the same ultrafiltration rate (CVVH) and effluent dialysate flow rate (CVVHD) of 25 ml/min (1.5 liter/hr) is used [19].

Removal of inflammatory mediators and other plasma proteins in CRRT

The identification of β_2m as a precursor molecule in the development of dialysis-related amyloidosis established low-molecular weight proteins as a new class of uremic toxins [20]. In response to this discovery, significant effort has been directed toward developing membranes and treatment strategies that optimize β_2m removal. However, efforts to enhance β_2m removal by

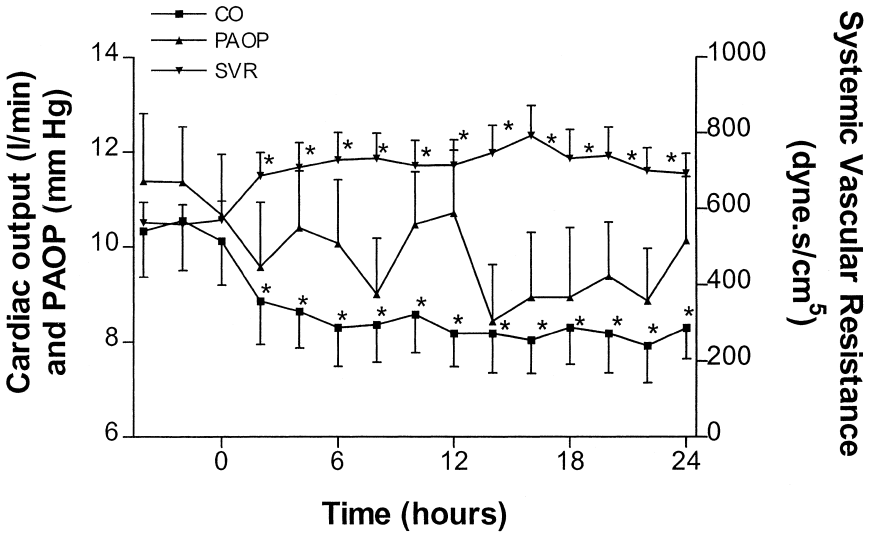

Fig. 2. Effect of continuous venovenous hemofiltration on hemodynamic parameters in patients with septic shock. Symbols are: (■) cardiac output; (▲) pulmonary artery occlusion pressure; (▼) systemic vascular resistance. Reprinted with permission from the American Society of Nephrology [22].

increasing membrane permeability have been limited by the concomitant need to minimize the loss of other proteins, such as albumin [21].

In some critically ill patients with ARF, low-molecular weight proteins also represent a class of molecules considered "toxic." However, specifically in the case of patients with sepsis or multi-system organ failure, the specific toxins are inflammatory mediators, such as cytokines and complement pathway products. The issue of inflammatory mediator removal with CRRT has been the topic of numerous recent investigations [22–29]. These studies have convincingly demonstrated that a number of inflammatory mediators can be removed by convection or adsorption during CRRT. However, data indicating that the ability to remove these mediators translates into lowered plasma concentrations are not nearly as convincing.

De Vriese et al recently performed an elegant study addressing the issue of cytokine removal during CRRT [22]. In patients receiving CVVH with AN69 filters (0.9 m^2), these investigators quantified removal of numerous pro-inflammatory and anti-inflammatory cytokines and the effect on plasma concentrations. The study design consisted of using two filters sequentially, each for 12 hours, at blood flow rates of 100 and 200 ml/min, respectively (or vice versa). Simultaneous sampling of the arterial, venous, and ultrafiltrate lines at multiple time points permitted mass balance assessments of adsorptive versus convective removal. Cytokine removal was found to be highest during the first hour of use of a new filter, corresponding to approximately 25 to 50% of the cytokine mass presented to the filter in this time period. This resulted in a significant decrease in the serum concentration of all cytokines. In addition, a significant decrease in cardiac output and a significant increase in systemic vascular resistance were observed during this early time period (Fig. 2). Particularly at early time points, adsorption accounted for the majority of cytokine removal and, in the specific case of interleukin (IL)-10, was the only removal mechanism at any time point. However, the rate of adsorptive removal decreased rapidly thereafter, suggesting a saturable phenomenon and corroborating previous data [23]. Because the CVVH mode was post-dilution, mean ultrafiltration rate was significantly higher at Qb = 200 versus Qb = 100 ml/min (44.3 ± 1.5 vs. 25.4 ± 0.7 ml/min, respectively). Under the higher blood flow and ultrafiltration rate condition, the convective removal rate of all cytokines increased along with the adsorptive removal rate of most cytokines. These data suggest that the combination of a relatively high ultrafiltration rate and frequent filter changes results in clinically measurable decreases in systemic cytokine concentrations.

The above data indicate that adsorption is the primary mechanism by which cytokine removal occurs during post-dilution CVVH performed with an AN69 hemofilter. It should be emphasized that this finding may not pertain to hemofiltration performed with other filters. Indeed, although convective cytokine removal appeared to play a relatively small role in the De Vries et al study, studies employing other filters suggest convection is the primary elimination mechanism [24, 27]. Consequently, there is a growing interest in the use of hemofiltration therapies that use unconventional methods to enhance convective removal of inflammatory mediators. One technique involves use of ultrafiltration rates (4 liter/hr or more) that are significantly higher than those typically used in clinical practice [24]. A second technique consists of using a hemofilter which has a mean pore size that is significantly larger than that of conventional hemofilters

[29]. Although animal data to date have been reasonably encouraging, the clinical efficacy of both of these types of therapies remains to be determined.

SUMMARY

A review of solute removal during various types of CRRT has been presented. For small solutes, the importance of dialysate flow rate in CVVHD and the mode of substitution fluid administration in CVVH have been discussed. For larger molecules, the solute removal mechanisms of convection and adsorption have been emphasized. An understanding of these issues is important when choosing a specific CRRT modality for an individual patient.

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