Modalities of Continuous Renal Replacement Therapy: Technical and Clinical Considerations

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ABSTRACT

Continuous renal replacement therapies (CRRT) are continuous forms of renal functional replacement used to manage acute kidney injury (AKI) in the critically ill patient. Depurative mechanisms include convection, diffusion, and membrane adsorption utilizing high-flux highly permeable biocompatible dialysis membranes. The simultaneous infusion of replacement fluid permits fluid removal without intravascular volume contraction and better hemodynamic stability, metabolic control to almost normal parameters, and removal of large-size toxins and cytokines. Moreover, CRRT allows better long-term clearance of small and middle molecules than other dialysis modalities. This article focuses on the different modalities of CRRT and reviews both the basic concepts and the newest approaches to the management of the critically ill patient with AKI.

Most hospital-acquired acute kidney injury (AKI) occurs in the intensive care unit (ICU) and is associated with elevated morbidity and mortality (1,2). Continuous renal replacement therapies (CRRT) provide extracorporeal treatment of these hemodynamically unstable, critically ill patients, who are often hypercatabolic and fluid overloaded. A recent international survey showed that 80% of patients with AKI in the ICU are currently treated with continuous therapies, 17% with intermittent therapies, and 3% with peritoneal dialysis or slow continuous ultrafiltration (3). These novel techniques of renal substitution therapy have permitted a conceptual shift from renal "replacement" to renal "support" therapies (4), whereby the strategies to treat AKI have become an integral part of overall critically ill patient management, with "renal" and "nonrenal" applications such as sepsis and acute respiratory distress syndrome (ARDS).

In their simplest definition, CRRTs are continuous forms of renal functional replacement used to manage AKI in the critically ill patient. CRRT techniques commonly use three types of depurative mechanisms: convection, diffusion, and membrane adsorption. The simultaneous infusion of replacement fluid permits fluid removal without intravascular volume contraction, metabolic control to almost normal parameters, and removal of large size toxins and cytokines. By and large, CRRT modalities require the use of high-flux, highly permeable biocompatible dialysis membranes.

Most systems are designed with a desire to "keep things simple" (Table 1); such need for simplicity is essential when these techniques are to be implemented by critical care personnel with variable degrees of dialytic expertise and nephrological support. Unfortunately, the various system designs are often daunting to the uninitiated and inhibit a more widespread use of their most powerful modality variations.

When a new renal replacement therapy (RRT) is started, practitioners must simultaneously decide on dialysis modality, membrane biocompatibility, dialyzer performance, and dialysis delivery (Table 2). CRRT has made possible the delivery of RRT to hemodynamically unstable patients. In practice, hemodynamic stability of the critically ill patient is the main determinant of the choice of dialysis modality (5) (Table 3). In addition to the patient's hemodynamic stability, the choice between the various RRTs rests on solute clearance goals, volume control, and anticoagulation (Table 4).

This article will focus on the different modalities of CRRT and emphasize the basic concepts and the newest approaches to this technology and its application in the ICU. The discussion will center on the use of diffusive and convective mechanisms, and briefly address the use of membrane adsorption as an additional valuable method of large molecule removal. Previous reviews (6,7) have discussed the fundamental operational characteristics of CRRT and will not be reiterated here. More recently, the acute dialysis quality initiative (ADQI) published a consensus on fluid (8) and volume management in AKI (9) relevant to the present discussion.

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TABLE 1. Characteristics of the "ideal" treatment modality of AKI in the ICU

Characteristic
Preserves homeostasis
Does not increase co-morbidity
Does not worsen patient's underlying condition
Is inexpensive
Is simple to manage
Is not burdensome to the ICU staff

From Lameire et al. (61)
AKI, acute kidney injury; ICU, intensive care unit.

TABLE 2. Considerations in renal replacement therapy for AKI

Consideration	Components	Varieties
Dialysis modality	Intermittent hemodialysis	Daily, every other day, SLED
	Continuous renal replacement therapies	AV, VV
	Peritoneal dialysis	
Dialysis biocompatibility	Membrane characteristics	
Dialyzer performance	Efficiency	
	Flux	
Dialysis delivery	Timing of initiation	Early, late
	Intensity of dialysis	Prescription versus delivery
	Adequacy of dialysis	Dialysis dose

AKI, acute kidney injury; SLED, sustained low efficiency daily dialysis; AV, arterio–venous; VV, veno-venous.

TABLE 3. Indications for specific renal replacement therapies

Therapeutic goal	Hemodynamics	Preferred therapy
Fluid removal	Stable	Intermittent isolated UF
	Unstable	Slow continuous UF
Urea clearance	Stable	Intermittent hemodialysis
	Unstable	CRRT
		Convection: CAVH, CVVH
		Diffusion: CAVHD, CVVHD
		Both: CAVHDF, CVVHDF
Severe hyperkalemia	Stable/ Unstable	Intermittent hemodialysis
Severe metabolic acidosis	Stable	Intermittent hemodialysis
	Unstable	CRRT
Severe hyperphosphoremia	Stable/ Unstable	CRRT
Brain edema	Unstable	CRRT

From Murray et al. (62)
UF, ultrafiltration; CRRT, continuous renal replacement therapies; CAVH, continuous arterio–venous hemofiltration; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration.

Arterio–Venous (AV) or Veno-Venous (VV) Blood Circuits

Arterio–venous (AV) systems are not currently used except in emergent situations such as earthquakes or other environments where appropriate machinery is not available (6,10,11). Their advantages include their ease of setup and operation and low extracorporeal volume. Unfortunately, AV systems require arterial cannulation and expose the patient to the risk of main arterial damage, atheroembolism, or distal limb ischemia. Furthermore, AV systems cannot control blood flow adequately, as they are dependent on the patency of the vessel and the patient's hemodynamics, thus making dose and ultrafiltration (UF) management very difficult.

Conversely, veno-venous (VV) systems offer a decreased risk of vascular damage, maintain blood flow independent of mean arterial pressure, and achieve greater blood flows regulated safely by blood pumps, thus obtaining higher clearances. For these reasons, VV is preferred to AV modalities, and AV is not recommended except in emergent situations where other alternatives are not accessible, such as unavailability of appropriate blood pumps or venous access (6). Multiple VV access options are offered, as discussed elsewhere in this issue (see section on Vascular Access).

Choice of CRRT Modality

The different modalities of CRRT (Fig. 1) are defined by the main mechanism with which clearance is achieved: simple diffusion (continuous veno-venous hemodialysis, CVVHD), convection (continuous veno-venous hemofiltration, CVVH), or a combination of both (continuous veno-venous hemodiafiltration, CVVHDF). See Table 5.

Many intensivists and nephrologists prefer to use CVVH in the belief that pure convection will remove a greater number of larger molecules than diffusion-based CVVHD. Others argue that CVVHD is easier and, given the lack of comparative evidence, prefer this mode. Still a third school favors CVVHDF on the basis that without evidence, providing both modes are safe (12). The choice of CRRT modality rests on the available equipment (membranes, pump systems) and appropriate fluids and cost and conceptual considerations.

The main feature of convective treatments is the use of high-flux membranes, characterized by high permeability for water as well as low- and middle-molecular weight solutes (in the range of 1000–12,000 Daltons) and high "biocompatibility." It is a widespread opinion that convective treatments like high-flux hemodialysis, hemodiafiltration, and hemofiltration offer a clinical advantage over standard dialysis when considering physiological outcomes. The crucial point is that up until now, studies have not been able to demonstrate superiority of these techniques on morbidity, mortality, and quality of life (6,13–18).

Comparison of CRRT with Other Renal Replacement Modalities

Continuous renal replacement therapies techniques offer better long-term clearance of small and middle molecules than IHD or SLED. Liao et al. (19) modeled a comparison between IHD, SLED, and CVVH and

TABLE 4. Advantages and disadvantages of various renal replacement modalities

Modality	Use in hemodynamically unstable patients	Solute clearance	Volume control	Anti-coagulation
PD	Yes	+ +	+ +	No
IHD	Possible	+ + + +	+ + +	Yes/no
IHF	Possible	+ + +	+ + +	Yes/no
Intermittent IHF	Possible	+ + + +	+ + +	Yes/no
Hybrid techniques	Possible	+ + + +	+ + + +	Yes/no
CVVH	Yes	+ + +/+ + + +	+ + + +	Yes/no
CVVHD	Yes	+ + +/+ + + +	+ + + +	Yes/no
CVVHDF	Yes	+ + + +	+ + + +	Yes/no

HDF, hemodiafiltration; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration; IHD, intermittent hemodialysis; IHF, intermittent hemofiltration; PD, peritoneal dialysis.
Modified from Davenport (33).

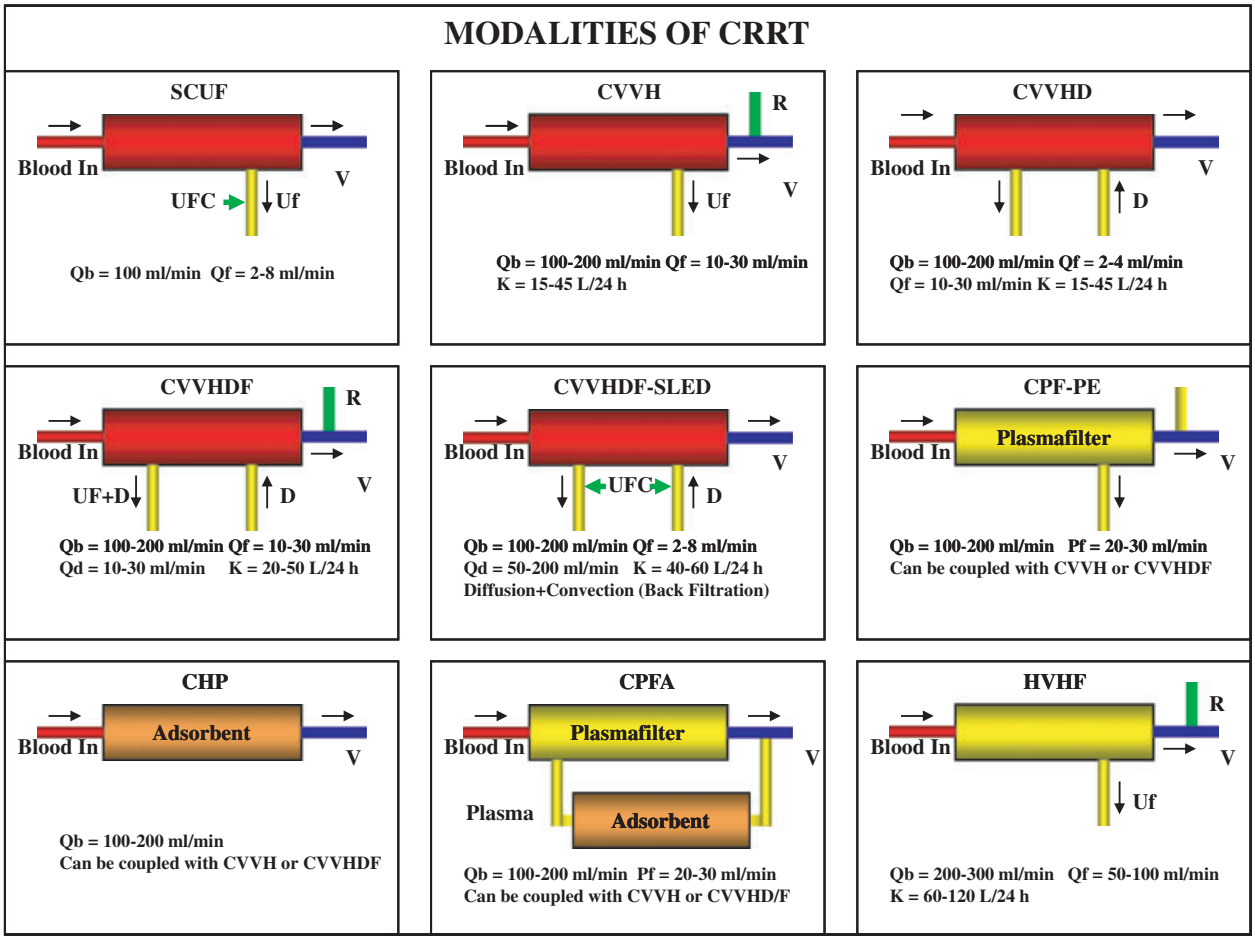

FIG. 1. Modalities of continuous renal replacement therapies (CRRT). Techniques available today for renal replacement in the intensive care unit. CAVH, continuous arterio–venous hemofiltration; CHP, continuous hemoperfusion; CPFA, plasmafiltration coupled with adsorption; CPF-PE, continuous plasmafiltration-plasma exchange; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration; CVVHDF, continuous high-flux dialysis; D, dialysate; HVVF, high-volume hemofiltration; K, clearance; Pf, plasmafiltrate flow; Qb, blood flow; Qd, dialysate flow; Qf, ultrafiltration rate; R, replacement; SCUF, slow continuous ultrafiltration; SLED, sustained low efficiency daily dialysis; UFC, ultrafiltration control system.

demonstrated that CVVH had 8% and 60% higher small solute clearance than SLED and IHD, respectively. Both SLED and CVVH were predicted to provide very effective azotemic control in hypercatabolic AKI patients, while IHD controlled azotemic peaks and time averaged concentration poorly.

Differences were more pronounced for middle and large solute categories, and equivalent renal clearance (EKR) in CVVH was approximately two to fourfold greater than daily IHD and SLED, respectively. The superior middle and large solute removal for CVVH was due to the powerful combination of convection and continuous operation. In their model, Liao et al. showed that as a consequence of ongoing production and poor clearance, the plasma concentration of β2-microglobulin actually increased in patients modeled to undergo IHD

TABLE 5. Modalities of continuous renal replacement therapy

	Clearance	Mechanism	Vascular	Fluid
Technique	Convection	Diffusion	Access	Replacement
SCUF	+	–	Large vein	0
CAVH	+ + + +	–	Artery and vein	+ + +
CVVH	+ + + +	–	Large vein	+ + +
CAVHD	+	+ + + +	Artery and vein	+ + +
CVVHD	+	+ + + +	Large vein	+/0
CAVHDF	+ + +	+ + +	Artery and vein	+ +
CVVHDF	+ + +	+ + +	Large vein	+ +
CAVHFD	+ +	+ + + +	Artery and vein	+/0
CVVHFD	+ +	+ + + +	Large vein	+/0

CAVH, continuous arterio–venous hemofiltration; CAVHD, continuous arterio–venous hemodialysis; CAVHDF, continuous arterio–venous hemodiafiltration; CAVHFD, continuous arterio–venous high-flux hemodialysis; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration; CVVHFD, continuous veno-venous high-flux hemodialysis; SCUF, slow continuous ultrafiltration.

0, not required; +, negligible; + +, some; + + +, marked; + + + +, major control system.

or SLED, while it reached a lower steady-state level after the third day of CVVH.

The importance of the clearance of larger compounds is suggested by the Ronco et al. study (20) and an earlier CRRT study (21) correlating dose (i.e., ultrafiltration rate) with survival. Both studies were performed in the purely convective mode, and large molecular clearance may have contributed substantially to the salutary effect of higher doses in these therapies. More recently, Saudan et al. (14) showed that the addition of diffusion to convective clearance resulted in further improvement in patient outcome. Because the daily versus every other day IHD study by Schiffl et al. (22) was performed with high-flux dialyzers, the clearance of compounds significantly larger than urea may have played a role in the improved survival among the patients dialyzed daily. In spite of these suggestive findings, there is no firm evidence that enhanced removal of mid- or high-molecular weight patients leads to better patient outcomes (see below).

Convection and Diffusion

Convection-based replacement techniques (hemofiltration and hemodiafiltration) using high-flux membrane filters are aimed at maximizing the removal of so-called medium and high-molecular weight solutes (higher than 1000 kDa up to several thousand kDa), as opposed to the so-called low-molecular weight toxins (15,16,23).

Hemofiltration, a predominantly convective technique, removes larger quantities of hydrophilic large molecular-weight compounds than diffusion-based hemodialysis. In the ICU setting, hemofiltration leads to greater cytokine removal by a combination of membrane adsorption and convection, but does not remove bacterial endo- and exotoxins. It has been postulated that removal of inflammatory mediators could influence patient outcome (24).

Hemodiafiltration has recently become widely available not only for the treatment of end-stage renal disease patients but also for the management of patients with AKI (25). Partially hydrophilic high-flux membranes with high sieving coefficients and reduced wall thickness have made it possible to combine diffusion and convection. Accurate ultrafiltration control systems have made the system safe to apply large volumes of fluid turnover. Continuous veno-venous hemofiltration/hemodiafiltration was made possible by the advent of a machine specifically designed for CRRT (Prisma) featuring four pumps, which allow separate management of dialysate flow and ultrafiltration/reinfusion flow. Recently, the development of on-line production of large amounts of ultrapure dialysate and replacement fluid has made the procedure safe and less expensive.

With current CRRT machines, solute removal can be obtained by convection, diffusion or both, with easier and more precise control over each component of the therapy. Blood (QB), dialysate (QD), and ultrafiltrate (QUF) flow rates can be controlled accurately with integrated pumps with greater dialysate or convective flows; therefore greater diffusive and convective solute fluxes can be achieved. During CRRT, diffusion is limited by QD, in contrast to intermittent hemodialysis (IHD) (26,27); the addition of convection may improve the clearances or middle-molecular weight solutes.

Diffusion

Whether in solution or in an extracorporeal membrane, the diffusivity of a solute is inversely proportional to its molecular weight. Consequently, as solute molecular weight increases, diffusion becomes a relatively inefficient solute removal mechanism and the relative importance of convection increases (28).

Diffusion occurs whenever a concentration gradient (dc) exists for solutes not restricted by the porosity of the membrane. The diffusion flux is influenced by the characteristics of the membrane including surface area (A) and thickness (dx), the temperature of the solution (T) and the diffusion coefficient of the solute (D). The diffusion flux of a given solute (Jx) will therefore result from the equation (28):

$$Jx = D.T.A\ (dc/dx) \qquad (1)$$

Other factors may influence the final clearance values including protein binding or electrical charges of the

solute. Increased convection may contribute to greater solute transport, especially in the higher molecular weight range.

Convection

Convection requires movement of fluid across the membrane driven by a transmembrane pressure gradient (TMP). The fluid transport is defined as ultrafiltration and can be described by the equation:

$$Jf = Kf.TMP \quad (2)$$

Where Kf is the coefficient of hydraulic permeability of the membrane and TMP = (Pb−Puf)−π. Pb is the hydrostatic pressure of blood, Puf the hydrostatic pressure of ultrafiltrate or dialysate and π the oncotic pressure of plasma proteins.

The convective fluid of a solute x will therefore depend on the amount of ultrafiltration (Jf), on the concentration of the solute in plasma water (Cb), and by the sieving characteristics of the membrane for the solute (S):

$$Jx = Jf\ Cb(1 - \sigma) = Jf\ Cb\ S \quad (3)$$

The sieving coefficient (S) is regulated by the reflection coefficient of the membrane σ according to the equation:

$$S = 1 - \sigma \quad (4)$$

In clinical practice, however, because plasma proteins and other factors modify the original reflection coefficient of the membrane, the final observed sieving coefficient is smaller than expected from a simple theoretical calculation (28).

The membranes used in convective treatments are high-flux, semisynthetic, and synthetic and possess high permeability, which allows for convective removal of water and electrolytes and a higher clearance of middle and larger molecular-weight solutes (see below). These membranes are more biocompatible, minimizing the inflammatory response induced by the blood–membrane interactions (18,29).

According to their ultrafiltration coefficient and solute sieving profile, dialysis membranes are classified as high-flux and low-flux (28). In clinical practice, membranes are incorporated into devices designed to optimize their performance. These devices are either designated as "dialyzers," working predominantly in diffusion with a countercurrent flux of blood and dialysate, or as "hemofilters," working prevalently in convection. Newer designs have allowed the performance of concomitant diffusive and convective mass transport, leading to therapies such as high-flux dialysis and hemodiafiltration where the advantages of both mechanisms are significantly enhanced.

Predilution or Postdilution

In hemofiltration, replacement fluid can be infused either before the hemofilter ("predilution") or after the hemofilter ("postdilution").

In postdilution CVVH, a purely convective therapy, the three primary determinants of solute clearance are ultrafiltration rate, membrane sieving coefficient, and dilution mode (28). Convection occurs by "solvent drag": solutes are swept (dragged) across the membrane in association with ultrafiltered plasma water, such that

$$K = Q_F.S \quad (5)$$

where K is clearance (ml/minute), Q_F is ultrafiltration rate (m/minute), and S sieving coefficient. For small solutes, as S approaches unity clearance equals the ultrafiltration rate in postdilution.

In postdilution CVVH, filtration fraction (FF), the ratio of ultrafiltration rate (Quf) to plasma water flow rate is determined by blood flow (Qb) rate and patient hematocrit (Htc):

$$FF = \frac{Quf}{Qb(1 - Htc)} \quad (6)$$

Clinical practice indicates that a FF greater than 0.3 should be avoided because of hemoconcentration and protein–membrane interaction (30). Greater ultrafiltration rates require larger blood flows to avoid elevated FF and filter clotting and coating with accumulated proteins. As higher blood flows are usually difficult to reach with the temporary dialysis catheters and hemodynamic conditions commonly prevalent among critically ill patients, achieving higher doses recently demonstrated to affect survival are difficult to do in postdilution mode.

Predilution mode has been introduced as a useful adjunct to prevent clotting of the extracorporeal circuit and to extend filter life, especially during high-volume CRRT, where filtration fraction would otherwise reach values greater than 0.3 and induce clotting and protein encroachment of the membranes.

Predilution CRRT allows freedom from the constraints in blood flow and filtration rate imposed by predilution. For small solutes dissolved in the water of the blood passing through the hemofilter (26), clearance equals

$$K = Q_F.S.[Q_{BW}/(Q_{BW} + Q_S)] \quad (7)$$

where Q_{BW} is blood water flow rate and Q_S the substitution (replacement) fluid rate.

At a given Q_F value, predilution is always less efficient than postdilution CVVH with respect to fluid utilization: while predilution attenuates hemoconcentration-related effects, it simultaneously reduces the efficiency of the treatment. Thus, the larger Qs is relative to Q_{BW}, the smaller the entire fraction, and the greater the loss of efficiency relative to postdilution. In CVVH, given the direct relationship that exists between Q_S and Q_F, great efforts are needed towards increasing the blood flow beyond the 150 ml/minutes that is traditionally used in CRRT.

In predilution mode, to attain doses of 35 ml/kg/hour as described by Ronco et al. (20) it is necessary to achieve

blood flows of 250 ml/minutes or higher, given that the decrease in efficiency inherent to predilution mode can be as high as 35 to 40–45% for urea and creatinine respectively, when QB is 125–150 ml/minutes and Q_S is fixed at 75 ml/minutes (31).

Utilizing modeling analysis, Clark et al. (30) have shown that when low blood flow rates are used with patients weighing more than 70 kg, the rate of replacement fluid required to achieve a postdilutional CVVH dose of 35 ml/kg/hour is impractically high. To achieve the dose target, the high predilutional replacement fluid infusion rates required have a substantial dilutive effect on solute concentrations at low blood flows. Conversely, higher blood flows allow the delivery of higher doses without loss of efficiency.

Brunet et al. (26) studied the diffusive and convective solute clearances during CVVHDF at various dialysate and ultrafiltration rates. To assess the impact of predilution on convective clearances, they demonstrated a progressive decrease in patient clearances for urea, urates, and creatinine of 15%, 18%, and 19% respectively, with predilution at a QUF of up to 2 l/hour. When comparing convective and diffusive clearances, for small solutes with an effluent to plasma ratio (E/P) of 1, clearances were equal to effluent rate, which became greater as the filter area increased. For larger molecules such as β2 microglobulin, diffusive clearance was very low and reached a plateau at a QD greater than 1.5 l/hour. Conversely, convective β2 microglobulin clearance increased nonlinearly up to 20 ± 2 ml/minute at a progressively greater QUF between 0.5 and 2 l/hour, due to an increase in E/P of almost 40% from a QUF of 0.5–2 l/hour. For small molecules, there was no interaction between diffusion and convection. For β2 microglobulin the addition of diffusion (QD 0.5–2.5 l/hour) did not result in significant increase in total clearance over convective clearance, suggesting that the diffusive clearances observed for β2 microglobulin at QUF 0 l/hour and at various QD probably occurs by convective fluxes across the membrane.

These results demonstrate that convection is more effective than diffusion in removing middle-molecular weight solutes during CRRT, and that high convective fluxes should be applied if the goal is to remove middle molecules more efficiently.

A recent modification of dialysis technique, continuous high-flux dialysis (CHFD), consists of high-flux dialyzers utilized in a continuous hemodialysis circuit with continuous ultrafiltration volume control (18,32–34). As the spontaneous filtration in the dialyzer would be much greater than the desired fluid loss, a positive pressure is applied to the dialysate compartment and the transmembrane pressure gradient is reduced. This results in high convective transport in the proximal port of the dialyzer and "backfiltration" of fresh dialysate in the distal portion of the dialyzer, in a convenient combination of diffusion and convection in a single procedure. The procedure requires continuous generation of ultrapure dialysate (33). Utilized in single pass or recirculation mode, CHFD can achieve a middle and large molecular clearance as high as 60% of the clearance of small molecules.

Interaction between Convection and Diffusion

At the slow flow rates normally utilized in CRRT, there is no interaction between diffusive and convective clearances. Recent studies (14) have shown that the addition of a diffusive component to dialysis "dose" resulted in improved survival.

Until recently, dose data were mainly limited to diffusion Schiffl et al. (22) and convection Ronco et al. (20). The results of Ronco et al. led to the definition of a "standard dose" of CRRT of 35 ml/kg/hour, which was applied indiscriminately to diffusive and convective continuous modalities. More recently, Palevsky et al. (5) utilizing a combined diffusive and convective modality (predilution CVVHDF) or intermittent hemodialysis (IHD) depending on hemodynamic stability, failed to demonstrate a beneficial effect of such dose, as discussed elsewhere (see Dose of Dialysis in this issue). It must be emphasized that the ATN study was "not" designed to evaluate the different RRT modalities, but rather to evaluate the effects of dose on survival and renal recovery function. The RENAL study, led by Bellomo et al. (35) to be reported later this year, will address similar dose questions utilizing postdilution CVVHD.

The premise of those studies is that dose is a solute clearance-related parameter (30). The studies were not designed to determine increased clearance of which toxin led to better survival. Although small solute clearance is a possible explanation, substantial clearance of relatively large molecular weight toxins may also explain the survival benefit in the high dose arm of the Ronco study (20).

Based on the dosing scheme of normalizing effluent flow rate to body weight, other forms of CRRT such as CVVHD and CVVHDF may provide equivalent or nearly equivalent small solute clearances as postdilution CVVH, but for a given effluent flow rate, the diffusive component of these therapies limits their ability to clear larger molecular weight toxins relative to hemofiltration (30). Consequently, extrapolating Ronco's data to other forms of CRRT, especially for dosing purposes, should be done with caution.

Nutrition and Outcome

Better management of volume and body fluid composition is easily achieved with CRRT. Given the importance of nutrition on the outcome of critically ill patients with AKI (36,37), CRRT could offer a theoretical advantage over IHD in this setting.

Hemodynamic Stability

Older (38) and very recent (34) studies have consistently shown that the main advantage of continuous modalities is greater hemodynamic stability. In their recently published study, Palevsky et al. (5) chose CRRT (CVVHDF) as the modality of choice for hemodynamically unstable patients, a decision that reflects current practice in the United States. In their study, although hemodynamically "stable" patients were allocated to

IHD, hypotension occurred more frequently among patients treated with IHD than CRRT and may have had an impact on their lower rate of recovery of renal function.

Continuous renal replacement therapies are associated with better tolerance to fluid removal for several reasons. First, the rate of fluid removal is much slower in CRRT than in IHD: if 3 l of fluid are removed in a 3-hour IHD session, the rate of UF is 1 l/hour, while the same volume can be removed at a rate of 0.125 l/hour in a 24 hour CRRT session. The main determinant of hemodynamic instability during RRT is the maintenance of intravascular compartment volume. The volume of that compartment is the result of the balance between convective removal of fluid (ultrafiltration) from plasma and the rate of replenishment from the interstitium. Therefore, whenever the UF rate exceeds the rate of interstitium-to-plasma flow (refilling), the patient will experience hypovolemia and hemodynamic instability (9).

Second, in IHD rapid diffusion of urea creates a plasma-to-interstitium and interstitium-to-cell osmotic gradient that drives water to the interstitium and to the intracellular compartment, such that plasma volume decreases and cell edema (including neuronal edema) occurs. With CRRT, the slower rate of urea clearance allows for equalization of urea concentrations between compartments and therefore, decreased water shifts and cell edema. This is particularly important in patients with intracranial hypertension, such as head trauma and severe liver failure (38–40).

Third, a decrease in core temperature and peripheral vasoconstriction has been shown to decrease hypotensive episodes and may play a role in hemodynamic stability (41).

Fourth, with either pre or postdilution hemofiltration, the magnitude of sodium removal is less than the amount of sodium removed with hemodialysis, a factor which may contribute to better cardiovascular stability in hemofiltration (9,42–45).

Finally, although hypovolemia is the first step in dialysis-related hypotension, the ultimate arterial pressure response to hypovolemia is the result of a complex interplay between active and passive mechanisms including decreased venous vessel capacity to sustain cardiac filling; increased arterial vascular resistances to ensure organ perfusion; and increased myocardial contractility and heart rate to maintain cardiac stroke volume (41). Any factor interfering with one or more of these compensatory mechanisms may foster cardiovascular instability. In this context, it is possible that convective removal of inflammatory mediators could contribute to hemodynamic stability, especially in the early phases of septic shock (see below).

Hemofiltration of Large Molecules

Middle molecules, consisting mostly of peptides and small proteins with molecular weight in the range of 1000–600,000 Daltons, accumulate in renal failure and contribute to the uremic toxic state (15,46). Beta-2 microglobulin, with a molecular weight of 11,000 Dalton is considered representative of these middle molecules (47). These solutes will not be well cleared by low-flux dialysis; high-flux dialysis will clear middle molecules partly by internal filtration (convection); the convective component of high-flux dialysis can be enhanced in a predictable way by hemodiafiltration (48,49).

In the last decade, it has been postulated that high convective dose therapies improve the management of sepsis (16,20,50–53). Severe sepsis and septic shock are the primary causes of multiple organ dysfunction syndrome (MODS), the most frequent cause of death in ICU patients. Many water-soluble mediators with pro and anti-inflammatory action such as TNF, IL-6, IL-8, and IL-10 play a strategic role in septic syndrome. In intensive care medicine, blocking any one mediator has not led to a measurable outcome improvement in patients with sepsis. CRRT is a continuously acting therapy, which removes in a nonselective way pro and anti-inflammatory mediators. The "peak concentration hypothesis" (54–56) is the concept that cutting peaks of soluble mediators through continuous hemofiltration may help restore homeostasis.

This latter development proposes to use increased volume exchanges in hemofiltration or the combined use of adsorbent techniques. High volume hemofiltration (HVHF) is a variant of CVVH that requires higher surface area hemofilters and ultrafiltration volumes of 35–80 ml/kg/hour, providing higher clearance for middle/high molecular weight solutes than simple diffusive transport (CVVHD) or convection-based transport at lower volumes (CVVH). This technique is associated with practical difficulties including machinery, replacement fluid availability and cost, and accurate monitoring systems to maintain safety (9). Studies utilizing this technique have shown preliminary evidence of benefit, but none of the studies are randomized trials of adequate statistical power to demonstrate effect conclusively. Alternative technologies have utilized high cut-off hemofilters with increased effective pore size (34). Drawbacks of such porous membranes include the loss of essential proteins such as albumin. Plasmafiltration coupled with adsorption (CPFA) has been recently utilized in septic patients (4), in a system that separates plasma from blood and circulates the plasma through a sorbent bed; blood is subsequently reconstituted and dialyzed with standard techniques, thus achieving normalization of body fluid composition and increased removal of protein-bound solutes and high-molecular weight toxins.

Recently, evidence has been obtained (56–59) that very high volume hemofiltration applied in pulses may improve the hemodynamic stability of patients in septic shock, but failed to show consistently improved survival. Larger multicentric evidence will be necessary before such techniques are widely implemented. If benefit is demonstrated, the use of very high-volume hemofiltration will require special equipment and very capable nursing able to manage such large volumes (i.e., up to 5–6 l/hour) of ultrapure replacement fluid without error (9,60).

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