CHAPTER 166

Continuous Renal Replacement Therapy: Modalities and Their Selection

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OBJECTIVES

This chapter will:

1. Review the principles of continuous renal replacement therapy.
2. Discuss the practical application of continuous renal replacement therapy and the consequences of such application.
3. Examine the consequences of technical modifications to continuous renal replacement therapy.
4. Provide information pertaining to choices and prescription of continuous renal replacement therapy.

Endogenous toxins accumulate in blood as a result of many biochemical processes.[1] If their concentration exceeds certain levels, they cause illness. Some toxins are volatile (CO_2, ketones) and can be excreted by the lungs through ventilation, others are lipophilic (bile acids, bilirubin) and can be excreted by the liver via the biliary system, and others are water soluble and nonvolatile and are excreted by the kidneys (Table 166.1).[1] When the kidneys fail acutely, removal of such water-soluble toxins requires acute artificial renal replacement therapy (RRT).[2]

Water-soluble toxins exist in blood at various concentrations. Blood is a complex fluid containing cells and

TABLE 166.1

Route of Blood Purification for Various Toxins

TOXIN	ROUTE
CO_2	Lung
Other volatile toxins	Lung
Ketones	Lung and kidney
Bilirubin	Liver and kidney
Biliary acids	Liver
Fat-soluble toxins	Liver and (after conjugation) kidney
Urea	Kidney
Water-soluble toxins	Kidney

plasma. Plasma is a complex solution, and it is the plasma compartment of blood that is available for purification by RRT. Plasma contains myriad solutes (electrolytes, proteins, lipids, carbohydrates, vitamins, amino acids), which are dissolved in plasma water (the solvent). Only those solutes that are water soluble and not protein bound (free solutes) are available for removal by classic RRT. This is because the conventional biosynthetic membranes used for RRT have an in vivo cutoff point of about 15 to 20 kilodaltons (kD), which does not allow the passage of anything beyond small proteins (such as β_2-microglobulin).[3] Accordingly, the following discussion of blood purification principles and techniques relates to free solutes of relatively small to small-medium molecular weight (<15 kD). The chapter does not discuss peritoneal dialysis, in which the dialyzing membrane is the peritoneum and some larger proteins are removed during the blood purification process. Also not discussed in this chapter are different forms of plasma therapies in which protein-bound solutes can be removed through high-porosity membranes.

Extracorporeal techniques are broadly named RRT and include continuous or intermittent hemofiltration, hemodialysis, or hemodiafiltration, each with its own technical variations. All of these techniques rely on the principle of removing unwanted solutes and water through a membrane separation process.

PRINCIPLES OF SOLUTE REMOVAL

The principles of RRT have been studied extensively and described.[2,4,5] This section provides a summary of some technical aspects of RRT, which are particularly relevant for the critical care physician.

Water Removal

The removal of excess solvent (water) is therapeutically at least as important as the removal of unwanted solutes (e.g., acid, uremic toxins, potassium). During RRT, water is removed through a process called *ultrafiltration*. This process is essentially the same as that performed by the glomerulus. It requires a pressure gradient (generated by blood flow and circuit resistance) to move water across a semipermeable membrane. This is because plasma water normally would be kept within the circulation because of oncotic pressure. This ultrafiltration is achieved by generating a positive hydrostatic pressure (as in hemofiltration or during intermittent hemodialysis) that is greater than oncotic pressure. The final result is a positive transmembrane pressure that drives fluid through the membrane at a rate dependent on the hydraulic permeability coefficient and the surface of the membrane.

Solute Removal

The removal of retention solutes can be achieved by creating a transmembrane pressure–driven "solvent drag," where solute moves together with solvent (convection) across a porous membrane. Solvent with unwanted solutes is discarded as effluent and then replaced with toxin-free fluid containing electrolytes (hemofiltration). The rate of transport of the solute depends on the relationship between solute radius (or molecular weight) and the radius of membrane pores. Solutes smaller than the pores will pass freely through the membrane and will not be "rejected" (rejection coefficient = 0), whereas solutes larger than the pores will be rejected fully (rejection coefficient = 1). Because it is difficult to establish a priori the rejection coefficient, in practice the physician can observe and measure the sieving coefficient, which is exactly the opposite of the rejection coefficient corrected for empiric factors. Solute clearance will be determined by the product of ultrafiltration rate by the value of measured sieving. Sieving is measured easily by the ratio between the concentration in the filtrate and that in plasma water.

Unwanted solutes also can be removed by creating a chemical gradient across the membrane using a "flow past" system with toxin-free dialysate (diffusion) as in hemodialysis.

The rate of diffusion of a given solute depends on (1) its molecular weight (diffusivity coefficient), (2) the porosity of the membrane, (3) its surface and its thickness, (4) the blood flow rate and the dialysate flow rate (which generates the concentration gradient and prevents equilibration resulting from blood and dialysate stagnation), (5) its concentration gradient across the membrane, (6) its binding to proteins, (7) its electrical charge, and (8) the temperature at which the process takes place. If standard, low-flux, cellulose-based membranes are used, middle molecules greater than 500 daltons (D) molecular weight can hardly be removed. If synthetic high-flux membranes are used (cutoff at 15 to 20 kD in molecular weight), larger molecules can be removed to a certain extent. However, with these membranes, convection is superior to diffusion in achieving the clearance of middle molecules.

CONTINUOUS RENAL REPLACEMENT THERAPY

First described in 1977, continuous renal replacement therapy (CRRT) has undergone several technical modifications. Initially, it was performed as an arteriovenous therapy (continuous arteriovenous hemofiltration [CAVH]), in which blood flow through the hemofilter is driven by the patient's blood pressure. However, clearances were low because blood flow was low (often <80 mL/min) and ultrafiltration was low. Thus countercurrent dialysate flow soon was added to double or triple solute clearances (continuous arteriovenous hemodialysis or hemodiafiltration [CAVHD or CAVHDF, respectively]), with or without spontaneous ultrafiltration. The need to cannulate an artery, however, is associated with 15% to 20% morbidity. Accordingly, double-lumen catheters and peristaltic blood pumps have come into use (continuous venovenous hemofiltration [CVVH]) with control of ultrafiltration rate. Because blood flow (often set

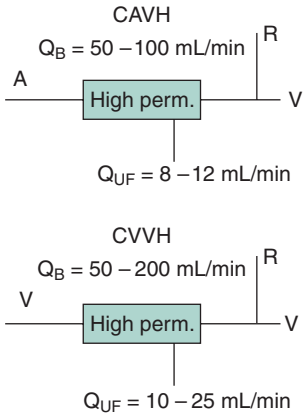

FIGURE 166.1 Diagrams illustrating an arteriovenous and a venovenous circuit for continuous hemofiltration. The top circuit represents continuous arteriovenous hemofiltration (CAVH) with spontaneous generation of ultrafiltrate (UF) and postfilter administration of replacement fluid (R). The bottom circuit represents continuous venovenous hemofiltration (CVVH). The letters A (arterial) and V (venous) refer to the source of blood. Ranges of possible values for blood flow (Q_B) and ultrafiltrate flow (Q_{UF}) are provided.

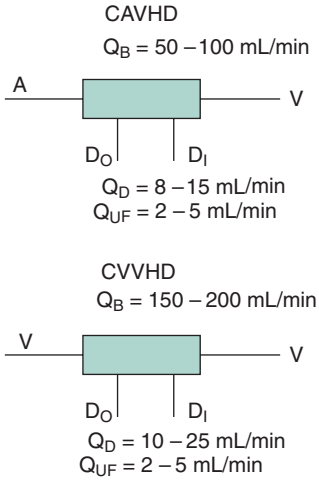

FIGURE 166.2 Diagrams illustrating an arteriovenous and a venovenous circuit for continuous hemodialysis. The top circuit represents continuous arteriovenous hemodialysis (CAVHD) with countercurrent dialysate flow. The bottom circuit represents continuous venovenous hemodialysis (CVVHD) with countercurrent dialysate flow. The letters A (arterial) and V (venous) refer to the source of blood. D_I and D_O represent the dialysate inflow and outflow ports. Ranges of possible values for blood flow (Q_B) and dialysate flow (Q_D) are provided.

at 200 mL/min) is no longer a limiting factor, venovenous technology has made hemofiltration easily able to deliver the necessary clearances again (Fig. 166.1). In the developed world, essentially all CRRT is now carried out in venovenous mode.[3]

In a venovenous system, dialysate also can be delivered countercurrent to blood flow (continuous venovenous hemodialysis [CVVHD]) to achieve almost purely diffusive clearance (Fig. 166.2). However, purely diffusive clearance is never possible because ultrafiltration is always necessary to remove some solvent. Accordingly, a degree of ultrafiltration with convective clearance always must occur, over a 24-hour cycle, even with CVVHD.

Furthermore, even without ultrafiltration, within the filter there are differences in hydraulic pressure and colloid

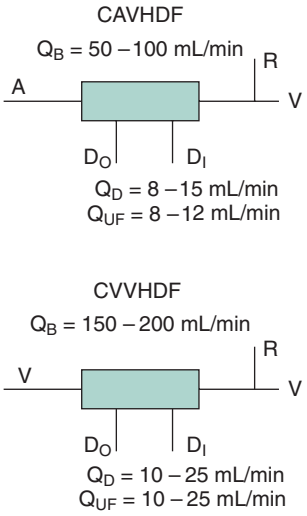

FIGURE 166.3 Diagrams illustrating an arteriovenous and a venovenous circuit for continuous hemodiafiltration. The top circuit represents continuous arteriovenous hemodiafiltration with countercurrent dialysate flow (CAVHDF) and postfilter replacement fluid (R). The bottom circuit represents continuous venovenous hemodiafiltration with countercurrent dialysate flow (CVVHDF) and postfilter replacement fluid. The letters A (arterial) and V (venous) refer to the source of blood. Q_B represents blood flow, Q_D, dialysate flow, and Q_{UF}, ultrafiltrate flow. D_I and D_O represent the dialysate inflow and outflow ports. Ranges of possible values for Q_B and Q_D are provided.

oncotic pressure relationship such that the hydraulic pressure is greater than the colloid oncotic pressure, and transmembrane pressure is positive. Thus there is a degree of convection within the membrane microenvironment in all patients. Also, depending on the type of membrane and the blood flow rate or dialysate flow rate and their relationship, other events such as backfiltration typically occur. Nonetheless, the feature that separates hemodialysis from hemodiafiltration is the fact that, in hemodialysis, no replacement fluid is given.

Finally, diffusion and convection can be coupled, as in continuous venovenous hemodiafiltration (CVVHDF) (Fig. 166.3).[6] In this mode, there may be, for example, ultrafiltration at 1 L/hr and dialysate flow at 1 L/hr, resulting in an effluent of 2 L/hr and the need for 1 L/hr of replacement fluid, if no fluid loss is planned. This approach would combine convection and diffusion in almost equal proportions.

These concepts, as discussed for continuous therapies, also apply to intermittent therapies. The only differences will, of course, relate to blood flow, dialysate flow, or ultrafiltration rate and replacement fluid rate. The possible combinations of blood flow rate, dialysate flow rate, ultrafiltration rate, and replacement fluid rate are almost infinite.

No matter what technique is used, the clinician needs to understand the solute clearance implications of using one versus the other and the solute clearance implications of using so-called predilution (the replacement fluid is administered before the filter) or postdilution (the replacement fluid is administered after the filter).

Hemofiltration, Hemodialysis, and Hemodiafiltration

If replacement fluid is given after the filter (postdilution) and 2 L of effluent (the fluid that is discarded) is generated

each hour, urea and creatinine clearance are essentially the same whether hemofiltration is performed with 2 L of replacement fluid per hour, hemodialysis with 2 L of dialysate fluid per hour, or hemodiafiltration with 1 L of dialysate fluid plus 1 L of replacement fluid per hour. That is because, for all three techniques, the effluent-to-plasma concentration ratio for urea or creatinine will be essentially 1. Thus, for small solutes, the choice of technique does not matter.

However, if replacement fluid is given postfilter, the hematocrit will rise within the filter as plasma water is removed (Fig. 166.4). For example, if blood flow is 150 mL/min and the hematocrit is 30% (50 mL), plasma flow will be 100 mL/min. If ultrafiltration is 2 L/hr, then 33 mL/min of plasma water will be removed. Thus, at the return end of the filter, the amount of plasma water will be 67 mL, which, added to 50 mL of cells, will deliver an intrafilter hematocrit of 42.7%. This is a significant increase, which also will be associated with a similar percentage increase in intrafilter platelet count and protein concentration. This concentrating effect on red cells, platelets, and proteins will, of course, be attenuated by any increase in blood flow. However, even with a blood flow of 200 mL/min, the statistical probability of filter clotting will rise and filter life will shorten (see Fig. 166.4).[7]

In addition, if the filtration fraction (effluent flow rate/plasma flow rate) is high (>30%), some loss of clearance (especially for middle molecules) will occur as proteins and cells are pushed against the membrane by transmembrane pressure and form a proteinaceous layer (so-called concentration polarization) on top of it, which decreases functional pore size and number. These observations have clear implications if a clinician moves to perform so-called high-volume hemofiltration (need to increase blood flow, need to maintain acceptable filtration fraction).[8,9]

Finally, these observations not only apply to CVVH but also to the convective component of CVVHDF and to any intermittent therapy that employs substantial convective clearance. They do not apply to CVVHD or conventional intermittent hemodialysis or diffusive sustained low-efficiency dialysis.[10]

Faced with the problem of hemoconcentration if postdilution is used, the clinician reasonably could turn to so-called predilution. This approach to fluid replacement essentially eliminates hemoconcentration and can be expected to increase filter life.

However, predilution also will dilute the very solutes that the clinician wishes to clear. The proportional dilution will be equal to the replacement fluid flow rate/plasma flow rate ratio (see Fig. 166.4). If replacement fluid is delivered pre–blood pump, dilution also will be greater than if it is delivered post–blood pump. For example, if blood flow is 150 mL/min and the hematocrit is 30%, plasma flow will be 100 mL. If predilution fluid is administered at 33 mL/min (2 L/hr) after the blood pump but before the filter, urea dilution will occur. If the rate was 30 mmol/L in the patient's plasma, it then will become 22.5 mmol/L when it enters the filter. Because the clearance is equal to ultrafiltration rate × urea in the ultrafiltrate, urea clearance will be decreased significantly with predilution as compared with postdilution (see Fig. 166.4). However, other events happen that tend to attenuate this decrease in clearance. They include diminished concentration polarization resulting from protein dilution, increased wall shear rate (i.e., an increased velocity gradient at the blood membrane interface, which keeps the inner membrane clean), minimized filtration fraction, and the movement of urea from red cells into plasma following dilution. Clearly, no such dilution would occur with CVVHD, and only half the dilution would occur with CVVHDF, if half the effluent was replaced prefilter (Table 166.2).

The final outcome of these processes has been measured in vivo by Brunet et al.[11] These investigators compared urea and creatinine clearance with predilution CVVH, CVVHD, or CVVHDF (50% in predilution), all with an equal 2 L/hr of effluent generation and a blood flow of 150 mL/min. They found that, with CVVH, urea clearance was 28.5 mL/min compared with 33.1 mL/min with CVVHD and 29.8 mL/min with CVVHDF. For creatinine the values were 26.3, 30.1, and 28 mL/min, respectively.[11]

Given that dilution is dependent on blood flow, these differences would be reduced further if blood flow were 200 or 250 mL/min. Nonetheless, at 150 mL/min of blood flow, it would appear that CVVHD should be the preferred

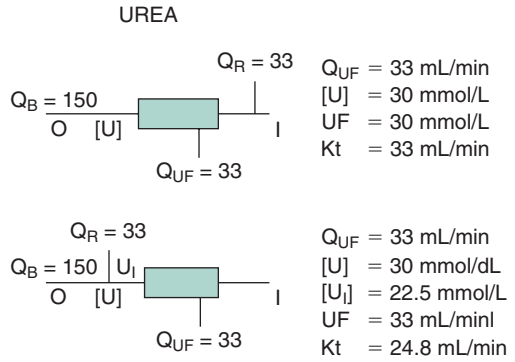

FIGURE 166.4 Diagrams illustrating the differences between continuous venovenous hemofiltration (CVVH) in postdilution and CVVH in predilution. The letters U and U_I refer to the concentration of urea in the patient's blood entering the circuit (U) and the same blood after dilution with prefilter replacement fluid (U_I) at the inlet of the filter. *I,* Inflow port of the catheter; *Kt,* clearance; *O,* outflow port of the double-lumen catheter; Q_B, blood flow; Q_R, replacement fluid rate; Q_{UF}, ultrafiltration rate; *UF,* ultrafiltrate.

TABLE 166.2

Estimated Clearances of Small Solutes With Various Techniques of Continuous Renal Replacement Therapy at Zero Fluid Balance[a]

TECHNIQUE	PLASMA FLOW (mL/min)	PREFILTER RF FLOW (mL/min)	EFFLUENT FLOW (mL/min)	DIAYSATE FLOW (mL/min)	CLEARANCE (mL/min)
CVVH	100	33.3	33.3	0	25
CVVH	100	0	33.3	0	33.3
CVVHD	100	0	33.3	33.3	33.3
CVVHDF	100	16.6	33.3	16.6	29.1
CVVHDF	100	0	33.3	16.6	33.3

[a]Effluent = the replacement fluid rate, the dialysate flow rate, or both. When the prefilter replacement fluid (RF) flow = 0, then the RF is given postfilter for CVVH and CVVHDF. If it is 16.6 mL/min, the other 16.6 mL/min is given postfilter.
CVVH, Continuous venovenous hemofiltration; *CVVHD,* continuous venovenous hemodialysis; *CVVHDF,* continuous venovenous hemodiafiltration.

therapy, given that the costs of replacing the effluent would be the same for all three approaches and that small solute clearance is about 20% better than with CVVH and close to 10% better than with CVVHDF.

However, this assessment only tells part of the story. The picture is different with larger molecules. For example, one can use urate as a marker for somewhat larger small molecules because urate has a molecular weight of 168 D compared with 113 D for creatinine and 60 D for urea. As may be expected, the clearances for urate found by Brunet et al. were 26.2 versus 27.4 versus 27.1 mL/min for CVVH, CVVHD, and CVVHDF, respectively. Using β_2-microglobulin (11.2 kD in molecular weight) as a marker for middle molecules and the same operative settings, CVVH delivered a clearance of 17.4 mL/min compared with 8.3 mL/min with CVVHD and 10.7 mL/min with CVVHDF.[11]

Thus, for a 20% loss of small solute (molecular weight <150) clearance, CVVH appears to lose little at any molecular weight greater than 150, while achieving a 100% increase in middle-molecular clearance. This observation is important. A recent review of free, water-soluble uremic toxins identified 45 low-molecular-weight toxins.[1] Only 17 of these had a molecular weight below 150 D. The same review also identified 22 middle-molecular-weight toxins. Thus, even with predilution, CVVH (convective clearance) reasonably can be expected to double the clearance of 22 toxins compared with CVVHD, while having essentially equal clearance for another 28 and a 20% decrease in clearance for another 17. Given that the individual toxicity of each uremic toxin is unknown, a score of 1 could be allocated for its expected clearance with pure diffusion (CVVHD). With this approach, CVVHD would have a "uremic burden clearance" score of 67 (1 multiplied for all uremic toxins removed). Compared with this, predilution CVVH would score 0.8 for 17 molecules (loss of 20% clearance), 1 for 28, and 2 for 22 (doubled clearance compared with CVVHD). Thus its uremic burden clearance score would be 85.6. This analysis does not take into account the fact that, in critically ill patients, a whole array of potentially pathologic middle molecules accumulate (cytokines, myocardial depressant factors, chemokines, complement anaphylatoxins), which are of middle molecular weight and can be expected to show a clearance pattern similar to that of β_2-microglobulin.[12,13] Accordingly, on the basis of the clearance measurements and given the knowledge available at this time, from a blood purification point of view, postdilution CVVH offers more "bang for the buck" at the same cost compared with CVVHD or CVVHDF. The limitations of CVVH are dependent only on the amount of ultrafiltrate one can achieve in a given time. Because of a sieving of 1 for several solutes, clearance equals ultrafiltration rate in postdilution mode. When ultrafiltration rate equals the effluent rate in CVVHD or CVVHDF, CVVH is always superior. There is no need to go with CVVHD or CVVHDF if CVVH offers the ultrafiltration rate requested. The problem may arise when filtration fraction increases too much. At this point, either blood flow can be increased or diffusion can be used additionally. However, once again, diffusion must consider the degree of effluent saturation. This is why CVVH was used in a recent CRRT dose randomized controlled trial.[8]

Accordingly, we have long been using and continue to use CVVH as the technique of choice.[14]

These observations apply to intermittent therapy as well, because the principles of convection and diffusion and solute clearance are the same. However, one must consider that, as a result of the high efficiency of these intermittent therapies, the blood compartment often is cleared faster than it can be replenished from tissues. Slower therapies, which are of intermediate efficiency and are applied for longer periods of time, offer greater potential for mass removal and may represent an ideal compromise.[15]

Impact on Outcomes

The final pertinent question is whether the differences in solute clearance discussed earlier in this chapter generate differences in outcomes. There is evidence that they generate differences in biochemical outcomes when compared in vivo.[16] Such differences favor hemofiltration when one focuses on middle-molecular-weight solutes such as cytokines.[16]

There are limited comparative data in terms of physiologic outcomes (blood pressure, peripheral vascular resistance, headaches, need for fluid resuscitation, muscle cramps) for intermittent therapy.[17,18]

There are no data on the filter survival effect of using one technique versus another. There are no clinical outcome data (duration of intensive care unit or hospital stay or survival) comparing different techniques of solute clearance applied at equal levels of intensity.

CONCLUSION

The techniques of hemofiltration, hemodialysis, or hemodiafiltration, either continuously or intermittently, achieve excellent small-solute clearances. If postdilution is used, such small-solute clearances are essentially identical. If predilution is used, hemofiltration will be less efficient for small-solute removal than hemodialysis. However, such limited efficiency loss will come with a major gain in middle-molecular solute clearance. There are no differences in cost or ease of use among these techniques. Given the minimal differences in small-solute clearance, the same cost, and the major gain in middle-molecular solute clearance, continuous hemofiltration appears to be the most logical technical approach to CRRT at this time. For intermittent therapies, because of the high blood flow requirements needed, hemofiltration is technically more demanding and may best be coupled with a degree of diffusive clearance (intermittent hemodiafiltration).

Key Points

1. Hemofiltration is equivalent in efficacy to hemodialysis for small-solute clearance.
2. Hemofiltration leads to better middle-molecular-weight solute clearance than hemodialysis.
3. Hemofiltration with prefilter replacement fluid administration leads to some loss of solute clearance because of dilution.
4. Hemodiafiltration with predilution is not as efficient as hemodiafiltration with postdilution.
5. Although postdilution increases solute clearance, it also leads to hemoconcentration.
6. Hemoconcentration increases the statistical probability of filter clotting.
7. Filter clotting is greater with postdilution compared to predilution.
8. Because of filter clotting, predilution delivers equivalent clearances over a 24-hour cycle with fewer episodes of filter clotting.

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A complete reference list can be found online at ExpertConsult.com.

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