# Hemodialysis Systems for Intermittent, Semi-Continuous, and Continuous Therapies in Acute Renal Failure

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*A*s is the case in end-stage renal disease (ESRD), both intermittent and continuous renal replacement therapies (RRTs) are employed in acute renal failure (ARF). In fact, a continuum of treatment options is available in ARF. At one end of the ARF RRT spectrum is conventional intermittent hemodialysis (IHD), in which relatively high blood and dialysate flow rates are used (typically ≥250 and 500 mL/min, respectively). Continuous renal replacement therapies (CRRTs), which employ much lower flow rates, comprise the other end of the spectrum. Finally, hybrid therapies, which combine characteristics of both IHD and CRRT, have recently been described. These therapies' removal mechanisms for solutes over a broad molecular weight range are discussed. An understanding of these mechanisms is important when determining the amount of therapy that can be provided by any RRTs. Additional studies are required to improve the understanding of solute removal by the various RRT used in ARF.

## Key words

Solute, diffusion, convection, backfiltration, acute renal failure

## Introduction

As is the case in end-stage renal disease (ESRD), both intermittent and continuous renal replacement therapies (RRT) are employed in acute renal failure (ARF) (1). In fact, a continuum of treatment options is available in ARF (Table I). On one end of the ARF RRT spectrum is conventional intermittent hemodialysis (IHD), in which relatively high blood ($Qb$) and dialysate ($Qd$) flow rates are used (typically ≥250 and 500 mL/min, respectively). In addition, due to the relatively short (total weekly) treatment times, the net ultrafiltration rate ($Qf$) is high (typically 1000 mL/hr or more) in IHD-treated patients. Continuous renal replacement therapies (CRRT) comprise the other end of the spectrum. In these modalities, although the *absolute Qf* can be 2000 mL/hr or higher in convective therapies, the *net Qf* is generally only 25–100 mL/hr. This large difference between absolute and net $Qf$ is due to the

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administration of substitution fluid which "replaces" a large fraction of the ultrafiltered plasma water. The use of substitution fluids not only permits hemodynamic stability in the continuous therapies (by maintaining low net $Qf$ values), but also results in the reduction of plasma solute concentrations, particularly in convection-based therapies [e.g., continuous venovenous hemofiltration (CVVH)]. Diffusion-based CRRTs [e.g., continuous venovenous hemodialysis (CVVHD)] usually employ $Qd$ values (≤2000 mL/hr) that result in approximate equilibration of concentrations of small solutes in the effluent dialysate and blood ("dialysis equilibrium"). Finally, hybrid therapies that combine characteristics of both IHD and CRRT have recently been described and are discussed below.

## Solute removal mechanisms for RRT used in ARF

In Table II solute removal mechanisms for IHD and CRRT are compared. Several solutes can serve as prototypical

TABLE I    RRT options in ARF

| RRT | Time (hr) | Frequency (/week) | Qb/Qd (mL/min) | Qf (L/hr) |
|---|---|---|---|---|
| IHD | 3–5 | 3–7 | 300/500 | 1.0–1.5 |
| CRRT | 24 | Daily | 150/17–34 | 1.0–2.0 |
| Hybrid | 8–16 | Daily | Variable | Variable |

RRT = renal replacement therapies; ARF = acute renal failure; IHD = intermittent hemodialysis; CRRT = continuous renal replacement therapies.

TABLE II    Determinants of solute removal in IHD and CRRT

| | IHD | CRRT |
|---|---|---|
| Small solutes (MW <300) | Diffusion: $Qb$ $Qd$ Membrane thickness | Diffusion: $Qd$ Convection: $Qf$ |
| Middle molecules (MW 500–5000) | Diffusion Convection: $Qf$ SC | Convection: $Qf$ Diffusion |
| LMW proteins (MW 5000–50 000) | Convection Diffusion Adsorption: site availability | Convection Adsorption: site availability |
| Large proteins (MW >50 000) | Convection | Convection |

IHD = intermittent hemodialysis; CRRT = continuous renal replacement therapies; MW = molecular weight; $Qb$ = blood flow rate; $Qd$ = dialysate flow rate; $Qf$ = ultrafiltration rate; SC = sieving.

molecules (surrogates) in the various categories shown: urea, creatinine, and amino acids (small solutes); vancomycin and inulin (middle molecules); inflammatory mediators, such as C3a, factor D, and cytokines (low molecular-weight proteins); and albumin (large proteins).

As Table II indicates, the mechanisms by which solute removal within a particular category occurs may differ significantly between the two types of therapies. In IHD, diffusion is almost entirely responsible for small solute removal (2). Therefore, measures such as high flow rates and thin membranes (3) that minimize mass transfer resistances enhance the removal of solutes in this category. Likewise, all solutes in the middle-molecule category and many low molecular weight (MW) proteins are predominantly removed by diffusion during high-flux IHD (4). Of note is the fact that low MW protein removal by high-flux dialyzers can also be achieved primarily by convection or adsorption, depending on the specific membrane type (5). Finally, solutes having a MW similar to or larger than that of albumin are almost exclusively removed by convection during high-flux IHD. However, (large) protein losses for IHD have not been quantified in the ART setting.

For a given solute, mass transfer mechanisms may differ significantly for the slow continuous therapies. Small solute removal can occur exclusively by convection, diffusion, or a combination of these mechanisms (6–9). Small solute clearances in CVVH are determined primarily by the ultra-filtration rate and the mode of replacement fluid administration (predilution vs postdilution) (10). For the diffusion-based continuous therapies [CVVHD or continuous venovenous hemodialfiltration (CVVHDF)] employing dialysate flow rates of 2 L/hr or less, urea and creatinine clearances are approximately the same as the effluent dialysate flow rate (9). For middle-molecule removal, a recent study (11) has shown that convection is more important than diffusion for a surrogate solute (vancomycin, MW 1448) for the same ultrafiltration and dialysate flow rates in CVVH and CVVHD, respectively. As opposed to IHD, transmembrane removal of low MW proteins by the slow continuous therapies occurs almost exclusively by convection. However, adsorptive removal of inflammatory mediators in this MW class may also occur, depending on the specific membrane type. Finally, a recent study (12) quantified total protein losses in CRRT to be a modest 1.6 g/day (mean).

### Hybrid RRT systems used in ARF

Recently, ARF therapeutic systems combining features of both IHD and CRRT have been described. An example is the system recently described by Ronco (13,14) designed to enhance solute removal over a wide MW spectrum. The system, which is called continuous high-flux dialysis (CHFD) and is shown in Figure 1, has a number of unique features. Blood and dialysate flow rates of 100 and 50–200 mL/min, respectively, are employed with a high-flux dialyzer or hemofilter. Sterile dialysate can be pumped in a single-pass or recirculation mode.

For a 10-L total volume of dialysate used in a recirculation mode, small solute saturation of the effluent dialysate occurs after 2–4 hr with a concomitant degree of saturation for inulin (MW 5200) of approximately 0.6. When fresh dialysate is provided every 4 hr (total daily volume of 60 L), urea and inulin clearances of approximately 60 L/day and 36 L/day, respectively, can be provided. These solute clearances surpass those achievable with conventional pumped CRRT systems employing an ultrafiltration rate or dialysate flow rate of 2L/hr. In addition, these daily clearances are markedly superior to those of IHD, in which solute removal is limited not only by the relatively low treatment time. but also by solute disequilibrium related to intercompartment mass transfer resistances (15). Although use of a dialysate flow rate of 75 mL/min in a single-pass mode can provide even higher daily clearances (approximately 72 L and 46 L for urea and inulin, respectively), nearly twice the volume of dialysate (108 L) is required.

For the CHFD system, some inulin removal occurs by diffusion, which is the primary removal mechanism for this solute in high-flux IHD, as discussed above. However, significant convective removal also is achieved because of the pressure-flow relationship within the filter (Figure 1). The specific blood and dialysate flow rates used in the CHFD system result in forward and reverse transmembrane pressures in the proximal and distal parts of the filter, respectively. Therefore, convective elimination of inulin occurs proximally in the filter, a process augmented by the phenomenon of Starling's flow (16). As recently discussed by Tetta *et al.* (17), the removal of mediators having MWs similar to that of inulin may be particularly important in septic ARF patients.

### Significance of backfiltration in ARF therapies

For a conventional (low-flux) dialyzer ($K_{uf} < 8$ mL/hr/mm Hg) used in intermittent HD, the relationship between blood flow rate and axial pressure drop ensures that the blood compartment pressure is greater than the dialysate compartment pressure along the entire length of the filter. Therefore, reverse ultrafiltration (backfiltration) of dialysate is not a concern for these dialyzers. However, for high-flux dialyzers ($K_{uf} > 20$ mL/hr/mm Hg), greater membrane permeability dictates that the average difference in hydrostatic pressure between the blood and dialysate compartments (transmembrane pressure) be relatively small to prevent excess fluid removal. Due to this small difference in transmembrane pressure and the axial pressure drop that occurs within the blood compartment, the hydrostatic pressure of the blood compartment becomes less than that of the dialysate compartment at some point along the (axial) length of the dialyzer under normal clinical conditions of IHD (ultrafiltration rate < 20 mL/min) (18,19). From this transition point to the distal (venous) end of the dialyzer, backfiltration of dialysate can occur. Associated with this backfiltration process is the potential "back convection" of inflammatory mediators from the nonsterile dialysate to the blood. The issue of backfiltration in ESRD patients has

# CONTINUOUS HIGH FLUX DIALYSIS
## FILTRATION-BACKFILTRATION SYSTEM
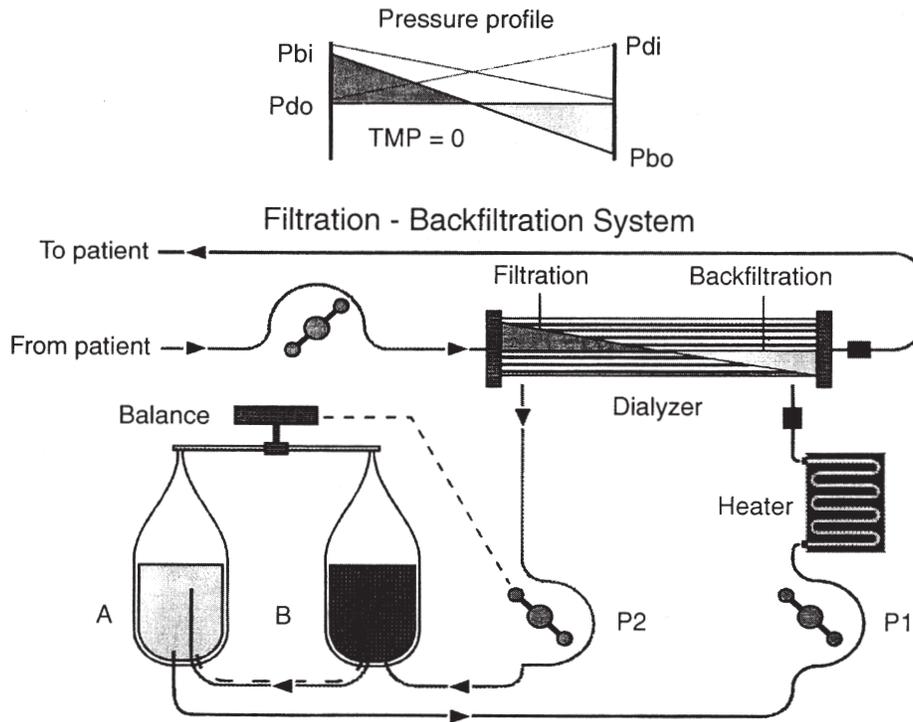


FIGURE 1    Schematic representation of the system for continuous high-flux dialysis. Reprinted with permission from Reference 13.

been debated, and currently no consensus exists on its clinical implications. However, a general recommendation for dialysis-based therapies employing nonsterile dialysate is the avoidance of conditions favoring excessive backfiltration, both in ESRD and ARF patients.

Despite having blood and dialysate flow rates that differ significantly from those in IHD, CRRT may also be associated with backfiltration under certain clinical conditions. This is demonstrated by the following theoretical analysis. For this analysis, linear pressure gradients were assumed for both the blood and dialysate compartments, and the rate of back-filtration was determined as described by Soltys *et al.* (18). The CRRT device was assumed to have performance characteristics of a polysulfone F60 hemodialyzer (Fresenius Medical Care). The extent of backfiltration was determined for two sets of operating conditions. Each set of operating conditions represented an extreme end of the operating range for absolute ultrafiltration rate, blood flow rate, and dialysate flow rate. The conditions were grouped according to those that favor greater backfiltration (i.e., low absolute *Qf*, high *Qb* and *Qd*) versus those in which less backfiltration occurs. The backfiltration estimates, shown in Table III, are based on a patient hematocrit of 28%. A sensitivity analysis demonstrated that, in order of significance, the absolute *Qf* has

the greatest effect on backfiltration, followed by *Qb* and then *Qd*. These theoretical estimates suggest that for the operating conditions typically used in CVVHD (absolute *Qf* = 300 mL/hr), backfiltration can be very significant. However, use of an absolute *Qf* similar to that typically used in CVVHDF (700 mL/hr) essentially eliminates the possibility of any backfiltration.

The potential clinical significance of backfiltration during a diffusion-based CRRT is dictated by the choice of dialysate. If sterile, nonpyrogenic dialysate prepared commercially or by a hospital pharmacy is used, the risk of backtransfer of bacteria-related products from dialysate to blood is eliminated. However, the above analysis

TABLE III    Backfiltration (BF) in ARF RRT systems

| *Qf* (mL/hr) | *Qd* (mL/hr) | *Qb* (mL/hr) | *Qbf* (mL/hr) |
|---|---|---|---|
| 300 | 2000 | 200 | 116 |
| 700 | 1000 | 150 | <1 |

ARF = acute renal failure; RRT = renal replacement therapies; *Qf* = ultrafiltration rate; *Qd* = dialysate flow rate; *Qb* = blood flow rate; *Qbf* = backfiltration rate.

demonstrates that the use of nonsterile dialysate for CVVHD, as has recently been described (20,21), may be associated with this risk of backtransfer. Therefore, the issue of backfiltration should be considered when selecting dialysate for CRRT.

## Summary

A continuum of therapies ranging from IHD to CRRT is available in the management of critically ill ARF patients. Their removal mechanisms for solutes over a broad MW range have been discussed. An understanding of these mechanisms is important when determining the amount of therapy that can be provided by a RRT. Additional studies are required to improve the understanding of solute removal by the various RRTs used in ARF.

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