What Is the Renal Replacement Method of First Choice for Intensive Care Patients?

RAYMOND VANHOLDER, WIM VAN BIESEN, and NORBERT LAMEIRE
Nephrology Unit, Department of Internal Medicine, University Hospital, Gent, Belgium.

Abstract. Renal replacement therapy for the patient with acute renal failure on the intensive care unit can be offered in several different formats: intermittent hemodialysis (IHD), continuous renal replacement therapy (CRRT), and slow low-efficient daily dialysis (SLEDD). It is frequently claimed that CRRT offers several advantages over IHD, but most of these, such as correction of metabolic acidosis, better recovery of renal function, better clinical outcome due to application of biocompatible dialysis membranes, correction of malnutrition, and better removal of cytokines, are not corroborated by the results of controlled prospective studies. There is also no evidence that CRRT results in a better survival, compared with IHD. The only potential advantages of CRRT that stood the test of clinical evaluation (hemodynamic stability, correction of hypervolemia, better solute removal) can be offered as well by SLEDD. In addition, the latter strategy is less expensive because the same infrastructure is used as for IHD, while the patient is not immobilized continuously, which leaves time free for other activities such as nursing care and technical investigations. SLEDD is a relatively young technique, so thorough clinical studies are lacking. Nevertheless, the hypothesis is proposed that SLEDD offers a valuable alternative to the classical dialysis strategies, applied in the intensive care patient.

The conceptual philosophy behind the treatment of acute renal failure (ARF) with dialysis differs from that governing maintenance therapy of patients with chronic renal failure. The sudden unexpected need for dialysis among severely ill patients frequently results in therapy-related complications, such as bleeding, inadequate fluid removal, volume depletion, and enhanced susceptibility to infection, which might become life-threatening. Specific therapeutic goals, such as the removal of fluid overload or the correction of wasting and malnutrition, influence the practical implementation. However, dialysis, at least in theory, is only temporary, because most acutely failing kidneys recover after some time.

In view of the often-precarious condition of the patients, the ideal extracorporeal strategy for ARF treatment should be simple to implement and should induce minimal work with limited cost; its capacity to remove accumulated water and solutes should be reliable and predictable. Survival rates after the dialysis treatment should be optimal, with an acceptable complication profile and an optimal recovery of renal function.

For ARF hemodialysis, two classic options are currently available, i.e., intermittent hemodialysis (IHD), whereby relatively short (3- to 4-h) dialysis sessions are performed every day or every other day, and continuous renal replacement therapies (CRRT), which are performed without interruption, at least in theory. Some of the characteristics of these two strategies are summarized in Table 1. Recently, slow low efficient daily dialysis (SLEDD) was introduced as a third possibility. This alternative method combines the advantages of CRRT with those of IHD; classic IHD is performed at low dialysate and blood flow rates, resulting in an improvement in tolerance at the expense of longer dialysis times (1).

Few data on the efficacy and reliability of SLEDD are available. Therefore, this report mainly compares the characteristics of IHD and CRRT. Although CRRT has some remarkable theoretical advantages, to date these have not been translated into convincingly better clinical outcomes. The hypothesis is that a valuable alternative dialysis strategy for intensive care patients with ARF has been introduced with SLEDD, especially because SLEDD helps to eliminate several drawbacks of both IHD and CRRT.

A number of different CRRT strategies are available, depending on the driving forces that produce the pressure gradient in the filter. This process is based either on the natural BP differences between large arteries and veins (continuous arteriovenous strategies) or on mechanically induced pressures (pump-driven continuous venovenous strategies). In addition, some strategies are based on dry ultrafiltration, with substitution of the ultrafiltrate by an isotonic electrolyte solution (continuous hemofiltration, mainly based on convective solute removal), whereas in other variants solute removal is essentially based on dialysate contact with the blood (continuous hemodialysis, mainly diffusive).

The concept of continuous blood purification strategies has been continuously evolving in the past decade. The technically simple but less efficient continuous arteriovenous hemofiltration (CAVH) and continuous arteriovenous hemodialysis (CAVHD) strategies have been gradually replaced by the technically complex but more adequate continuous venovenous hemofiltration and hemodialysis strategies (CVVH and CVVHD).
Despite an increase in adequacy, the venovenous strategies have resulted in the loss of one of the main advantages of the original techniques; CAVH(D) was introduced to eliminate the need for complex and expensive hardware. The venovenous approaches necessitate the reintroduction of more sophisticated equipment, resulting in substantial cost increases.

**Theoretical Advantages of CRRT**

**Hemodynamic Stability**

Hemodynamic stability is considered to be one of the main assets of CRRT (2). Nevertheless, studies of this issue yielded conflicting results. Only a few of those studies were randomized. In a retrospective analysis, van Bommel and Ponsen (3) demonstrated that the mean arterial BP (MAP) was lower 1 h after the start of renal replacement therapy with IHD, compared with CRRT. At 4 h (the end of the IHD session) and at 24 h, no differences could be observed, however. In a prospective analysis, Davenport et al. (4) observed a lower cardiac index for IHD, compared with CRRT, but no significant differences in MAP were noted. Neither Manns et al. (5), in a nonrandomized study, nor Misset et al. (6), in a prospective analysis, observed differences in MAP between IHD and CRRT. Problems with this type of study are the preferential use of CRRT for hemodynamically unstable patients and the choice of the time points at which BP should be compared.

Even if CRRT offers a hemodynamic advantage, this protection is relative, not absolute (2). Hypotension can still occur if too much fluid is removed, if fluid is removed too quickly, or if substitution lags behind removal.

**Recovery of Renal Function**

Hemodynamic stability is related to the recovery of renal function. Studies by Conger (7) revealed that renal damage was prolonged if the kidneys were subjected to repeated hypotensive episodes, especially because kidneys from patients with ARF have a limited ability to autoregulate. Hence, a reduction of hypotensive episodes should have a positive effect on the recovery of renal function. In a retrospective study by van Bommel et al. (8), however, the same percentages of patients exhibited recovery of renal function, whether they were treated with IHD or CRRT. The time until recovery was shorter with CRRT (11 ± 2 d versus 18 ± 3 d with IHD, P < 0.05).

**Correction of Metabolic Acidosis**

Metabolic acidosis, which is a frequent problem in the intensive care population, with sometimes extreme metabolic disturbances, might be corrected more accurately during CRRT, because of the continuous availability of buffer. In the study by van Bommel et al. (8), a significantly greater base excess was observed for patients undergoing CRRT, but the difference was maximally 2 mEq/liter and was observed only from the third day of renal replacement onward. However, lactate is the most frequently used buffer in substitution fluids for CRRT; this might be a cause for concern, because of the frequent occurrence of lactate acidosis, tissue hypoperfusion, and liver failure in the intensive care unit population. In the study by Heering et al. (9), however, the acid-base status was the same, irrespective of whether the substitution fluid contained lactate, bicarbonate, or acetate as a buffer.

**Biocompatibility**

Many of the dialyzers used for CRRT contain synthetic membranes; the majority of these are biocompatible toward the complement and leukocyte systems. For IHD, both synthetic and cellulosic dialyzers are used. Unmodified cellulosic dialyzers are bioincompatible with respect to the complement and leukocyte responses. It has been hypothesized that this biocompatibility of unmodified cellulose might slow the recovery of renal function, because of the induction of inflammatory responses and the intrarenal release of free radical species, and increase morbidity and mortality rates. At least as many studies, however, do not indicate an effect of biocompatibility on final outcomes (10). In a recent randomized study that compared unmodified cellulose dialyzer membranes with polymethylmethacrylate in an IHD setting, no differences in renal and patient outcomes could be demonstrated (11). However, it should be stressed that, among the synthetic membranes, polymethylmethacrylate is probably one of the strongest inducers of complement (12); in addition, several of the contributing centers had limited experience with dialysis treatment of ARF.

**Correction of Malnutrition**

Because of the high ultrafiltration rates associated with CRRT, important volumes of calorie-containing fluids can be administered for the prevention of malnutrition. It has therefore been hypothesized that CRRT offers possibilities for unlimited energy support. When too many calories are administered, however, overnutrition might itself cause a metabolic imbalance, especially if the nutritional support consists primarily of protein or amino acids. However, high-flux membranes, which are often used for CRRT, are associated with substantial transmembrane nutrient losses (13).

**Removal of Cytokines**

One of the most frequently mentioned advantages of CRRT is the presumed capacity of filters to remove and adsorb cytokines and other agents that play a role in the inflammatory
status of septic patients with ARF. A recent study by De Vriese et al. (14) demonstrated, however, that this elimination occurs only during the first 1 h after the application of a new filter. In addition, the removal of proinflammatory cytokines (e.g., tumor necrosis factor α, interleukin-1β, and interleukin-6) and that of anti-inflammatory cytokines or factors (e.g., interleukin-10, interleukin-1 receptor antagonist, and soluble tumor necrosis factor receptor) were equivalent. Therefore, the cytokine removal capacity of currently available membranes hardly matches the production observed in severely affected septic patients. In agreement with this hypothesis, Heering et al. (15) observed no change in the plasma concentrations of tumor necrosis factor α in 72 h of CRRT, despite substantial convective removal through the CRRT filter.

Solute Removal

Because of its continuous application, CRRT might offer more adequate solute removal. In a mathematical analysis, Clark et al. (16) demonstrated that it was impossible to maintain blood urea nitrogen levels of 60 mg/dl with daily IHD (maximum of 4-h dialysis) in patients with body weights of >80 kg. Such low levels could be obtained with CRRT, but with daily volume exchanges (ultrafiltration versus substitution) of >40 liters. This goal is difficult to reach, for practical and economic reasons. Moreover, these values were calculated for full 24 h/d applications of CRRT, which are virtually impossible in the daily intensive care setting.

Overall Outcomes

The final argument for the superiority of CRRT could be made if controlled studies could demonstrate significantly better patient survival rates, compared with IHD. Until now, such proof has not been provided (8,17–19) (Table 2). In the recently published multivariate analysis by Swartz et al. (20), the odds of death for CRRT, compared with IHD, exceeded 2 if no corrections were made for comorbid conditions. After correction, the odds of death decreased to 1.09, but these data do not indicate a significant difference between CRRT and IHD.

One of the main problems for a prospective evaluation of this issue might be appropriate randomization in such a heavily affected population. Treating physicians might be reluctant to initiate CRRT for patients with bleeding tendencies or IHD for patients in hemodynamically unstable condition. As a result, an inevitable selection bias could be expected for the enrollment of many patients. For comparative outcome studies, the optimal design would probably involve an intention-to-treat approach, in which patients who are not able to start with the technique to which they were randomized would represent failures of the respective technique; in such a situation, a large number of dropout subjects could probably be expected.

Disadvantages of CRRT

With the potential advantages of CRRT, there are also a number of potential disadvantages (21). To obtain vascular access, the originally proposed CAVH(D) strategy necessitates arterial puncture, which might be a source of complications. Continuous venovenous hemofiltration (and hemodialysis) requires less hazardous access approaches but is technically more complex.

The continuous need for anticoagulation therapy is a potential source of problems for patients with bleeding tendencies. Some authors propose the locoregional application of sodium citrate, with equimolar calcium infusion at the dialyzer outlet to neutralize the anticoagulant effects of citrate (22,23). Systemic anticoagulation can thus be avoided, if the neutralization is performed correctly. Citrate anticoagulation therapy for CRRT remains, however, a labor-intensive procedure that can be performed only by well-trained and experienced personnel. The immobilization of the patient is a potential source of problems. It might be necessary to uncouple the patient for nursing procedures or complex investigations that cannot be performed in the intensive care unit. Every time this uncoupling is performed, the dialysis process is interrupted. With IHD, such procedures can be performed in the dialysis-free periods.

Finally, CRRT is more expensive than IHD, because of the need for specific dialysate solutions, substitution fluids, and filters and because of its labor-intensiveness.

SLEDD as an Alternative

Only three potential advantages of CRRT have stood the test of clinical evaluation, i.e., hemodynamic stability, correction of hypervolemia, and solute removal.

These advantages can, however, also be obtained with SLEDD (24), a recently introduced dialysis strategy. In this technique, classic dialysis hardware is used at low blood and
dialysate flow rates, for prolonged periods of time (6 to 12 h/d). This modality offers more hemodynamic stability, better correction of hypervolemia, and more adequate solute removal, compared with IHD. The costs are lower than for CRRT, because the same equipment is used as for IHD. Unfortunately, no controlled studies comparing this new modality with the classic approaches are available. The preliminary results of the initial studies are promising, however (24,25).

Conclusion
In conclusion, CRRT has at least theoretically been considered to be superior to IHD. This superiority has not been translated into more favorable survival rates. The only potential advantages of CRRT that have withstood criticism are its better hemodynamic stability, easier correction of hypervolemia, and better solute removal. These advantages can, however, also be obtained with SLEDD. In addition, SLEDD is less expensive than CRRT and does not continuously immobilize the patient, leaving time open for other activities (e.g., technical investigations).

References