

Renal Replacement Therapy in the Intensive Care Unit

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ABSTRACT

Objective: To present an overview of the principles of renal replacement therapy, its application in the critically ill patient, and an update of recent research in this area.

Data sources: Articles and published peer-review abstracts on the beneficial effects of continuous renal replacement therapy (CCRT) in the critically ill patient.

Summary of review: Renal replacement therapy utilizes dialysers that enable solute and solvent to move across semipermeable membranes in either a convective or diffusive fashion. In the critically ill patient, percutaneous vascular access and improvement in dialysis machines, have facilitated the intensive care unit management of acute renal failure in these patients. Currently, CCRT is most often used to manage the critically ill patient with acute renal failure, as it is less likely to produce hypotension when compared with intermittent haemodialysis. However, CCRT has been expanded to manage critically ill patients with multiple organ failure, with the demonstration that it is able to remove or adsorb putative mediators of organ dysfunction. While there are experimental and uncontrolled clinical data that have suggested that this form of therapy is beneficial, currently there are no prospective randomised, controlled trials that have confirmed this benefit when used in these patients.

Conclusions: Continuous renal replacement therapy has become commonplace in the management of critically ill patients with acute renal failure. It has the advantage of causing less hypotension and a more gradual return of the fluid and electrolyte status, when compared with intermittent haemodialysis. Recent evidence suggests that it may also be a useful immunomodulator and may be beneficial in the management of patients with multiple organ failure. (**Critical Care and Resuscitation 1999; 1: 13-24**)

Key words: Renal replacement therapy, dialysis, haemofiltration, haemoperfusion, immunomodulator

Continuous haemofiltration was first described more than 20 years ago.¹ Over this period, it has undergone many changes, which have made it one of the great therapeutic successes of intensive care medicine. As we approach the turn of the century, it is useful to understand the principles involved and the reasons for its evolution. We will consider the present status of continuous haemofiltration (or continuous renal replacement therapy) and the trends in thinking and

practice that appear likely to bring about further modifications in this novel form of extracorporeal therapy.

However, focusing on continuous haemofiltration alone provides only a partial understanding of this important field of intensive care medicine. It is also important for the intensivist to appreciate the continuing evolution of intermittent forms of renal replacement therapy, as this continues to play a role in the treatment

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of critically ill patients in many units. The evolution in membrane technology and thinking in this area will also continue to influence the use of continuous haemofiltration in the future.

This review is aimed at providing an overview of the principles of renal replacement therapy (RRT), a description of the evolution in its application in the intensive care unit (ICU), an update of recent research in this area, and an insight into what the future may bring.

The principles of renal replacement therapy

To understand the development of continuous renal replacement therapy (CRRT) there needs to be an understanding of the principles of blood purification by means of semi-permeable membranes. First, one must appreciate the mechanisms of fluid and solute transport across such membranes; they are diffusion, convection and ultrafiltration.

Diffusion. During diffusion, the movement of solute depends on its tendency to reach the same concentration in the available distribution space on each side of the membrane. The result is the passage of solutes from the compartment with the highest concentration to the compartment with the lowest concentration.¹ The principle of diffusion is summarised in figure 1

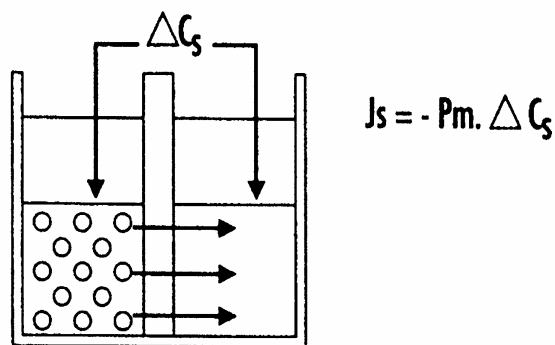


Figure 1. Illustration summarising the principle of diffusion, where the diffusive solute flux (J_s) is proportional to the membrane diffusive permeability (P_m) and the concentration gradient (ΔC_s)

Convection. During convection, the movement of solute across a semipermeable membrane takes place in conjunction with significant amounts of ultrafiltration and water transfer across the membrane. Stated another way, during convection, solute is ‘carried’ by solvent, as the solvent (water) is forced across the membrane (a process called ultrafiltration) in response to a transmembrane pressure gradient. The principle of convection is summarised in figure 2.

The porosity of the membrane is a major determinant of the solutes removed during any blood purification therapy. In some situations, the two modes of solute

transport occur simultaneously and in near equal proportions (i.e. haemodiafiltration).²

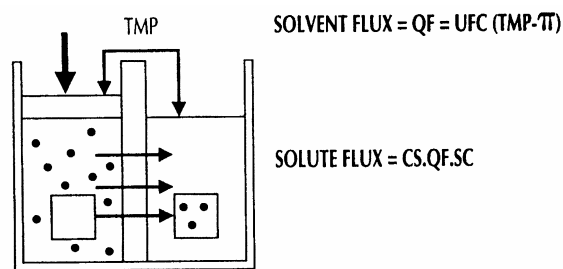


Figure 2. Illustration summarising the principle of convection, where the solvent flow rate (Q_f) is proportional to the dialyser ultrafiltration coefficient (UFC) and the transmembrane pressure (TMP) corrected for the protein oncotic pressure (π), and where the solute mass transfer is proportional to the solvent flow rate (Q_f), to the solute concentration (CS), and the sieving coefficient (SC)

Ultrafiltration is a process by which plasma water and crystalloids are separated from whole blood across a semipermeable membrane in response to a transmembrane pressure gradient. The process is governed by the following formula:

$$Q_f = K_m \times TMP$$

Where,

Q_f = the ultrafiltration rate (ml/min)

K_m = membrane ultrafiltration coefficient, which is derived from the ratio Q_f/TMP and expressed in (ml/h) x (m²/mmHg)

TMP = transmembrane pressure gradient generated by pressures on both sides of the membrane.

The hydrostatic pressure in the blood compartment is dependent on blood flow. The greater the rate of blood flow, the greater the transmembrane pressure. In a spontaneous ultrafiltration system based on convective clearance, measures that maximise blood flow rate, will maximise ultrafiltrate production and solute clearance. Equally, measures which increase the negative pressure on the ultrafiltrate compartment of the membrane will also increase ultrafiltration as will measures that decrease the oncotic pressure of plasma (e.g. pre-dilution, or the administration of replacement fluid before the filter).

As ultrafiltration proceeds, and plasma water is reduced, oncotic pressure is increased as hydrostatic pressure decreases.³ Thus, if the filter is long enough, a condition of filtration/pressure equilibrium is achieved where the oncotic pressure is equal to, or greater than, transmembrane pressure and ultrafiltration ceases. However, in modern filters this rarely, if ever, occurs. The relationship between transmembrane pressure and

oncotic pressure will determine the filtration fraction (i.e. the fraction of plasma water that is removed from blood during haemofiltration).

The optimal filtration fraction for patients with a haematocrit of approximately 30% ranges between 20-25%. This degree of filtration prevents excessive haemoconcentration at the filter outlet, which in turn would promote filter clotting. Ultrafiltration control can also be obtained by applying a negative pressure generated by a pump (volumetric or peristaltic) to the ultrafiltration side of the filtering membrane. If such pressure is applied, attention must be paid to the maintenance of a safe filtration fraction.

With modern filters, the initial effect of controlling ultrafiltration is to retard ultrafiltration and to generate a positive pressure on the ultrafiltrate side of the haemofilter. Thus, TMP is initially decreased. As the filter fibres start to 'foul', a negative pressure becomes necessary to maintain a constant ultrafiltration rate. It is important, especially if one is using haemofiltration pumps to achieve continuous plasmfiltration, to keep the transmembrane pressure within the range specified by the manufacturers. If this is not done, filter clotting becomes likely and membrane rupture may occur.

Blood purification technology

The membrane

Membranes employed during RRT can be divided into two categories: cellulose-based and synthetic membranes.⁴

Cellulose-based membranes. These membranes (e.g. cuprophane, hemophane, cellulose acetate) are generally considered 'low flux' membranes with a membrane permeability coefficient to water (K_m) of less than $10 \text{ ml/h} \times \text{mmHg/m}^2$. Cellulose-based membranes are very thin (e.g. 5 to 15 microns thick), they have a symmetric structure with uniform porosity, and are strongly hydrophilic

Synthetic membranes. These membranes (e.g. polysulfone, polyamide, polyacrylonitrile, polymethylmethacrylate) are high flux membranes with a $K_m > 30 \text{ ml/h} \times \text{mmHg/m}^2$. The wall thickness ranges between 40 and 100 microns with an asymmetric structure composed by an inner skin layer and a surrounding sponge layer. Synthetic membranes have large pores (e.g. 10,000 to 30,000 daltons) and are hydrophobic. They also have high sieving coefficients for solutes with a wide range of molecular weights, and are much more suitable for convective treatments. Convective high filtration rates always take place when these membranes are used, and such extracorporeal RRT is not adequately defined by the use of the term 'haemodialysis'. This treatment is more appropriately called 'haemofiltration'

in the absence of diffusive clearance, 'haemodiafiltration' if replacement solution is needed in addition to diffusive clearance or 'high flux dialysis' if a filtration-backfiltration mechanism is present and no replacement is required.⁵

Vascular access and the extracorporeal circuit

Extracorporeal blood treatments also require vascular access and a specific extracorporeal circuit design. Two different approaches are in use for extracorporeal treatments: arteriovenous and veno-venous.

Arterio-venous. In this system, the arterio-venous pressure gradient of the patient is the driving force moving blood through the circuit. An artery and a vein are cannulated with large bore catheters (e.g. 10-14 French) and no blood pumps are utilised.⁵ Maximal care is taken to avoid unnecessary resistances along the length of the circuit, so large short catheters, short blood lines and short filters are used. The determinants of ultrafiltration are different from those generally considered in pumped circulations. Haematocrit, plasma protein concentration (i.e. oncotic pressure) and the distance between the filter and the ultrafiltrate collection system become critical factors. In this system, blood flow generally ranges between 50 and 150 ml/minute. In some patients, vascular access may require the surgical construction of a 'Scribner' shunt. Blood flow under these circumstances tends to be between 60-80 ml/minute. In our opinion, this system carries an excess of vascular access-related morbidity, and should only be used if peristaltic pumps are unavailable.

Veno-venous. This requires a roller pump in the prefilter line segment and a drip chamber in the line returning the blood from the filter.⁶ Typically, a single central vein is cannulated with a double lumen catheter. Such double lumen catheters (11.5 to 13.5 French) are now available commercially, and can be easily inserted percutaneously using the Seldinger technique. In critically ill patients, the choice for the insertion site for these catheters is usually determined by the patients underlying disease and other clinical considerations. For example, patients who have a coagulopathy are more safely managed using a femoral catheter, because the femoral site is more amenable to compression in the event of an inadvertent arterial puncture.

A common feature of all double lumen catheters is the presence of a lumen which functions as the 'arterial' or outflow limb of the circuit, and of a lumen which functions as the 'venous' or inflow limb of the circuit. Blood lines can be longer than in A-V circuits and a pressure measurement is required before the pump and after the filter to ensure safe use of the blood pump, and to avoid any damage to the cannulated vein. In this system, blood flow can usually be kept between 150 and

200 ml/minute.

The delivery of replacement fluid and dialysate

With continuous haemodialysis and haemodiafiltration, a dialysate flow rate between 10 and 30 ml/minute is generally considered sufficient. Dialysate delivery can be performed by gravity, an infusion pump or roller pump. The same system can be applied to the dialysate and ultrafiltrate outlet line in order to achieve fluid control. In continuous high flux dialysis, two pumps are required to maintain effective ultrafiltration control. Sterile dialysate can be recirculated or run in a single pass. In those treatments where replacement solution is needed to maintain patient fluid balance (e.g. continuous arterio-venous haemodialysis, continuous veno-venous haemodialysis, continuous arterio-venous haemo-diafiltration, and continuous veno-venous diafiltration), substitution fluid can be infused both in post-dilutional or pre-dilutional mode. Pumps to control fluid replacement and removal are commonly used as they offer the advantage of decreasing the nursing workload.⁶

It is otherwise possible to operate a spontaneous system of filtration with the replacement being based on frequent (e.g. at least hourly) measurements of ultrafiltrate production. Sterile replacement/dialysate fluids for haemofiltration are now commercially available and contain different buffers, including bicarbonate, lactate and acetate.

Anticoagulation

In all forms of RRT blood comes into contact with a non-biologic surface, and activates the clotting cascade. Anticoagulation of the extracorporeal circuit is therefore desirable and often necessary if one wants to perform RRT safely and effectively.

Several approaches to anticoagulation during RRT have been described although most of them rely on the use of heparin.^{7,8} However, in many critically ill patients, systemic anticoagulation is undesirable. In these patients, low dose (e.g. 5-10 IU/kg/h) heparin can be administered into the circuit in a pre-filter position. Such therapy is often sufficient to perform intermittent haemodialysis or to achieve an adequate circuit life (i.e. approximately 20 - 24 hours) during CRRT, and has the advantage of inducing very little change in the patient's bleeding risk.

In some patients, a more aggressive anticoagulation of the dialysing or filtering membrane may be necessary, while also seeking to avoid systemic anticoagulation. In these patients, 'regional' anticoagulation is often effective. Such 'regional' anticoagulation can be achieved by the pre-membrane administration of heparin

at full anticoagulation doses and the post-membrane administration of protamine to reverse its effects prior to returning the blood to the patient. Typically, this results in a heparin:protamine ratio of 100 IU to 1 mg. Both are given by continuous infusion.⁷ Another form of 'regional' anticoagulation is based on the use of citrate, to achieve a pre-membrane chelation of calcium, with a post-membrane calcium infusion to re-establish blood coagulability.⁸ This approach is very effective, although it requires a specially made dialysate and calcium to be added separately. The infused citrate often causes a metabolic alkalosis. However, this technique may be used to advantage in patients suspected of having serious heparin-induced thrombocytopenia.

In high-risk patients, (e.g. liver coagulopathy, severe thrombocytopenia, etc) it is possible to perform RRT without any coagulation and still achieve an adequate circuit performance and survival.^{7,9} Low molecular weight heparin can also be used to maintain circuit function but limited controlled data are available on its usefulness in comparison with standard heparin.

Techniques and their nomenclature

It is important for the critical care physician to understand and appreciate the differences between renal replacement therapies and the reasons for the relatively complex nomenclature that describes them. The following definitions reflect the principles and technical requirements of the various types of RRTs as recently agreed upon during a consensus conference.¹⁰

Haemodialysis (HD)

This term defines a predominantly diffusive treatment, in which blood and dialysate are circulated in a countercurrent mode and a low permeability cellulose-based membrane is employed. The ultrafiltration rate is approximately equal to the scheduled weight loss. This treatment can be performed intermittently (i.e. intermittent haemodialysis or IHD), three times per week (for 4 hours), daily (from 2 - 4 hours)¹⁰ or continuously, both in arteriovenous or veno-venous mode.^{11,12}

Peritoneal dialysis (PD)

This term refers to a predominantly diffusive treatment in blood circulating along the capillaries of the peritoneal membrane which are exposed to dialysate. Access is obtained by the insertion of a peritoneal catheter, which allows the abdominal instillation of dialysate. Solute and water movement are achieved by means of variable concentration and tonicity gradients generated by the dialysate. This treatment can be performed intermittently or continuously.¹³

Haemofiltration (HF)

This term defines an essentially convective treatment with highly permeable membranes. The ultrafiltrate produced is replaced completely or in part by a sterile solution of water and electrolytes. Any net fluid loss will result from the difference between ultrafiltration and reinfusion rates. This treatment can be performed intermittently (e.g. 30 litres/session, three times per week), daily (using a 10 to 30 litre exchange) or continuously, both in arteriovenous or venous-venous mode.¹⁴

Haemodiafiltration (HDF)

This term defines a treatment in which diffusion and convection is combined utilising a highly permeable membrane. Blood and dialysate are circulated as in haemodialysis but typically an ultrafiltration rate in excess of the scheduled weight loss is produced. To achieve fluid balance, a sterile solution of water and electrolytes is reinfused into the patient at an adequate rate. This treatment can be performed intermittently (e.g. 3 - 4 hours using a 9 to 15 litre exchange/session, three times a week), daily (e.g. over 3 hours with a 9 litre exchange) or continuously, both in arteriovenous or veno-venous mode.¹⁵⁻¹⁹

High Flux Dialysis (HFD)

This term describes a treatment that utilises highly permeable membranes in conjunction with an ultrafiltration control system. Blood and dialysate are circulated as in haemodialysis, but due to the high permeability coefficient of the membrane, ultrafiltration would exceed the required patient weight loss. Therefore, a positive pressure is applied to the dialysate compartment to reduce the amount of ultrafiltration, and to avoid the need for replacement solution.

Due to the peculiar structure of hollow fibre dialysers, filtration takes place in the proximal part of the filter, while back-filtration occurs in the distal part of the filter. Diffusion and convection, therefore, are still combined. The high filtration rate, which occurs in the proximal part of the dialyser, is masked by back-filtration in the distal part. Replacement is avoided as it occurs inside the filter by the mechanism of back-filtration. Such back-filtration implies that during HFD, dialysate must be sterile and pyrogen free.⁴

Ultrafiltration (UF)

This term defines a treatment in which fluid removal is the main target of therapy. Highly permeable filters are utilised and fluid is removed from the body without providing any replacement solution. UF can be performed intermittently or daily, and a maximum of 3 litres per session is generally removed over a period of 4

- 6 hours. In clinical practice, ultrafiltration has also been used in sequence with haemodialysis to improve cardiovascular tolerance. In critically ill patients, it can also be performed continuously at very low filtration rates (e.g. 1 - 2 ml/minute) with or without the addition of dialysate to remove oedema fluid. Both arteriovenous and veno-venous modes can be used.

Plasmapheresis (PF)

This term describes a treatment, which uses a particular plasmafilter. In these filters, the molecular weight cut-off of the membrane is much higher than that of haemofilters. Plasma is filtered, and blood is reconstituted by the infusion of plasma products such as fresh frozen plasma, albumin or other fluids. This treatment is performed in an attempt to remove plasma proteins or protein bound solutes that cannot be removed by simple haemofiltration.^{21,22}

Haemoperfusion (HP)

This term describes a form of treatment in which blood is circulated on a bed of coated charcoal powder to remove solutes by adsorption. The technique is specifically indicated in cases of poisoning or intoxication with agents that can be effectively removed by charcoal (e.g. theophylline). This treatment causes frequent platelet and protein fraction depletion and therefore it is utilised only in specific cases, and under intensive and continuous monitoring.²³

Initiating and maintaining renal replacement therapy

Many intensivists feel that renal replacement therapy is best initiated early in the course of the patient's illness. This view holds that it is physiologically unsound and clinically dangerous to wait for any of the complications of uraemia to develop before dialytic therapy is undertaken. Now that CRRT is available and haemodynamic instability can be avoided, there is little morbidity associated with initiating RRT early, even in the sickest of patients. However, there are no scientific studies to help the physician decide when to start RRT. Time-honoured criteria are simply descriptors of uraemic complications such as pulmonary oedema, severe fluid overload, hyperkalaemia, uncontrolled uraemia, uraemic complications and severe uncontrolled metabolic acidosis. Attempts are usually made to prevent such complications by means of various conservative manoeuvres (e.g. diuretics, medical treatments for hyperkalaemia, bicarbonate administration, fluid restrictions and nutritional restrictions). When they fail, treatment is escalated to IHD or other forms of renal replacement.

A different and more aggressive approach to the above problems, however, has recently been advocated in the ICU, where maintenance of homeostasis and prevention of complications are an important therapeutic goal.²⁴ According to such an approach, prevention is superior to treatment of complications. Early intervention is desirable and CRRT offers the ideal form of RRT for such an approach. According to a more prevention-based approach, different criteria for initiating RRT in the ICU should now be considered (Table 1)

Table 1. Indications for initiating RRT in adult critically ill patients

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- Oliguria (urine output < 200 ml/12 h)
 - Anuria or extreme oliguria (urine output < 50 ml/12 h)
 - Hyperkalaemia ($[K^+]$ > 6.5 mmol/L and rising)
 - Severe acidaemia (pH < 7.1)
 - Azotaemia (plasma urea > 30 mmol/L or creatinine > 300 μ mol/L)
 - Pulmonary oedema
 - Uraemic encephalopathy
 - Uraemic pericarditis
 - Uraemic neuropathy or myopathy
 - Severe dysnatraemia (plasma Na^+ > 160 or < 115 mmol/L)
 - Hyperthermia
 - Drug overdose with filterable toxin (lithium, vancomycin, procainamide, etc.)
 - Anasarca
 - Diuretic-resistant cardiac failure
 - Imminent or ongoing massive blood product administration
-

NB: The presence of one of the above criteria is sufficient to initiate RRT. The simultaneous presence of two of these criteria makes the prompt initiation of RRT highly desirable. The presence of three criteria makes the prompt initiation of RRT mandatory. In all cases, CRRT is the preferred technique.

Once RRT has been instituted, there are no scientifically established biochemical or clinical measures of so-called dialytic adequacy. However, most clinicians using CRRT seek to maintain a urea concentration of at least < 30 mmol/L and preferably < 25 mmol/L. Normalisation of electrolytes, phosphate and calcium, is also pursued. The ideal therapy should achieve these goals with a minimum of morbidity and at reasonable cost. The ideal dialysis dose in critically ill patients, however, remains unclear and we still have

little information on the relation between the 'dose' of dialysis and outcomes in ARF.

Early randomised controlled trials comparing intensive dialysis to a less aggressive treatment were of insufficient statistical power to come to any conclusions, although some positive trends were reported. Moreover, the gap between dialysis prescribed and dialysis delivered may be in excess of 20% or more in end stage renal disease (ESRD). It may be even more pronounced with acute renal failure (ARF), due to haemodynamic instability, reduced blood flow, shortened dialysis time because of scheduled procedures or diagnostic tests, and suboptimal vascular access.

Despite these caveats, preliminary reports from Paganini *et al*, are informative.²⁵ In the first report, the authors examined the influence of dialytic modality (IHD vs. CRRT, not randomly allocated) in 856 critically ill patients with ARF. Among the 280 patients treated with IHD, there was no significant association between prescribed dialysis dose and the odds of death. Mortality was strongly associated with severity of illness and comorbidity. In a more recent report, however, patients were categorised into risk quartiles based on an institution-specific severity of illness and comorbidity score.²⁶ Dialysis dose was not associated with mortality at either extreme of risk (e.g. very low or very high risk). However, mortality was reduced in intermediate-risk patients treated with more intensive dialysis, defined as a urea reduction ratio in excess of 58% in patients on IHD, and a time-averaged urea concentration below 45 mg/dL in patients treated with CRRT. Renal recovery and other outcomes were not reported.

Schiffel *et al*,²⁷ recently reported the preliminary results of a randomised clinical trial in which 72 patients with ARF were randomised to either daily or alternate day IHD. Mortality was significantly reduced in the daily IHD group (21% vs. 47%). These data are provocative, but require confirmation. Nevertheless, on the basis of data derived from ESRD patients, and limited data in ARF patients, it can be said, in general, that more dialysis is better.

The prescription of dialysis should be individualised. Patients who are hypercatabolic or experience a large obligate fluid intake will most likely need daily IHD to control azotaemia and hyper-volaemia. Until a more refined tool is available, it is reasonable to use the urea reduction ratio (i.e. pre-BUN minus post-BUN divided by pre-BUN x 100). One should aim for at least a 65%-70% reduction per session. This reduction corresponds to a time-clearance product (Kt/V) of approximately 1.2 per treatment, or 4.2 per week, assuming alternate day therapy. This goal should be increased in hypercatabolic

patients. The dangers of using moderate or low BUN or creatinine levels (which may potentially be the result of low dietary protein intake, and diminished body protein mass, respectively) as measures of treatment adequacy, cannot be overemphasised.

The use of CRRT, can solve all of the above problems of dialysis delivery and Kt/V calculations, and can always maintain a steady and high level of control of uraemia, twenty-four hours a day.

Which dialyser?

Commonly used dialysers are composed of a variety of materials, including regenerated cellulose, modified cellulose (e.g. cuprophane, hemophan, cellulose acetate), and newer synthetic materials such as polymethylmethacrylate, polyamide, polysulfone and polyacrylonitrile. These materials vary widely in their capacity for solute transport (i.e. flux) and ultrafiltration, and their degree of interaction with cellular and soluble components of the blood (i.e. biocompatibility), as well as cost (e.g. synthetic membranes are more expensive).

Intermittent haemodialysis has been associated with several potentially adverse biophysical and inflammatory changes in humans. These changes include enhanced cell surface expression of leukocyte adhesion molecules such as MAC-1 and LAM-1,²⁸ stimulation of superoxide synthesis,²⁹ systemic release of thromboxane,³⁰ and augmented monocyte elaboration of interleukin 1, interleukin-6, and tumour necrosis factor.^{31,32} Many of these molecules are abundant in multiple organ failure, although the effect of their modulation by haemodialysis remains unknown. Cuprophane haemodialysers appear to initiate these processes more than synthetic dialysers.³³

Two recently published prospective trials compared cuprophane with polymethylmethacrylate or polyacrylonitrile in the treatment of acute renal failure.^{34, 35} In terms of patient survival, neither study reached conventional levels of statistical significance but a trend toward increased patient survival with non-cellulosic membranes was reported. Furthermore, the proportion of patients who recovered renal function was significantly higher, and the time to renal recovery significantly shorter, in patients dialyzed with non-cellulosic membranes. These findings are consistent with the knowledge that high-flux dialysers/filters (continuous haemofiltration can only be performed with such filters) are capable of removing or binding the anaphylatoxins C3a and C5a,³⁶ as well as inflammatory cytokines, such as tumour necrosis factor alpha (TNF), and interleukin-1.³⁷ Nevertheless, it is difficult to separate the specific effects of membrane flux from the concordant effects of biocompatibility.

Controversies in the choice of RRT in the ICU

Currently, there are no randomised, controlled trials to guide the clinician in his or her choice of the best form of RRT for a given critically ill patient. In the absence of such trials, there is much controversy and disagreement.

In the adult population, peritoneal dialysis is now only infrequently used in developed countries. This lack of application is due to several factors which include insufficient solute clearance,³⁸ limited control of hyperkalaemia, a high incidence of peritonitis, poor fluid removal, unpredictable fluctuations in glycaemia, abdominal leaks and respiratory dysfunction. Because of these factors, the major controversy pertains to the preferential use of CRRT vs. IHD, with Australian and European intensivists increasingly adopting CRRT and American nephrologists choosing to remain with IHD. Although this controversy is likely to remain unresolved, some observations may assist the intensivist in appreciating the pros and cons of the options available.

The first observation is that haemodialysis is associated with several clinically important complications (Table 2). The most important of which, in critically ill patients with multiorgan dysfunction, is the development of hypotension. This is most severe in those patients who are cardiovascularly unstable.^{34, 39} The physiological cost of hypotension in the critically ill can be significant, as IHD may precipitate ischaemia in specific organs including kidneys recovering from acute tubular necrosis which have temporarily lost pressure-flow autoregulation. The effects of these hypotensive events can be seen histologically as fresh ischaemic lesions occurring with each episode of IHD,^{40, 41} potentially delaying renal recovery.

Table 2. Major complications of intermittent haemodialysis

Systemic hypotension
Arrhythmia
Hypoxaemia
Haemorrhage
Infection
Line-related complications (e.g. pneumothorax)
Seizure or dialysis disequilibrium
Pyrogen reaction or haemolysis
? Delay in recovery of renal function

In addition to haemodynamic instability, the other major problem associated with episodic fluid removal during IHD is the intermittent fluid overload that occurs between treatments. In the extreme case, this may be life

threatening, particularly in oliguric patients with ARDS who will not easily tolerate excess extravascular water. CRRT is the obvious choice in such patients. Indeed it may also improve respiratory function in patients with multiorgan failure and acute lung injury.

An important practical benefit of CRRT is its ability to continuously remove as much water and sodium as desired. This ability particularly impacts on patient nutrition, which can be delivered without restriction.^{42,43} The importance of feeding the critically ill adequately has been borne out by studies demonstrating a correlation between mortality and a progressive calorie deficit as well as an association between patient morbidity and cumulative protein intake. The advantage of CRRT is that uraemic control can always be achieved and maintained even in septic patients,⁴³ while providing sufficient nutritional support. Nevertheless, the daily loss of free amino acids during CRRT is similar to that seen during a 4-hour haemodialysis session, i.e. approximately 1 - 2 grams of nitrogen or 10% of the usual daily intake.⁴⁴ No hormonal or trace element losses of significance take place during CRRT, and vitamin losses are minimal, except for vitamin C, which is lost in amounts roughly equivalent to its recommended daily allowance.

Additional benefits of CRRT include its ability to reduce energy expenditure by cooling the febrile patient, and, in the patient with heart failure resistant to diuretics, continuous ultrafiltration can produce a rise in cardiac index, while avoiding a fall in arterial pressure. The haemodynamic improvement is mostly due to a change in preload which optimises myocardial contractility on the Starling curve. Many patients with congestive cardiac failure not responding to conventional therapy are now successfully treated in this way.⁴⁴ The rationale of using a continuous therapy is to achieve a physiological, safe and progressive removal of fluid and solute. The cumulative clearance of urea and creatinine by a continuous method is superior (clinically and statistically) to that achieved by intermittent haemodialysis applied up to 4 times per week, even in septic patients. Indeed, IHD applied 6 times per week would be necessary to achieve the same uraemic control seen with standard CRRT.⁴⁶ The net result is that uraemic control is superior during CRRT.²⁴

Another disadvantage of the faster, diffusive clearance of solute with IHD is that it causes solute disequilibrium, because solute is extracted from the intravascular space by the dialyser at a rate that is substantially faster than solute movement into blood from the intracellular and interstitial compartments. Such solute disequilibrium may be responsible for brain oedema⁴⁷ and has even more pronounced ill effects in the critically ill; particularly those with increased

intracranial pressure.⁴⁸ In high risk patients, rapid solute movements may cause tonsillar herniation and death. CRRT, on the other hand, does not induce such increases in intracranial pressure and, as it maintains cerebral perfusion pressure,⁴⁸ it is the treatment of choice in all patients with, or who are at risk of, cerebral oedema.

Other practical considerations regarding differences between CRRT and IHD include thermal loss, anticoagulation, and patient mobilisation. The ability to cool febrile patients may be beneficial as it is often accompanied by amelioration of tachycardia and vasodilatation. However, because this effect conceals some clinical signs of infection, the clinician should have a lower threshold for suspecting ongoing sepsis.

Anticoagulation of the haemofiltration circuit with heparin is safe and adequate in the vast majority of patients. In those at risk of bleeding, various alternative approaches are used, including low dose heparin, regional heparinisation, low molecular weight heparin, prostacyclin, citrate or no anticoagulation. It is not uncommon that persisting difficulties with circuit clotting are due to problems with vascular access. This can occur irrespective of whether continuous or intermittent treatment is being employed. Overall, the need for anticoagulation does not pose a sufficient obstacle to the use of CRRT in contrast to IHD.

Despite the demonstrable physiological benefits of CRRT in critically ill patients, there are some who believe that, in the absence of a proven effect on mortality, IHD should be regarded as the standard approach. The difficulty, however, is that to demonstrate such a difference would require the randomisation of more than a thousand patients in a multicenter study with standardisation of other clinical management. Two attempts have been made to conduct such studies. Both have had difficulty with methodology, randomisation and with recruitment of patients; neither has yet been published in full and neither has achieved conclusive results so far. Furthermore, as more ICUs change to using CRRT, such a trial will be increasingly difficult to undertake.

Of all ICU patients, those receiving RRT have the poorest prognosis and also cost the most. It is important to consider the costs of the treatments used in these patients including those of renal replacement and to relate them to the gains in life-years. Although the general principles of cost estimation apply throughout, they must be calculated for individual units to account for local factors such as salaries, costs of replacement or dialysate fluids, methods of anticoagulation and rates of depreciation on equipment purchased. One such costing analysis was carefully performed at Guy's hospital in London. The costs of the two methods were found to be

very close, with the IHD being only 6% cheaper.⁴⁹ CAVHD would be cheaper overall as a blood pump would not be required. In addition, recent data from a randomised controlled trial show that complete renal recovery is significantly more common with CRRT than with IHD. This finding suggests that there may be hidden costs in association with an IHD-based approach.⁵⁰

Septic shock, multiorgan failure, acute renal failure and renal replacement therapy

Many patients with ARF have severe sepsis, multiorgan dysfunction and a major systemic inflammatory response. In these patients, the blood purification achieved with CRRT may provide additional advantages that go beyond renal replacement therapy *per se*, and move into the area of immunomodulation. The ability that CRRT has to remove or adsorb putative mediators of organ dysfunction may represent yet another reason for its preferential application.⁵¹

Recent investigations in animals and humans suggest that CRRT in sepsis may increase survival in patients with sepsis-associated ARF,⁵² although if haemofiltration is to have an additional role, the rate of plasma water exchange may have to be increased.^{53,54} In response to these developments, investigators are now seeking to augment the blood purification efficacy of CRRT in a direction more clearly aimed at immune system modulation. Initial experience is accumulating in the treatment of severe sepsis with organ dysfunction

using high volume haemofiltration⁵⁵ or coupled plasmafiltration with adsorption^{5,6} Such experience suggests that, at the very least, these more aggressive approaches to blood purification can decrease the need for vasopressor therapy during septic shock.

More recently, the concept that convective CRRT in the form of CVVH is more effective at lowering circulating levels of soluble inflammatory mediators than diffusive CRRT in the form of CVVHD has been tested in a randomised controlled study.⁵⁷ This study demonstrated that for equal amounts of dialysate/replacement fluid administration rate, convective therapy achieves lower serum TNF concentrations than diffusive therapy (Figure 3). Such data lend further support to the preferential use of convective therapy.

Another area where haemofiltration is proving useful is in the control of fluid balance in patients requiring extracorporeal membrane oxygenation for cardiogenic shock after cardiac surgery. These patients often require massive amounts of clotting factors, which can only be given safely in the presence of continuous haemofiltration. Under these circumstances, fluid can be removed as the clotting factors are being administered, and the development of ARDS or pulmonary oedema can be prevented while the bleeding is controlled. Also, haemofiltration can be performed without any need for circuit anticoagulation. We have also used haemofiltration to treat patients with ARDS in whom attempts to induce a negative fluid balance with loop diuretics result in a water diuresis but not a salt diuresis. In these

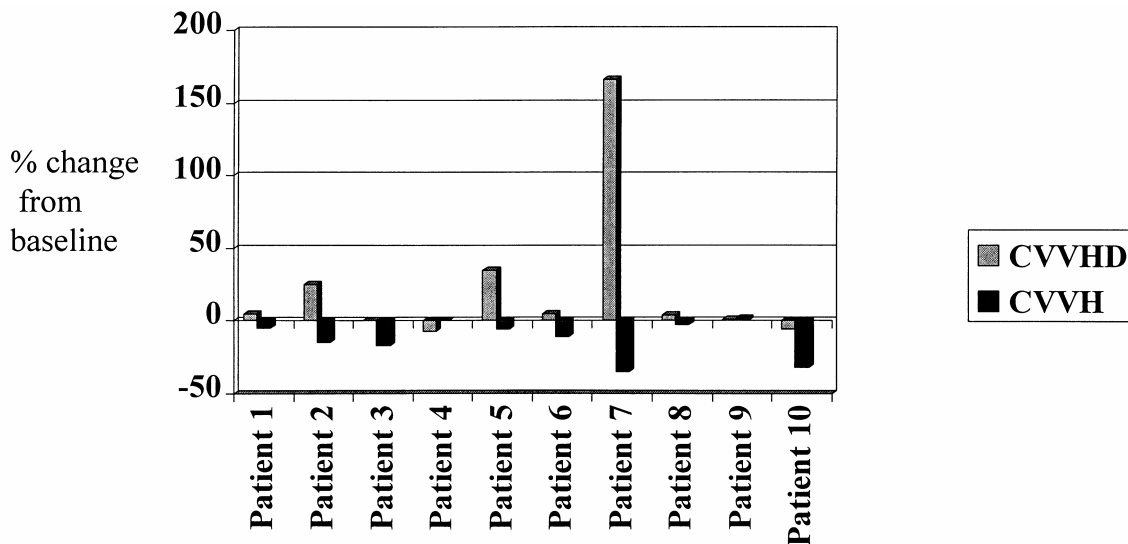


Figure 3. Graph displaying the different response of serum TNF levels in septic patients receiving either CWH (convective therapy) or CWHHD (diffusive therapy). Convective therapy lowers TNF levels while diffusive therapy is associated with a slight increase in serum NF concentration. (modified from Kellum JA, et al. Crit Care Med 1998;26:1995-2000)

patients, hypernatraemia may develop and extravascular lung water is not decreased. Continuous haemofiltration achieves the normalisation of serum sodium levels and the removal of extravascular water while maintaining full haemodynamic stability. This process often achieves substantial improvements in gas exchange and lung compliance.

In conclusion, the physician taking care of critically ill patients with multiorgan failure including severe ARF now needs to be aware of a myriad of issues and to understand the implications of recent changes in the area of renal replacement technology.⁵⁸ It is likely that the application of CRRT will continue to grow in intensive care units around the world and that the intensivist will be called upon to play an increasingly important role in its prescription and implementation. Furthermore, as the knowledge in this area expands, it is increasingly desirable for such physicians involved in what can be now called 'critical care nephrology' to develop a unique level of expertise in order to improve patient outcomes.⁵⁹ As artificial renal support remains a large component of the practice of critical care and may expand to the adjunctive management of septic shock, the clinician can no longer neglect it or delegate its management to others. In order to move forward, attention needs to be focussed on this component of the care of critically ill patients and co-operation between nephrologists and intensivists needs to be strongly promoted; only then will we see the mortality of these patients decline significantly.

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