

Continuous Renal Replacement Therapy: Continuous Blood Purification in the Intensive Care Unit

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Abstract

Severe acute renal failure (SARF) occurs when renal dysfunction is such that haemodialysis or haemofiltration becomes necessary to maintain homeostasis. SARF is increasingly seen in association with multiorgan failure and has become a predominantly Intensive Care Unit disorder. Because of this change in epidemiology, the treatment of SARF has evolved from being exclusively nephrologist and intermittent haemodialysis-based to being mostly intensivists and continuous haemofiltration-based, particularly in European countries with a strong ICU tradition and in Australia.

Continuous renal replacement therapy (CRRT) has several advantages in critically ill patients, including greater flexibility, excellent haemodynamic tolerance, outstanding fluid balance control, excellent control of uraemia, prevention of cerebral oedema, ability to provide full and aggressive nutrition, and a possible anti-inflammatory effect.

The blood purification effect of CRRT may, in fact, go beyond the simple control of uraemia. Several animal studies have now shown that CRRT attenuates the haemodynamic consequences of bacteraemia or endotoxaemia. Such studies have also shown that increasing the intensity of fluid exchange may offer further beneficial effects in the setting of sepsis. In the light of these findings, CRRT is moving into the area of adjuvant treatment of sepsis, and pilot randomized controlled trials are being conducted to test the hypothesis that CRRT, either in standard or high fluid exchange volumes, attenuates the inflammatory effects of sepsis in humans. In the future, the use of CRRT may extend beyond its initial scope into the area of adjuvant management of sepsis and continuous blood purification may become part of a complex multifaceted approach to multiorgan dysfunction.

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Introduction

The last decade has seen a progressive change in the style of management of severe acute renal failure (acute renal failure which requires the use of renal replacement therapy) as well as in the epidemiology of this condition.¹ Severe acute renal failure (SARF) is now most commonly seen in the intensive care unit and is part of the syndrome of multiorgan failure.¹ Patients with SARF are typically on artificial ventilation, have severe sepsis or septic shock and/or require the administration of inotropic or vasopressor agents to maintain an adequate cardiac output and an adequate mean arterial blood pressure. These patients do not easily tolerate "conventional" forms of renal replacement therapy such as standard intermittent haemodialysis or peritoneal dialysis. The former often results in serious haemodynamic instability, arrhythmias, and fresh ischaemic injury to the recovering kidney, the latter is associated with a high risk of intraperitoneal infection and often cannot achieve the degree of solute and fluid removal necessary to control uraemia and volume overload.² Because of the

shortcomings of standard nephrological patient management, two trends in medical practice have recently developed, particularly in countries with a strong and independent intensive care tradition (Australia, Holland, and Austria): one directed toward the predominance of intensivist-led SARF management and the other toward an increased use of CRRT (any form of continuous haemofiltration). These two trends have been in response to the changing epidemiology of SARF, are complementary, and have moved blood purification therapy from the dialysis unit and the renal ward into the intensive care unit.

The Changing Epidemiology of SARF

The recent change in the epidemiology of SARF is being increasingly documented.¹ Previously, relatively common causes of SARF such as renal outflow obstruction, multitrauma, haemorrhage, or postpartum renal failure have become uncommon because of prompt and aggressive fluid resuscitation. On the other hand, the performance of more and more complicated major sur-

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gery (solid organ transplantation and cardiac surgery) in an older population with diminished renal reserve recurrently exposes fragile patients to the risk of SARF. A recent prospective survey in the state of Victoria, Australia³ has shown that critically ill patients with SARF now have a mean age of approximately 65 years and that chronic renal impairment is present in up to a third of such patients. In more than 70% of these patients, there is the concomitant need for mechanical ventilation and inotropic support (i.e. failure of at least 3 organs). Sepsis is now the most common aetiology of SARF. In the three intensive care units of the Austin & Repatriation Medical Centre, close to 100 such patients are treated with CRRT every year with a prevalence of SARF of approximately 5% and approximately 30 patients receive acute dialytic treatment for isolated acute renal failure outside the ICU. The consequence of this epidemiological shift has been well documented in Australia: intensive care specialists now see most SARF and manage it with little or no nephrological input.³ Such a shift in practice threatens established attitudes and entrenched interests, and is seen with much ambivalence in several countries, particularly the USA but has been embraced without problems in Australia. This steady change in practice is also part of the process of a new specialty (critical care medicine) coming of age. In addition, given the growing complexity and increasingly expanding role of CRRT (see below), it is also likely that, over time, new physicians will emerge with combined training in nephrology and intensive care, and with strong interest and expertise in this area of medical practice (critical care nephrology). The consequences of such possible shifts in practice style and training cannot yet be predicted.

Continuous Renal Replacement Therapy

As argued above, critically ill patients with SARF require a renal replacement therapy which is particularly suited to their degree of physiological fragility. The only therapy that currently meets their needs is CRRT, also known as continuous haemofiltration.^{4,5} The advantages of CRRT over conventional treatment have been discussed in detail elsewhere.⁵ It is useful, however, to emphasise those with major clinical relevance. Firstly, unlike standard intermittent haemodialysis,⁶ CRRT is associated with outstanding haemodynamic stability.⁷ Secondly, CRRT can achieve the removal of large amounts of fluid without inducing hypotension. This is because it does so steadily and over a 24-hour period. It is therefore possible to remove up to 5 to 6 litres of isotonic fluid from a grossly oedematous patient without any haemodynamic alterations.⁸ In addition, such ability to safely modulate the fluid status of critically ill patients can be used prophylactically. For instance, if an ICU patient has been adequately resuscitated and has severe disseminated intravascular coagulopathy requiring large amounts of fresh frozen plasma, this can be given safely

while CRRT is operative because fluid can be simultaneously removed to make "space" for the blood products being administered. This prevents the development of pulmonary oedema. Thirdly, uraemic control is predictable, steady and superior in degree to that achieved by other therapies^{9,10} (Figs. 1 & 2). Fourthly, once the setting up of a continuous haemofiltration circuit has become part of the intensive care routine just like inserting a right heart catheter or initiating and regulating mechanical ventilation, the filter can be changed from a haemofilter (pore size approximately 30 000) to a plasmafilter and continuous plasmapheresis can be carried out as part of the treatment of such conditions as

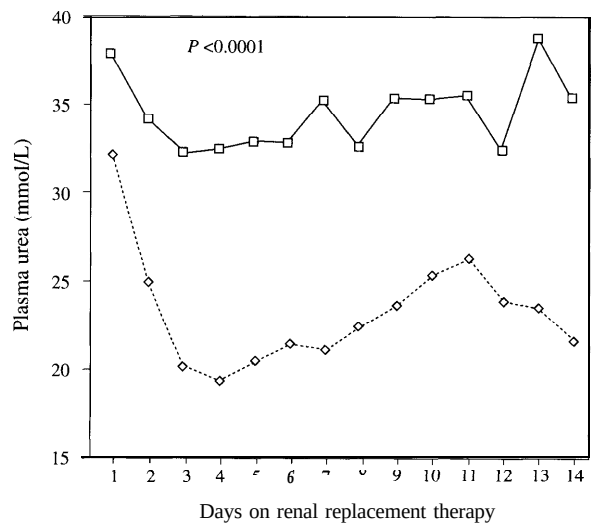


Fig. 1. Diagram illustrating the difference in mean urea concentration between a group ($n = 46$) of critically ill patients receiving intermittent haemodialysis (squares) and a group ($n = 46$) of similar patients receiving CRRT (diamonds) over a period of 14 days. As can be seen, uraemic control is vastly superior with CRRT.

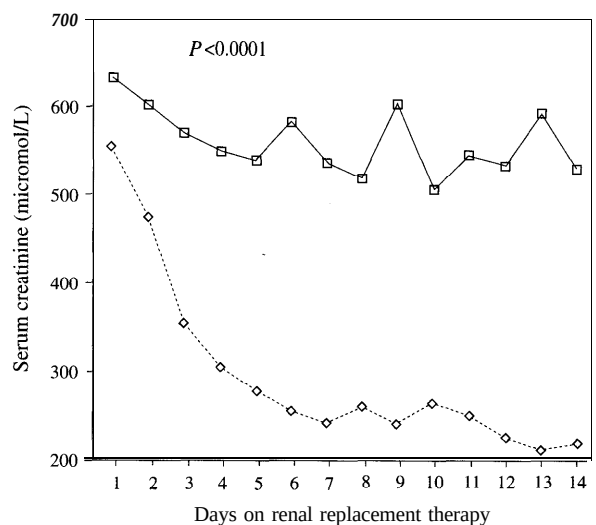


Fig. 2. Diagram illustrating the difference in mean creatinine clearance between a group ($n = 46$) of critically ill patients receiving intermittent haemodialysis (squares) and a group ($n = 46$) of similar patients receiving CRRT (diamonds) over a period of 14 days. Serum creatinine is rapidly lowered by CRRT and kept at much lower levels throughout the duration of therapy.

myasthenia gravis, Guillan-Barre syndrome, Good pasture syndrome and the like. Last but not least, because fluids and uraemia can always be easily controlled, nutritional therapy can proceed unhindered to the same degree that one would offer it to a patient without renal failure.”

In particular patients, the evidence for CRRT is so strong¹² that it has almost become mandatory. These patients are those with acute renal failure and cerebral oedema, particularly patients with combined acute liver and renal failure. In these patients, intermittent haemodialysis causes an increase in intracranial pressure, while CRRT reduces the severity of intracranial hypertension.”

There are several techniques of CRRT which can be used in critically ill patients. Their nomenclature and features have been recently reviewed in detail.¹⁴ Vascular access for continuous haemofiltration can be obtained by the insertion of a femoral artery cannula (or the creation of a Scribner shunt) and a femoral vein cannula for the return of purified blood to the patient (arteriovenous haemofiltration). More recently, however, double lumen catheters have been used for vascular access. When such catheters are used, blood must be pumped from a central vein to the filter and back to the same vein via the catheter (veno-venous haemofiltration). Such veno-venous therapy is technically more complex than arteriovenous haemofiltration because it requires the use of a peristaltic blood pump. It is important, however, to realise that veno-venous therapies which use double lumen central venous catheters for vascular access, are significantly safer than those which require cannulation of an artery (arteriovenous therapies).¹⁵ A diagram of 2 standard veno-venous circuits is shown in Figures 3 and 4. It is also important to realise that, whatever therapy one chooses, clearance of small solutes (urea, creatinine, phosphate and other small molecular weight substances) can always be increased by simply regulating the amount of dialysate delivered to the non-blood compartment of the filter by countercurrent flow. Under such circumstances, which effectively represent a form of “slow continuous dialysis”, solute removal occurs by diffusion. Diffusion is a mode of solute transfer in which molecular movement across a semipermeable membrane occurs according to the concentration gradient of that molecule. If a diffusive therapy (continuous veno-venous haemodialysis) is used, solute clearance will be different in content from that achieved by means of convection. Convection is a form of solute transfer in which molecular movement across a semipermeable membrane is driven by a transmembrane pressure gradient. Such transmembrane pressure is essentially generated by the hydrostatic pressure associated with blood flow through the filter. Such pressure induces plasma water movement across the membrane with solutes also

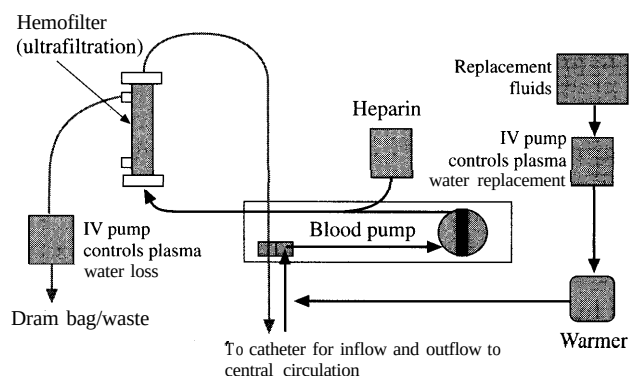


Fig. 3. Diagram of a continuous veno-venous haemofiltration (CWH) circuit with pump control of ultrafiltration. Blood is driven by a peristaltic pump into the filter and returned to the patient. The rate of ultrafiltration is controlled by a volumetric pump as is the replacement fluid rate.

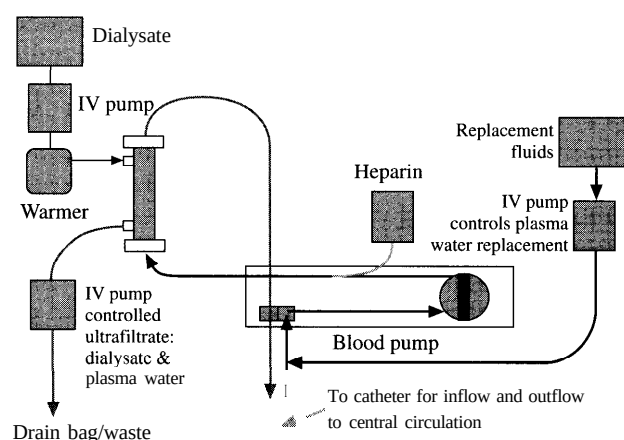


Fig. 4. Diagram of a continuous veno-venous haemodiafiltration (CWHDF) circuit with pump-controlled ultrafiltration. Dialysate is pumped counter-current to blood and the resulting ultrafiltrate is also pumped off the volumetric pump. The blood path is the same as in CWH.

moving across the membrane as part of the mass movement of plasma water (“solvent drag”). Convective therapy (continuous veno-venous haemofiltration), is slightly inferior to diffusive therapy in achieving small solute clearance but it is vastly more effective in achieving middle molecular clearance.¹⁶ Such middle molecular clearance may be important in the setting of sepsis. Recent data indicate that convective therapy is associated with the removal of several soluble inflammatory mediators. The clinical significance of this remains unclear, but these findings suggest that convective therapies may be preferable to diffusive therapies.^{16,17} The mode of solute removal is therefore important as is the type of filtering membrane in use. Recent evidence, in fact, suggests that certain membranes like polyacrylonitrile for instance, have a high absorptive capability and can rapidly reduce the circulating levels of complement factor D as well as absorb a variety of cytokines^{18,19} (Table I). These novel insights into the immunological effects of CRRT and several anecdotal reports of a beneficial haemodynamic effect of CRRT in

septic patients have raised the possibility that continuous haemofiltration techniques may provide a degree of blood purification that goes beyond the simple control of uraemia. This development would then make CRRT a potential form of adjuvant therapy in severe sepsis and septic shock. Several animal experiments conducted by different groups around the world have indeed shown a beneficial effect of CRRT in endotoxaemic or gram-positive shock, further supporting the concept that the role of CRRT in the treatment of sepsis should be formally explored.²⁰ A pilot randomised controlled study is being conducted in Australia to test the hypothesis that CRRT applied for 48 hours in patients with severe sepsis or early septic shock would lead to a decrease in the severity and duration of organ dysfunction. More recent studies also suggest that standard approaches to haemofiltration may not be enough, and that increasing the degree of convective clearance will lead to even greater benefits. In that regard, Grootendorst et al²⁰ have conducted animal experiments in endotoxaemic pigs and have been able to reverse the hypotension and cardiac dysfunction seen in this setting by performing high-volume continuous veno-venous haemofiltration (HV-CVVH - fluid exchange rate: 6 L/h). In the light of these findings, it has now become justifiable to test the efficacy of HV-CVVH in humans with established septic shock. A pilot randomised controlled multicentre study of the haemodynamic consequences of HV-CVVH in this setting is now being conducted in Australia and the Netherlands. In addition, even more efficient blood purification may be achieved if plasmfiltration instead of haemofiltration is performed and the plasmfiltrate is passed through absorptive resins that remove mediators during single pass.²¹ Initial *ex vivo* experiments suggest that this strategy should be tested in animals and humans.

Clearly, the arrival of CRRT in the intensive care unit has opened new horizons as well as addressed old unsolved problems. The role of blood purification in human disease is being reassessed as techniques develop to increase depurative efficiency and as we gain

further insights into the role of soluble mediators in a variety of human conditions, particularly sepsis. It is likely that the future will bring further major advances and applications for CRRT and that the intensivist, rather than the nephrologist will be exploring their consequences and increasing their application.

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TABLE I: INFLAMMATORY MEDIATORS SHOWN TO BE AFFECTED BY CONTINUOUS RENAL REPLACEMENT THERAPY

IL-1	: absorbed and filtered
IL-6	: absorbed and filtered
IL-8	: filtered
TNF	: absorbed and filtered
Platelet activating factor	: absorbed and filtered
C3a	: filtered
C5a	: filtered
Factor D	: absorbed
Endothelin	: filtered
Thromboxane	: filtered
Prostaglandins	: filtered
Myocardial depressant factors	: filtered