Continuous renal replacement therapy in critically ill patients

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Abstract
Acute renal failure is an evolving syndrome in which new pathogenetic mechanisms have recently been elucidated. The evolution of the field of haemodialysis has led to a parallel development in the therapeutic approach to patients suffering from this syndrome. In particular, acute renal failure is more frequently seen as part of a more complex syndrome, defined as multiple organ failure. In this clinical setting, patients are almost inevitably confined to intensive care units and sepsis is a frequent underlying mechanism of organ failure. The use of new devices and new machines, together with a better understanding of the underlying mechanisms of solute and water removal, have allowed us to achieve higher levels of efficiency and clinical tolerance during artificial renal replacement therapy. The first objective has been reached by increasing the automation of the extracorporeal circuits and the operational levels of the different techniques; the second has been achieved by means of a new generation of monitoring techniques and new machines equipped with specific interfaces and alarms. This progress has made continuous forms of renal replacement (CRRT) possible and easy to perform without major problems or complications. The most promising and effective options for treating acute renal failure in critically ill patients are today offered by continuous renal replacement therapies. Classic indications, but also alternative non-renal indications, have been proposed for these techniques. The most advanced indication is the multiple organ dysfunction occurring in septic patients. The possible removal of proinflammatory mediators may permit a blockade of the systemic inflammation, a modulation of the altered immune response in these patients, and it may lead to a partial or total restoration of the lost homeostasis.

Keywords: acute renal failure; continuous renal replacement therapy; critically ill patients

Continuous arteriovenous haemofiltration (CAVH) in critically ill patients with acute renal failure (ARF) was first reported ~ 20 years ago [1]. Since that time, continuous renal replacement therapies (CRRT) have undergone a remarkable evolution [2]. The major aspects of this evolution include the introduction of countercurrent dialysate flow [3], the use of double lumen central venous access (with pump technology for the control of blood flow) [4], the growing application of CRRT in the intensive care unit (ICU) in preference to intermittent haemodialysis (IHD) [5], the growing interest in the use of haemofiltration as an adjuvant therapy in sepsis [6] and, finally, the modification of CRRT techniques with the intention of maximizing their potential anti-inflammatory role [7]. We will briefly describe the current state and role of CRRT in the ICU, address some of the controversies about its application in the critically ill, and speculate on the future of the technique in intensive care medicine.

The technical evolution of CRRT

Initial assessment of CRRT involved studying its effectiveness and the clinical consequences of its application. Clinical experience was also gained using the first technique of CRRT: CAVH. It was clear from the start that CAVH had important advantages over IHD. These were particularly apparent in the areas of haemodynamic stability, control of circulating volume and nutritional support. However, CAVH also had serious shortcomings, including the need for arterial cannulation (or construction of a Scribner arteriovenous shunt) and the limited solute clearance that could be achieved even under optimal operating circumstances (10–12 ml/min for small solutes such as urea) [8]. Initial technical modifications, such as pre-dilution (i.e. the infusion of the replacement solution before the filter instead of after it), did improve creatinine clearance but the next major technical advance was the creation of an additional side port to the haemofilter. Through this port, countercurrent dialysate could be infused at slow flow rates (i.e. 1 l/h) to achieve...
additional diffusive solute clearance: this modified technique was named continuous arteriovenous haemodiafiltration (CAVHD) [9]. With the arrival of CAVHDF, IHD became even less utilized, as uremic control could be achieved in all patients irrespective of their weight or catabolic state simply by increasing countercurrent dialysate flow rates to 1.5 or 2 l/h as necessary [10]. Arteriovenous therapies are simple because they do not require a peristaltic blood pump, but the morbidity associated with arterial cannulation is substantial [11]. For this reason, veno-venous techniques utilizing a double lumen central venous catheter for vascular access are safer and considered preferable [12,13]. When veno-venous therapy is applied, blood flow is controlled by a peristaltic pump module with appropriate air bubble trap and pressure monitors. In this setting, continuous veno-venous haemofiltration (CVVH) or continuous veno-venous haemodiafiltration (CVVHDF) can be chosen: either technique achieves excellent uremic control. In fact, by using adequate blood flows (≥150 ml/min) and membrane surface areas (≥0.8 m²), CVVH without pump-driven ultrafiltrate control delivers high ultrafiltration rates (1.5–3 l/h) and, therefore, high solute clearance without the need for countercurrent dialysate flow [14]. However, to facilitate nursing care, ultrafiltration can now be pump-controlled with reasonable precision for clinical purposes and solute clearance can thereby be fully regulated to achieve the desired therapeutic aims [15]. Continuous renal replacement techniques may differ significantly according to the membrane used, to the mechanism of solute transport utilized, to the presence or absence of dialysis solution and to the type of vascular access. Membranes can have high or low hydraulic permeability. The former type is mainly cellulose-based and it is used mostly for diffusion. In this case, a dialysis solution is circulated in the filter countercurrent to blood and the technique is named continuous veno-venous haemodialysis (CVVHD). The technique is efficient in removing urea and other small molecules but not molecules in the middle-large molecular weight range. The other type of membrane is mostly synthetic and it can be used for convection or for mixed convective-diffusive therapies. If the transport is purely convective, the technique is named haemofiltration (CVVH). If the transport is both diffusive and convective the technique is named haemodiafiltration (CVVHDF). While in haemofiltration the solute clearance is limited by the amount of ultrafiltrate produced, in haemodiafiltration the additional solute transport provided by the presence of dialysate permits the best combination of small and large solute removal. Once staff know in-depth the performance of different techniques, the best therapy for a given patient can be chosen depending on the target solutes to be removed. A consensus nomenclature is now available to achieve uniformity of communication and more precise exchange of ideas and clinical experience [16].

Specific machines have now been designed to permit safe and reliable conduction of the therapy. These new machines are equipped with a friendly user interface that allows easy conduction and monitoring. The apparent complexity of the circuit is made simple by a self loading circuit or a cartridge that includes the filter and the blood and dialysate lines. Priming is performed automatically by the machine and pre- or post-dilution (reinfusion of substitution fluid before or after the filter) can easily be performed by changing the position of the reinfusion line. These new machines permit all CRRTs to be performed by programming the flows and the total amounts of fluid to be exchanged or circulated as a countercurrent dialysate at the beginning of the session.

Our preference is towards techniques that permit high volumes of convective transport such as CVVH with pump-driven ultrafiltrate control because of their greater ability to remove middle molecules (most soluble mediators of sepsis are middle molecules), their safety, and the ease of operation by nursing staff. Such a CVVH-based approach to the treatment of ARF has now been extended to the experimental clinical application of high-volume haemofiltration [7,17] and other techniques [18] aimed at increasing the potential ability to assist physicians in the management of septic shock [19]. Finally, haemofiltration circuits have been modified for connection to ECMO circuits (extracorporeal membrane oxygenation) and veno-venous bypass circuits, and have been effectively used to control circulating blood volume and total body water during cardiac surgery in infants [20]. The versatility of continuous haemofiltration and its increasing application suggest that new indications and technologies will develop in the near future.

CRRT: clinical issues

CRRT is ideally suited to the renal support of critically ill patients. It was developed and evolved, and has become successful precisely because alternative therapies (peritoneal dialysis (PD) and standard IHD or even daily haemodialysis) are deficient in many ways, especially in adult patients. Thus, we suggest that PD is not suited to the care of adult critically ill patients because of the high rate of associated peritoneal infection, and poor or inadequate solute clearances leading to less than optimal uremic control. PD, also impeding diaphragmatic movement, is associated with mechanical pulmonary and cardiac dysfunction. Finally, PD fluids contain high concentrations of glucose used as an osmotic agent; in the presence of high peritoneal membrane permeability this may result in rapid glucose absorption with unpredictable and highly variable levels of hyperglycaemia [21]. Although no randomized controlled trials have been conducted, intermittent haemodialysis may also be profoundly inferior to CRRT, if applied in the typical way (for 4 h every second day), to the care of these patients. This inferiority manifests itself at many levels [22]. The first and most important is that of haemodynamic instability. Thus, severe hypertension still accompanies 20–30% of haemodialysis
sessions in patients with ARF [23] and is precisely the reason that CRRT was developed. Such hypotension is highly undesirable and is likely to be damaging to the recovering kidneys [24]. As a consequence, adequate circulating volume control can only be episodic using IHD. With CRRT, volume control is continuous and immediately adaptable to changing circumstances (e.g. the immediate need for blood or blood products in a patient at risk of ARDS). Because of this adaptability, volume overload can be immediately treated or prevented, and volume depletion does not occur. The avoidance of swings in intravascular volume and blood pressure is likely to prevent renewed treatment-associated renal injury which, on the other hand, has been well documented with IHD [24,25].

Uraemic control with CRRT is vastly superior to that achieved with standard IHD [26]. IHD could hardly achieve the level of efficiency delivered by CVVH at 2 l/h. Even assuming the same clearance per week, the amount of solute removal will always be greater by CRRT because of the steady concentration of the solutes in plasma water in contrast to the wide variations occurring during IHD. Furthermore, the reality of daily clinical practice throughout the world is that, for logistic and financial reasons, IHD is rarely performed with the duration and the frequency that could permit such high levels of efficiency. Consequently, patients treated with CRRT consistently maintain lower urea and creatinine levels throughout the duration of renal replacement therapy [27] and they also are not exposed to the high concentration of uraemic toxins as occurs with intermittent treatments.

There is now emerging data suggesting that such inadequacy of dialysis [28] has significant adverse effects on patient outcome. Investigators from the Cleveland Clinic, for instance, have shown that the larger the delivered dialysis dose (expressed by litres of whole body clearance for various solutes such as urea) is associated with better outcome in critically ill patients [29]. Furthermore, recent results of a randomized prospective trial comparing different doses of ultrafiltration in CVVH show a statistically significant survival advantage to patients treated with higher doses [30]. It therefore seems reasonable to speculate that the better level of uraemic control provided by CRRT may also offer a survival advantage. There are other ways in which CRRT offers superior metabolic control over IHD. Comparative studies, for instance, demonstrate more rapid improvement and control of metabolic acidosis and more rapid and reliable control of serum phosphate levels [31]. In fact, CRRT is so effective at phosphate removal that hypophosphatemia develops frequently unless phosphate levels are monitored and prevented from falling below normal values. The superiority of CRRT in terms of uraemic control, volume control and overall metabolic control has important repercussions for the provision of nutritional support. In the era of traditional second daily IHD (as tolerated), adequate uraemic control was difficult and protein-restricted diets were applied to prevent high levels of blood urea. The consequences of such nutritional restriction were similar to those of protein starvation with highly negative daily nitrogen balances [32]. By contrast, because volume control and uraemic control are not a problem, an aggressive, protein-rich nutritional policy can be implemented in the care of ARF patients receiving CRRT [33], resulting in a marked improvement in daily nitrogen balance [34], with possible favourable effects on immune function and overall outcome. Finally, while amino acid losses through the filter do occur, they represent at most ~10% of overall amino acid supplementation and are not appreciably greater than those seen during IHD or PD [35].

In a particular group of critically ill patients, the use of CRRT in preference to IHD is sustained by controlled studies and is essentially mandatory. These patients are all those who are at risk of, or who already have increased intracranial pressure (neurosurgical patients, patients with encephalitis or meningencephalitis or acute liver failure). In a series of studies [36,37], CRRT has been shown to prevent the surge in intracranial pressure associated with intermittent renal replacement therapies. Because surges in intracranial pressure can be lethal in some of these patients, IHD should not be used.

Another group of patients ideally suited to CRRT are those with significant cardiac disease. In patients with diuretic resistant congestive cardiac failure, for instance, CRRT has been shown to restore dry body weight, improve urinary output, decrease neurohumoral activation and prolong symptom- and oedema-free time [38]. Clinical benefits have also been reported for cardiac surgical patients [39]. The possible mechanisms of action of such beneficial effects include decreased myocardial oedema, a decrease in left ventricular end diastolic pressure with optimization of the Starling relationship and increased myocardial performance, and also the removal of circulating myocardial depressant factors [40]. Furthermore, an increasing number of patients develop ARF after cardiac surgery or in relation to cardiac mechanical support as a bridge to heart transplant. Such patients typically require inotropic and vasopressor drugs and are haemodynamically fragile. Under these circumstances, standard IHD seems to be hazardous and almost impossible to carry out because of the severe treatment-induced hypotension. Such concepts also apply to patients receiving solid organ transplantation (especially lung and liver) in whom complications develop that require either aggressive isotonic fluid removal to attenuate reperfusion pulmonary oedema or liver dysfunction-associated ARDS, or in whom haemodynamic instability has developed in association with severe sepsis. Once again, optimal fluid and nutritional management and control of uraemia in these patients can only be achieved with continuous therapies.

Such speculations led us to the consideration of another large group of patients who are logically suited to CRRT: those with severe sepsis or septic shock-associated renal dysfunction. In these patients, haemodynamic instability is again very common and oliguria
or anuria typical. If appropriate fluid resuscitation, supplementation of nutrition and blood products administration is to take place under optimal physiological circumstances, CRRT is the renal replacement modality of choice. There are other reasons for choosing CRRT in this setting. A number of experimental studies have now shown that haemofiltration has beneficial effects on haemodynamics in animal models of sepsis [41]. Other animal and human studies have also indicated that haemofiltration membranes can bind and remove soluble inflammatory mediators and that the process of haemofiltration per se can induce convective removal of such mediators [42]. These observations have suggested a further rationale for the use of CRRT in this setting. The continuous contact of blood with such artificial membranes with great capacity of adsorption may in fact contribute to eliminate the peaks of concentration of proinflammatory mediators in the circulating blood. More recently, further advances have been made in this field thanks to the modification of standard CRRT technology by using more porous membranes [43], coupling continuous plasma filtration with continuous sorption [44] or increasing the plasma water exchange rate [45]. These recent investigations not only lend further support to the preferential use of CRRT over standard IHD in septic patients with ARF, but also suggest that there may be a role for CRRT as an adjuvant treatment of septic shock.

Controversial issues

Several controversies surround the use of CRRT. The most frequently debated and most clinically relevant are: does CRRT increase survival compared with standard IHD? Does CRRT increase cost compared with standard IHD? Who should run CRRT, the intensivist or the nephrologist? Should CRRT be used in septic patients even when there is no ARF?

The issue of the effect of CRRT on survival is clearly important. The best way to address this would be to conduct a randomized controlled trial comparing CRRT with IHD in critically ill patients with ARF. However, such a trial would not be easy to conduct. An appropriately sized population would have to be studied (probably 600–800 patients from multiple centres) [46], and randomization would have to be blocked according to illness severity, cause of ARF and hospital. Techniques of CRRT as well as IHD would have to be standardized. The task of designing and conducting such a trial is daunting. Nonetheless, a randomized controlled trial has been conducted and completed in the USA in three hospitals in San Diego, California. The results of the trial have been reported at meetings and published in abstract form [47]. Several issues concerning the trial make it impossible for it to provide clear cut guidance to clinicians. The first issue is that randomization failed to divide patients into comparable cohorts: those randomized to CRRT were more severely ill according to APACHE II and APACHE III severity of illness scores and had a higher percentage of males. Secondly, the study assumed a mortality of 70% for the ‘control’ group of IHD-treated patients for the purpose of pre-trial power analysis. Mortality was, in fact, in the range of 40–50%, resulting in a study that had limited statistical power. Thirdly, patients with a mean arterial pressure <70 mmHg were excluded from the study, the very population most likely to benefit from CRRT. Fourthly, patients were allowed to cross-over (32 of 131 who had an adequate trial of therapy), making analysis even harder. One interesting finding, however, did emerge: patients treated with CRRT who survived their illness were significantly more likely to show renal recovery to a pre-defined end point than those treated with IHD (92.3 vs 59.4%; P < 0.01) [48]. These findings suggest that mortality may not be an appropriate and achievable end point for future trials, but that renal recovery could be. The only other randomized controlled trial of some size (100 patients) has been conducted by Kierdorf and colleagues and showed a 15% (non-significant) survival advantage with CRRT [49]. In this study, however, five patients randomized to IHD were excluded from the analysis due to severe haemodynamic instability. Their inclusion and the use of therapeutic failure as an outcome measure would have given CRRT a >20% advantage over IHD. As pointed out in a recent review [49], when renal recovery is used as the outcome measure, and recent patient series are analysed, CRRT appears significantly superior. In addition, of all the retrospective series or prospective comparisons published so far, none has shown a trend in favour of IHD [22], but all have shown a trend in favour of CRRT.

The issue of cost has been analysed by several authors [49–51]. The general consensus is that differences in cost between CRRT and IHD are minimal. Furthermore, issues of cost relate to multiple variables such as the degree of renal recovery, the speed of renal recovery, and, most importantly, the structural organization of the hospital and ICU. In our hospitals, there is no appreciable cost difference between CRRT and IHD.

Severe ARF is a disease of critically ill patients. In many countries, such as Australia, intensivists have taken over the task of treating ARF without reference to nephrological opinion or intervention [52]. By contrast, in the USA, the prescription and application of CRRT is mostly controlled by nephrologists. In Europe, there may be a combined approach or a predominance of one group over another. We suggest that the ideal arrangement is one of full collaboration between intensivist and nephrologist [53]. If such a model is not possible, we strongly encourage the combined training of physicians in both disciplines, possibly leading to the development of a new area of medical specialization termed ‘Critical Care Nephrology’ [54].

Finally, there has been much debate about whether CRRT should now be used in patients without ARF
who have severe sepsis or septic shock [55, 56]. The rationale for such use rests upon the beneficial effects shown in animal models of sepsis [7, 41–43] and its ability to remove or adsorb many of the soluble inflammatory mediators of sepsis [57]. The concept that ‘blood purification’ may provide a form of adjuvant treatment for septic shock is conceptually appealing; however, much works remains to be done before we can understand the effects of CRRT in severe sepsis/septic shock [58]. In addition, we still have to define what kind of CRRT (high volume exchange, haemofiltration with higher porosity of membrane, maximal use of the adsorption capacity of the membrane with frequent filter changes, coupled plasmapheresis, sorption, or others) provides the level and type of blood purification best suited to severe sepsis/septic shock. Accordingly, we do not believe the case exists yet for using CRRT as adjuvant treatment for severe sepsis. The case certainly exists, however, for exploring this area with great attention and enthusiasm over the next decade.

References


