Continuous versus intermittent renal replacement therapy in the treatment of acute renal failure

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Introduction

Acute renal failure (ARF) can occur in intensive care patients due to several pathological events. Isolated ARF, treated with intermittent or daily haemodialysis, generally has a favourable outcome [1,2]. In patients with severe infectious complications or sepsis, however, ARF is often part of a more complex clinical entity generally described as multiple organ dysfunction syndrome (MODS). These patients have a severe prognosis, and haemo- or peritoneal dialysis may sometimes be contraindicated or present potential hazards [2–4]. To overcome these problems, continuous renal replacement therapies have been introduced into clinical routine and applied since 1977 [5,6].

Adequacy and tolerance of renal replacement for critically ill patients with ARF are the main aims of the dialysis technique. Adequacy of dialysis in the critically ill is determined by a number of variables which range from blood biochemistry and control of homeostasis, to nutrition and anabolism. Tolerance is seen mainly as a synthesis between a good haemodynamic response, and a minimal interaction between the host and the artificial circulation.

The heterogeneity of the patient population [7–12] makes it nearly impossible to evaluate the impact of different approaches to dialytic therapy in the absence of very large multi-centre studies. The variability in severity of illness, the ‘bounded physiological chaos’ inherent in intensive care unit (ICU) therapeutic interventions, and the small numbers seen in single institutions further aggravate the problem of defining adequacy in this setting.

While the problems described above have not disappeared, progress has been made in several directions. We now have several safe, effective and flexible forms of renal replacement therapy [13–20]. Illness severity scores have been developed and validated [21–24], even though they seem to be only partially adequate to describe the condition of the patient with complic-ated ARF. Nevertheless, such scores now make it possible to make more accurate comparisons of populations of critically ill patients from the same or different ICUs. Ventilator techniques, haemodynamic manipulations and approaches to the management of sepsis are performed increasingly according to consensus principles [25–28]. The ability to organize multi-centre studies is increasing because of recent advances in telecommunications. These changes open the door to the possibility of testing the concept of adequacy of dialysis for ARF in the near future.

At present, however, any discussion of the concept of adequacy of dialysis in the critically ill with ARF has to rely on indirect data and physiological principles. Such principles are helpful in defining ‘a priori’ the necessary properties of an adequate renal replacement therapy.

The first, indirectly established, principle in the management of critically ill patients is that the degree of physiological disturbance in the first 24 h after admission to the ICU (but also thereafter) ‘drives’ prognosis to hospital discharge.

This principle has been tested widely and demonstrated by multiple studies of illness severity scoring systems which evaluated it prospectively in thousands of ICU patients [21–28]. A corollary of this principle is that early correction or prevention of any physiological disturbance is a very important therapeutic goal in critical care medicine. ARF should be no exception.

Adequate therapy, therefore, means a renal replacement therapy that is applied early to prevent hyperkalaemia, hyponatraemia, uraemia, acidosis and pulmonary and peripheral oedema. It also means a therapy that does not generate derangements of its own.

The second principle is that the adequacy of any artificial organ support in the ICU is measured by how closely such support mimicks the flexibility, versatility and efficacy of the organ system it seeks to substitute. This is true for mechanical ventilation, cardiac assist devices and artificial oxygenators. It should be true of any artificial kidney.

The third principle is that the use of any artificial
organ support should not delay the recovery from injury of the native organ, or, as in some cases, of the transplanted organ.

The fourth principle is that, particularly in the setting of multi-system organ failure, any organ replacement therapy should have absent or minimal proinflammatory effects.

The critically ill patient

The typical features of MODS can be summarized as follows: the syndrome is one of the major cases of death in intensive care; patients are on different life support systems, and monitoring, together with the maintenance of homeostatic parameters, becomes extremely complex.

Vasoactive drugs are utilized to counterbalance haemodynamic instability or shock conditions; mechanical ventilation or extracorporeal CO₂ removal are often required to sustain tissue oxygenation. Cardiac support frequently is achieved not only with inotropic drugs but also with mechanical devices. ARF is a common finding in this complex clinical picture. Finally, humoral and cellular mediators of inflammation are generally present in tissues and systemic circulation at very high concentrations.

Under such circumstances, an effective renal replacement therapy must provide adequate blood purification from uremic toxins, correction of fluid, electrolyte and acid–base disturbances, maintenance of the highest level of homeostasis, protection of the kidneys from further injury and, possibly, accelerated recovery of renal function after ARF.

Renal replacement strategies

The clinical pattern and the history of patients affected by MODS have changed over the years. For a long time these patients were unable to survive more than a few hours, and renal replacement was not even instituted or only instituted at the last minute. Subsequently, with the advent of different life support systems, critically ill patients could be maintained at a sufficient level of stability to permit the institution of renal replacement therapy. The outcome in these cases did not change significantly, and in some cases it apparently worsened. Of course, this was not the case, and the reason for this observation was that more seriously ill patients were treated with resuscitation procedures which were not available in the past. Therefore, a population of patients with higher severity indices is now treated with renal replacement therapies. In these cases, both haemo- and peritoneal dialysis display some limitations and appear inadequate to treat such complicated patients.

In 1977, Kramer described a new treatment he named continuous arterio-venous haemofiltration (CAVH) [5]. This treatment was based on a highly permeable haemofilter connected to an artery and a vein by modified haemodialysis blood lines. The arterio-venous pressure gradient moved the blood through the extracorporeal circuit and no pumps were utilized. Slow continuous production of ultrafiltrate was achieved, and substitution fluid was administered in post-dilutional mode to maintain the patient’s fluid balance.

The technique subsequently was modified and newer options were made available. The use of a blood pump with a venous blood access became popular, and the arterio-venous treatments were partially abandoned. At the same time, the haemofilters were equipped with a second port in the ultrafiltrate compartment, thus permitting the countercurrent circulation of dialysate. In such cases, the treatment was named continuous haemodialysis or continuous haemodiafiltration. All these modifications are available today as routine treatments, and special machines have also been designed to facilitate the clinical application of these techniques (Figure 1).

Recently we have utilized several of these new equipments both in haemofiltration and in haemodiafiltration modes, using single-pass or even recirculation techniques. Sterile fluid bags are employed both as a replacement solution and as a dialysate to be circulated countercurrent to blood flow in high-flux hollow fibre dialysers. The machines are equipped with a weighing system and pumps for the dialysate inlet and outlet flow [29–32]. Urea and creatinine, clearances as high as 60 l/24 h can be achieved with these systems. Larger molecules are also cleared at high speed thanks to the high convective transport, and inulin clearances of up to 36 l/24 h have been obtained. Several companies have now undertaken to build newly conceived machines, based on the principle that specifically designed equipment should be used in intensive care patients as an alternative to classical, more sophisticated dialysis machines. The approach is a user friendly interface, beyond which the sophisticated complexity of the machine is maintained with advanced functions. Self-priming procedures and self-loading of the circuit are some of the new features that contribute to the simple use of the machine even by nurses who have not specialized in haemodialysis.

Efficiency of treatment

When continuous haemofiltration is utilized, solute clearance is equal to the amount of ultrafiltrate obtained over 24 h. Assuming in CAVH a maximal clearance of 16 l in a given patient with 100 mg/dl of blood urea nitrogen (BUN), 16 g of urea nitrogen can be removed daily. When severely catabolic patients are involved, higher amounts of ultrafiltrate are needed to control azotaemia and, (CVVH) frequently is used. In such conditions, clearances of up to 30–40 l/24 h are required, and the use of a blood pump in the circuit permits the required level of efficiency to be obtained. Urea is also effectively removed when a countercurrent flow of dialysate is utilized in the circuit and diffusion
is added to convection, thus obtaining a treatment defined as continuous arterio-venous haemodialysis (CAVHD) or continuous arterio-venous haemodiafiltration (CAVHDF). The first utilizes a low-flux membrane while the latter uses a synthetic high-flux membrane. As mentioned above, to avoid problems related to fluid control and to maintain the efficient removal of small and large molecules, we now utilize a system derived from use in the chronic patient in which filtration and backfiltration take place in a highly permeable dialyser during several hours of recirculation of sterile bicarbonate dialysate (Figure 2). The system is called continuous high-flux dialysis, and allows the optimal use of dialysate fluid since the 10 l batch is discarded only when urea nitrogen has been equilibrated with the patient’s blood levels. Clearances of up to 60–70 l per day can be obtained for urea, while larger molecules can be cleared at a rate of 36–40 l per day. The weighing system of the machine allows for an accurate and precise fluid control in the patient. Despite a lower clearance, continuous therapies are more efficient at removing urea nitrogen compared with intermittent daily haemodialysis (Figure 3). The explanation for this is the stable concentration profile of urea in blood during continuous therapies. On the contrary, during intermittent haemodialysis, the treatment is very efficient in the first hour but the amount of solute removal decreases significantly later on. In fact, despite a higher clearance being maintained, the solute concentration in blood is reduced and the relevant amount of solute removal decreases. Additionally, a remarkable rebound in concentration after dialysis can be observed.

**Clinical aspects**

The complexity of the patient with ARF associated with multiple organ failure suggests that continuous therapies probably should be utilized as a first choice treatment in intensive care settings.

Clinical conditions other than ARF, such as congestive heart failure, respiratory distress syndrome, cerebral oedema, etc., could also probably benefit from this
Fig. 2. Schematic representation of the continuous high-flux dialysis system (Braun Carex, Mirandola, Italy). Once the patient has reached the dry body weight, net filtration is minimal due to the mechanism of filtration and backfiltration occurring inside the hollow fibre dialyser. The two pumps placed on the dialysate compartment, and the gravimetric control, provide for an accurate fluid balance. The system can be used in single-pass or in recirculation mode.

form of treatment when oliguria is present or early signs of renal insufficiency are associated.

The patient with severe haemodynamic instability cannot be controlled with intermittent treatments such as haemodialysis or haemodiafiltration carried out for 3–4 h per day. On the other hand, peritoneal dialysis can be inadequate to obtain the ultrafiltration volumes and solute clearances necessary to control overhydration and severe catabolism. The slow continuous fluid removal achieved with continuous therapies such as CAVH/CVVH or CAVHD/CVVHD is generally well tolerated, and an optimal hydration status generally can be reached in a relatively short period of time with adequate constancy of measured haemodynamic parameters. Direct measurements of haematocrit and blood volume during treatment, carried out with an optical red light absorption device (Crit-Line, Riverdale, UT), demonstrated that even in presence of small volumes of ultrafiltration, a significant reduction in circulating blood volume can be observed in intermittent treatments. This phenomenon is not observed in continuous treatments (Figure 4). This aspect may be of tremendous importance in the phase of recovery from ARF. The recovering kidney is extremely sensitive to variations in perfusion pressure and blood flow. Accordingly, intermittent treatments may be unphysiological and may contribute to possible further damage to the renal parenchyma. On the contrary, continuous renal replacement therapies may be well tolerated and may contribute to a constant and progressive recovery of the kidney without major haemodynamic alterations.

These features present particular benefits for patients with severe cardiac contractility failure. Several mechanisms have been considered important in the amelioration of the haemodynamic conditions of patients
Continuous vs intermittent renal replacement therapy in ARF

**Fig. 3.** Urea kinetics in continuous haemofiltration and daily haemodialysis. Despite a higher clearance and higher daily Kt/V, intermittent haemodialysis removes less urea nitrogen per week. The explanation lies in the stable concentration profile of urea nitrogen during continuous therapy, compared with the yawning profile in intermittent treatments. Furthermore, patients on intermittent haemodialysis spend a remarkable number of hours per day with a higher degree of uraemic intoxication due to higher level of uraemic toxins.

**Fig. 4.** Blood volume and arterial pressure during CVVH and intermittent haemodialysis in the same patient. Haemodynamic instability is frequently observed during intermittent haemodialysis. The process of ultrafiltration obtained within a few hours leads to a reduction in the circulating blood volume and hypotensive episodes. This is not the case in continuous therapies where a slow progressive ultrafiltration is accompanied by a continuous refilling of the intravascular fluid volume.

With congestive heart failure treated with continuous haemofiltration; the improvement of the ventricular filling pressures, the reduction of the pre-load, the maintenance of the blood volume and the modulation of the renin–angiotensin axis, the reduction of afterload and the possible clearance of myocardial depressant substances. Another factor considered important has been the possibility of a dissociation of sodium and water transport during haemofiltration techniques. This, together with the isotonic characteristics of the ultrafiltrate, may lead to a continuous vascular refilling and an improved haemodynamic condition.

Continuous therapies can also effectively correct various forms of acidosis. In fact, while intermittent haemodialysis produces a dramatic alkalinization during treatment and frequent observation of a subsequent rebound of acidosis (the same effect is seen for urea removal), continuous therapies are slowly but continuously acting and reach a steady-state concentration both for uraemic solutes and organic acids in the blood (Figure 5).

**Fig. 5.** Bicarbonate kinetics in continuous haemofiltration and daily haemodialysis. Intermittent treatments provide a sudden correction of acidosis with a transient period of alkalaeemia. After dialysis has ceased, the patients experience a rapid rebound of bicarbonate, returning to a condition of definite acidosis. This has been shown to affect protein metabolism, albumin levels and enzyme function. A stable correction of acidosis is reached in continuous haemofiltration due to a constant infusion of buffer via the replacement solution.

More recent studies have confirmed that patients with ARF frequently show baseline values of brain density near to normal or slightly decreased. Intermittent haemodialysis further decreases brain density values, leading to the condition of transient post-dialytic oedema. These alterations induced by intermittent treatments are not observed with continuous therapies that can therefore be utilized to maximal advantage in these patients (Figure 6).

Several mechanisms have been proposed to explain the improvement of adult respiratory distress syndrome (ARDS) patients treated with continuous haemofiltration. The continuous fluid withdrawal from the interstitium due to a progressive vascular refilling represents a major advantage. However, the modulation of the vascular inflammation thanks to the clearance or adsorption of specific proinflammatory substance onto the membrane recently has been hypothesized. This mechanism has also be invoked as an interesting possibility for patients with systemic immunoresponsive syndrome (SIRS) or septic shock.
The concept of renal support

The current era of critical care practice has witnessed the evolution of challenging new trends. Today, serious manifestations may arise in transplanted patients due to surgical or medical complications, immunosuppressive therapy and renal failure. A clinically important infection or acute sepsis may occur in these patients, alone or as a major complication of ARF.

Roughly 50% of such infections are caused by Gram-negative bacteria and, of these cases, 10–20%, may result in a documented period of bacteraemia, 'renal protection' or 'renal support' would be exploited before the extracorporeal removal of cytokines is unanimously accepted as clinically relevant. Possible advancements in the extracorporeal therapies dedicated to critically ill patients should take into account the need for (i) higher convective rates, (ii) the type of reinfusate and (iii) removal of protein-bound cytokines.

Conclusions

While isolated ARF can be treated advantageously with standard intermittent treatments, continuous renal replacement therapies appear to be the appropriate treatment in patients with ARF complicated by different clinical problems. In patients with ARF and other organ system failure, continuous treatments appear to be the only possibility for obtaining positive results from an extracorporeal therapy. Finally, if adequate modulation of chemical mediators of the septic syndrome could be achieved with these treatments, the whole concept of 'renal protection' or 'renal support' would be exploited and a real possibility of preventing or shortening ARF would probably be in our hands. There is no question, however, that continuous therapies seem to meet the criteria for adequacy we proposed in the introduction. Such treatments should be provided to all patients in which standard therapies represent less benefits or even a potential hazard.

References

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