Continuous Renal Replacement Therapy: Challenges and Evidences

7

Giorgio Berlot and Antoinette Agbedjro

7.1 Introduction

The aetiology of the Acute Kidney Injury (AKI) in critically ill patients admitted to the Intensive Care Unit (ICU), and especially in those with sepsis and sepsis-related Multiple Organ Dysfunction Syndrome (MODS), is multifactorial, being variably associated with hypovolemia, the use of nephrotoxic substances including some classes of antibiotics and radiologic contrast media and the production and release of a number of mediators occurring during the host-infecting agent interaction [1–3]. According to the balance between pro- and anti-inflammatory mediators, the final effect can range from a relatively localized process (i.e. pneumonia) to a devastating systemic process [4, 5], related to the individual genetic predisposition [5]. The final clinical scenario includes the exhaustion of all reactive capabilities ultimately leading to immunoparalysis and death [2]. The kidney is commonly involved in sepsis, as its function can be compromised either directly by the very same mediators acting in other organs and indirectly due to their systemic hemodynamic effect [6].

Independently from the cause(s), the occurrence of AKI is associated with a worse prognosis as compared to AKI-free patients [1]. In the early 1980s the Renal Replacement Treatments (RRT) of critically ill patients with AKI was revolutionised by the introduction of techniques based on the convective transport of water and solutes, as opposed to the diffusive process which is suited for intermittent haemodialysis (IHD) [7]. The fluid removed by convection (a) is qualitatively iso-osmotic with the blood and contains equal amount of electrolytes; and

G. Berlot (✉) · A. Agbedjro
Department of Anaesthesia, Intensive Care and Pain Therapy, University of Trieste, Strada di Fiume 447, 34149, Trieste, Italy
e-mail: berlot@inwind.it

A. Gullo (ed.), *Anaesthesia, Pharmacology, Intensive Care and Emergency A.P.I.C.E.*,
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(b) is quantitatively replaced by water and solutes deriving from the extracellular space thus reducing, albeit not eliminating at all, the cardiovascular disturbances associated with IHD. As the former treatments are supposed to run on a 24-h basis they are collectively known as Continuous Renal Replacement Therapy (CRRT) to differentiate from Intermittent Renal Treatments (IRT), which include the IHD and the Slow Low Efficiency Dialysis (SLED) and whose durations are much shorter. Since then, a number of modifications to the initial technique, which was based on the patient's own arterial pressure, have been developed, including the interposition of a roller pump and a negative pressure in the extracorporeal circuit, making thus the procedure independent from the patient's hemodynamic conditions (Continuous Veno-Venous Hemofiltration-CVVH) [8]. Further developments included mainly (a) the exchange of elevated volumes of fluids (High Volume Continuous Veno-Venous Hemofiltration-CHVVVH); and (b) the association of diffusion to the convection, leading to the Continuous Veno-Venous Hemodiafiltration (CVVHD) (Table 7.1) [8]. The large popularity of these techniques is mainly due to the relatively good hemodynamic tolerance in critically ill patients, which has been ascribed to the diffusive transport. In the same period, as it became clear that the molecular weight (MW) of the sepsis mediators was compatible with their passage through the membrane used in CRRT, indeed, several investigators hypothesized that these techniques could treat at the same time the cause and the effects of the sepsis-associated AKI by removing these substances and by eliminating the uremic toxins [9, 10]. Since then on, the CRRT has been used either with renal as well as non-renal indications, being these latter addressed more at the removal of septic mediators than to the treatment of AKI-associated derangements. However, in most studies published on its use in critically ill patients, it is difficult to separate one effect from the other.

7.2 Experimental Evidence

As far as the non-renal indications are concerned, the CRRT could be valuable in the neutralization of sepsis mediators provided that:

(a) Their MW lies within the cut-off value of the membrane used, thus causing their removal through the filter down in the collecting bag where they can be measured in the ultrafiltrate (UF), whose production for unit of time (Qf) becomes the key factor [8, 9];
(b) as an alternative, the mediators can be removed from the blood circulating inside the chosen CRRT by their adsorption on the surface of the filter [11]; of course, this process is time-limited and ceases once the sticking capabilities of the membrane are saturated;
(c) the filtered molecule(s) must constitute the active form of a given mediator: as an example, although the MW of monomeric TNF is 17,000 kD, the biologically active form is trimeric, thus exceeding the cut-off of most of the commercially available filters used in CRRT [12];

Table 7.1 Principal variants of RRTs. Legend: Qb: blood flow, Qf: ultrafiltrate flow

Denomination	Abbreviation	Class	Principle of functioning	Driving forces		Replacement fluid[a]
				Qb	Qf	
Continuous arterio-venous hemofiltration	CAVH	CRRT	Convection	Patients's own arterial pressure	Patients's own arterial pressure	Yes
Slow continuous ultrafiltration	SCUF	CRRT	Convection[a]	Patients's own arterial pressure/roller pump	Patients's own arterial pressure/aspiration	No
Continuous veno-venous hemofiltration	CVVH	CRRT	Convection	Roller pump	Aspiration	Yes
Continuous veno-venous hemodiafiltration	CVVHD	CRRT	Convection + diffusion	Roller pump	Aspiration	Yes
Continuous high-volume venovenous hemofiltration	CHVVVH	CRRT	Convection	Roller pump	Aspiration	Yes
Intemittent hemodyalisis	IHD	IRT	Diffusion	Roller pump	Aspiration	Yes
Sustained low efficiency dialysis	SLED	IRT	Diffusion	Roller pump	Aspiration	Yes

[a] The amount and composition of the replacement fluids vary according to the clinical conditions

(d) they are present in the bloodstream in relevant concentrations when the procedure is running, since both too early or too late treatments can be ineffective: in the former case because the burst of the mediators could not have occurred (yet), whereas in the second because an irreversible end-organ damage could have already occurred [11, 13, 14], making any treatment futile.

Since the reduction in the blood concentration of sepsis mediators represents the ultimate goal of non-renal indications of CRRT, their measurement before and after the initiation of the treatment became the issue addressed by many studies. Indeed, several investigations, aimed to demonstrate an effect of CRRT techniques on the blood values of different inflammatory and counter inflammatory mediators have been carried out, but the overall results were not uniform. The reduction of the blood concentration of septic mediators by means of the techniques commonly used in CRRT has been demonstrated by several investigators, who were also able to demonstrate that healthy animals and/or isolated tissues challenged with the fluid removed from septic organisms undergo similar cardiac, respiratory and metabolic derangements [15–17]. Moreover, it appears that both Qf and time of initiation play a major role, as either the decrease in mediators or the peripheral effect are more marked with higher volumes of UF and when the treatments started in the early phase of sepsis [18–21]. However, other studies failed to confirm these results, as mediators remained stable or even increased [10, 22] during the treatment. To add to the confusion, a substantial hemodynamic improvement was observed in the absence of any change in the blood concentration of the measured mediators [23].

Different factors can account for these somewhat puzzling results. First, inflammatory mediators can be produced during the process itself, due to the interaction between the blood and the membrane [22]; as a matter of fact, this phenomenon accounts for most of the physiologic derangements commonly observed during IHD using less recent membranes [24]. The same consideration applies to the production of inflammatory mediators observed during cardiopulmonary bypass, which, by the way, can be efficiently removed by means of CRRT [25]. Second, the mechanisms responsible for this reduction can differ according to the membrane used: as a consequence, one cannot expect a marked or prolonged decrease in circulating mediators once the adsorptive capabilities of the membrane have been exhausted [10]; the latter being a time-dependent process, it is likely the concentration of septic mediators will show a bimodal course, with an initial decay followed by a subsequent increase [13]. Third, although a substantial reduction in the circulating levels of several mediators, including the Platelet Activating Factor, (PAF), the Tumour Necrosis Factor-α (TNF-α) and various Interleukins, has been demonstrated [15] in different models of sepsis, the impact on the natural history of sepsis may be hard to evaluate since the blood concentrations of septic mediators (a) can fluctuate during the septic challenge (as well as during the clinical course); (b) as stated by Cavaillon [14], their blood values can be considered the tip of an iceberg, poorly reflecting what is going on at the tissue level; and, finally, (c) the biologically active forms of some mediators can be different from that assayed in the UF [12]. Finally, different membranes can exert

different results in terms of neutralization of sepsis mediators: as an example, Rogiers et al. demonstrated that TNF was more efficiently removed by polyacrilonytrile (PAN)-made membrane as compared with polysulphone [26].

7.3 Clinical Evidence

When looking at clinical investigations using CRRT in the treatment of critically ill patients with AKI, some relevant issues arise including:

(a) Is the CRRT superior to IRT in terms of outcome improvement?
(b) Should this be the case, its effect can be entirely ascribed to the removal of mediators or other factors, including a better hemodynamic tolerance compared with IRT, play a role?
(c) Does a dose–response effect exist? and, finally,
(d) Does the timing of initiation of treatment influence the outcome?

As far as the first question is concerned the results of clinical studies carried conflicting results, with older investigations favouring CRRT over IHD, whereas more recent meta-analyses failed to demonstrate any advantage. In a non-recent review Kellum et al. [27] reviewed 13 studies involving 1,400 patients and did not find any significant difference in the overall mortality between CRRT and IRT-treated patients. However, when the six studies in which only patients with comparable severity of illness at time of initiation of the treatment were considered, the outcome was significantly better in those treated with CRRT. Different factors likely accounted for these results, including the heterogeneity of patients included, the causes of AKI, the amount of volume exchanged, the membrane used, the timing of the procedures and the underlying conditions. The author concluded that there is no sufficient evidence to demonstrate definitely a superiority of CRTT over IHD and advocated a large, controlled randomized trial (RCT) encompassing the rules of the Evidence Based Medicine (EBM). In a meta-analysis contemporaneous to the Kellum's one, also Tonelli et al. [28] were unable to demonstrate any superiority of CRRT over IHD in terms of both survival and recovery of renal function in critically ill patients. Other more recent studies that have been completed after the publication of these meta-analyses failed to demonstrate any superiority of CRRT over IRT [29–31]. Yet it should be remarked that some factors other than CRRT could have influenced the results and thus a definitive evaluation on their real efficacy is probably still premature. This issue has been recently discussed by Bagshaw et al. [32] in a meta-analysis which failed to find any superiority of CRTT over IRT. The authors enlighten several factors able to impede to draw definite conclusions. First, the poor quality of many studies, which prompt the authors to evaluate only 9 RCTs out of the 1,550 investigations initially screened. Second, it is likely that more unstable patients could have been treated by means of CRRT which offers clear advantages in terms of cardiovascular stability, thus causing a selection bias [33]. Third, even if an improvement in survival is obvious of exceeding importance when studying a novel approach for sepsis, still it

could be a too hard endpoint if one considers the extreme heterogeneity of sepsis population, whose prognosis can be influenced not only by the acute organ dysfunction(s) but also, if not predominantly, by the underlying conditions, the age, genetic factors predisposing to sepsis and AKI [34, 35] and by therapeutic options other than the type of renal replacement treatment used [36]. Third, the impact of AKI on the outcome is different according to its time of occurrence, being worse when it appears in an advanced stage of a critical condition [37], and in the advanced phases of MODS any kind of treatment unlikely influences the outcome.

The possible effects of the removal of septic mediators are the subject of intense debate. As stated above, most, if not all, the mediators implicated in the septic process can be eliminated through the filter via the convective transport or can be absorbed on the membrane, even if the efficacy of this latter process is subjected to decay. Unfortunately, sepsis appears to be a dynamic process, during which mediators with different properties are produced at the same time. This polymorphism is likely responsible for the repeated negative results of clinical trials aimed to study the effect of the neutralization of a determined mediator [2]. In different time frames, one class of substances can prevail on the other, leading to a systemic inflammatory response syndrome (SIRS), associated or not with an infection, or, conversely, to a status characterized by the progressive blunting, till the exhaustion of this response [2–5, 38]. Although oversimplified, this is a reasonable model to understand the bizarre clinical course of many septic patients, in whom an anergic status often follows, and sometimes concludes, a critical illness initiated with a typical inflammatory process (e.g. pneumonia or peritonitis). Several investigations were addressed to assess the efficacy of CRRT in terms of mediators' removal. Not differently from what has been already described for the outcome, results have been not unequivocal [9, 15]. Again, it should be recalled that, the mediators being involved are subjected to ample individual and time-related variations, the difference observed in many studies could be ascribed to different time frames of initiation of the CRRT itself. In other words, it is unlikely that elevated amounts of TNF, which is a powerful pro-inflammatory cytokine, could be extracted during the advanced phase, in which anti-inflammatory mediators predominate.

The intensity of treatment represents another hot point. Actually, the dose of RRT represents the most important determinant for the control of uraemia in patients with chronic renal failure. Some authors demonstrated that also in sepsis-associated AKI the intensity of the treatment influences the outcome independently of the technique used. In a group of critically ill patients with AKI of different origins Ronco et al. [39] used CRRT performed with different amounts of volume exchanged (20, 35 and 45 ml/kg/h, respectively) and demonstrated a significant reduction in mortality in the group of septic patients more aggressively treated. A dose-dependent improvement of survival has been demonstrated also in another study using high-volume hemofiltration [40]. Almost at the same time, Schiffl et al. [41] demonstrated that daily IHD as compared with IHD performed on an alternate day basis was associated with an improved outcome in a group of critically ill patients with AKI.

Then, from these studies it appears that the outcome is influenced more by the intensity of the treatment than by the treatment in and by itself. Other investigators [42] demonstrated that in critically ill patients with multifactorial AKI receiving CVVH with different Qf (1.0 vs. 1.5 l/h) the more aggressive regimen was associated with a better control of uraemia even if the outcome was not different in the two groups; however, it is clear that in both groups the Qf was much lower than in Ronco's study. More recently, a large observational study involving 553 patients with AKI treated either with CRRT or IHD at different intensities failed to demonstrate any beneficial effects on the outcome by higher dose RRT, although there was a reduction in ICU stay and duration of mechanical ventilation in the more intensely treated patients [43]. In a recent meta analysis, Pannu et al. [44] who scrutinized 38 out of 173 published studies comparing the effect either of the type of treatment and its intensity, concluded that CRTT and IHD are equally effective in the treatment of AKI, but should be a CRTT used, a dose of at least 35 ml/kg/h should be provided.

Also, the issue of the timing of initiation is somehow controversial Similar to other therapeutic approaches recommended in sepsis, including the administration of antibiotics and the achievement of determined hemodynamic goals [45], the timing of initiation of CRRT appears to be a key factor in influencing the outcome of patients with sepsis-associated AKI. Actually, the term "timing" can be misleading, as, according to the study considered, it applies either at a time interval from the diagnosis and to the severity of organ dysfunction at or before the start of CRRT. Piccinni et al. [46] used the Risk Injury Failure Loss and End-stage kidney disease (RIFLE) criteria [47] to subdivide patients with septic shock treated with CVVH and demonstrated a significantly better survival in those treated on the "Acute Renal Injury" phase as compared with those in the "Acute Renal Failure" phase. Similar results have been demonstrated also by other investigators who used pulsed, short-term (4 h) high volume (35 l) hemofiltration followed by CVVH at a standard intensity; responders (patients whose cardiovascular and acid base status improved during the 4 h period) were treated earlier than non-responders and the survival rate was significantly higher in the former (9/11) than in the latter group (0/9) [48]. However, these findings have not been confirmed in another study [49] addressed to elucidate the role of early high volume CVVH compared with early-low volume CVVH and late-low volume CVVH in which the authors failed to demonstrate any difference in "hard" endpoints including 28-days survival and recovery of the renal function. Despite these controversial results, a recent meta-analysis demonstrated that an earlier initiation of RTT could exert a positive effect on the outcome [50]; however, as stated by the authors, once again this conclusion is based on studies of variable quality enrolling patients with AKI from heterogeneous causes.

7.4 Final Considerations

On the basis of the available results, some conclusions can be reached on the role of CRRT techniques for the treatment of sepsis-associated AKI. First, despite roughly 20 % of patients treated with CRRT experiencing arterial hypotension during the procedure [51], yet the principle of functioning confers an advantage in terms of hemodynamic stability, making them suitable also in severely compromised subjects, making CRRT the preferred renal treatment in critically ill patients with AKI [52]. Second, although the results are not uniform, there are suggestions indicating that either an early start of treatment, possibly associated with elevated volumes of exchange can be associated with a better outcome (or of a surrogate of outcome, such as the decreased need for catecholamines to support the hemodynamic functions). This can be summarized and transferred into the clinical practice with "the sooner and the more, the better" concept. Finally, it should be recalled that all meta-analyses take into consideration only a small fraction of the published studies, thus weakening the related conclusions.

7.5 Conclusions

Despite extended experimental and clinical investigations, the role of CRRT in the treatment of sepsis is still under scrutiny. As far as AKI is concerned, despite a better hemodynamic tolerance associated with the convective removal of fluid and solutes, mortality remains high in the treated patients, and the place occupied by IHD is going to be re-evaluated. The feasibility of removal of sepsis mediators is based on sound experimental bases, yet there is no evidence that this feature exerts any major effect on the outcome. It is likely that a more in-depth knowledge of the chemico-physical characteristics of the membranes could be valuable in enhancing the elimination of these substances via their removal with the ultrafiltrate or their absorption on the filter surface by implementing the Qb or the Qf, respectively.

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