

Commentary

Recent evolution of renal replacement therapy in the critically ill patient

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Abstract

The epidemiology of severe acute renal failure has dramatically changed in the past decade. Its leading cause is sepsis and the syndrome develops mostly in the intensive care unit as part of multiple organ dysfunction syndrome. After the significant improvements obtained from the mid 1970s to the mid 1990s, the past decade has seen a dramatic evolution in technology leading to new machines and new techniques for renal and multiple organ support. Extracorporeal therapies are now performed using adequate treatment doses, which have resulted in improved survival in the general population. At the same time, patients with sepsis seem to benefit from the use of increased doses, as in the case of high-volume hemofiltration or of increased membrane permeability and sorbents as in the case of continuous plasmafiltration adsorption. The humoral theory of sepsis and the peak concentration hypothesis have spurred a significant interest in the use of such extracorporeal therapies for renal support and possibly for the therapy of sepsis. Ongoing research and prospective studies will further elucidate the role of such therapies in this setting.

In the past decade, the change in the epidemiology of acute renal failure has made critical care nephrology an emerging sub-speciality of intensive care medicine. Dedicated literature and a series of physicians and nurses have made an effort to bridge the knowledge and experience from nephrology and critical care medicine in response to an increased incidence of acute kidney injury in intensive care unit (ICU) patients [1].

The origin of this process can definitely be found in the mid 1970s, when continuous arteriovenous hemofiltration (CAVH) appeared on the scene. CAVH has been a tool that has permitted the treatment of patients with acute kidney injury in which peritoneal dialysis or hemodialysis were clinically or technically precluded [2]. This opened the doors of ICUs to a dedicated dialysis technology that experienced a flourishing evolution in subsequent years. Within a few years, continuous veno-venous hemofiltration (CVVH) replaced CAVH because of its improved performance and safety. The advance was

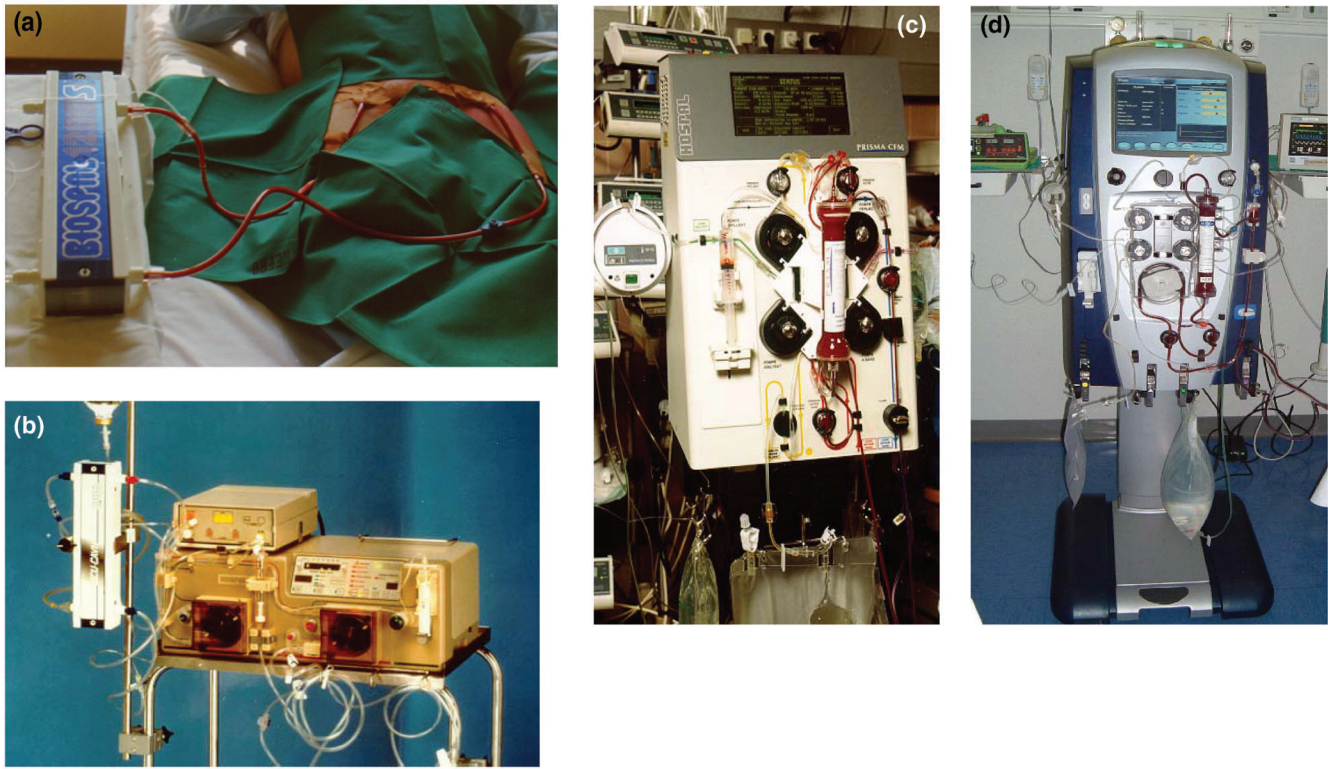
made possible by the use of blood pumps, calibrated ultrafiltration control systems and double lumen venous catheters. In the late 1980s, specific machines for continuous renal replacement therapies (CRRTs) were designed and a new era of renal replacement in the critically ill patient began [3]. The therapy started to be standardized and clear indications began to be defined.

The evolution of technology did not stop, however, and the recent demand for higher efficiency and exchange volumes has spurred new interest in a further generation of machines with better performance, integrated information technology and easy to use operator interfaces. An example of such technological evolution is represented by the passage from CAVH systems to the BSM 22 and Prisma machines to the most recently developed Prismaflex machine (Gambro Dasco, Mirandola, Italy; Fig. 1). A schematic drawing of different techniques available today for the therapy of the critically ill patient with renal and other organ dysfunction is given in Fig. 2. The last generation of machines available on the market today and representing the evolution of the past decade of research and development is shown in Fig. 3.

Two interesting aspects of the evolution of renal replacement therapy (RRT) in the ICU over the past decade are represented by the definition of an 'adequate' dose of dialysis in acute kidney injury and the potential of high dose therapies for the treatment of sepsis [4]. The first of these has identified 35 ml/kg/h as a dose of dialysis capable of improving survival, whereas higher doses do not seem to give additional benefits in the general population [4]. The second concept introduces the rationale for high-volume hemofiltration (HVHF) in patients with acute renal failure and sepsis [5]. In this setting, the most important advance of the past decade has been the use of either increased exchange volumes in hemofiltration, or the combined use of adsorbent techniques in systems where the

CAVH = continuous arteriovenous hemofiltration; CPFA = plasmafiltration coupled with adsorption; CRRT = continuous renal replacement therapy; CVVH = continuous veno-venous hemofiltration; HVHF = high-volume hemofiltration; ICU = intensive care unit; RRT = renal replacement therapy.

Figure 1



The technological evolution from continuous arteriovenous hemofiltration (CAVH) to the last generation of continuous renal replacement therapy machines. (a) CAVH machine; (b) the BSM32 machine; (c) the PRISMA machine; (d) the Prismaflex machine.

cut-off of the membrane was increased to the level commonly seen in membranes for plasmfiltration [6]. HVHF is a variant of CVVH that requires higher surface area hemofilters and employs ultrafiltration volumes of 35 to 80 ml/kg/h.

This technique is associated with practical problems, including the requirement of adequate hardware, significant amounts of re-infusion fluid and monitoring systems accurate enough for the high volumes exchanged and the relatively high blood flows used.

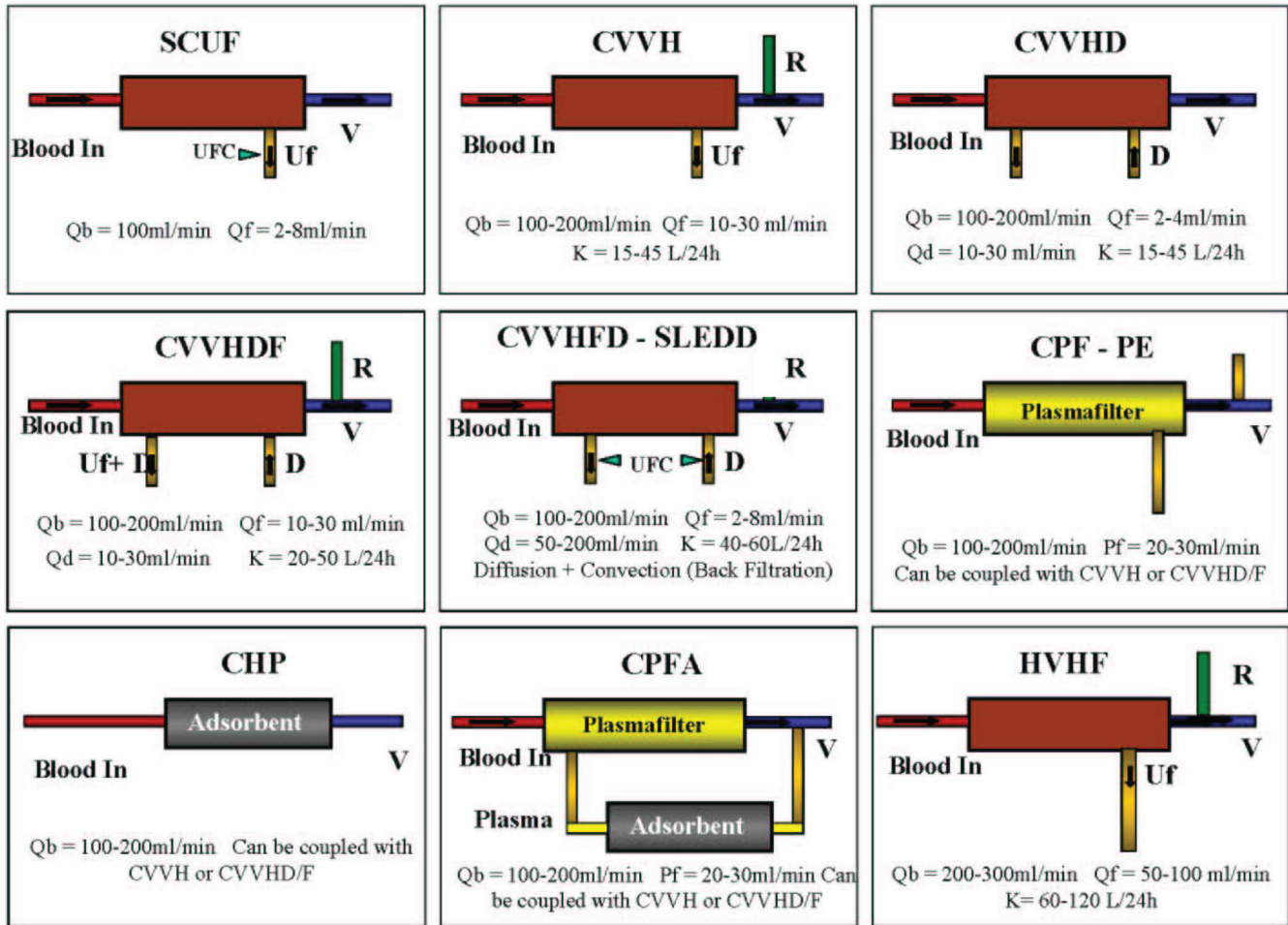
In the past five years, many studies have been conducted to evaluate and demonstrate benefits of increasing the volume of ultrafiltration and replacement fluid during CRRT [7,8], particularly in complex and very severe syndromes such as severe sepsis and septic shock, associated or not with acute renal failure.

In general, the high-volume approach provides higher clearances for middle/high molecular weight solutes than a simple diffusive transport (CVVHD) or a convection-based transport at lower volumes (CVVH). These solutes seem to be primarily involved in the systemic inflammatory response syndrome, which characterizes the sepsis syndrome, and their efficient removal may thus be beneficial [9].

Alternative approaches have been based on more efficient removal of inflammatory mediators by high cut-off hemofilters, which are characterized by an increased effective pore size. Most commercially available hemofilters do not permit a substantial elimination of cytokines because of the low cut-off point of their membranes. The use of high cut-off hemofilters is a new and effective approach to cytokine removal, but it has potentially harmful side effects, such as the loss of essential proteins like albumin [10]. To prevent this side effect, plasmfiltration coupled with adsorption (CPFA) has been designed and experimentally used with beneficial effects in septic patients [11]. CPFA is a combined therapy in which plasma is separated from blood and circulated through a sorbent bed. After this purification phase, blood is reconstituted and dialyzed with standard techniques. The final effect is an increased removal of protein bound solutes and large molecular weight toxins.

These therapies are not selective in removing specific mediators (pro- and anti-inflammatory mediators are equally removed) and, consequently, their role is not completely understood and their usefulness remains the subject of much debate. Early data are encouraging but additional data are required before they could become part of the standard management of sepsis. More statistically powered studies are

Figure 2



Techniques available today for renal replacement in the intensive care unit. CAVH, continuous arteriovenous hemofiltration; CHP, continuous hemoperfusion; CPFA, plasmfiltration coupled with adsorption; CPF-PE, continuous plasmfiltration – plasma exchange; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration; CVVHFD, continuous high flux dialysis; D, dialysate; HVHF, high-volume hemofiltration; K, clearance; Pf, plasmfiltrate flow; Qb, blood flow; Qd, dialysate flow; Qf, ultrafiltration rate; R, replacement; SCUF, slow continuous ultrafiltration; SLEDD, sustained low efficiency daily dialysis; UFC, ultrafiltration control system.

needed to confirm the preliminary results on the positive effect of HVHF and CPFA on outcome. Except for the beneficial effect of dialysis dose, no randomised trial has evaluated the effect of HVHF on clinical outcome, or the effect of different modalities of CRRT on length of stay and recovery of renal function in patients with sepsis. This research is needed. Adequate technical support becomes mandatory, therefore, to fulfil all these expectations. The evolution of understanding of the above mentioned concepts has led to the improvement of technology and the generation of new machines and devices compatible with the demand for increased efficiency, accuracy, safety, performance and cost/benefit ratio.

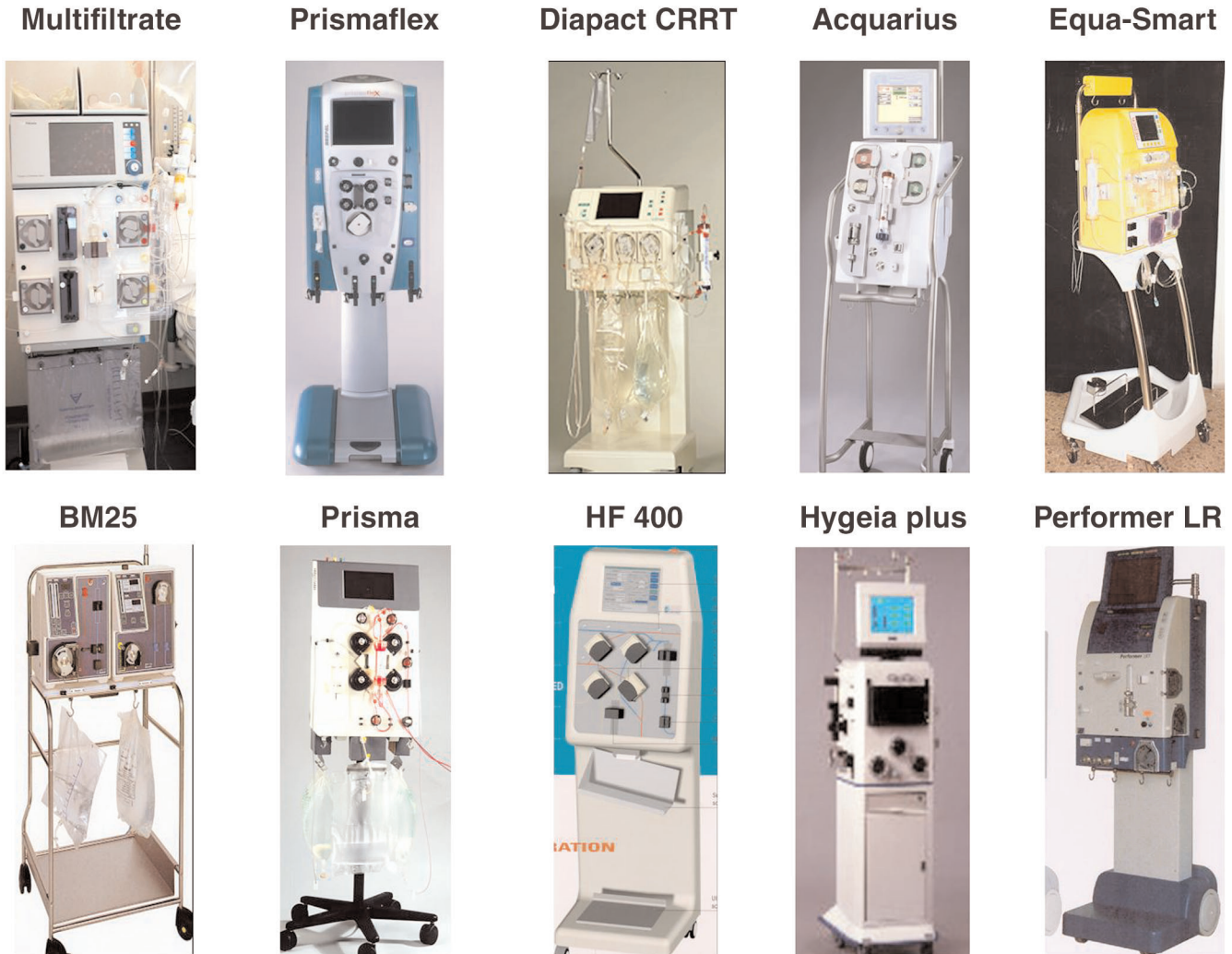
At present, almost all CRRT therapies can be delivered in a safe, adequate and flexible way, thanks to devices specifically designed for critically ill patients to a point that multiple organ

support therapy is envisaged as a possible therapeutic approach in the critical care setting [12].

HVHF or CPFA can be seen as a potent powerful immunomodulatory treatment in sepsis. Since sepsis and systemic inflammatory response syndrome are characterized by a cytokine network that is synergistic, redundant, autocatalytic and self-augmenting, the control of such a non-linear system can not be approached by simple blockade or elimination of some specific mediators. Therefore, non-specific removal of a broad range of inflammatory mediators by HVHF and CPFA may be beneficial, as recently suggested on the basis of the 'peak concentration' hypothesis [9].

The high dose that characterizes HVHF can be delivered either using a constantly high exchange rate or by delivering a 'pulse' (for 6 to 8 h) of very high-volume hemofiltration (85 to

Figure 3



The last generation of machines available on the market for continuous renal replacement therapy.

100 ml/kg/h) followed by standard doses [13]. In both cases, cytokine half-lives and concentrations are affected, the first by the continuous modality and the second by the non-specific decapitation of peaks. Therefore, rather than a detailed analysis of each molecule involved, we envisage as much more interesting and useful a teleological analysis of the impact of HVHF on more integrated events such as monocyte cell responsiveness, including apoptosis, neutrophil priming activity and oxidative burst [14-16]. More studies are needed to define its role in hyperdynamic septic shock, with or without acute renal failure. A last comment should be dedicated to the use of sorbents and especially those cartridges dedicated to the adsorption of endotoxin and related material. A great deal of evolution has occurred in this field but it seems we are only at the beginning of a long and possibly fruitful journey [16].

At the end of this commentary we might speculate that although improvements have been made, a lot remains to be done. For sure, the progress of technology in critical care nephrology has been enormous and more will come in the near future.

Competing interests

The author declares that they have no competing interests.

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