Acta clin Croat 2000; 39:99-116 Review

CONTINUOUS RENAL REPLACEMENT THERAPY

Petar Kes

Department of Nephrology and Dialysis, Sestre milosrdnice University Hospital, Zagreb, Croatia

SUMMARY - Acute renal failure (ARF) is currently more frequently seen as part of a more complex syndrome defined by sepsis and/or multiple organ failure. Evolution in the field of hemodialysis has led to a parallel development of new systems for continuous renal replacement therapy (CRRT) in critically ill patients. The various CRRT modalities differ in the type of vascular access, application of diffusive or convective clearance (or a combination of both), and location where the replacement fluid enters the circuit. CRRTs have certainly facilitated the management of critically ill patients with ARF combined with cardiovascular instability, severe fluid overload, hypercatabolism, cerebral edema, adult respiratory distress syndrome, lactic acidosis, sepsis or other inflammatory syndromes, crush syndrome, congestive heart failure, and cardiopulmonary bypass. Continuous therapies incorporate several advantages including improved hemodynamic stability, optimal fluid balance, gradual urea removal, elimination of septic mediators, and the possibility of unlimited parenteral nutrition. Major difficulties and unsolved problems of CRRT are the ongoing necessity for continuous anticoagulation, considerable loss of amino acids, vitamins, trace elements, potassium, phosphate, and some drugs as well as immobilization of the patient. The advantages of CRRT should theoretically translate into improved outcomes of critically ill ARF patients, but the superiority of continuous modalities in terms of outcomes is still controversial, despite encouraging results in some clinical trials.

Key words: *Kidney failure, acute; Kidney failure, acute - therapy; Renal replacement therapy; Renal replacement therapy - economics*

Introduction

Despite improved medical care and support, and better technological aspects of renal replacement therapy (RRT), the mortality rate for patients with acute renal failure (ARF) has remained high and stable over more than two decades, often exceeding 50%[1-3]. In particular, ARF is more frequently seen as part of a more complex syndrome defined as multiple organ failure (MOF). In this clinical setting, patients are almost inevitably confined to intensive care units (ICU), and sepsis is a frequent underlying mechanism of organ failure[4]. Thus, the main causes of death are the underlying disease and infection, not ARF itself[5]. The mortality of RRT also may affect the outcome. For many years, intermittent hemodialysis (IHD) has been a standard form of dialysis to treat ARF. However, as a majority of patients with ARF are hemodynamically unstable and have severe concomitant diseases (sepsis, shock, MOF, acute respiratory distress syndrome (ARDS)), many develop hypotension during IHD. Because of cardiovascular instability, it is often not possible to accomplish the desired volume removal which, in turn, renders parenteral nutrition and the administration of vasopressors more difficult[6]. The evolution in the field of dialysis has led to a parallel development in the therapeutic approach to patients suffering from the syndrome of ARF. This progress has made possible to perform continuous renal replacement therapy (CRRT) without major problems or complications characteristic of IHD.

The aim of this paper is to descriebe and summarize the most effective and promising options for treating ARF in critically ill patients.

Correspondence to: *Professor Petar Kes, M.D., Ph.D.,* Department of Nephrology and Dialysis, Sestre milosrdnice University Hospital, Vinogradska c. 29, HR-10000 Zagreb, Croatia

Received January 31, accepted May 31. 2000

History

Inability of ARF patients to tolerate the hemodynamic effects of IHD was the very reason that motivated Kramer et al.[7] to initiate a new approach of continuous CRRT. In March 1977, Kramer[7] installed hemofiltration in a patient and by mistake punctured femoral artery instead of the vein. His presence of mind was the starting point of the continuous arteriovenous hemofiltration (CAVH). The driving pressure in the extracorporeal arteriovenous circuit was sufficient for an effective continuous hemofiltration, and ultrafiltrate was eliminated through the filter synchronously with the pulsations in the systemic circulation[8].

The initial technique was simple. The high-flux hemofilter (Amicon Diafilter 20) was perfused (75 to 150 mL/min) via an extracorporeal arteriovenous circuit between the femoral vessels introduced by Seldinger technique. The ultrafiltration rate (UFR) was 200 to 600 mL/h, and continuous anticoagulation was performed by adding a 1,000 to 1,500 IU/h dose of heparin.

In the following years, the technique found wide use in ICU. The special benefits of the method included its technical simplicity and lack of any pumping device, a remarkable stability of the systemic circulation, an effective elimination of fluid, and an easy way for managing overhydration.

In the initial period, some severe and even fatal complications resulted from the arterial access of the extracorporeal circuit, which included unintentional and unnoticed disconnection of the blood line, bleeding and infection of hematoma, arterial thromboembolization in arteriosclerotic vessels, and other events. The limited removal capacity of CAVH and the complications related to the arterial access were the main reasons to look for a venovenous pump-driven technique in order to become independent from the systemic circulation and arterial access. As early as 1982, Bischoff et al.[9] used a continuous venovenous hemofiltration (CVVH) pump-driven technique. With a single roller pump, it was possible to increase the UFR to up to 1,000 mL/h, and the removal of urea nitrogen was effective even in severely catabolic septic patients. When higher flow rates were necessary, the substitution fluid was kept warm by a heating device. Another way to improve the solute clearance was to combine the convective principle of hemofiltration with the benefits of the diffusive transport of dialysis, which is more effective for the removal of small molecules. Geronimus and Schneider[10] using a cuprophane dialyzer, and independently Ronco[11] using a polysulfone filter, developed a modification called continuous arteriovenous hemodialysis (CAVH) or hemodiafiltration (CAVHDF). In these systems, a dialyzer was connected to the patient using a circuit similar to CAVH. In addition, dialysate was circulated through the dialyzer. Adequate urea clearance was achieved by diffusion with a remarkable cardiovascular stability. It was evident that the addition of the diffusive principle considerably improved the removal capacity of the hemoflitration[8]. Today, this combination with the dialysis principle is integrated in all automatic pump systems for CRRT.

Definitions and Nomenclature

Recently, a series of publications dealing with a temptative standardization of definitions, nomenclature and abbreviations in the specialized area of CRRT have appeared on the international scene[12]. The recommendations based on currently published articles and discussions incorporate two basic premises: 1) definitions are to be based on the operating characteristics of each method with emphasis on the primary forces for solutes and fluid removal; and 2) description of the components are not considered in the definitions but should be mentioned in the method section of any publication.

CRRT

CRRT is any extracorporeal blood purification therapy intended to substitute for impaired renal function over an extended period of time, and applied for or aimed at being applied for 24 h/day. The various CRRTs differ in the type of access (arteriovenous or venovenous), application of convective clearance (continuous hemofiltration), diffusive clearance (continuous hemodialysis), or a combination of both (continuous hemodiafiltration), and location where the replacement fluid enters the circuit (predilution or postdilution) (Table 1).

CAVH

CAVH is a technique of CRRT whereby blood is driven by the patient's blood pressure through a filter containing a highly permeable membrane via an extracorporeal circuit originating from an artery and terminating in a vein. The ultrafiltrate produced during membrane transit is replaced in part or completely with appropriate replacement solutions to achieve blood purification and volume control (Fig. 1, left panel). Ultrafiltration (UF) is in excess of patient weight loss[12].

Table 1. Comparison of different continuous renal replacement modalities

Type of therapy	Abbreviation	Physicochemical basis of therapy	Urea clearance (L/d)		Convective (mL/min)	
			Diffusive	Convective	Diffusive	Convective
Continuous arteriovenous hemofiltration	CAVH	Convection	-	10-15	-	7-10
Continuous venovenous hemofiltration	CVVH	Convection	-	22-28	-	15-20
Continuous arteriovenous hemodialysis	CAVHD	Diffusion plus small amount of convection	22-24	2-6	14-16	2-5
Continuous venovenous hemodialysis	CVVHD	Diffusion plus small amount of convection	22-24	2-6	14-16	2-5
Continuous arteriovenous hemodiafiltration	CAVHDF	Diffusion plus convection	22-24	14.4	18-20	10
Continuous venovenous hemodiafiltration	CVVHDF	Diffusion plus convection	22-24	14.4	18-20	10-13
Slow continuous ultrafiltration	SCVF	Convection	-	3.0	-	2-5

CVVH

CVVH is a technique of CRRT whereby blood is driven through a highly permeable membrane by a peristaltic pump via an extracorporeal circuit originating from a vein and terminating in a vein. The ultrafiltrate produced during membrane transit is replaced in part or completely with appropriate replacement solutions to achieve blood purification and volume control. UF in excess of replacement results in patient weight loss[12] (Fig. 1, right panel).

Slow Continuous Ultrafiltration

Slow continuous ultrafiltration (SCUF) is a form of CAVH or CVVH not associated with fluid replacement and often used in the management of refractory edema with or without renal failure. Its primary aim is to achieve safe and effective management of fluid overload (Fig. 2). In venovenous SCUF, a volumetric control of UF may be required to maintain UFR below the values that would require fluid reinfusion[12].

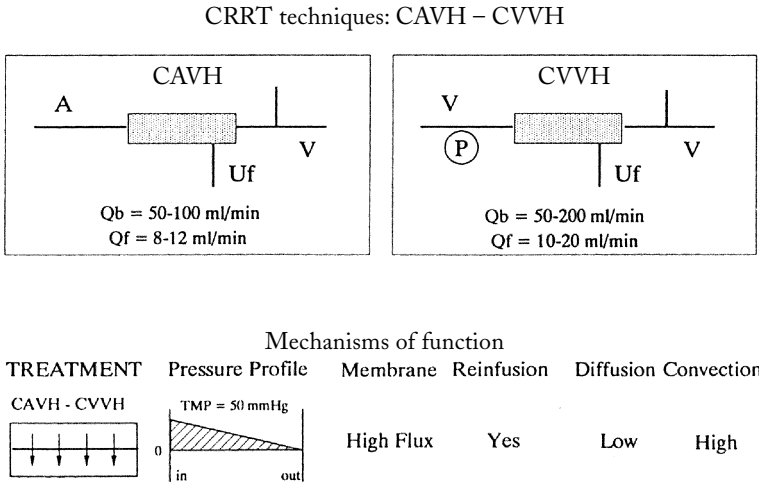

Fig. 1. Schematic presentation of CAVH and CVVH therapy.
Abbreviations: A=artery, V=vein, Uf=ultrafiltrate, R=replacement fluid, P=peristaltic pump, Qb=blood flow, Qf=ultrafiltration rate, TMP=transmembrane pressure, in=dialyzer inlet, out=dialyzer outlet.

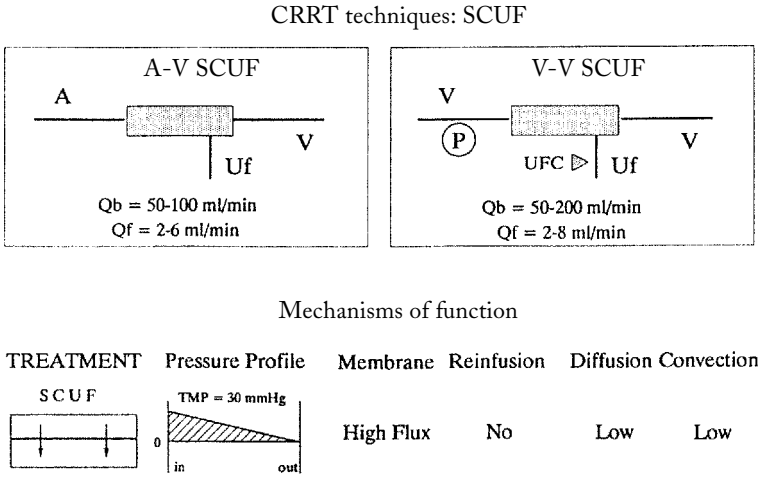

Fig. 2. Schematic presentation of SCUF therapy.
Abbreviations: A=artery, V=vein, Uf=ultrafiltrate, R=replacement fluid, P=peristaltic pump, Qb=blood flow, Qf=ultrafiltration rate, TMP=transmembrane pressure, in=dialyzer inlet, out=dialyzer outlet, UFC=ultrafiltration control system.

CAVHDF

CAVHDF is a technique of CRRT whereby the CAVH circuit is modified by the addition of slow countercurrent dialysate flow into the ultrafiltrate-dialysate compartment of the hemofilter. UF volumes are optimized to exceed the desired weight loss to take advantage from convection. Fluid replacement is routinely administered as clinically indicated to replace fluid losses either in part or completely. Solute removal is both diffusive and convective[12] (Fig. 3, left panel).

CVVHDF

CVVHDF is a technique of CRRT whereby the CVVH circuit is modified by the addition of slow countercurrent dialysate flow to the ultrafiltrate-dialysate compartment of the membrane. UFR is greater-than-expected patient weight loss. Therefore, fluid replacement is routinely administered as clinically indicated to maintain desired fluid balance. Solute removal is both diffusive and convective[12] (Fig. 3, right panel).

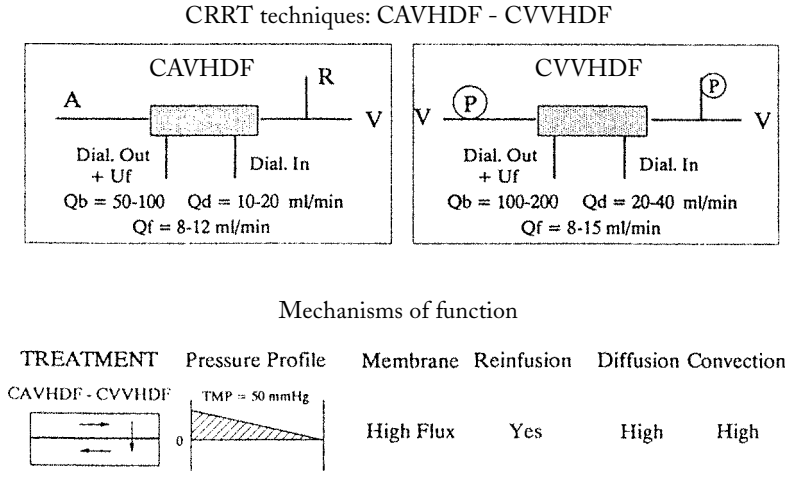

Fig. 3. Schematic presentation of CAVHDF and CVVHDF therapy.
Abbreviations: A=artery, V=vein, Uf=ultrafiltrate, R=replacement fluid, P=peristaltic pump, Qb=blood flow, Qf=ultrafiltration rate, TMP=transmembrane pressure, in=dialyzer inlet, out=dialyzer outlet, Dial=dialysate, Qd=dialysate flow rate.

CAVHD

CAVHD is a technique of CRRT whereby the extracorporeal circuit is characterized by slow countercurrent dialysate flow into the ultrafiltrate-dialysate compartment of the dialyzer. Blood flow through the blood compartment of the dialyzer is driven by the patient's blood pressure through a circuit beginning in an artery and terminating in a vein. Fluid replacement is not routinely administered. Solute clearance is mostly diffusive[12] (Fig. 4, left panel).

CVVHD

CVVHD is a technique of CRRT whereby the extracorporeal circuit is characterized by slow countercurrent dialysate flow into the ultrafiltrate-dialysate compartment of the dialyzer. Blood flow through the blood compartment of the dialyzer is driven by a peristaltic pump through a circuit beginning and terminating in a vein. Fluid replacement is not routinely administered. Solute clearance is mostly diffusive[12] (Fig. 4, right panel). It should be emphasized that the mechanism by which solutes are removed from the circulation in continuous hemodialysis may be substantially different depending on the choice of the membrane. If a low-flux cellulosic membrane is used, solutes are mainly removed by diffusion, and ultrafiltration volume equals patient weight loss. In case of a synthetic high-flux membrane, solutes are removed both by diffusion and convection. The UF would exceed the patient weight loss but is limited by an UF-dialysate outlet control system that avoids the need for postdilutional reinfusion. In this case, the pressure profile inside the dialyzer leads to a proximal filtration and distal backfiltration by which convective transport is maintained even though it is absolutely not apparent. This treatment has been defined as continuous high-flux dialysis (CHFD).

CVVH/DF - extracorporeal membrane oxygenation or

CVVH/DF - Venovenous Bypass CVVH/DF - extracorporeal membrane oxygenation (ECMO) and CVVH/DF - venovenous bypass are techniques of CRRT where the driving force to blood flow across the filter is obtained from a circuit derivation of the larger blood pump circuit used from ECMO or venovenous bypass (as may occur during liver transplantation)[12].

Indications

CRRT is often regarded as one of the more important advances in ICU in recent years. ARF combined with cardiovascular instability, severe fluid overload, hypercatabolism or cerebral edema are widely accepted indications for CRRT. Less well established indications include sepsis and other inflammatory syndromes, crush injury, ARDS, tumor lysis syndrome, chronic heart failure, lactic acidosis, cardiopulmonary bypass, and ARF combined with acute or chronic liver failure and after hepatic transplantation. Recently, CRRT has been used in critically ill pediatric patients[6].

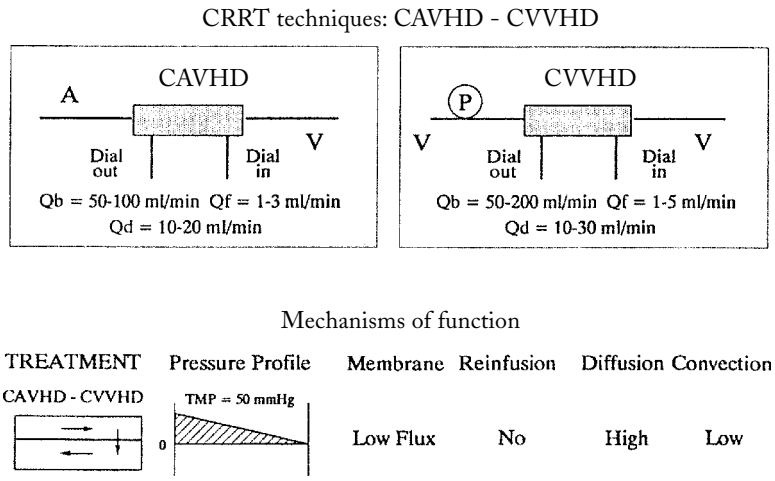

Fig. 4. Schematic presentation of CAVHD and CVVHD therapy.
Abbreviations: A=artery, V=vein, Uf=ultrafiltrate, R=replacement fluid, P=peristaltic pump, Qb=blood flow, Qf=ultrafiltration rate, TMP=transmembrane pressure, in=dialyzer inlet, out=dialyzer outlet, Dial=dialysate, Qd=dialysate flow rate.

ARF with cardiovascular failure

The most frequently failing organ in critically ill patients is the circulatory system. During RRT, the circulating volume is reduced by UF that is followed by replenshment from the interstitial compartment. CRRT allows slow and isotonic fluid removal that results in an excellent hemodynamic tolerance, even in patients with severe fluid overload or septic shock. Fluid removal and solute clearance in CRRT may be modified at any time allowing adaptation to the rapidly changing hemodynamic situation of critically ill patients. Improved hemodynamic stability during CRRT may have a beneficial effect on the preservation and recovery of renal function[13].

ARF with hypercatabolism

There is general agreement that hypercatabolic patients require substantial caloric and nitrogen supply in order to preserve lean body mass. This results in a high obligatory fluid input. CRRT permits a safe and adequate control of hydration, allowing the delivery of full dose nutrition[13]. The hypercatabolic state of ARF patients requires efficient removal of nitrogen waste products. Inadequate azotemia control has for a long time been regarded as one of the drawbacks of CRRT. However, this shortcoming only applies to CAVH. The addition of dialysis and the use of pump driven techniques allow urea clearances of 20 to 50 mL/min to be achieved[12]. For the same adequacy of azotemia control (Kt/V) CRRT achieves a better metabolic control than IHD[14]. This superior metabolic control results from continuous equilibration between the different body compartments, allowing access to the total distribution volume of the solute, thus increasing the amount of solute removed. During IHD, solute concentration decreases resulting in a decrease in the amount of solute removed (even if clearance is constant). This intermittent treatment is followed by a rebound of the solute concentration due to redistribution from the peripheral compartment to the central compartment. In critically ill patients, post-treatment rebound of solute concentrations is aggravated by disturbances of the regional circulation that may further decrease tha actual volume of distribution to which the intermittent treatment has access[15].

ARF with cerebral edema

Life-threatening elevations of the intracranial pressure may occur during IHD in patients with pre-existing cerebral edema secondary to ischemia, metabolic disorders (such as liver failure), trauma or surgery. CRRT induces a slow and gradual decrease of plasma osmolality and thus prevents dialysis disequilibrium. The improved hemodynamic stability further contributes to the preservation of cerebral perfusion pressure. Patients with renal failure combined with cerebral edema should therefore be treated with CRRT.

Sepsis and other inflammatory syndromes

Extracorporeal removal of several inflammatory mediators including proinflammatory cytokines, activation products or components of the complement system, and arachidonic acid metabolites has been demonstrated in a great number of uncontrolled clinical studies. However, a decrease in the plasma concentration during CRRT is more an exception than the rule, possibly due to the ongoing production and the high endogenous clearance limiting the contribution of extracorporeal elimination. Two recent controlled clinical studies did not establish an effect of hemofiltration on the plasma concentrations of TNF-(and interleukin-6 (Il-6)[16,17]. The use of high volume hemofiltration might increase the contribution of extracorporeal clearance, whereas frequent filter changes might increase the elimination of mediators adsorbing to the membrane.

Many uncontrolled clinical studies report on a remarkable hemodynamic and respiratory stability, and occasionally improvement of septic patients on hemofiltration. Only a limited number of small controlled clinical trials evaluated the effect of zero-balanced hemoflitration in hyperdynamic inflammatory syndromes and demostrated no effect or attenuation of the hyperdynamic situation. A reduction of body temperature or correction of metabolic disorders might have contributed. Clinical application of high volume hemofiltration has only been reported in uncontrolled trials, suggesting an improvement of hemodynamics in patients with septic shock or inflammation after cardiopulmonary bypass[15]. An improvement of the survival or a reduction of organ failure during CRRT in patients with inflammatory syndromes remains to be confirmed in controlled clinical studies. The underlying mechanism of this amelioration also requires further investigations. Awaiting the results of this research, widespread application od CRRT in patients that have not yet developed ARF cannot be recommended.

Crush syndrome

Hemofiltration has been suggested to contribute to the prevention of ARF in crush injury by extracorporeal elimination of myoglobin (MW 17. 8 kD)[18]. However, adequate fluid resuscitation combined with urinary alkalization remain the mainstays in the treatment of crush syndrome.

Acute respiratory distress syndrome

Elimination of inflammatory mediators and an excess of extravascular lung water have been suggested to improve the outcome of ARDS[19,20]. CRRT-induced hypothermia may be used in patients with ARDS in order to reduce $C0_2$ production. The decreased ventilatory requirement may reduce ventilator-induced lung injury.

Tumor lysis syndrome

Tumor lysis syndrome may lead to ARF due to tubular obstruction by hyperphosphatemia with precipitation of calcium and phosphate complexes or uric acid crystals in renal tubuli and interstitium[21]. The prevention of ARF in tumor lysis syndrome relies on the stimulation of diuresis combined with allopurinol, and high-risk patients who have low urine output and high plasma LDL-cholesterol concentration may be treated with CRRT[22].

Congestive Heart Failure

In congestive heart failure, low cardiac output promotes a variety of compensatory neurohumoral mechanisms (activation of the sympathetic system, and the renin-angiotensin-aldosterone system, and release of vasopressin), resulting in both sodium accumulation and water retention, as well as in arteriolar vasoconstriction (Fig. 5). The treatment of congestive heart failure requires an interruption in the vicious neurohumoral hemodynamic circle, and this may be mostly achieved with diuretics, vasodilatators, and beta-blocking agents. Some patients with congestive heart failure will not respond to medical treatment, and even more fluid removal with diuretics may further enhance the neurohumoral stimulation and aggravate heart failure. The removal of fluid with UF has been reported to interrupt this vicious circle and represents an alternative approach in the treatment of refractory heart failure[23]. The data suggest that fluid removal by UF shifts the abnormal set point for fluid balance to a more physiological level, resulting in an increase of diuresis and sodium excretion, stabilizing blood pressure, and a further decrease of body weight after interruption of the procedure. Continuous therapies are particularly suited for patients with severe heart failure, to bridge the time until heart transplantation can be performed[24].

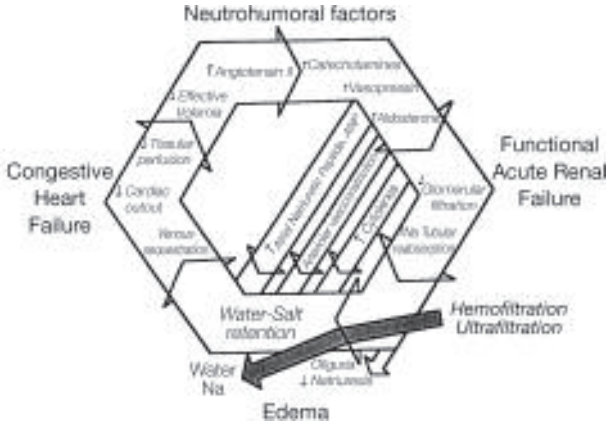

Fig. 5. Schematic presentation of the vicious circle relating cardiac failure and functional ARF, and the role of isolated UF.

Lactic acidosis

Continuous bicarbonate hemodiafiltration may eliminate lactate, and minimize hypernatremia and hypervolemia (both of which are side effects of bicarbonate administration) contributing to the correction of lactic acidosis[25].

Cardiopulmonary bypass

The primary goal of continuous UF during cardiopulmonary bypass is to remove excess fluid from overhydrated patients, to reduce blood loss and transfusion requirement, to improve pulmonary vascular resistance and oxygenation, to improve left ventricular systolic and diastolic function, and to remove inflammatory mediators by convective solute transport[26].

ARF with acute or chronic liver failure

CRRT is now established as the treatment of choice for the management of ARF in the setting of either acute or chronic liver failure, and after hepatic transplantation. The treatment alone does not provide adequate compensation, as the amount of hepatic toxins such as ammonia removed during CRRT is small. However, CRRT does have a role in the management of both acute and chronic liver failure awaiting transplantation by allowing the correction of sodium and other electrolyte imbalances, providing space for parenteral nutrition and albumin, and controlled extracellular fluid removal. A biocompatible membrane such as polysulphone or polyacrylonitrile should be used to minimize both adverse cardiovascular and intracranial effects. The anticoagulant of choice is prostacyclin because it not only reduces the risk of hemorrhage, but may also increase tissue oxygenation.

Critically ill pediatric patients

CRRT either driven in the arteriovenous or venovenous mode is an effective method of renal support in critically ill infants and children. Both methods allow good control of fluid, acid-base, and electrolyte balances. The pump-

driven CRRT mode allows constant blood flow and UFR with excellent control of azotemia even in hypercatabolic states (urea clearance may increase up to 300%). The use of a pump makes the CRRT more complex, but it can be performed in every pediatric ICU. CVVH, CVVHDF or CVVHD, because of the highest urea clearance rates are indicated in emergency conditions such as severe tumor lysis syndrome or severe metabolic crisis due to an inborn error of metabolism. All CRRTs allow adequate nutrition and unlimited medication of critically ill pediatric patients[26].

Prophylactic use of CRRT

The prophylactic initiation of CRRT is not justified in a patient with completely normal renal function, with an unimpaired water excretion and normal hemodynamic function. Potential advantages cannot outweigh the risks associated with this invasive therapeutic approach, and there is no evidence that prophylactic CRRT will prevent the development of renal failure in such a patient. However, prophylactic CRRT in modern critical care medicine may be viewed in the more complex context of a multiorgan approach with effects on various additional, but not only renal, organ functions. This may become especially important in sepsis, septic shock and MOF, the most frequent causes of ARF in the critically ill. Any therapeutic approach in these conditions in preventing the development of multiple organ dysfunctions such as heart failure, ARDS, intestinal failure aside from renal failure must take into account the basic pathophysiologic pancellular disturbance. In the critically ill patient with compromised water excretion, cardiovascular instability, and sepsis at risk of progression to MOF, and patients with ARDS and progressive water accumulation, the early institution of CRRT is warranted even when laboratory values would only suggest a mild impairment of renal function[27].

New Technology and New Techniques for CRRT

The CRRT Equipment

Minimal technical requirements for CRRT are a blood pump, a dialyzer or hemofilter, arterial and venous pressure monitors, a venous air bubble chamber, an air detector, and a balancing system for dialysate inflow and outflow, replacement fluid inflow, and filtrate outflow (Fig. 6).

The *Prisma* (Hospal, France) consists of 4 pumps for blood, dialysate, replacement fluid and effluent, and 3 weighing devices. The touch screen along with software

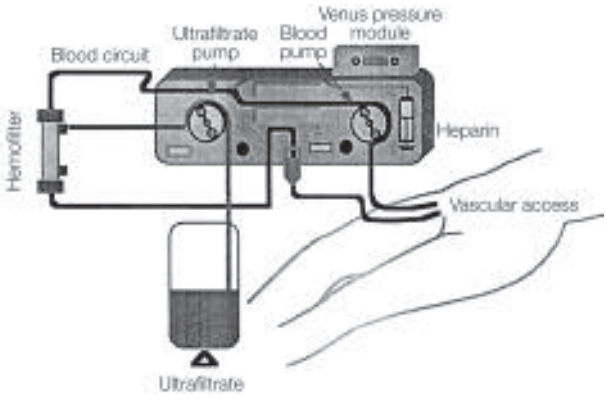

Fig. 6. Schematic diagram of the system for continuous high-flux dialysis.
The module used for either slow continuous UF (SCUF) or slow daily UF (SDUF) consists of two independent pumps (one for blood, and one for UF) plus venous pressure monitoring module and air detector with safety clamp.

provides step-by-step instruction and online assistance. A disposable tubing set with a preconnected AN69 filter allows an easy set-up.

The *BM 25* (Baxter Healthcare, USA) consists of 2 integrated modules, i.e. a blood monitor BM 11, and a balancing monitor BM 14 with 2 pumps for the inflow of dialysate and replacement fluid, and outflow of dialysate and filtrate, as well as 2 integrated scales.

The *Trio* (Braun, Germany) is composed of a blood module and 2 fluid balance monitors operated by interfaced roller pumps. The front panel resembles the infusion pumps. A disposable measuring chamber with an ultrasound sensor controls fluid balance, and the pumps are recalibrated after each measurement cycle.

The *Diapact* (Braun, Germany) performs CVVHDF. The blood is pumped into a high-flux dialyzer in which proximal part UF-induced convective clearance occurs. In addition, diffusive clearance is applied by a dialysate flow between 20 and 100 mL/min countercurrent to the blood flow. As blood courses down the hollow fiber and plasma water is filtered, the pressure in the dialysate compartment exceeds in the distal part the pressure in the blood compartment. This causes backfiltration of sterile dialysate into the blood and compensates for the UF in the proximal part. Equilibration between the dialysate and plasma is achieved by optimal recirculation of the dialysate and 10 L of dialysate can be recirculated in approximately 4 hours. The machine produces high small-molecule clearance (the combined diffusive and convective clearance for urea is about 60 L/day), and a high middle-molecule clearance.

The *EQUAsmart* (Medica, Italy) is equipped with 2 peristaltic pumps for blood and replacement fluid, 2 intelligent clumps (one for control of dialysate and the other for effluent flow during SCUF), and 3 accurate load cells (for UF, replacement solution, and dialysate). A thermal printer is integrated in the EQUAsmart body to enclose treatment data in patient clinical report. EQUAsmart has been specifically developed to improve the working condition for the filter, to ensure its proper function along with the treatment duration, and to avoid undesired and premature replacement. For these reasons, the blood flows from the bottom to the top avoiding the build up of air bubbles on the hemofilter top. In addition to this, when dialysate flow is needed also the dialysate flows from the bottom to the top in a concurrent way, giving, at low dialysate flow, similar results to the traditional countercurrent flow. The UF of the hemofilter is not forced by the use of a pump but is free depending on the characteristics of both the filter and patient, and ensuring a spontaneous, unforced UF, less stress for the patient, users work load reduction, and saving of economic resources.

The *Acu-men* (Fresenius Medical Care, Germany) uses a pneumatic blood pump to drive the blood through the extracorporeal circuit, and the venous air bubble chamber is replaced by 2 hydrophobic membranes. Negative pressure behind these membranes continuously removes the air entering the system. Accurate balancing is achieved by a volumetric balancing chamber. The extracorporeal circuit is integrated in a disposable cartridge, which ensures an easy set-up.

Slow continuous dialysis (SCD) is defined by the following parameters: 1) blood flow from 100 to 500 mL/min; 2) dialysate flow from 100 to 300 mL/min; 3) utilization of a modified 2008H hemodialysis machine (Fresenius Medical Care, Germany) with controlled UF and online production of bicarbonate-based dialysate; and 4) continuous or daily treatment for at least 8 to 12 hours. SCD provides a sustained high rate of solute clearance in the range of 70 to 80 mL/min. Preliminary clinical data demonstrate the safety, simplicity, and efficiency of the treatment.

The purpose of the *technique of coupled sequential hemofiltration and hemodialysis* is to accomplish sequential

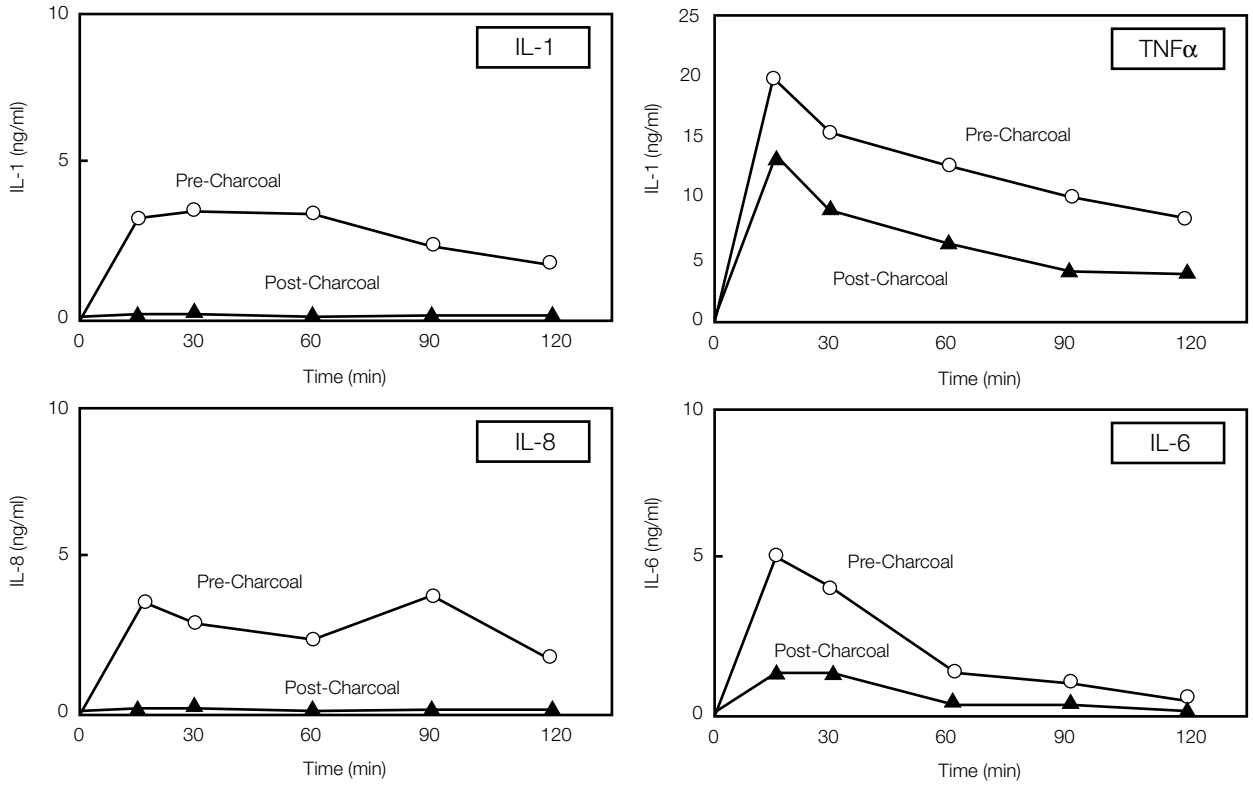

Fig. 7. Cytokine removal from ultrafiltrate by charcoal cartridge used in coupled filtration-adsorption system.
Cytokine concentration in the inlet ultrafiltrate is increasing during the first 15 min of treatment, because at the beginning adsorption onto hemofiltration membrane occurs. When the membrane is saturated, cytokines appear in the ultrafiltrate and they are almost totally retained by charcoal cartridge.

fluid removal and then solute removal in patients who are unable to tolerate simultaneous UF and diffusive solute clearance as it occurs during routine IHD. With the advent of computed volumetric controlled UF machines and sodium modeling, the incidents and severity of hypotension are decreasing, and the above methods are used much less frequently.

In the *coupled filtration–absorption technique* used in the treatment of sepsis, a plasma filter is used in a continuous hemofiltration circuit. The plasma filtrate passes through an uncoated charcoal cartridge and is reinfused to the patient. The system offers the ability to remove inflammatory mediators in sepsis[28] (Fig. 7), protein-bound or lipid-soluble toxins in combined renal and liver failure[29].

Temporary vascular access for CRRT

Initially performed spontaneously via an arteriovenous circuit, CRRT modalities have progressively become venovenous with the circulatory assistance of a blood pump. At present, double lumen catheters represent the most common vascular access for CRRT. Semirigid polyurethane catheters currently used in case of emergency are limited in short term use, and flexible silicone catheters, less aggressive for the vessels, seem better suited for the medium and long-term run. The internal jugular vein, particularly the right one, seems to warrant proper functioning of the catheter while reducing the risk of stenotic complications. Subclavian access should be limited in time and reserved for silicone catheters in order to limit the risk of stenosis and/or thrombosis. Femoral access, very useful in case of respiratory problems and in case of emergency, should also be limited in time to prevent thrombosis and/or infection. Performance standards of catheters are less of a limiting factor in CRRT modalities than in IHD ones[30]. Finally, careful handling of the catheter is essential to prevent infections[31].

Anticoagulation

Patency of the extracorporeal circuit requires the use of continuous anticoagulation, which adds to the risk of complications (bleeding) and requires monitoring. Several methods of anticoagulation are now in use, and it is possible to minimize the risks (Table 2).

The most commonly used method of prevention clotting is *continuous administration of heparin* in the arterial line of the extracorporeal circuit. The hemofilter is primed with one to 2 L of heparinized saline containing 2,500 to 5,000 U heparin. This is followed by an initial loading heparin dose of 1,000 to 2,000 U. Routine coagulation parameters guide the subsequent continuous heparin administration of roughly 400 to 800 U/h (5 to 10 U/kg body weight)[32]. A partial thromboplasin time or activated clotting time (ACT) of 1.5 to 2 times the normal is the usual target level of anticoagulation. The incidence of heparin-induced major bleeding complications may be as high as 50%, and approximately 4% of such patients die as a result of hemorrhages during CRRT.

Priming the extracorporeal circuit with *2 L saline with 20,000 U heparin for one to 4 h before initiation* of treatment leads to significant heparin adsorption onto the hemofilter surface, which seems to reduce the need for heparin during CRRT.

Regional heparin anticoagulation with protamine neutralization at a ratio of 100:1 aims to minimize the systemic effect of heparin. The method requires frequent monitoring to optimize the heparin to protamine ratio.

Table 2. Anticoagulation for continuous renal replacement therapy

Anticoagulation	Advantages	Problems	Efficacy	Monitoring
Heparin	Good anticoagulation	Bleeding, thrombocytopenia	Good	PTT/ACT
Low molecular weight heparin	Less thrombocytopenia	Bleeding	Good	Anti-Xa activity
Regional heparinization + protamine neutralization	Reduced bleeding	Complex	Good	PTT/ACT
Citrate	Lowest risk of bleeding	Metabolic disorders, special, dialysate	Excellent	PTT/ACT
Prostacyclin + (low-dose heparin)	Reduced bleeding risk	Severe hypotension	Insufficient	Thrombelastograph
Saline flush	No bleeding risk	Filter clotting	Insufficient	

Abbreviations: PTT = partial tromboplastin time, ACT = activated clotting time.

Low molecular weight heparin in a dose to achieve a concentration of 0.3 to 0.6 antiXa U/mL is less likely to cause thrombocytopenia compared with ultrafractionated heparin.

Regional citrate anticoagulation is associated with the lowest risk of bleeding and dialyzer clotting, but it is only suitable for methods that use diffusive clearance (convective clearance during CRRT removes insufficient amounts of citrate), and a special alkali- and calcium-free dialysate with low sodium concentration (calcium supplementation is necessary during CRRT).

Prostacyclin is a potent inhibitor of platelet aggregation, and in comparison with heparin it appears to reduce bleeding frequency and to increase hemofilter life. It is also a potent vasodilatator and may induce a marked decrease in the mean arterial pressure (up to 15 mm Hg). Furthermore, the drug is expensive and monitoring of platelet function is difficult[6].

Dialysis membranes used in CRRT

It has been increasingly recognized that significant side effects may occur as a result of interactions of blood with the dialysis membrane itself[32,33]. The use of unmodified cellulosic HD membranes results in a potent activation of the alternative pathway of complement, granulocyte activation and degranulation, protease release, production of reactive oxygen species, and modulation of granulocyte cell adhesion molecules, contributing to the prolongation of ARF, and increasing the morbidity and mortality[32-34]. Most of the studies[32-35] suggest that dialysis (IHD or CRRT) with more biocompatible membranes (modified cellulosic or synthetic) in patients with ARF leads to better outcome.

In a complex disease such as sepsis or ARDS, down-regulation of the ongoing systemic inflammatory response may be beneficial. The use of highly adsorptive membranes in CRRT procedure results in simultaneous inhibition of different biological systems (e.g., complement, coagulation, cytokines, kinins)[36], and frequent changes of dialyzers or development of new devices with greater adsorptive capacity may represent therapeutic advances for critically ill patients with MODS.

The technical aspects of CRT have set the minimal requirements for hemofilters and hemodialyzers. CVVH uses a TMP of 100 to 150 mm Hg. A desired UF of 25 mL/min (1. 5 L/h) requires a TMP of 120 mm Hg and a membrane with an UF coefficient of 12. 5 mL/h/mm Hg. In SCD, the blood flow rate (100 to 150 mL/min) is many times greater than the dialysate flow rate (14 to 30 mL/min), which results in almost complete saturation of the dialysate. The minimal requirement for dialysis membranes is a mass transfer coeffcient (KoA) high enough to provide a urea clearance of up to 30 mL/min. All current membranes by far exceed this KoA, and most of the filters also can be used for combined filtration and dialysis (CVVHDF)[6].

Replacemet fluid and dialysate

Any fluids with the following concentrations of electrolytes are adequate as substitution fluid for CVVH: sodium 140 mmol/L, potassium 0 to 4 mmol/L, calcium 1.5 to 1.75 mmol/L, magnesium 0.5 to 0.75 mmol/L, chloride 108 to 112 mmol/L, and glucose 0 to 83.3 mmol/L. Most of the available replacement solutions contain lactate (3 5 to 45 mmol/L) to compensate for bicarbonate losses in the filtrate (up to 1,000 mmol/day during CVVH or CVVHD). Under physiologic conditions, lactate is converted to bicarbonate on an equimolar basis at a rate of roughly 100 mmol/h. Severe impairment of lactate metabolism or enhanced lactate production in patients with sepsis, liver failure, or severe hypoxia may result in lactate accumulation with decreased myocardial performance. The negative metabolic and hemodynamic effects of lactate make the buffer bicarbonate preferable[37] (Fig. 8). In a twocomponent system, a bicarbonate solution (160 mL 8.4% HCO_3) is mixed immediately before use with 4,500 mL electrolyte solution containing calcium, magnesium, and lactic acid (3 mmol/L). Lactic acid increases pCO_2 and prevents precipitation of insolubile calcium and magnesium carbonates. The solution is stable for 24 hours.

For SCD, replacement solutions for hemofiltration or peritoneal dialysis fluid with the abovementioned electrolyte concentrations are frequently used as dialysate[6]. Some peritoneal fluids contain less than 140 mmol/L sodium, and hypertonic saline must be added to increase the sodium concentrations and to avoid hyponatremia.

UF control during CRRT is achieved by means of gravity, by using an ultrafiltration pump, or by two identically calibrated pumps (one for UF/dialysate inflow and one for the replacement fluid and dialysate outflow). Newer devices with gravimetric or volumetric balancing systems provide a more accurate fluid balance.

The continuous blood flow through extracorporeal system and cool replacement fluid cause a reduction in body temperature, and an energy loss (about 1,000 kcal/day). The reduction of body temperature may be desirable in certain critically ill patients, in whom hypothermia is associated with a reduction of oxygen consumption, an increase in pO_2, and increase in systemic vascular resistance and blood pressure. In most patients, it is recommended to use a heat-

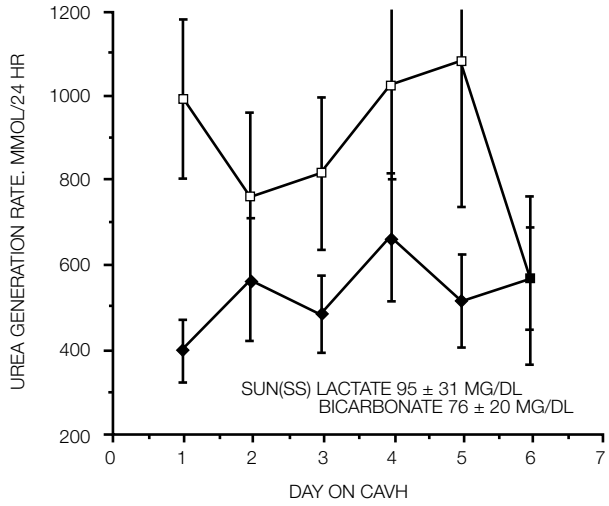

Fig. 8. Urea generation rate obtained from critically ill patients treated with CAVH using either lactate- or bicarbonate-based fluids. The use of bicarbonate-based fluids was associated with a lower urea generation rate. Symbols: ◆ bicarbonate; □ lactate.

ing device to warm the substitution fluid and to prevent hypothermia during CRRT.

Metabolic control and dialysis dose in CRRTs

Urea clearance in CRRT is equivalent to the UF. During CAVH and CVVH, roughly 10 to 15 L and 22 to 24 L of plasma water are filtered per day, which corresponds to a urea clearance of 10 to 15 L/day and 22 to 24 L/day, respectively. Because the blood flow during CRRT is much greater than the dialysate flow, the dialysate is fully saturated with urea. The urea clearance in CAVHD or CVVHD equals the dialysate flow rate plus UF. Roughly 24 to 30 L of plasma water are cleared per day during continuous HD. Continuous HDF, a combination of convective and diffusive clearance, is the most efficient CRRT modality, providing a urea clearance of 36 to 38 L/day. If it is not sufficient, the dialysate flow rate may be increased to 4 L/day, which amounts to a urea clearance of 3 L/day[6].

The standards for dialysis adequacy in ARF are not currently defined. Considering the fact that ARF is a catabolic state due to concomitant sepsis, wasting, acidosis, and increased nutritional support, it would appear that ARF patients may require large dialysis dose delivery for metabolic and azotemic control. Recently, urea kinetic modeling (UKM) has been applied to estimate dialysis dose delivery in ARF patients[38]. Clark et al.[38] studied the control of azotemia in 11 oliguric ARF patients treated by CVVH, and compared these results with those of 11 ARF patients treated by IHD. These studies have shown that intensive IHD (with a urea clearance of 160 mL/min, performed for 4 h) would be required 5 days per week to reach the dialysis dose and to achieve the metabolic control equivalent to those achieved with CVVH[38].

Solute removal during CRRT is determined by convec-

Table 3. Mean results for weights, urea clearances, ultrafiltration rates, and daily and weekly Kt/V obtained with four different continuous replacement modalities and intermittent hemodialysis

Technique	Weight (kg)	Urea Cl (mL/min)	UF (L/h)	Daily Kt/V	Weekly Kt/V
4-h HD daily	71.6	175	Variable	1.07	7.5
4-h HD 3x/wk	7.16	175	Variable	1.07	3.2
CAVHD; DFR at 1 L/h					
Multiflow-60 (PAN 0.6 m^2)	73.0±3.0	23.0±2.2	0.5±0.1	0.88±0.12	6.2
CAVHD; DFR at 4 L/h					
Multiflow-60	67.6±17.9	49.0±1.3	0.6±0.1	2.03±0.51	14.2
CVVHD; DFR at 1 L/h					
Multiflow-60	81.2±7.4	34.8±4.3	1.1±0.3	1.14±0.25	8.0
CVVHD; DFR at 1 L/h					
Multiflow-100 (PAN 0.9 m^2)	63.9±12.4	43.7±3.2	1.6±0.2	1.83±0.39	12.8

Kt/V obtained with 4 hr IHD sessins are theoretical, assuming dialyzer urea clearance of 175 mL/min and considering mean weight of all patients.
Abbreviations: IHD = intermittent hemodialysis, DFR = dialysate flow rate, UF = ultrafiltration, CAVHD = continuous arteriovenous hemodialysis, CVVHD = continuous venovenous hemodialysis

tive fluxes relating to UF, with urea clearances approaching 10 to 15 mL/min. Perfusing the dialysate compartment with dialysate increases solute clearances by adding a diffusive component to clearance. Bonnardeaux et a1.[39] showed that urea clearance increased from 24.6±1.3 mL/min with a dialysate flow rate of 1 L/h to 48.5±3.4 mL/min when the dialysate flow rate was increased to 4 L/h.

Leblanc et al.[40] compared dialysis dose delivery by CRRT and IHD in 25 critically ill ARF patients. Dialyzer urea clearance was calculated directly by dialysate quantification, and urea clearances were calculated taking into account dialysate and ultrafiltrate outflow rate, as well as outlet dialysate and ultrafiltrate urea concentration. Volume distribution of urea was estimated at 55% of the mean body weight for each patient during CRRT. The mean Kt/V obtained with the various CRRT modalities was compared with a theoretical Kt/V of 1.1 provided by IHD (4 h/session utilized 3 times per week, or daily). The data presented in Table 3 show that CRRT may provide a greater dialysis dose to ICU ARF patients[40]. Even more, because of relatively large pore membranes used in CRRT modalities, and of very high UF, CRRT methods are very effective in the removal of toxic middle molecules, which may be important in the treatment of patients with MOF and ARF.

Drugs and dosage during CRRT

Most drugs have a MW up to 0.5 kD and easily pass through typical high-flux membranes (pore size 0.2 to 30 kD) used for CRRT. Because of the pore size of the dialysis membranes, only protein-bound drugs will not pass through the membrane. In postdilution hemofiltration, the drug clearance equals the ultrafiltration rate, while in predilution hemofiltration, the dilution prior to filtration needs to be considered when calculating clearance. In continuous HD, drugs are eliminated by diffusion (Fig. 9). The clinical relevance of a given drug clearance caused by CRRT will mainly depend on the competing drug clearance by other elimination pathways. Even a high clearance for a drug may

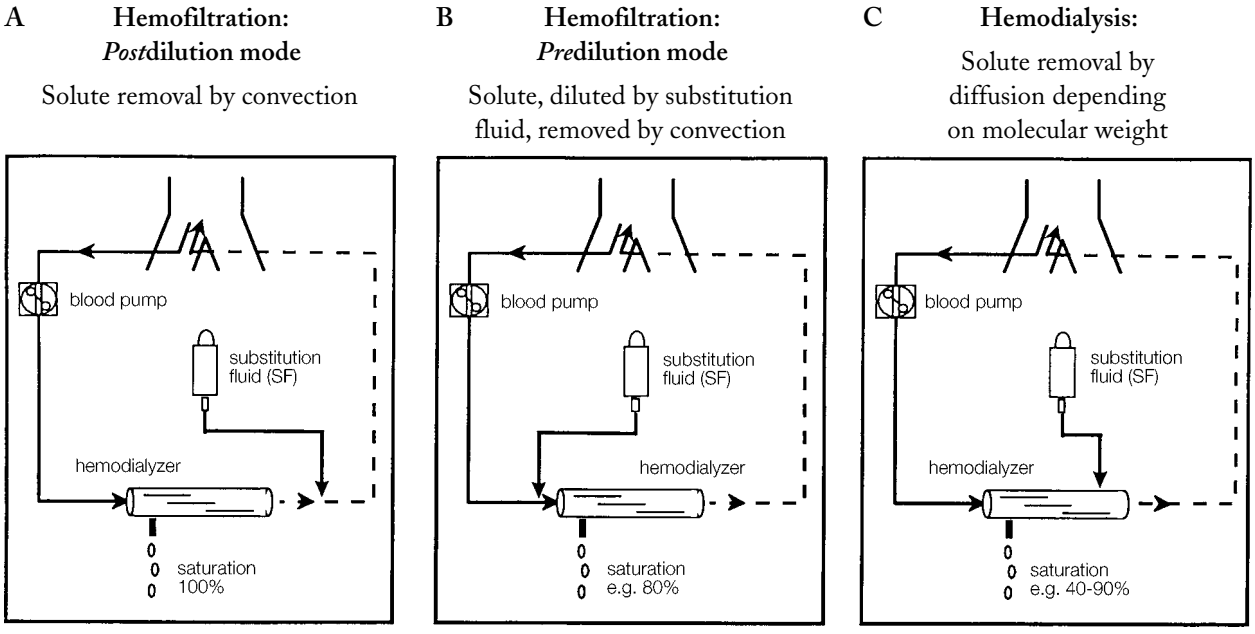

Fig. 9. Continuous renal replacement therapy results in different drug clearance rates depending on the treatment modality used.
A) In postdilution hemofiltration, ultrafiltrate is saturated to 100% compared with the drug concentration in plasma water. The drug clearance equals the UFR.
B) In predilution hemofiltration, the drug concentration is diluted by substitution fluid prior to entry into the dialyzer, resulting in lower saturation of ultrafiltrate compared with the patient's plasma water. The clearance is lower than the UFR.
C) In continuous hemodialysis, diffusion of the free non-protein-bound fraction of the drug is variable and depends mainly on the molecular weight[41].

be irrelevant for overall drug removal if nonrenal clearance pathways provide a much higher clearance rate. The ideal drug to be removed by CRRT that requires dose adjustment has low protein binding, low volume of distribution, and low nonrenal clearance (e.g., aminoglycosides, flucytosine, fosfomycin, and vancomycin)[41].

Depending on the drug, it may be more appropriate to increase the dose or to shorten the dosing interval. In the antibiotics in which the bactericidal effect correlates with peak concentrations (e.g., aminoglycosides), after beginning CRRT, it is preferable to increase the single daily drug dose to achieve high peak levels, while at the same time CRRT treatment helps decrease the drug levels to low trough concentrations and thereby reduces the risk of side effects. The efficacy of other antibiotics (e.g., beta-lactams) may be related to plasma concentrations above the minimal inhibitory concentrations of the bacteria, whereas side effects occur if high peak concentrations are reached with the use of high single doses. In these drugs it may be useful to shorten the dosing intervals instead of increasing the individual dose[41]. Whenever feasible, the measurement of drug concentrations should be used to guide the therapy. The dose adjustments in CRRT patients are mostly based on clinical studies in ICU patients[42].

Advantages of CRRT

CRRT avoids nonphysiological volume overload, and large fluctuations of the urea, creatinine, electrolyte and acid-base balance, which occur because of intermittent nature of HD treatment.

Fluid balance

Patients with MOF or sepsis require large amounts of volume in the form of blood products, vasopressors, and parenteral nutrition. Continuous therapies provide an almost unlimited ability to remove fluid which, in most patients, achieves an optimal volume balance.

Unlimited alimentation

The unrestrained fluid removal permits adequate parenteral nutrition without the fear of inducing volume overload. Bellomo et al.[43] demonstrated that 90% of patients received the prescribed nutrition during CRRT, as oposed to only 54% of patients during IHD. A subsequent study showed that 91% of the patients were able to receive more than 1.5 g protein/kg/d during CRRT, oposite to IHD and peritoneal dialysis treated ARF patients who received only up to 1.0 and 0.8 g/kg/d, respectively. CRRTs have also a direct impact on amino acids and calorie loss. Depending on the UFR during CVVH the body loses approximately 5 to 8 g/d amino acids (0.25 to 0.4 g/L). The administration of amino acids should therefore be increased by 0.2 g/kg/d to compensate for these losses. CVVH also filters 40 to 80 g/d glucose, which should be substituted by the replacement fluid or parenteral nutrition. If dextrose-containing peritoneal dialysis fluid is used as dialysate in CVVHD, roughly 45% to 60% of the dextrose are adsorbed resulting in daily uptake of 700 to 1,300 kcal[6]. McDonald et a1.[44] and Barlett et a1.[45] observed that CRRT patients received 12% more protein than prescribed, as well as an optimal caloric intake, which was associated with a trend toward a lower mortality rate, compared with IHD (72% vs 88%).

Gradual urea removal

Continuous therapies avoid the fluctuations in blood urea and sodium concentrations with a decrease in blood osmolality and creation of an intracellular to blood concentration gradient, which may lead to an osmotic shift of intravascular water to the interstitial and intracellular space. This disequilibrium may cause cerebral edema with nausea, vomiting and headache. During CRRT, serum osmolality does not change significantly.

Hemodynamic stability

Hypotension is one of the most common and severe complications of IHD, occurring in 20% to 50% of all treatments[6]. The repeated episodes of hypotension during IHD might aggravate renal injury and delay recovery from renal failure[46]. It has been shown that HD associated hypotension and the increased need of catecholamines result in increased oxygen consumption, decreased splanchnic blood flow, and increased interstitial, intramucosal acidosis[47]. In comparison to patients treated with IHD, ARF patients treated with CRRT experianced a significantly lower decrease in creatinine clearance (-7% vs -25%) and urine output (-10% vs -50%)[48]. Improved hemodynamic stability during CRRT seems to have a protective effect on residual kidney function, and improve cardiovascular stability.

Lower intracranial pressure

CRRT modalities appears to be beneficial in patients with combined fulminant hepatic failure and ARF, and in patients with increased intracranial pressure[49].

Elimination of septic mediators

The role of CRRT as a method of reducing serum cytokines in septic ARF patients is still controversial. Many inflammatory mediators (complement and cytokines) have a molecular weight (up to 50 kD) below the cutoff point of hemofilters, and have been detected in the filtrate of septic patients as well as at the surface of dialysis membranes[50,51], suggesting removal by convective clearance as well as membrane adsorption. An effective removal is only possible with a highly permeable membrane (sieving coefficient approximetely 1.0), high filtrate volume (>2 L/h), and when the halflife of the substance to be eliminated is greater than 60 min. Adsorption of TNF-α, IL-1β, factor D, and platelet activation factor onto PAN69 membrane is relatively high[6,36,50-52]. However, because the membrane surfaces are saturated after a few hours, frequent filter changes are necessary for them to generate effective adsorption of these mediators. Despite filter changes, only a brief and transient drop in the inflammatory mediators plasma level has been observed[50,51]. This does not mean that CRRT (especially CVVHDF) cannot positively influence sepsis or systemic inflammatory response syndrome (SIRS) in other ways. Controlled clinical trials are needed to determine whether or not CRRT actually has a beneficial effect on outcome in septic ARF patients.

Difficulties and Unsolved Problems with CRRT Modalities

CRRTs are generally well tolerated with a low rate of complications. The potential complications are illustrated in Table 4.

Table 4. Potential complications with CRRT

Technical	Clinical
Vascular access malfunction	Bleeding
Circuit clotting	Hematomas
Circuit explosion	Thrombosis
Catheter and circuit kinking	Infection and sepsis
Insufficient blood flow	Allergic reaction
Line-catheter disconnection	Hypothermia
Air embolism	Nutrient losses
Fluid balance errors	Insufficient blood purification
Loss of efficiency	Hypotension, arrhythmias

The most severe technical complications are mainly associated with the arterial access of the CAVH procedure. The *vascular access malfunction* (insufficient blood flow and circuit clotting) occurred frequently in CAVH when spontaneous arteriovenous gradient moved the blood through the circuit. Except in case of technical defects, the safety system excludes any *air embolism.* At the high perfusion rate of the extracorporeal circuit, any *accidental disconnection of the blood lines* acutely threatens life. It must always be assured that all connections are well locked and that the whole circuit is freely visible. If there is an alarm failure of blood pump, dangerous variations in the pressures may occur inside the circuit, and occasionally the *circuit may even explode.* A significant *reduction in membrane permeability* frequently occurs in CAVH (because of filter clotting), and it may occur even in CVVH over time[53]. The sieving coefficient of solutes tends to decrease, and the effective solute removal may be less than expected because of this phenomenon. Accidental *fluid overload* is a consistent danger of the CRRT, especially when a high fluid turnover is maintained[53]. Monitoring of fluid intake and output is mandatory.

The need for anticoagulation is regarded as the major clinical disadvantage of CRRT[53,54]. In addition, platelet-membrane interaction, turbulent blood flow, and shear stress may cause platelet dysfunction, which further increases the risk of bleeding[54]. The incidence of heparin-induced *bleeding complications* can be as high as 50%, and approximately 4% of such patients die as a result of hemorrhages during CRRT[33].

The degree to which *filter coagulation* occurs may be reduced by an uninterrupted blood flow, by monitoring of activated clotting time and prothrombin time, and by limiting the rates of volume depletion to about one L/h.

During CRRT treatment a considerable *loss of amino acids* occurs, while glucose is taken up from the substitution solution[6].

Deficiencies with respect to *potassium and phosphate* may frequently occur due to electrolyte filtration, but also due to a shift from the extracellular to the intracellular space when nutrition therapy is started and the acid-base balance is corrected[55].

CRRT may be accompanied by other unrecognized *deficiencies of vitamins, trace elements, and other micronutrients* as well as with loss of some drugs[55].

Significant disadvantages cited for CRRT are also *arterial puncture* (necessary in CAVH, CAVHDF and CAVHD) and *immobilization of the patient.* Arterial puncture can be avoided by pump-assisted venovenous methods, and critically ill patients are in any case generally im-

mobilized because of the primary disease. Hypothermia provided by the hemofilter/dialyzer (that can be considered a potent heat exchanger) must be taken into consideration when the caloric intake is scheduled and the nutritional and energy balances are evaluated[53].

Currently used CRRT with sophisticated treatment devices has become more *expensive* than IHD. This is also due to the amount of substitution solutions needed to obtain an adequate clearance (at least 15 L/day of filtrate are recommended)[6,55].

Influence of CRRT on Outcome of ARF Patients

The advantages of CRRT should theoretically translate into improved outcomes as the ultimate measure of treatment efficiency. Several studies have compared CRRT with IHD and reported a trend toward improved survival with CRRT[43,56]. In a study by Bellomo et a1.[43], a group of 24 CAVHDF/CVVHDF patients with a medium Apache II score of 24 to 29 demonstrated a significantly lower mortality rate of 53% compared with the IHD group (87%). These results were confirmed in a subsequent analysis in 234 ICU patients, in which continuously treated patients with Apache II score of 19 to 29 again had a significantly lower mortality rate than ARF patients treated with IHD or peritoneal dialysis (PD)[57]. It was noticed that CRRTs were started earlier and at lower mean plasma creatinine and urea concentrations, which might have contributed to the improved outcome[56]. Kresse et al.[58] compared demographics, severity, course, and prognosis of ARF during 36 months (period 1: 1991 to 1993; 128 patients) and 18 months (period 2: 1994 through 1995; 141 patients). There were no significant differences in patient demographics or etiology of ARF, but the therapeutic approach was different. During period 2, RRT was strated at earlier stages of renal failure, and in comparison with period 1, the mortality rate was reduced from 78.9% to 59.6% ($P<0.001$). The mortality in ARF patients treated with CRRT was in periods 1 and 2 higher than the mortality in patients treated with IHD, but these results are biased by a preferred use of CRRT in severely ill patients with unstable circulatory system. These data suggest that the early onset of RRT reduces the mortality rate of ICU ARF patients[58]. Mehta et al.[59] reporte on the results of a randomized, controlled multicenter trial of 166 ARF patients. Patients treated with CRRT had a significantly higher Apache II score (25.3 vs 20.6), and significantly higher mortality rate (59.5% vs 41.5%) compared with ARF patients treated with IHD[59]. CRRTs are predominantly used in hemodynamically unstable patients with higher Apache II score who would not tolerate IHD, and conversely, IHD is primarily performed in hemodynamically more stable patients with less complicated ARF, who have a much better prognosis. An analysis of such different patient populations where mortality is more dependent on the underlying disease than on ARF per se, will inevitably fail to show any survival benefits of different renal replacement therapies. Further evaluations are ongoing to gain deeper insights into the influence of renal replacement modality on ARF patient outcome.

CRRT Costs

Three recent studies provide evidence for the true cost differences between CRRT and IHD. Silvester and Bihari[60] compared CRRT and IHD and demonstrated that weekly costs of CRRT were approximately 1,213 USD (9,097.50 HRK), whereas IHD costs were l,136 USD (8,520 HRK). It can be seen that the costs of the two different methods at Guy's Hospital are very close, with the IHD being only by 6.3% cheaper[60]. Another recent trial compared weekly costs of CRRT and IHD and found CRRT cost of 1,915 USD (14,362.50 HRK) and IHD 867 USD (6,502.50 HRK)[61]. Cost per survivor was 2,872 USD (21,540 HRK) for CRRT, and 1,300 USD (9,750 HRK) for IHD[61]. Mehta et a1.[62] recently completed a prospective randomized multi-institutional trial that enrolled 166 ICU ARF patients treated with CRRT or IHD. There was no mortality advantage demonstrated by either therapy, and 25% of the patients crossed over during the trial. Significant factors that were demonstrated with this trial included achieving caloric and protein targets more often and better positive fluid balance with CRRT. When comparing direct costs for the randomized patients in the San Diego study, IHD led to an aggregate cost of 3,077 USD (23,077.50 HRK), and CRRT 3,946 USD (29,595 HRK) for 8.4 and 7.9 treatments, respectively. The cost analysis for labor and materials per treatment showed that the labor costs were not different between these two therapies, but there was a significant difference in material costs, with CRRT being 338 USD (2,535 HRK) and IHD 66 USD (495 HRK) per treatment. This study would suggest that cost differences are real and approximate 250 to 300 USD (1,875 to 2,250 HRK) per treatment[62].

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Sažetak

KONTINUIRANA NADOKNADA BUBREŽNE FUNKCIJE

P. Kes

Akutno zatajenje bubrega (AZB) danas se najčešće javlja u sklopu složenih sindroma poput sepse i/ili višestrukog zatajenja organa. Napredak na području hemodijalize doveo je do usporednog razvoja novih tehnika liječenja koje se temelje na kontinuiranoj nadoknadi bubrežne funkcije. Metode kontinuirane nadoknade bubrežne funcije razlikuju se s obzirom na krvožilni pristup, uporabu difuzije ili konvekcije u čišćenju krvi (ili kombinaciju obiju metoda), kao i prema mjestu u izvantjelesnom optoku na kojem se dodaje nadoknadna tekućina. Metode kontinuirane nadoknade bubrežne funkcije značajno su olakšale liječenje teških bolesnika s AZB koji imaju nestabilan srčanožilni sustav, suvišak tekućine, nalaze se u stanju pojačanog katabolizma, imaju edem mozga ili sindrom iscrpljenih pluća u odraslih, laktacidozu, sepsu ili sistemski upalni odgovor, nagnječenja, zatajenje srca ili srčanoplućno premoštenje. Postupci kontinuiranog liječenja AZB imaju niz prednosti koje uključuju poboljšanu hemodinamsku stabilnost, uravnoteženje tekućine u organizmu, postupno odstranjenje ureje, uklanjanje posrednika sepse i mogućnost neograničene parenteralne prehrane. Medu najznačajnije nedostatke i do danas neriješene probleme metoda za kontinuirano liječenje AZB spadaju potreba za trajnom primjenom antikoagulansa, značajni gubitci aminokiselina, vitamina, oligominerala, kalija, fosfata i nekih lijekova, kao i vrlo ograničena pokretljivost bolesnika. Prednosti metoda kontinuiranog liječenja AZB mogle bi teorijski rezultirati boljim ishodom liječenja vrlo teških bolesnika s AZB, ali su rezultati istraživanja na tome području još uvijek neujednačeni bez obzira na ohrabrujuće rezultate nekih kliničkih ispitivanja.

Ključne riječi: *Bubrežno zatajenje, akutno; Bubrežno zatajenje, akutno - terapija; Nadoknada bubrežne funkcije; Nadoknada bubrežne funkcije - ekonomičnost*