From Origin to Actual Trends

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The Pattern of Severe Acute Renal Failure

The incidence of acute renal failure (ARF) is approximately 50 – 100 new cases/year/million inhabitants [1]. ARF can be community acquired or hospital acquired and it may present with different clinical patterns. ARF can be isolated as a single disease or it may be part of a more complex syndrome involving other organs. Hospital-acquired ARF is an increasingly recognized condition, ranging between 2 – 5% of all patients admitted to general medical and surgical services, and increasing up to 23% in intensive care units (ICU) [2 – 4].

When ARF occurs without additional organ dysfunction, patients are treated in renal wards with standard dialysis techniques and outcome is generally favorable. When ARF occurs in "critically ill patients", severe cardiovascular, respiratory and metabolic instability, may contraindicate or preclude standard dialysis techniques. In such conditions, patients are generally followed in the ICU and continuous renal replacement therapies (RRT) are frequently employed (Table 1).

The ICU patient is critically ill and his monitoring and life support becomes extremely complex. Vasoactive drugs are utilized to counterbalance hemodynamic instability or shock conditions; mechanical ventilation or extracorporeal CO_2 removal are often required to sustain tissue oxygenation. Cardiac support is frequently achieved not only with inotropic drugs but also with mechanical devices. ARF is a common finding in this complex clinical picture. Finally, humoral and cellular mediators of inflammation are generally present in tissues and systemic circulation at very high concentrations and this may lead to the multiple organ dysfunction syndrome (MODS) due to systemic inflammatory response syndrome (SIRS) or sepsis.

Under such circumstances, an effective RRT must provide adequate blood purification from uremic toxins, correction of fluid, electrolyte and acid-base derangements, maintenance of homeostasis, protection for the kidneys from further injury and finally accelerated recovery of renal function after ARF (Table 2).

Evolution of Continuous Renal Replacement Techniques

The evolution in the field of hemodialysis has led to a parallel development of new systems for acute RRT in ICU patients. The use of new systems and techniques has permitted

Table 1. Approach to the Management of ARF

Prevention Measures	Conservative Therapy	Substitutive Therapy
– Maintain adequate volume repletion – Reconstitute circulating plasma volume – Carefully check patient's hydration when administering potentially toxic substances – Avoid potentially hazardous and risky diagnostic procedures – Consider the use of: – Mannitol – Furosemide – Dopamine – IV infusion – Other pharmacologic support – Adjust drug dosage to GFR – Undertake all specific measures in case of possible toxic exposure	– Metabolism Restrict protein intake (<0.5g/L/day) Maintain caloric intake (30-50 Cal/Kg/day) Provide adequate amount of carbohydrate to avoid ketosis and protein catabolism. Check daily nitrogen and phosphate balance – Fluid balance Make accurate intake/output balance Restrict fluid intake (if oliguria) to maintain BW Intake = Urine output + extrarenal losses Consider weight loss due to catabolism Monitor accurately fluid infusion rate – Electrolyte and Acid-base Prevent and treat hypo-hypernatremia, prevent and treat hyperkalemia Consider body pools and distribution spaces Correct metabolic acidosis (check K and Ca) Correct hyperphosphatemia and hypocalcemia – Consider initiation and choice of the RRT	– Peritoneal Therapy Consider: Peritoneal access schedule (IPD, CAPD, TPD) efficiency and prescription Respiratory problems Peritonitis risk – Hemodialysis Consider: Access to circulation schedule (HD, HF, HDF) efficiency & prescription Cardiovascular problems Poor clinical tolerance – Continuous therapies Consider: Access to circulation (A-V or (PUMP) schedule (CAVH, CAVHD, CVVH etc.) efficiency and efficacy and prescription Extrarenal effects Good clinical tolerance

to improve efficiency both in terms of blood purification and clinical tolerance. The first objective was reached by increasing the automation of the extracorporeal circuits and the operational levels of the different techniques; the second objective was reached by means of a new generation of monitoring techniques and new machines equipped with specific interfaces and alarms.

The Beginning of Continuous Arteriovenous Hemofiltration (CAVH)

In 1977 Kramer described this new treatment [5] based on a highly permeable hemofilter connected to an artery and a vein by modified hemodialysis (HD) blood lines. The arteriovenous pressure gradient was mov-

Table 2. General Criteria for the Initiation of RRT

- Oliguria (urinary output (< 500 mL/day)
- Anuria (no urinary output for 12 hours)
- BUN ≥ 70 mg/dL
- Creatinine ≥ 6 mg/dL
- Hyperkalemia (K ≥ 6 mEq/L)
- Pulmonary edema not responsive to diuretics
- Metabolic acidosis with acidemia (pH ≥ 7.2)
- Uremic encephalopathy
- Uremic pericarditis

ing the blood through the extracorporeal circuit and no pumps were utilized. Slow continuous production of ultrafiltrate was achieved and substitution fluid was administered in postdilutional mode to maintain patient's fluid balance. CAVH was a completely convective treatment, i.e. blood purification and volume control were only achieved by ultrafiltration and replacement of the fluid lost by filtration, while diffusion (the prevalent mechanism of standard HD) was totally absent (Figure 1).

The important achievement of CAVH in the early 1980s had been the ability to treat, with an extracorporeal technique for blood purification, those very ill patients in whom severe clinical conditions precluded any other form of renal replacement (Tables 3 and 4). Furthermore, CAVH enabled centers that were not equipped with HD facilities to perform acute RRT. However, while CAVH was an excellent tool for fluid control, the technique rapidly displayed its limitations in terms of solute removal and blood purification [6]. The maximal efficiency that could be achieved in CAVH was between 12 and 18 L of ultrafiltrate/day. Assuming a complete ultrafiltrate saturation and a sieving coefficient for urea close to 1, the daily urea clearance could not exceed those 18 L/day. In a patient with an

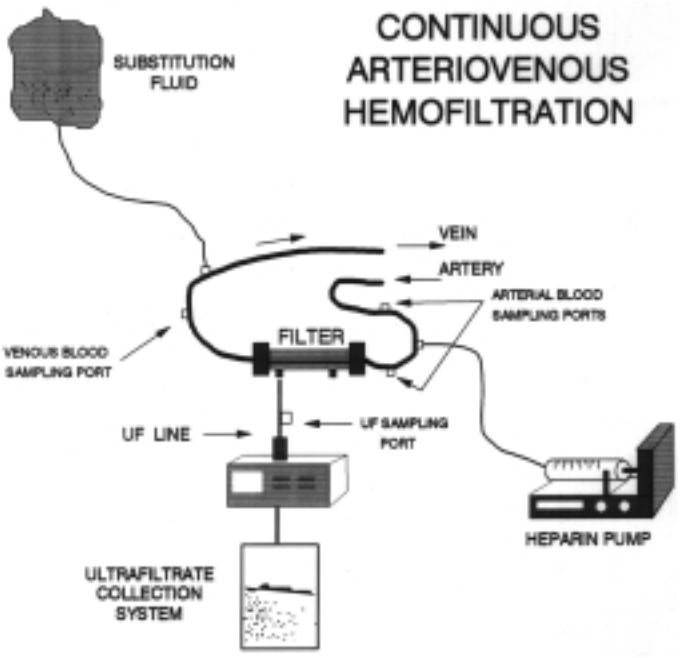

Figure 1. Schematic representation of the original CAVH Circuit.

Table 3. Intermittent Hemodialysis in Critically Ill Patients

Advantages	Disadvantages	Complications
– High efficiency – Shortness of the session – High ultrafiltration capacity – Low heparinization – Possibility to adjust therapy prescription – Clearances of drugs well known – Possibility of rapid and effective correction of hyperkalemia and other life threatening derangements	– Cardiovascular instability – High ultrafiltration /time – Need of a vascular access – Postdialytic solute rebound – Difficult solutes balance – Extracorporeal circulation – Contraindicated in hypotensive and critically ill patients – Large amounts of dialysate and replacement solutions – Body fluid and solute shifts and possible disequilibrium among body compartments – Machine required – Complex monitoring	– Infections and bacteremia – Access malfunction – Bleeding – Hypoxemia-hypoventilation – Cardiac arrhythmias – Severe hypotension – Air embolism – Disequilibrium syndrome – Worsening of brain edema – Machine dysfunction – Circuit coagulation – lines disconnection

* In chronic patients undergoing RRT, the relevant advantages and disadvantages may be significantly different

Table 4. Peritoneal Dialysis

Advantages	Disadvantages	Complications
– Cardiovascular stability – Gentleness of treatment – No need for machines – Easy monitoring – No need of heparin – Administration of nutrients – Administration of drugs – No need for vascular access – No risks of extracorporeal circulation – Steady state chemistry when CPD is performed	– Low efficiency – Low rate of ultrafiltration – Need for peritoneal access – Respiratory problems – Glucose load – Risk of infection – Contraindicated in burns and recent abdominal surgery – Large amounts of dialysate if IPD is performed – Protein losses – Increased intraabdominal pressure	– Bacterial or fungal peritonitis – Catheter malfunction – Leakage – Pulmonary atelectasis – Cardiac arrhythmias – Hypernatremia – Hyperglycemia – Intestinal perforation – Pneumoperitoneum – Hernias – Hydrothorax

average blood urea concentration of 100 mg/dL, a maximum of 18 g urea could be removed in 24 hours. Since most critically ill patients are severely catabolic, this amount of urea removal frequently resulted in an insufficient control of blood urea levels and inade-

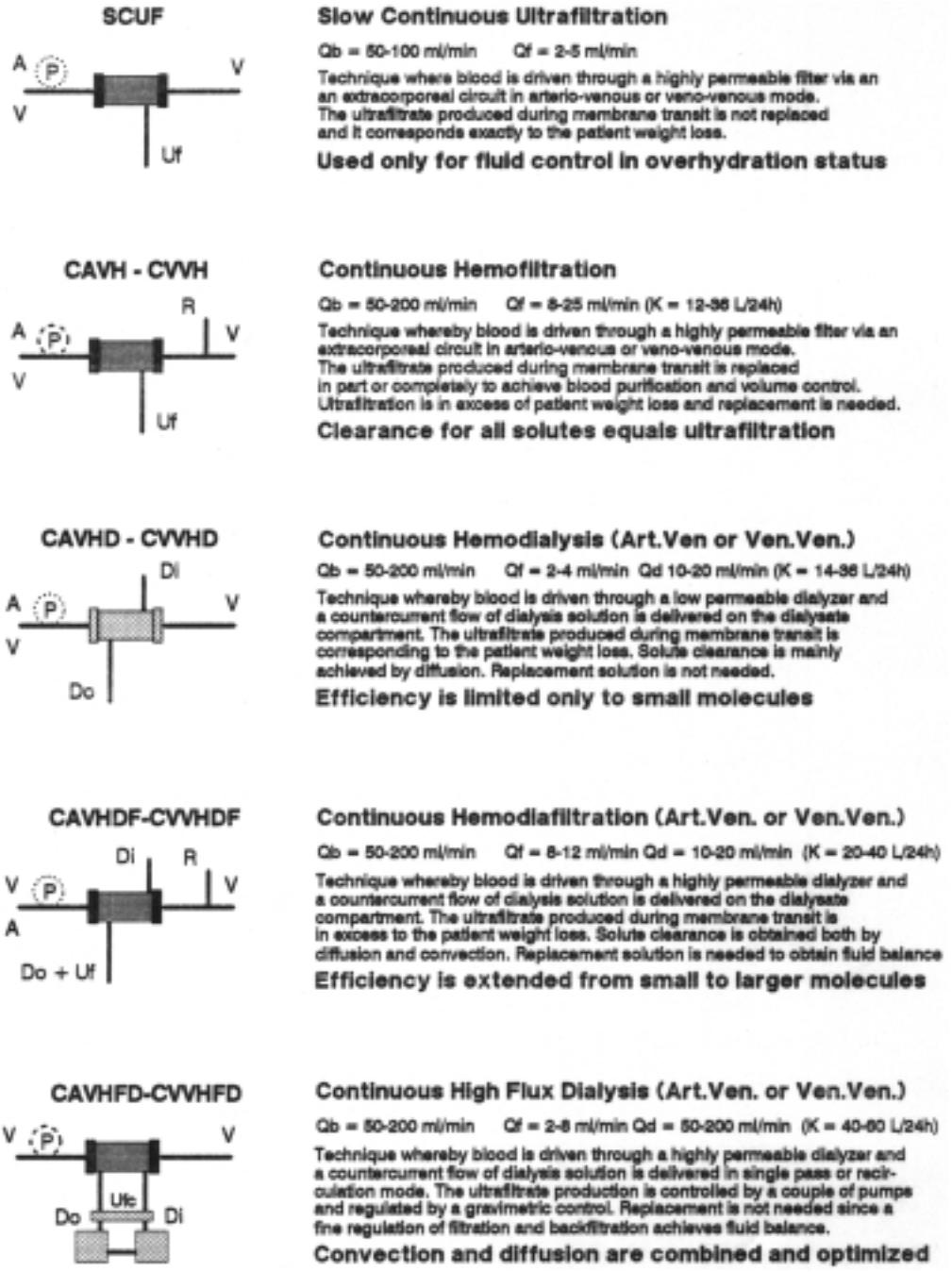

Figure 2. Schematic representation of the various techniques for continuous renal replacement therapy (CRRT). A = artery; V = vein; P = pump, R = replacement solution; Uf = ultrafiltrate; Di = dialysate inlet; Do = dialysate outlet; Ufc = ultrafiltration control system; Qb = blood flow; Qf = ultrafiltration rate; K = clearance; Qd = dialysate flow rate.

quate blood purification. For this reason, newer techniques were required and the use of continuous arteriovenous hemodialysis (CAVHD) has been introduced as a first alternative to classic CAVH (Figure 2) [7].

The treatment was similar to CAVH but a low permeability membrane could be employed and countercurrent dialysate flow was provided to increase transmembrane urea removal by the addition of diffusion. At the beginning, cuprophan (CU) hollow fiber devices were utilized, while in a second step, polyacrylonitrile (PAN) plate dialyzers were employed for CAVHD. Since a dialysate flow rate of 16 mL/min was programmed, almost complete saturation of the spent dialysate was obtained thus leading to an average urea clearance similar to dialysate flow, plus the small amount of ultrafiltration allowed from the patient. Thus a daily urea clearance in the range of 24 – 26 L could be achieved with CAVHD with an increased efficiency of treatment. In the same days, we applied the same concept to a highly permeable hollow fiber hemodiafilter, and we firstly described the treatment called continuous arteriovenous hemodiafiltration (CAVHDF) [8]. In this treatment, the higher permeability of the membrane (we were using polysulfone 0.4 – 0.7 m^2 hollow fiber hemodiafilters) allowed for a convenient combination of diffusion and convection, thus permitting not only an increased efficiency of removal of small molecules, but also an improved efficacy for the extraction of larger solutes. In our original description, a 40% increase in solute removal could be achieved in a day of treatment combining diffusion and convection. The amount of ultrafiltration exceeded the scheduled weight loss and replacement solutions had to be reinfused to maintain fluid balance.

From Arteriovenous to Pumped Circulation

One of the major limitations imposed by the arteriovenous approach was the unstable performance of the circuit due to possible reductions of extracorporeal blood flow secondary to the patient's hypotension, or circuit kinking and filter clotting. This frequently resulted in treatment interruptions, reduced daily clearance, and treatment failure. On the other hand, the perception of continuous renal replacement therapy (CRRT) had changed over time and, by the late eighties, CRRT had become more and more accepted in the ICUs as a standard form of therapy. Therefore, thanks to the recent development of double lumen venous catheters and a new generation of blood pump modules for continuous therapies, the era of CAVH started to decline and the more efficient continuous venovenous hemofiltration (CVVH) or venovenous hemodiafiltration (CVVHDF) became the golden standard (Figure 2). In CVVH, purely convective blood purification is achieved in a system where the production of ultrafiltrate is almost completely replaced by a substitution fluid. Higher amounts of fluid can be exchanged per day in CVVH, since blood flow can be maintained constant over time and the performance of the membrane is better preserved. CVVH can be performed in post-dilution mode reaching daily clearances for urea in the range of 36 L. When predilution is performed, the requirement of heparin may be remarkably reduced and ultrafiltration can be increased up to 48 – 56 L/day. It is clear, however, that since predilution decreases the effective concentration of the solute in the filtered blood, the amount of solute removal is not proportional to the volume of ultrafiltrate produced and it is reduced by a factor depending on the percentage of predilution flow vs. blood flow.

The increased amount of fluid exchanged per day in CVVH induced several units to utilize automated blood modules equipped with blood leak detectors, pressure alarms, and pressure drop measurement in the blood compartment of the dialyzer [9 – 10]. In the mean time, several machines began to use a second pump to control the rate of administration of the replacement solution and integrated systems for CVVH started to be proposed by the industry. It was clear, however, that despite the high efficiency achievable with this system, a low degree of safety and reliability was still present in these machines which were basically derived from hemodialysis blood modules but never reached the status of independent units for CRRT.

From CVVH to CVVHDF and More

More recently, a new generation of machines such as the Prisma (Hospal, Lyon, France), the Diapact CRRT (B. Braun Carex, Mirandola, Italy), EQUA-SMART (Medica, Medolla, Italy), the BM25 (Baxter Healthcare, USA) and the Multimat B-ICU (Bellco, Mirandola, Italy) have been designed as complete CRRT machines for acute renal replacement in ICU patients. These machines are all equipped with integrated safety alarms, fluid balancing controls, and connected blood modules with the possibility to perform CVVH, CVVHDF and continuous veno-venous hemodialysis (CVVHD). These machines allow smooth conduction of RRT in the ICU with increased levels of efficiency [9 – 10]. Blood flows up to 200 – 300 mL/min and dialysate/replacement fluid flow rates in the same ranges are leading to urea clearances that may reach 100 mL/min. At the same time, the highly permeable membranes utilized in these systems achieve improved clearances of the larger molecular weight solutes. Due to the higher blood and dialysate flow rates achievable in the system, higher surface areas can also be utilized and more efficient dialyzers can be applied.

The new machines are also equipped with a friendly user interface: this leads to an increased confidence of the personnel with the therapy and constant levels of efficiency can be applied without major problems or complications.

Continuous High-flux Dialysis (CHFD)

The metabolic control of ARF generally requires ≥ 20 L urea clearance/day. All attempts to add diffusion to convection have shown that, while satisfactory clearances of small molecules are generally achieved, the clearance of middle molecules might be insufficient. Since ICU patients with ARF, sepsis, multiorgan dysfunction and severe catabolism may present increased levels of substances in the middle molecular weight range (500 – 5000 Daltons), i.e. chemical mediators, vasoactive substances, cytokines such as tumor necrosis factor (TNF), Interleukin-1 (IL-1), and platelet activating factor (PAF), an adequate treatment should be oriented towards the control not only of urea nitrogen, but also of all these substances [11]. In this case the necessary amount of convection can only be obtained with high-flux synthetic membranes because of their higher sieving capacities. To come up with a compromise and to meet the requirements of adequate amounts of convection and diffusion, reduced quantities of replacement solution and easy monitoring, CHFD has recently been proposed [9 – 12].

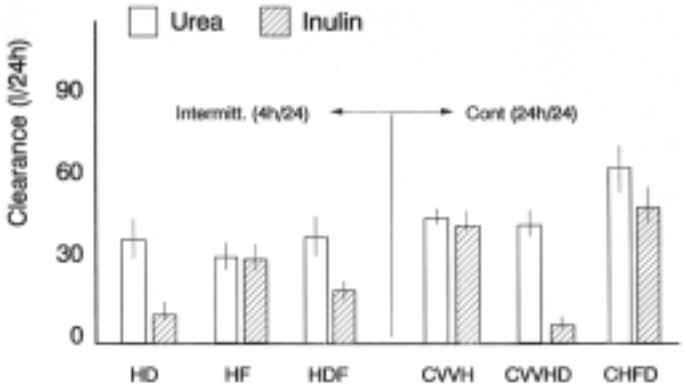

Figure 3. Efficiency of different renal replacement therapies in terms of urea and inulin clearance. (urea and inulin are taken as marker molecules for small and middle molecular weight substances respectively)

The name derives from the chronic treatment (high-flux dialysis) where a dialyzer with high permeability is utilized in conjunction with an accurate ultrafiltration (UF) control system. The UF control achieves an adequate fluid balance without need for a replacement solution. High convective transport is still maintained in the proximal part of the filter, but it is compensated by the high rate of backfiltration that takes place in the distal part of the fibers (Figure 2). This treatment has been therefore created to combine the advantages of continuous HD and continuous hemofiltration (HF).

The system consists of a circuit for continuous HD modified to achieve a continuous dialysate volume control. A hemodiafilter (or high-flux dialyzer) is utilized and 2 roller pumps are applied to the dialysate circuit. Warmed dialysate is delivered by the first pump at a programmed flow rate. The second pump regulates the dialysate outlet flow rate and therefore the net ultrafiltration, in response to a specific controller and programming module. UF control is achieved by a continuous gravimetric control. The system may operate in conditions of single pass or recirculation of dialysate. In recirculation mode, the same amount of dialysate can be better utilized with a lower cost of the treatment. In this system, once the patient's dry weight has been achieved, the circuit may operate at zero net filtration using sterile dialysate at various flows (50 – 200 mL/min). In our experiments carried out with different operational conditions and dialyzers, dialysate/plasma equilibration for urea and creatinine is reached after a variable treatment time between 120 and 210 min, when 10 L of dialysate fluid are employed in recirculation mode. Interestingly, at the same time the dialysate/plasma ratio for larger molecules such as inulin is 0.6. Assuming a continuous treatment is performed and dialysate bags are changed every 4 hours, urea clearances up to 60 L/day and inulin clearances up to 36 L/day can be expected. This represents a very efficient blood purification with a daily clearance close to or even greater than the whole urea distribution space of the patient. In this case the fractional clearance over total body water (*K/V*) approaches or exceeds the value of 1 every 24 hours (t). If CHFD is performed continuously, the weekly *Kt/V* index may be in the range of 7 – 10 thus resulting in a treatment efficiency much higher than that achieved with other intermittent dialysis therapies (Figure 3). In fact, since a steady blood urea concentration is achieved during treatment, these clearances are leading to a greater amounts of urea removal if compared to intermittent therapies where the blood con-

centrations tend to fall significantly during treatment. When less efficiency is sufficient, the bags can be changed every 6 hours and, while urea equilibration is maintained, the equilibration for larger molecules will be in this case even higher. The high clearance for inulin is mostly achieved because of the convective transport taking place in the proximal side of the filter. Zero net filtration is in fact achieved thanks to a mechanism of proximal filtration and distal backfiltration. CHFD is therefore a hemodiafiltration-like system, where the ultrafiltrate is produced in the first half length of the fibers and the reinfusion is provided in the second half by the backfiltration of sterile dialysate. Variable increases in clearances can also be achieved if the system is applied in single pass conditions with large hemodiafilters. Furthermore, some newly designed machines are able to handle 20 L of fluid and therefore bags do not need to be exchanged as frequently.

High Volume Hemofiltration (HVHF)

Recent experimental findings have demonstrated the beneficial impact of increasing the volume of UF during continuous hemofiltration therapy [13]. In particular, hemodynamic improvement has been observed in the experimental animal injected with endotoxin. Although the possibility of preventing the septic shock syndrome in humans by this technique has not been proven yet, there is enough evidence that suggest the need for a pilot controlled randomized trial to test this hypothesis. To perform HVHF, however, a clear definition of the operational ranges of the technique and a precise description of the technical requirements imposed by this form of therapy are definitely needed.

According to present clinical practice, CVVH is generally performed with an average UF rate between 1 – 2 L/hour. Above 50 liters per day, the amount of UF is considered high and the treatment can be defined as HVHF.

There are 2 ways to perform HVHF: the standard CVVH treatment schedule is maintained and the rate of UF is maintained at 3 – 4 L/hour; or the standard CVVH therapy is maintained overnight, but during a few hours of the day, a large amount of UF is produced at rates > 6 L/hour. In both cases the amount of UF exchanged per day may exceed 60 L.

Technical Notes

Continuous therapies require special care and a series of specific measures to permit smooth and safe conduction of treatment.

Access to Circulation

CAVH was performed by placing large bore catheters in an artery and a vein to guarantee a sufficient arteriovenous pressure gradient to move the blood through the circuit. Several problems including hematomas, low blood flows, and low efficiency of treatment induced most groups to move towards venovenous pumped extracorporeal circuits.

Since arteriovenous HF has been almost abandoned, the developments in the field of vascular access mostly concern venous catheters. The use of double lumen venous catheters has practically solved the problem of vascular access, permitting the use of a single head blood pump [14]. Further studies should, however, be devoted to improve the clinical

tolerance to these catheters. In particular, special care should be placed to avoid skin infections or septic problems derived from the catheter itself. Subcutaneous tunnelling and exit site care represent adequate measures to achieve such results.

Double lumen catheters however may present a series of limitations due to their design. First of all, access recirculation cannot be avoided and, in some cases, this can reach dangerous levels. When recirculation exceeds 20%, hemoconcentration takes place in the extracorporeal circuit leading to an increased viscosity of blood and easy clotting of the system. Furthermore, the efficiency of the system may be dramatically reduced leading to inadequate blood purification. Access recirculation tends to increase as the blood flow increases. For this reason, blood flows > 150 – 200 mL/min are discouraged when double lumen catheters are utilized. However, since higher blood flows may be required in some cases to achieve higher volumes of fluid exchange, 2 separate venous catheters may be the solution in such conditions. Encouraging results have been obtained with the new split-catheters.

Circuitry and Equipment

When arteriovenous HF was used, special care had to be applied to reduce any resistance in the extracorporeal circuit. For this reason, ultrashort blood lines were created and short circuits were recommended (Figure 1). The use of a blood pump in the extracorporeal circulation has essentially removed such concerns, leading, however, to an increased complexity of the circuit. A bubble trap with active alarms is necessary to avoid air embolism. Pressure measurements before and after the filter are required to avoid vessel damage or circuit explosion (Figure 4).

In modern equipment, continuous measurement of the pressure drop inside the filter, obtained from adequate pressure measurements, achieves monitoring of filter function and detection of early clotting of the fibers.

Standard blood pumps for HD have shown to be inadequate for continuous therapies and a new series of machines specifically designed for CRRT have now been created.

The ideal machine should have a small volume, an easy interface and high flexibility (i.e. the ability to perform all types of treatments). The machine must be self-standing and easily transportable to the bedside. When a new machine is designed, a certain compromise must be reached between simplicity of use and flexibility of performance. For example, the number of pumps may vary from 1 – 5 depending on the functions of the system. A single pump apparatus may be designed assuming that fluid balance is achieved by gravity or external devices, heparin administration is performed periodically, in a different intravenous (IV) line, or with an external syringe pump. Finally, the single pump may often preclude the use of a single lumen catheter in a push-pull mode. The advantage of such systems, however, is the simple layout of the circuit and the easy interface with the operator. Such systems can be operated by nursing personnel without need for long training and learning procedures. Recently, new machines for CRRT have been designed with 4 – 5 pumps. Two pumps are utilized for blood flow (single or double lumen catheters) and 2 pumps are utilized for the ultrafiltrate and replacement in CVVH mode, or for inlet and outlet dialysate in CVVHD mode. The fifth pump is utilized for heparin or drug infusion. Despite maximal simplification or self-learning display, the layout of the lines is complex and a dialysis nurse is often required. Such machines are not utilized on daily basis, and, in some cases, the training of nursing person-

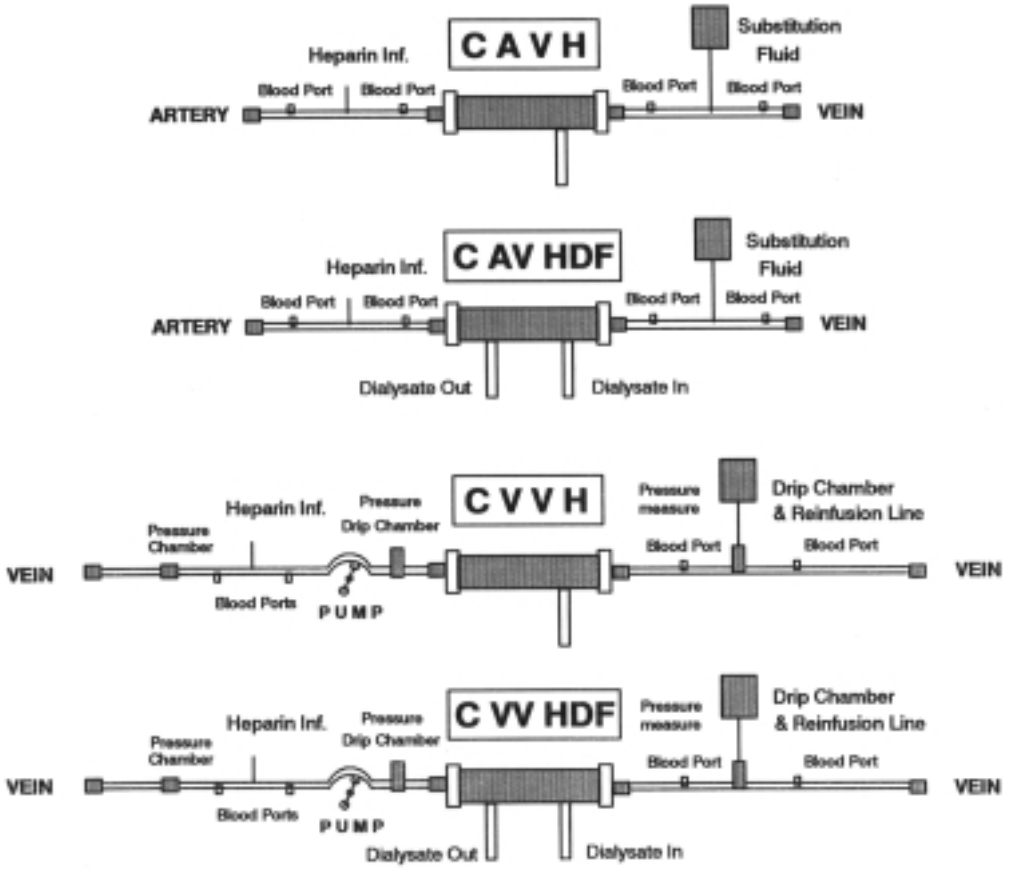

Figure 4. A series of typical CRRT circuits with blood and dialysate lines.

nel becomes difficult or prolonged. Furthermore, such machines are frequently big, difficult to move, and require costly maintenance. The cost of the lines and the entire treatment, including the machine, may significantly increase. The advantages of such systems, however, are represented by the possibility of carrying out all different treatments in the presence of any type of vascular access. Fluid balance is accurate and treatment is standardized, allowing the highest levels of efficiency and tolerance. All these machines utilize sterile dialysate. Recently, bicarbonate-based replacement fluids or dialysis solutions have been made available for this purpose. Acid and basic solutions are mixed before the treatment to avoid calcium precipitation during storage and stability of the solution is guaranteed up to 48 hours. The fluid can be warmed on line and it can be used both as a replacement solution or dialysis fluid.

Hemofilters and Dialyzers

In arterio venous HF the resistance of the hemofilter was a critical point to achieve adequate blood flows even in the presence of low arterio venous pressure gradients. For this

reason small short filters with a large cross-sectional area were identified as ideal devices for CAVHF. The search for an optimal compromise between surface and resistance has now become less important because of the extensive use of blood pumps. Blood flow is standardized and the filtration fraction (the ratio between UF and plasma flow rate) can be adjusted at the desired level in order to achieve optimal performance of the filters. High filtration fractions are leading to protein concentration polarization, and membrane clogging; therefore predilution is often used to minimize the increase in protein concentration inside the filter, and filtration rates are optimized at an average value of 20%. Anticoagulation is then achieved with lower amounts of heparin and in some cases, treatment can be carried out with no heparin at all.

All filters are now equipped with 2 ports in the ultrafiltrate compartment so that dialysate can be circulated when required. Filtration membranes have been improved beyond hydraulic permeability to achieve satisfactory diffusive properties. These membranes are in a continuous process of evolution towards reduction of thickness (i.e. reduction of diffusive resistance), optimization of pore size and distribution, hydrophilic structure, and biocompatibility properties.

Biocompatibility has been recently shown to improve patient survival and recovery of renal function [15]. Similarly, highly permeable membranes have been shown to adsorb and filter high amounts of chemical mediators of inflammation and sepsis [16 – 18]. These properties must be further explored, but they may represent a useful mechanism of renal support in critically ill patients.

Heparin-bound surfaces are still under evaluation, but this approach may further improve the biocompatibility of the membrane and reduce the risks related to heparin infusion including bleeding and heparin-induced thrombocytopenia. Substances other than heparin have been bound to artificial membranes in order to permit selective adsorption of certain molecules. This may represent an interesting therapeutic approach for the future.

Finally, when high volumes of ultrafiltrate are produced, it may be of interest to investigate the possibility of regeneration and reinfusion of the ultrafiltrate by on-line production of pyrogen-free replacement solutions from dry concentrated salts.

Clinical Aspects and Indications

Blood Purification

When continuous HF is utilized, solute clearance is equal to the amount of ultrafiltrate obtained over 24 hours. Assuming in CAVH a maximal clearance of 16 L, in a given patient with 100 mg/dL of blood urea nitrogen (BUN), 16 grams of urea nitrogen can be removed daily. When severely catabolic patients are involved, higher amounts of ultrafiltrate are needed to control azotemia and CVVH is frequently used. In such conditions clearances up to 30 – 40 L/day are required and the use of a blood pump in the circuit can achieve the desired level of efficiency. Urea is also effectively removed when a countercurrent flow of dialysate is utilized in the circuit and diffusion is added to convection, thus obtaining a treatment defined as CVVHD or CVVHDF: the first utilizes a low-flux membrane while the latter uses a synthetic high-flux membrane.

Solute concentration rebound as those seen after highly efficient intermittent treatments

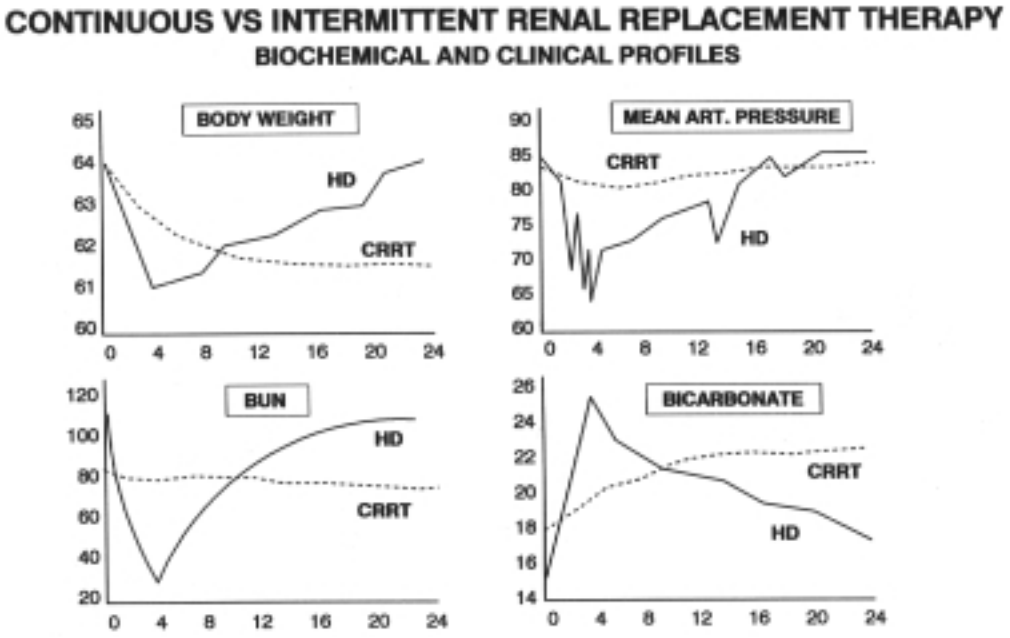

Figure 5. Continuous versus intermittent renal replacement therapy. Continuous venovenous hemofiltration is compared to intermittent hemodialysis in a critically ill patient. Continuous therapy allows for a steady control of body weight, BUN, Bicarbonate and mean arterial pressure while intermittent hemodialysis leads to remarkable fluctuations in the same parameters.

are not observed in continuous therapies; this represents a major advantage in terms of BUN time average concentration. While in intermittent hemodialysis BUN concentrations suddenly fall after one hour of treatment and solute extraction is reduced showing a remarkable postdialytic rebound, BUN concentrations are steadily controlled with continuous therapies and the average concentration over time is lower (Figure 5).

Fluid Overload, Heart Failure and Septic Shock

Clinical conditions other than ARF, such as congestive heart failure (CHF), Acute Respiratory Distress Syndrome (ARDS) and cerebral edema may benefit from continuous treatments when oliguria or early signs of renal insufficiency are present (Table 5).

The patient with severe hemodynamic instability cannot be controlled with intermittent treatments such as HD or hemodiafiltration carried out for 3 – 4 hours/day. On the other hand peritoneal dialysis (PD) cannot achieve the UF volumes and solute clearances necessary to control overhydration and severe catabolism. The slow continuous fluid removal achieved with continuous therapies such as CAVHF-CVVH or CAVHD-CVVHD is generally well tolerated and an optimal hydration status can generally be reached within a relatively short period of time with adequate constancy of measured hemodynamic parameters. Among the possible mechanisms that have been proposed to explain the steady hemodynamics in patients

Table 5.

Sequence of Events in Sepsis

Bacterial Invasion of the Host
Exo- and Endotoxin Presence in Blood
Activation of Humoral Pathways Response
Recognition of LPS via specific cell receptors
Activation of Specific Cellular Response
Production of Inflammatory Mediators

Clinical Consequences: Inflammation and Shock

Source of Endotoxins and Pyrogens	*Possible Therapeutic Approach*
Bacterial degradation and killing in the patient	Biological blockage of endotoxin (???)
Possible external contamination of the circuit	Endotoxin adsorptlon onto artificial membranes
Backdiffusion and backfiltration of LPS fragments	Endotoxin elimination by plasma filtration procedures
Signalling and cell activation without endotoxin	Intervention on endotoxin-induced biological effects
Additional transfer stimuli from membrane bioincompatibility	Modulation of humoral response
	Modulation of cellular response
	Clearance of mediators of inflammation

undergoing fluid removal by continuous HF, continuous fluid withdrawal from the interstitium with progressive vascular refilling that avoids significant relative blood volume changes has been considered a critical one (Figure 6).

This feature is particularly useful in patients with severe cardiac failure. Several mechanisms have been considered important in the amelioration of the hemodynamic conditions of patients with CHF treated with continuous HF: the improvement in ventricular filling pressures, the reduction of preload, the maintenance of the blood volume, the modulation of the renin-angiotensin axis, the reduction of afterload, and the possible clearance of myocardial depressant substances. Another factor considered important has been the possibility of a dissociation between sodium and water transport during HF. This, together with the isotonic characteristics of the ultrafiltrate, may lead to continuous vascular refilling and an improved hemodyamic conditions.

There is human and experimental evidence to indicate that continous HF beneficially affects cardiac function both in CHF and sepsis [19 – 30].

During severe CHF, fluid retention may lead to major increases in left ventricular diastolic volume. In these patients, removal of excess intravascular and extravascular fluid can be reasonably expected to optimize left ventricular filling and improve cardiac output once again. The patient's clinical status can then be expected to improve at the same time. Sufficient and safe fluid removal, however, is not always easily undertaken in these patients. There often is diuretic-resistant fluid retention and concomitant renal impairment. Furthermore, the patient's condition is such that excessive fluid removal may precipitate a severe low output state. Inadequate fluid removal, on the other hand, may result in delayed treat-

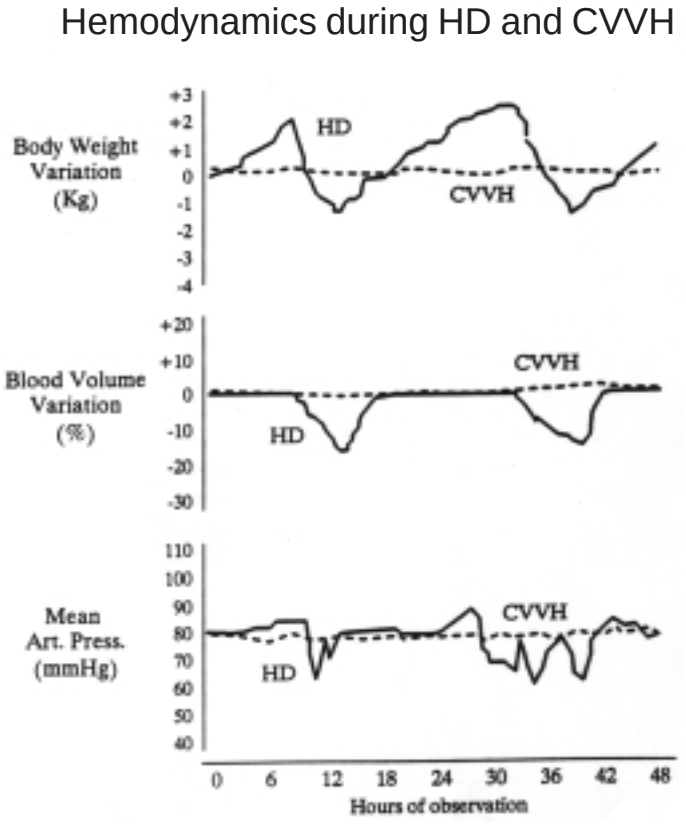

Figure 6. Continuous versus intermittent renal replacement therapy. Continuous veno-venous hemofiltration is compared to intermittent hemodialysis in a critically ill patient. Continuous therapy permits a steady control of body weight and arterial pressure. The better tolerance is explained by the absence of variation in the circulating blood volume.

ment and the development of pulmonary edema.

A possible answer to this therapeutic challenge has been provided by continous HF. The utility of such techniques in the management of episodes of refractory cardiac failure has been widely reported [19 – 30].

HF has also been shown to offer significant benefits in the setting of pediatric cardiac surgery [31], with reduced time spent on mechanical ventilation with improved hemodynamics and tissue oxygenation, accelerated recovery of renal function and significant reduction in circulating TNF, C3a – C5a and IL-6 levels.

By far the most exciting aspect of the beneficial effect of HF on hemodynamics and cardiac function pertains to the area of sepsis and septic shock. It is well known that septic shock is associated with significant myocardial dysfunction. Much evidence suggest that there may be circulating myocardial depressant substances during severe sepsis. Such depressant substances appear to have middle molecular weights and are potentially filterable. It is, therefore, possible that the use of HF in shock states would beneficially affect cardiac function. It has susequently been show that TNF is a major myocardial depressant and a likely candidate for this effect in vivo. Furthermore, it has also been recently shown that continuous HF removes TNF (and a number of other cytokines and autacoids) from the circulation of patients with sepsis [32 – 39].

Given that most removal of middle molecules during HF is convective, it is theoreti-

cally possible that increasing ultrafiltrate production and convective clearance will result in even more detectable beneficial cardiovascular effects [29 – 30]. Clearly, there is much more that we have to learn on the effect of HF in human sepsis, but its application to the management of human septic shock is already taking place particularly in the form of high-volume hemofiltration.

Recent experimental reports are promising and suggest the need for controlled studies in humans soon. Continuous HF may soon become a powerful tool in the adjunctive management of septic shock, not only to improve cardiovascular function, but also as a form of therapy directed at decreasing the effects of uncontrolled humoral inflammation on other organs.

Electrolyte and Acid-base Derangements

Continuous therapies may be used to correct water and electrolyte imbalances by changing the composition of the substitution fluids or of the dialysate. Hypo- and hypernatremia can be corrected not only by achieving a normal plasma sodium concentration, but also by restoring the normal body sodium content. Hyperkalemia can also be corrected: the efficiency in removing potassium is directly related to the amount of fluid removed during treatment and its replacement with potassium-free solutions. However, the efficiency of CAVH-CVVH in removing potassium is rather low, and continuous HD with a potassium-free dialysate may be more efficient.

Bicarbonate loss during CAVH can easily be measured directly in the ultrafiltrate or predicted using the formula:

$$[HCO_3^-]_{UF} = UF \times [HCO_3^-]_s \times 1.124$$

where $[HCO_3^-]_{UF}$ and $[HCO_3^-]_s$ are the bicarbonate concentration in the ultrafiltrate and in the serum; UF = total amount of ultrafiltrate and 1.124 = average bicarbonate sieving coefficient

When CAVH-CVVH are applied without fluid substitution to reduce fluid overload, bicarbonate losses are compensated by the reduction of the body volume distribution for the buffer and the serum concentration does not change significantly. On the contrary, when replacement solutions are infused to maintain body fluid balance, the same amount of bicarbonate lost in the ultrafiltrate must be administered to achieve stable serum levels of the buffer. Finally, to correct metabolic acidosis, the amount of HCO_3^- in the replacement solution must exceed the amount lost in the ultrafiltrate, providing a positive balance of the buffer [11]. In CHFD, bicarbonate dialysate provides an adequate buffer balance and smaller fluctuations of the acid-base status can be observed with a remarkable clinical stability.

Special Indications

In patients with cerebral edema, intermittent treatments may worsen the clinical condition because of a post-dialytic influx of fluid both in the grey and white matter. These alterations induced by intermittent treatments are not observed with continuous therapies that can therefore be utilized with maximal advantage in these patients.

Infants and neonates have been successfully treated with continuous therapies. The slow progressive action of the treatment may help achieve adequate RRT and the correction and maintenance of a homeostasis. For these treatments, special minifilters with reduced priming volumes have been utilized.

Several mechanisms have been proposed to explain the improvement of ARDS patients treated with continuous HF. Continuous fluid withdrawal from the interstitium due to isoosmotic ultrafiltration and progressive vascular refilling represents a major advantage. However, the modulation of vascular inflammation thanks to the clearance or adsorption of specific pro-inflammatory substances onto the membrane has been recently hypothesized. This mechanism has also be invoked as an interesting therapeutic possibility for patients with SIRS (systemic inflammatory response syndrome) or septic shock (Table 5).

Beyond RRT and Towards Renal Protection

Recently, several studies have provided evidence for inflammatory mediators to be of relevance in determining structural and functional changes capable of establishing ARF. Eicosanoids, cytokines (TNF, IL-1, IL-6, IL-8), endothelin (ET), and PAF may all contribute to the fall in renal blood flow (RBF) and GFR during sepsis.The biologic properties of these mediators alone or in combination may account for the metabolic and hemodynamic changes of sepsis.

Evidence that excess of TNF-α and/or IL-1β may be causally involved in the development or sepsis-induced MODS raises the possibility that removal of these cytokines from the circulation of clinically ill patients may be of benefit. CVVH provides extraction of significant quantities of circulating macromolecules (molecular weight 30 kilodaltons) with high permeability membranes currently in use. We have shown clearances of 30.7 and 36.1 L/day for TNF-α and IL-1β with a total excretion rate (ng/day) of 14.1 and 10.6. Excretion was mainly by ultrafiltration, although other authors have envisaged significant absorption by hydrophobic membranes. The relevance of convection in maximizing the performances of filter systems cannot be overemphasized and may cast doubts on studies where it might have been overlooked. However, several aspects have to be clarified before the extracorporeal removal of cytokines can be unanimously accepted as clinically relevant. First, TNF-α and IL-1β are not the sole cytokines to play a role in septic shock. Second, the incidence of detection of TNF-α in septic patients is variable and the concentration of IL-1β is usually not increased. Furthermore, IL-8, another important pro-inflammatory cytochine, is not ultrafiltered by all high-permeability membranes. The second aspect is the high "volume of distribution" and high endogenous clearance of cytokines. Much interest has recently emerged over membrane handling of different mediators. Deeper insights into the mechanisms at work may provide new ideas for more appropriate surfaces and dialytic strategies. We have already hinted at the relevance of convection in the removal of mediators of sepsis.

In a recent study, we evaluated the removal of PAF by experimental CAVH with respect to kinetics, absorption and ultrafiltration. These studies emphasized the role of plasma in enhancing removal of PAF from the distribution volume. In fact, removal of PAF by UF was significantly higher in the presence of plasma than in washed blood. Since PAF was absorbed onto the cell surface, plasma (which may bind one-third of the amount of PAF added to whole blood) may be relevant in rendering PAF available for UF. Moreover, PAF was ultrafiltered at a much lower rate when we used plasma-free washed blood cells suspended in physiologic concentrations of albumin instead of whole blood. These studies

suggest that convection in this setting increases the surface area available. Indeed CAVH membranes may function in vivo as "sponges" for mediators such as PAF and, as elsewhere demonstrated, for TNF. High amounts of PAF have been recovered from hemofilters used in patients with septic shock.

Possible advancements in the extracorporeal device dedicated to critically ill patients should take into account the need for higher convective rates , type of reinfusate, and removal of protein-bound cytokines.

Complications

Continuous therapies are generally well tolerated with a low rate of complications (Table 6) [40]. The outcome is partially related to such aspects as the severity of the illness, and the presence of concomitant factors such as mechanical ventilation or artificial cardiovascular support. The number of organs involved in the syndrome appears to be critical to the final outcome and the rate of mortality. In most series, mortality is still > 50% for critically ill patients treated with continuous therapies. As continuous HF is an invasive technique, certain typical risks have to be considered. The most severe complications were mainly associated with the arterial access in CAVH. Venovenous access reduces the complication rate considerably. Bleeding transcutaneous punctures and introduction of a large cannula by the modified Seldinger technique may lead to bleeding and even vessel perforation.With careful technique and experience, this happens only rarely.When local atherosclerosis is present, serious bleeding may occur by injuring the vessel wall and detaching plaques. Therefore, in suspected severe local atherosclerosis another access (e. g. venous) is preferred. During the course of HF, careful control of the anticoagulation (low-dose heparinization) reduces the risk of bleeding. However, at the end of the procedure, bleeding may even result from the removal of the arterial cannula. Careful and persistent compression is mandatory. If bleeding continues, the decision for surgical intervention should be made without further delay. The infection of a large persistent hematoma may cause an abscess which is difficult to treat the femoral region.

Table 6. Continuous Arteriovenous Hemofiltration vs. Intermittent Hemodialysis

- Slow continuous therapy and fluid removal
- Purely convective solute transport
- High biocompatibility of the system
- High sieving capacity of the membrane
- High adsorbtive capacity of the membrane
- Isotonic ultrafiltration
- Good clinical tolerance and hemodynamic response
- Possible manipulation of extracellular fluid composition with different substitution fluids
- No rebounds in solute concentrations -stability of the desired body hydration
- Possibility of hyperalimentation

Local thrombosis at the arterial cannula site occurs rather often (about 10%). Occasionally, this may critically restrain the perfusion of the leg; prompt surgical intervention is mandatory. Therefore, frequent and regular assessment of perfusion (e. g. by Doppler sonography) is highly advisable. Especially in severe atherosclerosis, local thrombosis becomes a considerable risk.

Local infections at the cannula site (especially infected hematomas) are serious complications because they may threaten arterial perfusion. Therefore, the extracorporeal circuit must be handled with extreme care: sterile handling with avoidance or reduction of disconnections for blood sampling.

At the high perfusion rate of the extracorporeal circuit (especially in the absence of alarms and monitoring), any accidental disconnection of blood lines acutely threatens life. Therefore all connections must be tightly locked in, and the whole circuit must be freely visible (e. g. not covered by blankets). Continuous surveillance by a competent nurse must always be ensured. It is generally accepted that the risk of technical complications clearly correlates with competence and intensity of nursing care.

Air embolism in modern pump driven systems is prevented by special monitoring and alarm systems which immediately stop perfusion when air enters the system. Except in cases of technical defects, this safety system excludes any air embolism. However, in the spontaneous CAVH technique without any alarm systems air embolism can indeed occur when a disconnection happens at the venous access and negative inspiratory pressures sucks air into the venous system.

Accidental fluid overload is a consistent danger of continuous HF techniques, especially, when a high fluid turnover is maintained. Meticulous monitoring and protocol-based assessment of fluid intake and output is mandatory. Everybody must be aware of the danger of possible fluid balance errors. Furthermore, the clinical condition of the patient must be carefully taken into account.

Hypothermia can occasionally occur when large amounts of ultrafiltrate are exchanged but simple warming of substitution fluid may correct this problem. On the other hand, continuous HF can effectively be used to reduce body temperature in cases of hyperthermia.

Hypophosphatemia has been observed and, as for other electrolytes, nutrients and drugs, solute imbalances can easily be avoided with frequent monitoring of ultrafiltrate and plasma concentrations and adjustments of the replacement fluid composition.

Treatment Outcome in Patients with ARF

Isolated ARF (e.g. caused by nephrotoxins, infections, and other renal diseases) generally has a good prognosis, with mortality reported < 10%. However, in critically ill patients treated in intensive care units, ARF is usually part of multiple organ failure arising during the hospital stay and treatment, often following complicated surgery and induced by sepsis. Here, mortality still remains extremely high, depending upon the number of other failing organs. Thus, mortality cannot directly be connected to renal failure, but is, in fact, the result of the multiple organ failure as a whole. Sepsis is the major cause of death in up to 70% of patients with ARF. Once multiple organ failure is established with respiratory and cardiovasculatory support, renal failure becomes only one problem among others. It seems therefore rather pointless to assign the mortality to ARF alone. Consequently, the positive effects of RRT cannot exclusively be compared and measured by mortality. The fact that the mortality of ARF in critically ill patients cannot significantly be improved yet, has often been used as an argument against CRRT. However, this is inappropriate. For correct comparison we need reliable methods for comparing the severity of illness of the patients involved. Scoring severity of illness, for instance by APACHE II or III, by simplified acute physiological score (SAPS), by mortality probability monitoring (MPM) or organ system failure (OSF), may help to prove the effect of renal support therapies. But, even then, all measures applied in the intensive care for the treatment of the multiple organ failure will contribute to the final outcome. In large studies from ICUs, including large numbers of patients with well-defined organ system

failure, the strong correlation between the number of failing organ systems and mortality has been clearly demonstrated: 2-organ failure for more than one day increased the death rate to 60%; 3-organ failure for > 3 days had a mortality of 92%. Furthermore, mortality tends to be higher in patients with ARF and poor previous health status, need for mechanical ventilation, and the presence of oliguria.

Certainly, scoring systems are a necessary tool for measuring severity of illness in controlled clinical trials. However, scores should not be used for decision on therapeutic interventions in individual patients. In the individual cases, prediction of outcome cannot be made from the severity of illness. Nevertheless, scores may help the intensivists have a better idea of what they were dealing with in an individual patient.

Conclusion

The above mentioned procedures represent a variety of reliable and efficient techniques for the treatment of patients with ARF. Some specific advantages such as simplicity, easy monitoring, and easy institution make CAVH a first choice treatment in several clinical conditions. For patients with severe cardiovascular instability, multiorgan failure or polytrauma, CAVH/CVVH may be the ideal treatment [41 – 45]. One of the main features of CRRT today is the flexibility of materials and techniques. Machines and devices can be utilized both for pure convective therapies and for combined diffusive-convective treatments without any complication. The circuit can be used with a blood pump or in arteriovenous driven mode. The choice of the technique and materials will therefore depend on the patient's clinical requirements, the hospital facilities, and the knowledge and training of the nursing staff. The institution of the above described procedures and the use of new devices and materials can now overcome the classic limits of low depurative efficiency or frequent clotting of filters and will make the use of CVVH and related techniques more and more common in the treatment of critically ill patients. The new possibilities offered by different membranes in terms of removal of special pro-inflammatory substances open the horizon to newer indications for extracorporeal blood treatment, such as the treatment of sepsis, multiple organ failure, and other pathologic conditions. Finally, the possible use of extracorporeal blood treatment to protect kidney function or to shorten oliguria and accelerate renal recovery represent a new challange for the coming years [46].

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