# Continuous Renal Replacement Therapy for Acute Renal Failure on the Intensive Care Unit

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# Continuous Renal Replacement Therapy for Acute Renal Failure on the Intensive Care Unit

Continue nierfunctievervangende
therapie voor acuut nierfalen
op de intensive care

**Proefschrift**

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*Als U begrijpt wat ik bedoel.....*
*(O.B.B., 1967)*

*Voor Carine, Willemijn, Florien en Emilie*

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# Contents

# List of Abbreviations

| | |
|---|---|
| APACHE | Acute Physiology and Chronic Health Evaluation |
| ARDS | Adult respiratory distress syndrome |
| ARF | Acute renal failure |
| C | Complement factor |
| CAVH(D) | Continuous arteriovenous hemo(dia)filtration |
| CRRT | Continuous renal replacement therapy |
| CUPID | Continuous ultrafiltration plus intermittent hemodialysis |
| CVVH(D) | Continuous venovenous hemo(dia)filtration |
| ERD | Estimated risk of death (%) |
| $FiO_2$ | Inspired oxygen content (%) |
| ICU | Intensive care unit |
| IHD | Intermittent hemodialysis |
| IL(1ß,6,8 etc) | Interleukin (1ß,6,8 etc) |
| J | Mass transfer (pg/min) |
| K | Clearance (mL/min) |
| MAP | Mean arterial pressure (mm Hg) |
| MDF | Myocardial depressant factor |
| MOSF | Multiple organ systems failure |
| OSF | Organ systems failure |
| PAF | Platelet activating factor |
| PAN | Polyacrylonitrile (AN 69) |
| $PaO_2$ | Arterial oxygen tension (mm Hg) |
| PD | Peritoneal dialysis |
| PG | Prostaglandin |
| $Q_b$ | Blood flow rate (mL/min) |
| $Q_d$ | Dialysate flow rate (mL/min) |
| $Q_{uf}$ | ultrafiltration flow rate (mL/min) |
| SC | Sieving coefficient |
| SIRS | Systemic inflammatory response syndrome |
| TNFα | Tumor necrosis factor alpha |
| TPN | Total parenteral nutrition |
| TX | Tromboxane |

Chapter I

# General Introduction

## Introduction

During the last decade, impressive advances have been made in the techniques available for the treatment of ARF in critically ill patients [1]. This has led to the increased use of continuous hemofiltration and its derived modifications on the intensive care unit (ICU) as opposed to the use of intermittent hemodialysis and peritoneal dialysis [1]. In spite of this, it has not been possible to demonstrate an improved outcome in these patients, which is ascribed to a change in patient characteristics [2]. One major reason for our failure to demonstrate enhanced survival may be the lack of validated and objective illness severity scores that would allow an adequate comparison of outcome data from different reports [3]. Today, ARF is most often encountered in the setting of the systemic inflammatory response syndrome (SIRS), usually as a result of sepsis, which is characterized by the release of a myriad of inflammatory mediators with vasoactive and cardiodepressant properties into the circulation.

It has been suggested that these middle- and large molecular weight mediators may pass the membranes that are used in continuous renal replacement techniques (CRRT) and that this may have a beneficial effect on the clinical course in critically ill patients with ARF [4]. There is, however, still much controversy as to which dialytic treatment modality should be preferred in the setting of ARF on the ICU [5].

## 1. Acute renal failure

ARF, defined as an abrupt decrease in previously stable renal function sufficient to result in retention of nitrogenous wastes in the body, is commonly encountered in the hospital setting. A prospective study of hospitalized general and surgical patients showed an incidence of almost 5% [6]. A higher incidence of ARF is seen in selected clinical settings, particularly in the critically ill, where ARF is reported to occur in 15 and 25% of patients admitted to the ICU [7,8,9]. After excluding prerenal azotemia, postrenal obstruction and inflammatory renal diseases ('nephritis'), the term can be used in a more restricted sense, referring to acute intrinsic renal failure ('acute tubular necrosis'[ATN]). This is more appropriate as ATN is by far the most common cause of ARF in the intensive care setting (60-80%)[9,10]. ARF is traditionally viewed as the result of either an ischemic or nephrotoxic renal injury.

Clinically more common, however, is a combination of various acute insults (Table 1), often on a background of preexisting chronic risk factors, all acting in concert to induce renal failure [11]. Several authors have studied the causes of ARF (acute insults and risk factors) in critically ill patients [12,13,14]. Sepsis is repeatedly shown as the major aetiologic factor for the development of ARF in the ICU. Another, often coexistent, major risk factor for the development of ARF is prolonged prerenal azotemia due to unrecognized intravascular volume depletion. It may be quite difficult to acertain whether a patient who is grossly edematous as a result of the 'capillary leakage syndrome' and hypoalbuminemia (*e.g.*, due to sepsis or trauma) is really overhydrated or that in fact this patient is suffering from severe intravascular

volume depletion, thereby being at risk for renal hypoperfusion. Several predisposing factors for nephrotoxic or contrast-media induced ARF have been identified and are depicted in Table 2 [15-22].

**Table 1. Insults Causing Acute Tubular Necrosis**

Hypotension
- Trauma and burns
- Surgical
- Sepsis
- Cardiac event
- Drugs
- Profound and prolonged volume depletion

Rhabdomyolysis with myoglobinuria
Haemolysis with haemoglobinuria

Nephrotoxins

Sudden decrease in renal blood flow
Cross-clamp of aorta or renal artery

Renal artery embolus

**Table 2. Predisposing Factors for Nephrotoxic Acute Renal Failure**

| Risk factor | Cause | Reference |
|---|---|---|
| Volume depletion | Pigment, contrast agents, aminoglycosides, NSAID's | [11,15,18] |
| Advanced age | Contrast agents, aminoglycosides, NSAID's | [15,16,17] |
| Diabetes, multiple myeloma | Contrast agents | [11,15] |
| Prostaglandin-dependency of GFR<br>Old age, cirrhosis, nephrosis, congestive heart failure | NSAID's | [11,19] |
| Angiotensin-dependency of GFR<br>Renal artery stenosis | Converting enzyme inhibitors | [11,20] |
| Pre-existing renal disease | Contrast agents, aminoglycosides | [11,15,16] |
| Sepsis, endotoxemia | Aminoglycosides | [21,22] |
| Fever | Aminoglycosides | [22] |

Abbreviations: NSAID's: nonsteroidal anti-inflammatory agents; GFR: glomerular filtration rate.

Despite impressive advances in medical care, survival from ARF in recent series (50-70%) appears to be no better than that reported two or more decades ago [7,8-13,23]. It has been suggested that this continuing high mortality is due to changes in patient characteristics, which may have masked an improvement in outcome [12]. These changes include: (1) a reduction of cases of uncomplicated ARF; (2) an increase in ARF as part of multiple organ systems failure (MOSF) resulting from extremely severe illnesses, accidents and operations, also affecting older patients. Indeed, it may be that patients are now treated for ARF who would formerly have died before the condition could occur [10,23,24]. Outcome in ARF patients is mainly dependent on the factors that determine failure of other organs as part of MOSF [25,26,27]. As well as being the major causative factor, sepsis is established as the principal cause of death in critically ill patients with ARF/MOSF [23,24,28]. This particularly relates to surgical ARF, as it is intra-abdominal sepsis that carries the highest mortality [25,26]. Giving the grave prognosis of these patients, efforts should thus be directed at preventing ARF, such as the recognition of predisposing factors and the identification of patients at risk of ischemic or nephrotoxic renal injury (Table 1,2). As there is no specific treatment for established ARF, management is directed at measures to prevent or treat complications associated with this condition. These complications are: (1) bleeding diathesis due to uremic platelet dysfunction; (2) acid-base and electrolyte (*e.g.*, hyperkalemia, hypocalciemia) disturbances; (3) fluid overload; and (4) uremic immunosuppression [29,30]. All this may lead to cardiovascular (tachy-arrythmias, pericarditis, myocardial infarction), pulmonary (pulmonary edema, ARDS), neurologic (encephalopathy, seizures) and infectious complications as well as life-threathening bleeding complications [29,30].

If conservative measures fail to correct uremic symptoms or fluid and electrolyte imbalances, kidney function should be replaced by intracorporeal or extracorporeal dialytic treatment modalities. Conditions that mandate initiation of dialytic support are shown in Table 3. It has been suggested that the initiation of early, intensive dialysis ('prophylactic dialysis') in ARF might avoid some of the abovementioned complications (*e.g.*, the occurence of gastrointestinal hemorrhage or septicemia) [31-34]. A recent controlled study failed, however, to show any significant benefit from intensive dialysis [35]. It may be that the possible beneficial effects of this approach are offset by the side-effects associated with IHD, such as hypotension and the prolongation of ARF (see below).

**Table 3. Conditions That Mandate Initiation of Dialytic Support**

| |
|---|
| Refractory acidosis |
| Serum urea > 35 mmol/l |
| Serum potassium > 6.5 mmol/l[@] |
| Diuretic-resistent fluid overload |
| Pericarditis |
| Encephalopathy |
| Haemorrhage |

[@]: despite conservative measures directed towards acutely lowering serum potassium level (cation-exchange resin, correction of acidosis, glucose and insulin infusion).

## 2. Dialytic modalities

Four main goals are to be achieved with blood purification techniques in ARF: to remove toxic substances presumably responsible for the uremic syndrome; to remove potassium for treatment or prevention of hyperkalemia; to administer buffer-anions to control metabolic acidosis; and to remove excess body water and sodium [36,37]. Various methods for blood purification in ARF are now available, including hemodialysis, peritoneal dialysis, hemofiltration and hemodiafiltration. All these methods can be performed either intermittently or continuously. Solute movement across a membrane occurs by two processes: (1) diffusion, where movement is passive, rapid and down a concentration gradient; and by (2) convection, where solutes are dragged with water as it moves across the membrane (ultrafiltration) down a hydrostatic pressure gradient. Small molecules, such as urea (60 Daltons [Da]) and creatinine (113 Da) move mainly by diffusion, whereas for molecules of size greater than 500 Da (so-called middle molecules) diffusion is less efficient and movement occurs predominantly by convective transfer. In dialysis solutes diffuse from blood through the peritoneal or dialysis membrane into a dialysis solution. Dialysis fluid represents an ideal plasmawater composition and provides the osmotic gradient for diffusion. Hemofiltration relies on solutes being carried along with the bulk flow of fluid in a hydraulic-induced ultrafiltrate of blood (*i.e*, convective transfer). As small molecules diffuse more rapidly than large molecules, higher molecular weight solutes are cleared much less efficiently with dialysis than small solutes. With hemofiltration, clearances are similar for all solutes that have molecular weights in the range to which the membrane is readily permeable.

### *Intermittent hemodialysis*

Before the advent of continuous hemofiltration and derived modifications, treatment of the acutely uremic patient usually consisted of every-other-day IHD or intermittent/continuous PD. IHD requires specialised equipment and personnel. Only short-term anticoagulation is needed. IHD is highly efficient in small solute removal, the urea clearance amounting to 160-200 ml/min with a blood flow of 150-250 ml/min and dialysate flow of 500 ml/min. Because treatment times can be kept short with IHD (usually 3-5 h), the patient is free to be mobilized and undergo other therapeutic or diagnostic procedures. However, its efficiency brings with it potential complications, especially when used in the setting of ARF. The so-called dialysis disequilibrium syndrome is a much feared complication and characterized by headache, nausea, muscle cramps, disorientation and eventually coma and seizures [38]. Its occurrence may lead to dangerous increases in intracranial pressure in patients with pre-existing cerebral edema (*e.g.*, traumatic, post-hypoxic, hepatic failure). Rapid volume and solute shifts may induce or aggrevate hemodynamic instability and prohibit the necessary ultrafiltration to control fluid balance. Indeed, fluid infused to maintain a mean arterial pressure sufficient to be able to perform IHD may result in the patient ending dialysis more fluid-overloaded than before

treatment. This often results in a tendency to restrict fluids and nutritional intake, thereby aggrevating catabolism. Several other factors, such as the buffer-anion used and the type of membrane, contribute to the side effects of IHD. Use of acetate as buffering-anion may aggrevate hemodynamic instability by inducing vasodilation [38,39,40]. The vasodilating effect of acetate might decrease pulmonary hypoxic vasoconstriction resulting in increased pulmonary shunting [38]. Furthermore, acetate metabolism leads to alveolar hypoventilation and an increase in oxygen consumption [38-41]. Lactate as buffering anion produces less vasodilation compared to acetate. However, unphysiological concentrations of lactate (usually D,L lactate) are needed to correct acidosis and may cause metabolic disturbances [42]. Bicarbonate seems to be the obvious buffer choice as it alleviates much of the symptoms associated with IHD [38,42,43]. Bioincompatibility of dialyser membranes may also induce deleterious side effects. Cellulosic membranes induce complement activation with generation of C3a and C5a which may result in pulmonary leuco-sequestration, (local) release of inflammatory mediators, micro-embolisation and increased pulmonary shunting [44,45]. In addition, IHD using cellulosic membranes aggrevates sepsis-induced neutrophil dysfunction, thereby contributing to susceptibility to infection in such patients [46]. Indeed, a higher incidence of sepsis was observed in ARF patients treated with IHD using cellulosic membranes when compared to similar patients treated with IHD using biocompatible (*i.e.*, synthetic) membranes [47]. In addition, use of cellulosic membranes prolonged the duration of ARF when compared to the use of synthetic membranes in experimental ARF [48].

It should thus be recognized that side-effects of IHD may be diminished by using bicarbonate as buffering anion and by using biocompatible membranes (as used in CRRT!). In addition, other simple and inexpensive maneuvers have been shown to stabilize blood pressure during IHD, *i.e.*, the use of high sodium dialysate [49,50] and the use of cooler-temperature dialysate [51]. Therefore, further studies are needed to assess the 'real' side effects of more contemporary IHD in ARF patients.

*Peritoneal dialysis*

Acute PD may be an alternative to IHD in certain patients with ARF. The main advantages of PD are that no anticoagulation is needed, there is minimal effect on hemodynamics and the ease of implementation. No specialised equipment or personnel is required. Therefore, in patients at risk of bleeding or patients who are at a greater risk from hemodialysis-induced hypotension, PD may be the preferred treatment modality. Other relative indications are difficult blood access and hypothermia, for which central core warming with intraperitoneal fluid may be desirable [52,53]. However, PD is less efficient at the removal of waste products, the urea clearance usually amounting to 7-14 L/day (5-10 ml/min)[52,53,54]. PD efficacy may be further compromised in the critically ill by reduced splanchnic flow during shock or use of vasoconstrictors, and low oncotic pressure due to hypoalbuminemia. Acute PD may not offer urea clearances sufficient to ensure azotemic control in catabolic patients and it may be inadequate for the ultrafiltration requirements needed

to maintain fluid balance. This disadvantage often precludes the provision of full nutritional support. Efforts to increase either solute or fluid removal include increasing volume/exchange, cycles/hour, or ultrafiltration/exchange [53,54], but all of this will substantially increase the work load. PD may be contra-indicated or impossible to perform because of intra-abdominal pathology such as infection or recent surgery. Large volumes of intra-abdominal fluid may lead to splinting of the diafragma, atelactasis, decreased functional residual capacity and respiratory insufficiency [52,54,55]. In addition, consecutive hypertonic exchanges to achieve high ultrafiltration rates may lead to 'overfeeding' hyperglycemia with detrimental effects on metabolism and respiratory function [56]. Other complications are protein losses with the dialysate (10-20 g/day), hypernatremia following aggressive ultrafiltration, blockage of the catheter with drainage failure, access infection and peritonitis [53-55]. Both intermittent and peritoneal dialysis, therefore, have significant disadvantages and potentially deleterious side-effects when performed in the setting of ARF on the ICU.

*Continuous renal replacement therapy*

As early as 1977, Kramer and co-workers described a method to treat diuretic-resistent fluid overload in critically ill patients with ARF: continuous arteriovenous hemofiltration (CAVH)[57]. This process of arteriovenous hemofiltration imitates glomerular function, a function of the natural kidney (Fig 1). The pumping force of the heart is utilized: blood is conducted through a bundle of capillaries, *i.e.*, the hemofilter, via a tubing system, from a large artery (usually the femoral artery) and returned to the patient through a large vein (usually the femoral vein). The driving force for blood flow and filtration is the difference between arterial and venous pressure: that is why this filtration method is called arteriovenous. To inhibit coagulation, heparin must be added continuously to the blood as soon as it enters the artificial circulation. The hydrostatic force acros the hemofilter membrane results in the formation of an ultrafiltrate, consisting of plasmawater and non-protein bound low- and middle molecular weight solutes [58,59]. Blood cells and proteins are too large to cross the filter membranes and thus remain within the hemofilter tubules and are returned to the systemic circulation. The composition of the ultrafiltrate is similar to that of the plasmawater. Non-protein bound electrolytes are present in the ultrafiltrate in concentrations similar to that observed in plasma. For non-electrolyte solutes the concentration in the ultrafiltrate progressively decreases with increasing molecular weight [58,59]. The concentrations of various electrolytes and solutes in plasma and ultrafiltrate and their sieving coefficient are shown in Table 4. The sieving coefficient represents the ratio of the solute concentration in the ultrafiltrate to the solute concentration in the retained plasma. The sieving coefficient depends on the particular membrane, molecular size and protein-binding properties of the solute. It is not affected by changes in either the blood flow rate through the hemofilter or the ultrafiltration rate [58,59]. It may be noted from Table 4 that cations have sieving coefficients slightly less than 1 and anions have values greater than 1.

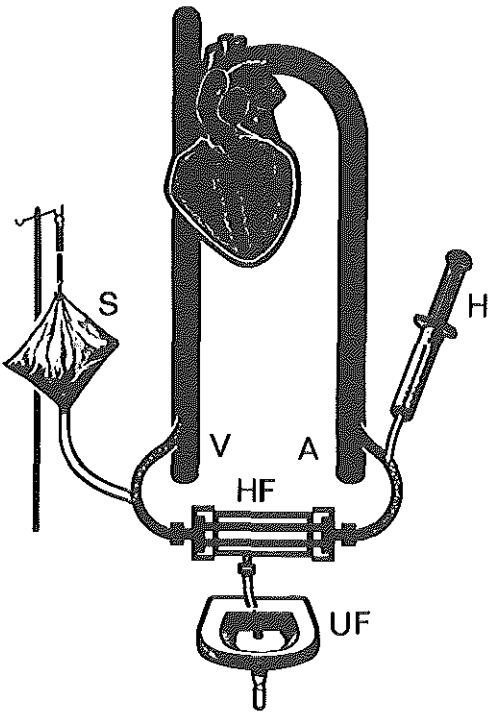


*Figure 1: Schematic representation of continuous arteriovenous hemofiltration (CAVH). Abbreviations: A, artery; V, vein; HF, hemofilter; S, substitution fluid; H, heparin pump; UF, ultrafiltrate. [From Günther Slabon. Arterio-venöse hämofiltration. In: Kramer P, ed. Arterio-venöse hämofiltration. Nieren-(ersatz)-therapie im intensivverpflegebereich. Vandenhoeck & Ruprecht Göttingen, Zürich, 1982:2]*

This phenomenon is caused by a small Gibbs-Donnan effect, in which the negatively charged proteins attract cations, thereby decreasing the transmembrane movement, and repels anions, increasing their transmembrane movement. Clinically, this effect is unimportant. During CAVH, fluids must be administered because of the large amount of plasmawater removed as ultrafiltrate (usually 10-15 L/day). Fluid replacement serves two purposes: (1) it prevents the patient from becoming too volume depleted as a result of ultrafiltration; and (2) it serves to decrease the concentration of nitrogenous wastes and creatinine by a dilutional effect [57-59]. Several commercially available (sterile) filtration replacement fluids are now on the market.

The technique of slow but continuous ultrafiltration (*i.e.*, isotonic dehydration !) avoids the rapid changes in osmolality and intravascular volume as seen with IHD. Indeed, in 1984 Paganini and co-workers reported its successfull use in 23 oliguric ARF patients who were unable to tolerate bicarbonate IHD [60].

**Table 4. Electrolyte and Solute Concentration in Plasma and Ultrafiltrate and Their Respective Sieving Coefficient**

| Solute | Concentration | | Sieving coefficient[@] |
|---|---|---|---|
| | Plasma ($n$ = 10) | Ultrafiltrate ($n$ = 10) | |
| Sodium (mmol/l) | 136.2 ± 10.4 | 135.3 ± 11.2 | 0.993 |
| Potassium (mmol/l) | 4.1 ± 0.7 | 4.1 ± 0.7 | 0.985 |
| Chloride (mmol/l) | 99.3 ± 10.8 | 103.7 ± 9.6 | 1.046 |
| Bicarbonate (mmol/l) | 19.8 ± 4.7 | 22.1 ± 5.1 | 1.124 |
| Glucose (mmol/l) | 9.2 ± 4.3 | 9.6 ± 4.8 | 1.043 |
| Urea (mmol/l) | 39.6 ± 18.1 | 41.5 ± 19.2 | 1.048 |
| Creatinine (µmol/l) | 570 ± 348 | 586 ± 353 | 1.020 |
| Albumin (g/l) | 26.5 ± 5.1 | 0.21 ± 0.43 | 0.008 |

[@]: represents the ratio of the solute concentration in the ultrafiltrate to the solute concentration in the retained plasma.

Due to its simplicity and its capability for physiologically continuous fluid removal, this new method was soon widely accepted in many ICU's [2,4,58]. Intravascular space for the unrestricted infusion of parenteral nutrition, blood products and drugs (*e.g.*, inotropics, antibiotics) was easily provided. Any existent overhydration could be easily corrected at any time of day or night. Disadvantages of the technique include the need for continuous anticoagulation, the requirement of arterial access, and the confinement to bed of the patient, which may interfere with other forms of patient care (*e.g.*, diagnostic or surgical procedures). Other disadvantages are the possible impact of CAVH on serum drug and nutrient levels [57-60]. In addition, the system of CAVH proved unable to produce a filtration rate (usually 10-14 L/day, *i.e.*, urea clearance 7-10 ml/min) capable of compensating azotemia in highly catabolic patients and additional isovolemic IHD was often required [59-62]. This has led to the development of pumped continuous venovenous hemofiltration (CVVH)[61] and continuous arteriovenous hemodiafiltration (CAVHD)[62,63]. In CVVH, enhanced solute clearance of both small- and middle molecular weight solutes is achieved by using a blood pump in the circuit, thereby increasing the blood flow and ultrafiltration rate (Fig 2a). In CAVHD, enhanced small solute clearance is achieved by adding a diffusional component to the continuous filtration of CAVH. Sterile dialysis fluid is pumped slowly through the ultrafiltrate compartment of the hemofilter, usually at a flow rate of 1-2 L/h (Fig 2b). These intensified continuous therapies regularly achieve a significant reduction in serum urea and creatinine production, even in highly catabolic patients [61-63]. For the purposes of clarity, all these forms of continuous therapy are shared under the acronyme 'continuous renal replacement therapy' (CRRT).

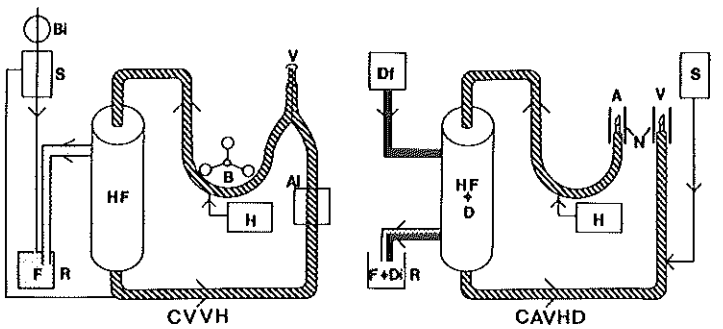


*Figure 2a,b: Schematic representation of (a) continuous (pump-driven) venovenous hemofiltration (CVVH) and (b) continuous arteriovenous hemodiafiltration (CAVHD). Abbreviations: A, artery; V, vein; H(D)F, hemo(dia)filter; B, blood pump; N, needle (double-lumen catheter in CVVH [b]); H, heparin pump; S, substitution fluid ($S_1$, prefilter; $S_2$, postfilter); F, filtrate; R, reservoir; Df, dialysis fluid; Di, dialysate; Bi, balancing system (regulating substitution fluid flow rate); Ai, air detector.*

## 2. Severity-of-illness scoring systems

The many choices available today of blood purification are in striking contrast to the limits on management of ARF three decades ago [37,38]. However, despite an impressive decrease in mortality following the introduction of dialytic treatment, recent mortality rates seem to be on the rise and comparable to that seen in the predialysis era [10,59,64]. Kjellstrand and Solez [65] suggested that maximal survival benefit was probably achieved with every-other-day IHD treatment and that no impact of a specific dialysis procedure on mortality is to be expected. Other authors have propounded the view that no survival advantage is to be expected from CRRT when compared to contemporary IHD and that improvements in outcome will depend on advances in the treatment of today's principal cause of ARF/MOSF, *i.e.*, septicemia [66,67].

Some authors, however, suggest that progress has been made but is masked by a change in patient characteristics (see chapter I.1)[64]. One reason for our failure to demonstrate progress unequivocally may be our failure to provide data in a form that allows a meaningfull comparison of outcome data. Indeed, many reports contain patients of varying qualifications (usually a case-mix of medical, surgical and/or obstetric ARF), not all of whom required dialysis or stay on the ICU [64,68]. ARF in the critically ill should be considered as a syndrome and not as a specific disease entity. Closer attention to other factors surrounding the course of the patient with ARF may aid in delineating any changes in mortality associated with changes in the severity of these other factors [64,69]. However, the incidence of ARF and the trend in terms of the population base has yet to be defined.

*Specific risk models for acute renal failure*

Considerable variability exists in the design of outcome studies in ARF: differences in inclusion criteria; large versus small patient groups; retrospective versus prospective; univariate versus multivariate analysis of risk factors [66,70-79]. Indeed, even when statistical methodology and patient numbers are similar, inclusion criteria can range from mild increases in creatinine to only dialysis-treated patients [70-79]. In addition, some authors studied a more general ARF population (*i.e.*, including nephritis), while others studied predominantly ATN cases [70-79]. Except for identifying risk factors influencing the development or recovery of renal failure and ultimate patient outcome, the need of measuring the severity of ARF is becoming increasingly important. This would provide us an objective method to risk-stratify patients in therapeutic trials (*e.g.*, different forms of dialytic support), for audit of clinical performance, and in the prediction of outcome. Its accuracy should be verifiable against clearly defined outcomes which do not form part of the criteria employed to construct the system. It should be reasonably easy to use, and applicable to as wide a population as possible [69,80]. Based on uni- and multivariate analysis, a multitude of risk factors for the development of ARF and mortality has been identified [70-79]. Results are, however, confusing. One particular example is the importance of age: some related age to mortality, while others did not [66,69]. The same inconsistency exists for several other variables [66,69]. Some studies [72,73,77-79,81] provided a severity-of-illness score and an equation by which the chance of survival in ARF patients could be predicted (Table 5). Most of these models, however, are not formally validated and do not reach a discriminative cut-off point allowing identification of the patients without hope of survival. In addition, none of these models is widely accepted. Furthermore, Paganini and co-workers recently showed that these risk models may be institution-specific [82].

**Table 5. Variables Found Significant in Outcome Prediction in Acute Renal Failure Patients**

| Author [Ref] | No of Patients | Type of ARF | Variables used in outcome prediction |
|---|---|---|---|
| Cioffi *et al.* [77] | 83 | Postoperative | Age, # of transfusions, cardiac surgery, cardiac failure, sex, vascular surgery other than AAA, interval from ARF to dialysis, preoperative hypotension |
| Liem *et al.* [78] | 59 | Only needing IHD | CNS depression, inotropic support, age |
| Corwin *et al.* [73] | 232 | ATN | Sepsis, recovery of renal function |
| Barton *et al.* [79] | 250 | Only needing CVVH | Age, ventilation, inotropic score, urine volume, bilirubin |
| Liano *et al.* [72] | 353 | ATN | Age, sex, nephrotoxic, oliguria, hypotension, jaundice, coma unconsciousness, assisted ventilation |
| Halstenberg *et al.* [81] | 512 | Only needing DS | Sex, intubation, platelet count < $50\text{-}10^9$/l, bilirubin, no surgery, low serum creatinine, organ system failure, change in urea |

Abbreviations: ARF, acute renal failure; IHD, intermittent hemodialysis; AAA, abdominal aortic aneurysm; CNS, central nervous system; ATN, acute tubular necrosis; CVVH, continuous venovenous hemofiltration; DS, dialytic support

*The APACHE II scoring system*

The need for measuring severity of illness and predicting outcome in ICU patients has long been recognised by intensivists. Using multivariate analysis, several risk models have been developed for use in the general ICU population [66,69]. Of these models, the acute physiology and chronic health evaluation (APACHE) II scoring system is the most widely used and validated form [83-87]. To quantify severity of illness, APACHE II generates a score for each individual patient (scoring range 0-71); the score is the sum of three parts of the evaluation, *i.e.*, the acute physiology score (0-60), an age-related score (0-6), and points for chronic illness (0,2, or 5). The acute physiology score is based on the worst values for 12 commonly measured physiologic variables obtained during the the first 24 h of ICU stay. The patients raw score is entered into a logistic regression equation together with a disease-specific coefficient that reflects the relative mortality of the underlying condition or pathology (Table 6).

**Table 6. APACHE II Equation to Predict Hospital Mortality (%) for an Individual Patient[@]**

Ln (R/1-R) = -3.517 + (APACHE II x 0.146) + D + S

Where

R = Risk of hospital mortality

D = Disease weight according to relative risk imposed by a specific disease (range: -3.35 to +0.89)

S = Additional weight (0.603) for emergency surgery

Ln = Log e

From [83]. [@]: The predicted death rate for groups is calculated by summing the individual risks and dividing them by the total number of patients

The equation than yields an estimated mortality risk for the individual patient. The expected deaths for a group of patients is the sum of the individual mortality risks. APACHE II has been used extensively in risk-stratification of patients in order to control for case-mix so that appropriate comparisons of therapy can be made [84,87]. It has also been used for comparing outcome of different ICU's, resource allocation and individual decision making [84,87,88]. The routinely use of APACHE II in many ICU's and the familiarity of the system to most physicians involved in the care of critically ill patients would also favor its use in patients with ARF.

To date, however, only few authors have used the APACHE II system in ARF patients [89,90]. In addition, while validated for use in the general and surgical ICU population, it is not clear whether its use is valid in specific disease groups such as those with ARF. One particular question arises as to whether the APACHE II system, originally intended for use during the first 24 h of ICU admission, is automatically transferrable for use in patients who develop ARF during their course of stay on the ICU.

## 4. Inflammatory mediators and acute renal failure

### *Mediators of the systemic inflammatory response syndrome*

Today, ARF on the ICU most commonly occurs in the setting of MOSF, usually as a result of septicemia [4,23,24,29]. Sepsis results in an extensive triggering of the bodies host defense mechanisms, resulting in the release of a myriad of mediators with vasoactive and cardiodepressant properties (Table 7) into the circulation [91,92]. However, non-infectious insults (*e.g.*, burns, trauma, pancreatitis, severe hemorrhage) may produce a similar response [93-95]. The acronyme 'systemic inflammatory response syndrome' (SIRS) was therefore proposed to describe this inflammatory state, irrespective of its cause [96].

**Table 7. Inflammatory Mediators of SIRS and Their Molecular Weight**

| Mediator | Molecular weight (Dalton) |
|---|---|
| Cytokines | |
| IL-1ß | 16,800 |
| IL-6 | 22,000 |
| IL-8 | 10,000 |
| TNFα | 16,800 (52,000)[@] |
| Platelet activating factor | 500 |
| Arachidonic acid metabolites | |
| $TXA_2$ | 350 |
| Leukotrienes | ~500 |
| Prostaglandins | ~600 |
| Humoral defense systems | |
| Complement (C3a, C5a) | 10,000; 11,200 |
| Kinins (Bradykinin) | 1,206 |
| Others | |
| Myocardial depressant substance(s) | 10,000 - 30,000[#] |
| Endorphins | ~4,000 |
| Histamine | 127 |
| Serotonin | 210 |

Abbreviations: SIRS, Systemic inflammatory response syndrome; [@]: bioactive TNFα may exist in the circulation as a trimer [100]; [#]: ultrafiltrate experiments for determining the molecular weight(s) yielded differing results. From [4,92,93,97,100].

Although endotoxin directly triggers the activation of a number of mediators, cytokines appear early in the sequence of reactions initiated by endotoxin and play a major role in amplifying the subsequent release of soluble mediators and the activation of different plasma cascades [91,94,97]. Cytokines exert their influences on diverse cell types, such as neutrophils, endothelial cells, and lymphocytes. A comprehensive discussion of these factors as well as a detailed account of specific cytokine functions is beyond the scope of this chapter and one is referred to several excellent reviews [97-100]. It appears that tumor necrosis factor-alpha (TNFα) is a central mediator in septic and non-septic shock. Infusions of TNFα into experimental animal models mimic many of the hemodynamic and vascular changes of septic shock, including hypotension, coagulopathy, leucocyte aggregation, vascular leakage and myocardial depression [97-99]. Numerous reports have documented elevated circulating levels of TNFα in a number of inflammatory and infectious conditions [98,101-103,105]. In addition, (persistently) elevated TNFα plasma levels has been found to correlate with poor outcome [99,101] and blocking TNFα might ameliorate some of the deleterious effects of SIRS [97,106]. Its short half-life, however, suggests that TNFα exerts regional and local effects rather than systemic effects [98,102,103].

Detection of TNFα in the circulation may therefore reflect excessive activity of this mediator at the tissue level [100,103]. Interleukin-1ß (IL-1ß) shares many functions with TNFα that are directed toward inflammatory responses, although less severe [97,100,102]. Blocking IL-1ß prevented some sequelae of severe endotoxemia or sepsis [106]. In one study [105], IL-1ß levels were associated with patient outcome; however, subsequent studies did not confirm these findings [107,108]. In addition, IL-1ß is only occassionally and transiently released into the circulation [95,97,108]. Unlike most other cytokines, interleukin-6 (IL-6) is more readily detected systemically and thus serves more of a classical endocrine function [97,100,101,107,109]. It has been suggested that the relative lack of toxicity of IL-6 in experimental models argues against a major causative role in SIRS [97]. However, increased plasma IL-6 levels have repeatedly been found to correlate with subsequent organ failure(s) [110,111] and poor outcome [102,107,109,112]. In addition, Gennari *et al.* [113] recently showed that blocking of IL-6 may reduce bacterial translocation from the gut and improve outcome in gut-derived sepsis. Interleukin-8 (IL-8) has also been suggested to play a role in SIRS [97,114]. In one study [97], plasma levels of IL-8 correlated with the severity of injury of multiple trauma patients. In another study, however, plasma IL-8 were higher in patients who survived compared to patients who died, suggesting a possible protective role in shock [114]. Further study to assess the role of this cytokine in SIRS is therefore needed. Principal effects of these cytokines are summarized in Table 8. Platelet activating factor (PAF) also appears to play a fundamental role in the pathogenesis of SIRS. Increased levels of PAF have been identified in animal models of endotoxemia and in human sepsis [91,92,115.116]. Many of the manifestations of endotoxemia, such as cardiovascular collapse and lethal pulmonary injury, can be mimicked by infusion of PAF [91,115].

**Table 8. Abridged List of the Pathogenic Effects of Cytokines in SIRS**

| Cytokine | Major pathogenic effects |
|---|---|
| TNFα | Neutrophil activation; amplification of mediator release (incl. itself); endothelial activation; increased microvascular permeability; decreased peripheral vascular resistence; myocardial depression; activation coagulation cascade and complement system; fever; lactic acidosis |
| IL-1ß | Neutrophil activation; amplification of mediator release (incl. itself); increased microvascular permeability; decreased peripheral vascular resistence; stimulates T- and B-cells; fever *(acts synergistically with TNFα)* |
| IL-6 | Stimulates synthesis of acute phase proteins; activates T- and B-cells; fever |
| IL-8 | Recruitment and activation neutrophils and lymphocytes |

Abbreviations: SIRS, systemic inflammatory response syndrome; TNFα, tumor necrosis factor alpha; IL-1ß, interleukin 1ß; IL-6, interleukin 6; IL-8, interleukin 8. From [92,93,94,97,98,99,100,103,104].

Use of PAF receptor antagonists in animal models attenuated many of the hemodynamic and metabolic sequelae of endotoxemia [91,115,116]. One important effect of PAF, like that of TNFα, is that it amplifies the release of various inflammatory mediators from cells (including cytokines and PAF), initially 'primed' by endotoxin [115]. PAF also strongly promotes platelet aggregation [92]. The complement system also participates in the inflammatory response by the generation and release of C3a and C5a. These factors, known as anaphylactoxins, stimulate neutrophils and enhance the permeability of endothelial cells [91,92,117]. Systemic administration of C5a into animals induce a fall in blood pressure and leukopenia, the latter being due to pulmonary sequestration [117]. This may contribute to the development of the 'adult respiratory distress syndrome' (ARDS). Anaphylactoxins may be able to induce production of cytokines by monocytes. In one study, plasma levels of C3a were found to correlate with outcome in septic patients [117]. Activation products of the contact system of coagulation (*e.g.*, bradykinin) have been found to contribute to SIRS by enhancing vascular permeability, decreasing vascular tone and stimulating aggregation and degranulation of neutrophils [91,92,117,118]. Both experimental and clinical studies have shown an early rise of bradykinin in septic ARDS and necrotizing pancreatitis [91,92,118]. Eicosanoids, *i.e.*, metabolites of arachidonic acid (AA), are also involved in the pathogenesis of SIRS [119]. Both TNFα and PAF promote AA metabolism. Conversely, AA derivates can prompt TNFα and PAF release from cells [92,119]. In several studies, plasma levels of thromboxane A2 ($TXA_2$) and 6-keto-prostaglandin-1α (6-keto-PG-1α) were found to correlate with patient outcome in septic shock [118,120]. AA metabolites such as leukotrienes and $TXA_2$ stimulate aggregation and degranulation of neutrophils, increase vascular permeability and produce vasoconstriction of several vascular beds. $TXA_2$ also promotes platelet aggregation. Leukotrienes and $TXA_2$ also promote the release of vasodilating prostaglandins (PG), *i.e.*, $PGI_2$ and $PGE_2$, which might be a protective mechanism. However, it can be detrimental when these levels are excessive by inducing or prolonging shock [119]. Several studies have documented a circulating (water-soluble) factor responsible for myocardial depression in various forms of shock [92,93,121-125]. This factor or factors, however, has yet to be identified. Ultrafiltration of sera from these patients to determine its molecular weight yielded differing results; some reported a molecular weight of 500-600 Dalton while others reported a molecular weight between 10 and 30 kDalton [93,121-125]. Increased levels of other vasoactive mediators, listed in Table 7, are also documented in both experimental and human shock but its precise role and relative importance in SIRS is less clear [91-93]. Thus it seems that all these mediators act in concert to produce microvascular collapse and tissue hypoxia, ultimately resulting in multiple organ dysfunction. However, it should also be recognized that tissue responses are dependent not only upon the absolute concentrations of mediators such as TNFα and IL-1ß, but also upon the concentrations of cytokine inhibitors (*e.g*, soluble TNF receptors, IL-1ß receptor antagonist [100,106,126]) and anti-inflammatory mediators [100].

*Specific mediators of renal dysfunction*

The pathophysiology of renal dysfunction in the setting of SIRS is not clearly understood. Patients dying of sepsis and ARF usually show no major structural damage at autopsy [23,127]. Renal blood flow (RBF) may be maintained because of renal vasodilation (*i.e.*, autoregulation) during systemic hypotension. However, when blood pressure continues to decline, the renal vessels constrict due to increases in sympathetic activity, activation of the renin-angiotensin-aldosteron system and release of vasopressin [23]. In an animal model of septic ARF, however, intense renal vasoconstriction was observed in the absence of hypotension [128]. In addition to altered systemic and intrarenal hemodynamics, specific mediator activity contributes to the development or persistence of ARF (Table 9).

Eicosanoids exert important (inter)actions in ARF [128-135]. In sheep with severe sepsis and renal impairment, urinary excretion of $TXB_2$, *i.e.*, the metabolite of $TXA_2$, correlated inversely with MAP and TX-synthetase inhibition conferred protection for renal function [128]. Urinary excretion of 6-keto-PG-1$\alpha$, a metabolite of vasodilating PGs was also increased. Renal impairment following bile duct ligation in rats was also associated with increased urinary $TXA_2$ excretion and could be restored by intraperitoneal administration of a specific $TXA_2$ blocker [135]. $TXA_2$ produces platelet aggregation, leads to a preferential afferent vasoconstriction and contracts glomerular mesangial cells.

**Table 9. Mechanisms Involved in the Development and Persistence of Acute Renal Failure and Proposed Responsible Mediators**

| Mechanism | Mediator |
|---|---|
| Arteriolar vasoconstriction | |
| afferent | $TXA_2$; PAF; endothelin |
| efferent | Endothelin; leucotrienes |
| Mesangial contraction | $TXA_2$; $PGE_2$; leucotrienes; PAF; endothelin |
| Microvascular thrombosis[@] | $TXA_2$; PAF; TNF$\alpha$ |
| Recruitment/trapping neutrophils | TNF$\alpha$; IL-1ß; C3a, C5a; leucotrienes |

Abbreviations: $TXA_2$, thromboxane $A_2$; PAF, platelet activating factor; $PGE_2$, prostaglandin $E_2$; TNF$\alpha$, tumor necrosis factor alpha; IL-1ß, interleukin 1ß. [@]: may be provoked by stimulating platelet aggregation ($TXA_2$, PAF) or by stimulating the coagulation cascade (TNF$\alpha$).
From [48,115,116,127-145]

Systemic or intrarenal administration of leukotrienes resulted in a decrease of RBF and glomerular filtration rate (GFR) by increasing efferent arteriolar resistance and contraction of mesangial cells [128-135]. Adverse renal effects of endotoxemia could be partially abolished by the systemic administration of a non-specific leucotriene antagonist [132,134]. Neutrophil activation by leukotrienes may also play a role [133]. It thus seems that different AA metabolites exert opposite actions in the kidney and that the ratio between $PGI_2$, $PGE_2$/ $TXA_2$, leukotrienes is critical. In addition, it should also be recognized that vasodilating PGs may induce mesangial contraction by stimulating the renin-angiotensin system [129,130]. PAF may also contribute to renal impairment in endotoxemia. PAF generation has been demonstrated in isolated perfused kidney and in various isolated renal cells [115,116]. PAF produces arteriolar vasoconstriction, contracts mesangial cells and promotes platelet aggregation [115,116,136]. Infusion of PAF in normal rats decreased GFR, RBF and filtration fraction (FF) in the absence of hypotension [115,116]. Systemic administration of a PAF receptor antagonist improved GFR, RBF and FF in endotoxin-induced ARF in rats without inducing significant changes in MAP [115]. Endothelin, a 21-amino-acid (2,500 Da), is also implicated in the reduction in GFR and RBF that characterizes septic ARF. It causes both afferent and efferent vasoconstriction and contracts mesangial cells [137-141]. It is not clear whether endothelin exerts endocriene actions or that renal effects result from locally produced endothelin [137,138,140]. In septic shock patients, plasma endothelin levels correlated inversely with endogenous creatinine clearance, independent from MAP, suggesting that circulating endothelin affects adversely intrarenal hemodynamics in septic ARF [140]. LPS-induced renal hypofiltration was prevented by intrarenal infusion of anti-endothelin antibodies [141]. Hypoxia and norepinephrine are important stimuli for endothelin release from endothelium [137,138]. Circulating or locally produced cytokines also adversely affect renal function. In glycerol-induced ARF in rats, *i.e.* an established model of acute trauma, a rapid rise was seen of plasma TNFα levels which correlated with the development of severe renal failure [142]. Systemic administration of TNFα-antisera prior to glycerol injection ameliorated renal impairment. TNFα may mediate renal dysfunction by stimulating local endothelin or PAF release, by stimulating the coagulation cascade, or by increasing leucocyte adhesion molecules, thereby causing entrapment of neutrophils and other inflammatory cells that release toxic mediators (*i.e.*, elastase, reactive oxygen products, cytokines) [141,143]. *In vitro*, endotoxin-induced ARF in rats was associated with increased production of TNFα and IL-6 by resident glomerular cells [143]. Clinically, a correlation was found between the occurrence of ARF after cardiac bypass surgery and preoperative plasma levels of IL-6 ($p = 0.02$) and sTNFR-I/II ($p < 0.05$), respectively [144]. Cummings and co-workers [128] showed expression of the IL-1ß gene in tubular and vascular structures within kidney, removed from a trauma patient. Activated complement may also contribute to renal impairment by inducing neutrophil activation in the ischemic kidney [48]. Indeed, Linas *et al.* reported that addition of endotoxin-activated polymorphonuclear cells to ischemic kidney, but not to non-ischemic kidney, caused severe renal injury [145]. Direct cellular damage may be induced by neutrophil products such as elastase or free oxygen radicals [133], whereas neutrophil-derived

vasoconstricting mediators such as $TXA_2$ and leukotrienes may affect adversely renal hemodynamics [48,133,145].

These combined data suggest that the reduction in GFR and RBF entirely depend on altered glomerular hemodynamics. The latter is regulated by the tone in afferent and efferent arterioles and in the mesangial cells. Mediators may be produced by intrinsic renal cells or by macrophages infiltrating the renal parenchyme. In addition, circulating mediators may be involved in impairment of renal function. Therefore, like ARDS [91,92], ARF may represent a target organ injury resulting from activation of the host's inflammatory cells and uncontrolled liberation of inflammatory mediators.

*The role of the kidney in mediator excretion*

Data upon the role of the kidney in mediator clearance and its clinical relevance in SIRS is scarce. Experimental animal data demonstrated an important role for the kidney in the clearance of sTNFR and TNFα/TNFR complexes in mice [146]. In undialysed patients with chronic renal failure, plasma concentrations of TNFα, IL-1ß and sTNFR strongly correlated with the degree of renal insufficiency, suggesting that inadequate renal clearance is at least partially responsible for elevated cytokine levels in these patients [147]. In a study of 20 septic ICU patients, it was found that TNFα and sTNFR-I levels increased when renal failure ensued and that these levels correlated with APACHE II scores and sepsis severity [148]. Graziani and co-workers [149] investigated the role of the kidney in cytokine elimination by comparing cytokine levels in septic patients with normal renal function, non-oliguric and oliguric ARF. Plasma IL-6 levels were significantly increased in oliguric ARF patients when compared to the other two groups (202 ± 13 *vs* 106 ± 16 and 103 ± 13 pg/mL; $p < 0.01$). However, from available data one can not exclude differences in disease severity as a possible explanation of these findings. They also reported a weak inverse correlation between plasma levels and urinary excretion of IL-1ß ($r^2 = -0.33$; $p < 0.07$) and a significant correlation between fractional urinary excretion of IL-6 and IL-1ß ($r = 0.885$; $p < 0.0001$). Froon *et al.* observed a significant correlation between plasma creatinine values and sTNFR-I ($r^2 = 0.60$; $p < 0.001$) and sTNFR-II ($r^2 = 0.44$; $p < 0.001$) levels [150]. No data are available upon the urinary excretion of other mediators in relation to plasma levels or on creatinine values in relation to specific plasma mediator levels.

It has been suggested that CRRT with highly porous membranes might simulate a kidney-like function in removing inflammatory mediators from the blood in critically ill patients and that this might have a beneficial influence on the clinical course in these patients [151,152]. In different animal models of septic shock, isovolemic hemofiltration improved hemodynamics and/or gas exchange [153-158]. The mechanism by which this occurred, however, was not entirely clear. As the most pronounced beneficial effects were seen in the study using high ultrafiltrate volumes (Fig 3a,b), convective removal of mediators with vasoactive and cardiodepressant properties might play an important role [151,157,158].

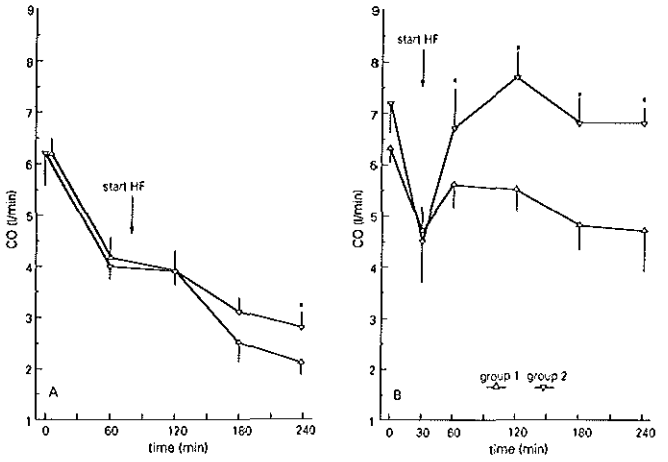


*Figure 3: The effect of (A) low volume (600 mL/h) [153] and (B) high volume (6 liters/h) [157,158] hemofiltration (HF) on the course of cardiac output in porcine endotoxic shock. High volume HF resulted in a more pronounced beneficial effect on cardiac output as compared to low volume HF. Differences in experimental protocol included the total amount of endotoxin infused (0.5 mg [A] vs 20 mg [B]) and the start of HF (75 min [A] vs 30 min [B] after the initiation of endotoxin infusion). Data (mean±SEM) of Group 2 (endotoxemia and HF treatment) are compared to those obtained in Group 1 (control group, endotoxemia only). *: $p < 0.05$. [From Grootendorst AF, Van Bommel EFH. The role of hemofiltration in the critically ill ICU patient: present and future. Blood Purif 1993;11:209-223]*

Uncontrolled clinical data support the contention that CRRT, in contrast to IHD, may improve hemodynamics and gas exchange in (non-renal) MOSF [4,151,152]. However, no proper designed clinical study has yet evaluated these possible beneficial effects of CRRT in patients with SIRS [151,152]. In addition, little is known as to the endogenous clearance in relation to this exogenous clearance of soluble mediators, the possible mechanisms (*i.e.*, convective transfer versus adsorption onto the membrane) and of the impact of prolonged blood-membrane interaction on mediator levels.

## 5. Aim and outline of the thesis

Despite impressive advances in the field of intensive care, patients who develop ARF carry a high mortality. One of the most rapidly evolving aspects of intensive care is the development of CRRT, which is now increasingly accepted as the preferred treatment modality in the hemodynamically unstable ICU patient. Indeed, an ever increasing number of reports have described the various aspects of different forms of CRRT.

Its superiority over conventional dialysis in terms of metabolic control, however, is not clearly established. In addition, despite its potentional beneficial effects, it is not clear whether the use of CRRT has resulted in enhanced survival of these patients. One explanation may be a change in patient characteristics, *i.e.*, a shift from patients with isolated ARF to (older) patients who developed ARF as part of MOSF, usually as the result of sepsis. MOSF is characterised by an exaggerated inflammatory response in which the body can not control its own defense mechanisms, resulting in the release of many mediators into the circulation. Direct comparison of mortality data from different reports is hampered by the lack of objective and validated illness severity scores. The **aim of this thesis** is to assess the efficacy of CRRT, to examine its proposed superiority over IHD, and to investigate the mechanisms involved in the possible beneficial effects of CRRT on hemodynamics and gas exchange. As we used the APACHE II scoring system to describe disease severity to allow a meaningfull comparison, it was also investigated whether its use was valid in ARF patients.

In **chapter II** a comprehensive review is given of the current knowledge of CRRT. Technical and clinical aspects of the various forms of CRRT, including their impact on serum drug levels and nutrient balance, are discussed. In addition, an attempt is made to clarify the possible beneficial role of CRRT in reducing patient morbidity and mortality in the ICU.

**Chapter III** describes the use of the APACHE II scoring system on the day of ICU admission and on the day dialytic support was initiated. Using logistic regression analysis, a comparison of the adequacy in terms of outcome prediction is made. In addition, using the APACHE II scoring system, the influence of several factors on outcome is examined.

In **chapter IV** the efficacy of the continuous treatment modality as employed in our hospital, *i.e.*, CAVHD, is examined. In addition, a detailed description of the patient population is provided, including APACHE II scoring and examination of factors influencing survival, to allow a meaningfull comparison with other reports.

In **chapter V** a direct comparison of CAVHD and IHD is made in ARF patients treated in the same ICU. A detailed description of the patient population, including biochemical and hematological data, is provided. Major variables examined are the control of fluid balance, acidosis and azotemia; hemodynamic tolerance; the duration of ARF; renal and patient outcome; and costs.

In **chapter VI** the hypothesis is tested that some of the beneficial effects of CRRT are attributable to the convective removal of factors that adversely affect hemodynamics during endotoxemia. This was investigated with a whole-animal bio-assay, *i.e.*, ultrafiltrate collected under sterile conditions during hemofiltration of endotoxemic pigs was infused into healthy pigs and their hemodynamics were compared with those of pigs who were infused with ultrafiltrate from healthy pigs.

**Chapter VII** describes the results of a study in which the impact of hemofiltration membranes on plasma cytokine kinetics (TNFα, IL-1ß, and IL-6) is investigated during both *in vitro* and *in vivo* CRRT, with emphasis on the possible mechanisms involved in mediator clearance (convective transfer *vs* adsorption onto the membrane surface) and the effects hereon of prolonged filter use.

In **chapter VIII** these findings are summarized and proposals for future research are given to further unravel the question whether the use of CRRT leads to improved survival of ARF patients and to provide a rational for the use of CRRT in the absence of conventional indications for dialytic support.

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Chapter II

# Continuous renal replacement therapy for critically ill patients: an update

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**Abstract**

Despite continuous progress in intensive care during the last decades, the outcome of critically ill patients who develop acute renal failure (ARF) is still poor. This may be explained partially by the frequent occurrence of ARF as part of multiple organ systems failure (MOSF). In this complex and unstable patient population, the provision of adequate renal support with either intermittent hemodialysis or peritoneal dialysis may pose major problems. Continuous renal replacement therapy (CRRT) is now increasingly accepted as the preferred treatment modality in the management of ARF in these patients. The technique offers adequate control of biochemistry and fluid balance in hemodynamically unstable patients, thereby enabling aggressive nutritional and inotropic support without the risk of exacerbating azotemia or fluid overload. In addition, experimental and clinical data suggest that CRRT may have a beneficial influence on hemodynamics and gas exchange in patients with septic shock and (non-renal) MOSF, independent of an impact on fluid balance. This review deals with both the technical and clinical aspects of the various continuous therapies, including their impact on serum drug levels and nutrient balance. In addition, an attempt is made to clarify the possible beneficial role of CRRT in reducing patient morbidity and mortality in the ICU.

## Introduction

Although treatment modalities for conditions predisposing to the development of acute renal failure (ARF) have increased and improved over the years, the incidence and outcome of ARF in the intensive care unit (ICU) has changed little [1,2]. This lack of change seems related to variations in the ICU population during the last decade with increasing numbers of elderly patients and patients with more complex conditions [1,3].

It is the complications associated with ARF that result largely in the death of patients [2,3]. Critically ill patients with ARF commonly have additional failing organ systems and mechanical ventilation is often required at some stage of the illness as a result of inadequate oxygenation due to infection, pulmonary edema and/or 'adult respiratory distress syndrome' (ARDS) [1,2,3]. It is likely that recent advances in intensive care medicine permits treatment of ARF patients who previously may not have been considered for renal support.

Renal replacement therapy is one of the most rapidly evolving aspects of intensive care. As the traditional forms of dialysis treatment have characteristics which limit their use in critically ill patients with ARF, continuous renal replacement therapy (CRRT) has been rapidly adopted as the preferred treatment modality [4,5,6]. However, whether this new form of continuous treatment for ARF is superior to conventional dialysis can currently only be answered by reference to theoretical advantages, by investigations of some single factors and by a few, mostly retrospective studies comparing the clinical outcome of ARF patients treated with continuous or conventional dialysis techniques.

We present an updated review of the various continuous renal replacement techniques, and we attempt to clarify the possible beneficial role of CRRT in reducing patient mortality in the ICU. To allow comparison between the procedures, conventional dialysis techniques are reviewed briefly.

## Intermittent Hemodialysis.

Intermittent hemodialysis (IHD) has been used most commonly for the management of ARF. It is the treatment of choice for patients who are cardiovascularly stable or when life-threatening hyperkalemia is present. The daily urea clearance of IHD (urea clearance 120-180 ml/min), calculated as the mean value of 4 hour, every-other-day treatment, amounts to 19 L/day. As small solutes (<500 Dalton [Da]) diffuse more rapidly than large molecules, clearance is less for solutes with higher molecular weights (MW).

IHD requires specialist equipment and personnel and, despite a number of technical modifications, may cause cardiovascular instability and solute disequilibrium [4,7,8,9]. In a retrospective study of critically ill patients with ARF secondary to abdominal sepsis, hemodialysis led to severe hypotension (mean arterial pressure [MAP] <50 mm Hg) in 52 of 163 (31.9%) procedures [8]. Fluid infused to raise the blood pressure may result in the patient ending dialysis more fluid overloaded than

pretreatment [5,7,8,9]. Possible explanations for the observed hemodynamic instability include impaired sympathetic response to fluid removal, the effect of dialysate bath components (*i.e.*, buffer-anion used, sodium content, the presence of cytokine-inducing substances) and rapid volume and osmolar shifts [4,10-13]. Kidneys affected by acute tubular necrosis may not be able to autoregulate blood flow and may so be susceptible to further ischemic insults during hypotensive episodes associated with IHD [8,14]. In addition, dialysis-induced arterial hypoxemia and an increase in oxygen consumption may occur with the use of acetate-containing dialysate [9,13] and because of membrane incompatibility [9,15]. To allow hyperalimentation and to remove uremic solutes, IHD needs to be performed with increased frequency. However, attempts to decrease the frequency of IHD often results in a tendency to restrict fluids and nutritional intake, thereby aggrevating catabolism [5,16]. All of these problems may potentially exacerbate the already precarious condition of the critically ill patient. In one study [17], a significant increase in vital organ dysfunctions was observed during IHD in ICU patients with ARF.

Recent advances in hemodialysis technology, such as bicarbonate dialysis, volumetric dialysis machines allowing controlled ultrafiltration and more biocompatible dialyzer membranes (as used for CRRT), have reduced, rather than prevented, hemodynamic instability during IHD [9,16].

**Peritoneal Dialysis**

Although less efficient in removing of fluid and waste products, acute (continuous or intermittent) peritoneal dialysis (PD) may be better tolerated in the critically ill patient [18]. PD is a relatively simple procedure and does not require the use of specialised equipment. The urea clearance of acute PD usually approximates 7-14 L/day (5-10 ml/min), but may be augmented by increasing volume/exchange, cycles/hr, and/or ultrafiltration/exchange [18,19,20]. However, factors such as reduced splanchnic blood flow during shock or the use of vasoconstrictors and low oncotic pressure due to hypoalbuminemia may compromise PD efficiency.

According to Nolph [18], there are no absolute indications for PD other than the inavailability of other techniques and the need for dialysis. If the hepatitis B or HIV status is unknown, then PD will result in less risk to medical and nursing staff than IHD where cross infection from the patients blood is possible. Relative indications include hemorrhage, for which anticoagulants are undesirable; hypotensive states, for which IHD is likely to exacerbate the problem; difficult blood access; and hypothermia, for which central core warming with intraperitoneal fluid may be desirable [18,20].

Acute PD may be contra-indicated or impossible to perform because of acute intra-abdominal pathology, such as recent abdominal surgery, peritonitis and the presence of abdominal drains. In addition, acute PD does not offer urea clearances sufficient to ensure adequate control of azotemia in catabolic patients and may be inadequate for the ultrafiltrate requirements needed to maintain fluid balance [18,20].

This often precludes the provision of full (par)enteral nutrition. Large volumes of intra-abdominal dialysis fluid may lead to respiratory compromise. Other complications are hypernatremia following aggressive ultrafiltration [18,20], 'overfeeding' hyperglycemia with consecutive hypertonic exchanges [21] and, most importantly, access infection and peritonitis [18,20,22]. It is for these reasons that acute PD is now rarely used in the ICU.

## Continuous Renal Replacement Therapy

CRRT has now been used in a wide variety of clinical settings. The basic technique involves placing a hemofilter in the extracorporeal blood pass of the patient, whose systemic blood pressure provides the main driving force for ultrafiltration (UF). Continuous renal replacement may take one of several forms: *continuous arteriovenous hemofiltration* (CAVH), first proposed by Kramer in 1977, depending on convective transfer of solute [23]; *slow continuous ultrafiltration* (SCUF), a technique of continuous slow ultrafiltration, most commonly performed without simultaneous fluid replacement [7]; *continuous venovenous hemofiltration* (CVVH), which, unlike CAVH, depends on the use of an external blood pump [24]; *continuous arteriovenous hemodiafiltration* (CAVHD), first described by Geronemus and Schneider in 1984 [25], which involves infusing sterile dialysis fluid through the hemofilter in a counter-current direction to the blood flow, thereby enhancing solute movement due to convection across the membrane by diffusion; *continuous venovenous hemodiafiltration* (CVVHD), ultrafiltration and dialysis combined as in CAVHD, but performed with the use of a pump-assisted venovenous extracorporeal circuit [26]; *continuous ultrafiltration periodic intermittent hemodialysis* (CUPID), intermittent hemodialysis performed against a background of continuous pump-driven ultrafiltation [27].

### *Principles*

Hemofiltration was first described by Henderson *et al.* [28]. This technique uses the principle of convective transport of solutes: venous blood is pumped from the patient through an artificial kidney and subsequently back to the patient and an ultrafiltrate of plasma water is produced by a hydrostatic pressure gradient across a highly permeable membrane (*in vitro* molecular cut-off point 40,0 kDa). Mass transfer occurs by convection, *i.e.* as water moves across the membrane ('ultrafiltration'), it drags with it solutes such as urea. The quantity of solute movement by convection depends upon molecular size, membrane permeability, hydrostatic pressure and the UF rate. Intravascular volume is preserved by replacing the ultrafiltrate with fluid that has an electrolyte composition similar to that of plasma [28].

Kramer [23,29] modified this principle by simply attaching a hemofilter to the femoral artery and vein, using the patient's own arterial blood pressure as a driving

force through the filter, thereby obviating the need for a pump to drive the system: CAVH. Over the last decade, this technique has gained increasing popularity as a way of treating critically ill patients with ARF in the ICU [4,5,6].

*Advantages of continuous renal replacement therapy*

Several potential advantages of CRRT relative to conventional hemodialysis in critically ill patients with ARF have been identified. Principle among these is the avoidance of cardiovascular instability [8,30]. Paganini *et al.* reported in 1984 that 23 of their patients, for whom IHD was not possible, could be treated effectively with CRRT [7]. CRRT is a slow, continuous form of therapy that avoids the rapid shifts in both blood volume status and electrolyte concentrations that result from rapid removal of solutes occurring with IHD [7,8,30]. The gradual, yet continuous, removal of intravascular water and toxic metabolites allows great flexibility in fluid and electrolyte management and creates 'space' for the (early) administration of full parenteral nutrition and intravenous medications [16,20,31]. In addition, an improvement of pulmonary gas exchange and cardiac performance may result from the readily reversal of any existing pulmonary edema and by the titration of left ventricular filling pressure [7,32]. Another advantage of continuous therapies is the metabolic 'steady state' of the ICU patients. CRRT prevents the peak/trough urea concentrations associated with IHD [33,34], and the steady-state urea concentration achieved may well reflect more adequate azotemic control [33]. By use of 'appropiate' filtration replacement fluid the patient's electrolyte concentrations can be decreased or increased gradually and independently of changes in total body water [32-37]. Other potential advantages relative to IHD include a lower circulating extracorporeal blood volume, less complement activation and less need for specialised personnel or equipment [4,6,35]. In addition, the ability of CRRT to remove mid- to high MW solutes (0,50-20,0 kDa) has led to the application of this technique in various clinical conditions (see section '*non-renal effects*')[38]. The effectiveness of CRRT, particularly its recently developed modifications (CVVH[D], CAVHD), is such that adequate metabolic control can be achieved even in severely hypotensive, hypercatabolic patients.

*Fluid and solute removal*

The capability of CRRT to remove plasma water and solutes is a function of the net pressure gradient across the membrane, *i.e.*, the difference between the hydrostatic and oncotic pressures present in the extracorporeal system. Positive hydrostatic pressure within the hemofilter is a function of the MAP but tends to be much lower because of resistance encountered by blood flow. This decrease is determined by the type of vascular access, the length and internal diameter of the blood tubing, the resistance of the hemofiltration membrane and the patient's venous pressure [35-37,39]. A MAP of 50-70 mmHg is generally required to produce an

adequate UF rate. A negative hydrostatic pressure component is generated by suction produced by the weight of the ultrafiltrate fluid column beneath the hemofilter. The pressure generated is equal to the height of the fluid column (cm) multiplied by 0.74 mm Hg/cm $H_2O$ (usually 15-30 mmHg). The oncotic pressure exerted by plasma proteins within the blood compartment of the hemofilter opposes the forces that favor filtration. As UF occurs, the oncotic pressure increases along the length of the filter and may subsequently become sufficient to offset the hydrostatic pressure, thus causing UF to cease (*i.e.*, 'filtration pressure equilibrium') [39]. However, filtration pressure disequilibrium (postfilter hydrostatic pressure > postfilter oncotic pressure) is probably present in the majority of patients [40]. As plasma water is removed, non-protein-bound solutes are transported across the membrane by convection. The degree of permeability of a hemofiltration membrane is indicated by the Sieving coefficient (*S*). The *S* represents the ratio of the solute concentration in the ultrafiltrate to the solute concentration in the retained plasma and varies from 0 to 1, depending on particular membrane, molecular size, and protein-binding properties of the solute [6,7,35]. The Gibbs-Donnan effect on small-solute and electrolyte transfer across the membrane is negligible; therefore, their concentration in the ultrafiltrate is identical to that in the plasma (*S* close to 1.0) and the overall concentration of these substances remains unchanged [6,7,35]. For larger non-protein-bound solutes the concentration in the ultrafiltrate progressively decreases with increasing molecular size (*S* approaching 0)(Figure 1).

Replacement of the ultrafiltrate with a 'balanced' electrolyte solution, which does not contain urea or creatinine, allows the overall clearance of these and other solutes from the blood. With ultrafiltrate volumes of 10-12 L/24h being removed and replaced, urea clearances of approximately 9 ml/min may be achieved [35,36]. In hypercatabolic or severely hypotensive patients, however, urea clearances with CAVH may be inadequate to achieve metabolic control and additional IHD may be required [8,41,39].

*Techniques for enhancing solute clearance*

Various modifications of CAVH have been developed to enhance solute clearance. These are either directed at increasing UF rate and thus convective solute transport (*i.e.*, vacuum suction, predilution, use of a venovenous pumped system) or at enhancing solute clearance by combining diffusive and convective solute transfer (*i.e.*, adding slow dialysis to CAVH).

•*Suction assist.* Applying suction (usually 150-200 mm Hg) to the UF limb of the filter will increase the hydrostatic pressure gradient across the membrane and so increase UF rate [42]. However, the increase in filtration fraction (sometimes exceeding 50%) may favor filter clotting despite adequate heparinization.

•*Predilution.* Adding replacement fluid to the blood within the extracorporeal circuit just before it enters the filter ('predilution') has the effect of reducing blood viscosity as it enters the filter by reducing hematocrit and plasma protein concentration and

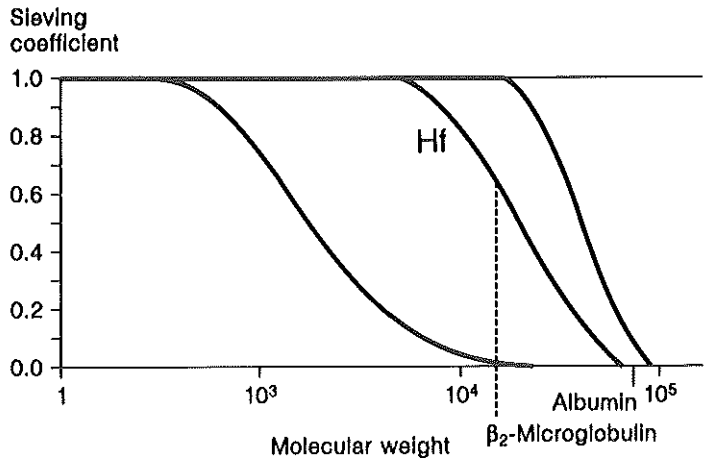


*Figure 1: Permeability characteristics of hemofiltration membranes (Hf) for solutes with different molecular weight (MW). The Sieving coefficient, representing the ratio of the solute concentration in the ultrafiltrate to the solute concentration in the retained plasma, of $\beta_2$-microglobulin (MW 11,6 kDa) is depicted in the figure. For comparison, the permeability profile of the glomerular basement membrane (right curve) and a low-flux dialyzer membrane (left curve) are shown. Note the progessive decline in permeability of hemofiltration membranes for large solutes with increasing molecular size (Sieving coefficient approaching zero).*

increasing the flow and hydrostatic pressure across the membrane [43]. In addition, predilution increases the availability of urea for convective transfer by favouring its movement from the erythrocyte [4,43]. All of this will increase the UF rate and may lead to a better preservation of sieving properties of the membrane [4,43].

•*Pumping.* The addition of a mechanical blood pump to a venovenous extracorporeal circuit (*i.e.*, CVVH) will increase blood flow through the filter (100-300 ml/min) and so increase the UF rate. With this technique, up to 50 litres of ultrafiltrate per day (urea clearance 34 ml/min) may be produced [44]. Longer effective filter life may result from the high blood flow through the filter. Monitoring and safety features of currently available systems include a venous pressure sensor, air detector and automatic vascular clamps. In addition, to avoid errors in fluid balance which could compromise the patient's clinical condition, computer-monitored systems have been developed which regulate substitution fluid volume by measuring ultrafiltrate volume [22,45].

Continuous pump-driven venovenous hemofiltration may also be performed with volumetric dialysis machines, allowing automatic switching between hemofiltration and hemodialysis modes and providing automatic and accurate control of fluid removal: CUPID [27].

•*Adding slow dialysis.* By running dialysate through the filtrate compartment of the filter, additional diffusive transfer occurs, the basis of CAVHD. Counter-current dialysate flow should be preferred as it provides more efficient small-solute clearance as compared to concurrent flow [46]. If dialysate flow is slow enough (<33 ml/min), small solutes will equilibrate completely between blood and dialysate and the urea clearance will approximate dialysate flow rate [25,47]. A high dialysate flow may result in declining increments in solute clearance because of incomplete solute equilibration. However, in contrast to Geronemus and Schneider's initial report [25], no ceiling was observed with dialysate flows up to 67 ml/min (4L/h) in a recent study (urea clearance approaching 50 ml/min)[48]. As diffusive clearance with CAVHD is independent of blood flow in the range of 50-190 ml/min, adequate control of uremia can be obtained in highly catabolic patients with hypotension [47]. In practice, the dialysis component (typically with dialysate flow 0.5-2 L/h) is used for correction of uremia and hyperkalemia, whereas the filtration component is used for net fluid removal [47-49]. Earlier reports suggested that the presence of dialysate reduced the transmembrane hydrostatic pressure gradient and consequently the UF rate [25]. However, with use of currently available hemofilters having high hydraulic permeability, the UF rate with CAVHD is not reduced when compared with CAVH [47,49]. The combination of a pump-driven venovenous extracorporeal circuit with counter-current dialysate flow (CVVHD) provides excellent small-solute clearance [26,50]. The UF rate is usually limited to 4-7 ml/min and, as with CAVHD, the urea clearance is predominantly determined by the dialysate flow [26,50]. However, UF rate and thus convective solute transport may be enhanced significantly by increasing the (pump-driven) blood flow.

Figure 2 shows the urea clearance of the different continuous treatment modalities, calculated as the mean value (± SD) from 26 published reports. Both CAVHD and CVVH(D) compare favourably with IHD (when calculated as the mean value of 4 hour, every-other-day treatment, *i.e.*, the usual setting). In addition, the limited urea clearance obtained with CAVH is illustrated. Whilst urea clearance of IHD can be doubled by daily treatment, the effectiveness of continuous methods can be improved either by increasing dialysate flow rate or by increasing daily filtration rate.

### *Hemofiltration membranes*

Available membranes for use in CRRT are characterized by a small internal volume (40-70 ml), low resistance to flow and high permeability. Because of increased biocompatibility, synthetic membranes (either made of polyacrilonitrile, polyamide or polysulphone) should be preferred [9,70]. This may especially relate to its use in critically ill patients. Experimentally, cuprophane membrane, but not polyacrilonitrile membrane, exposed blood delayed resolution of ischemic ARF [71].

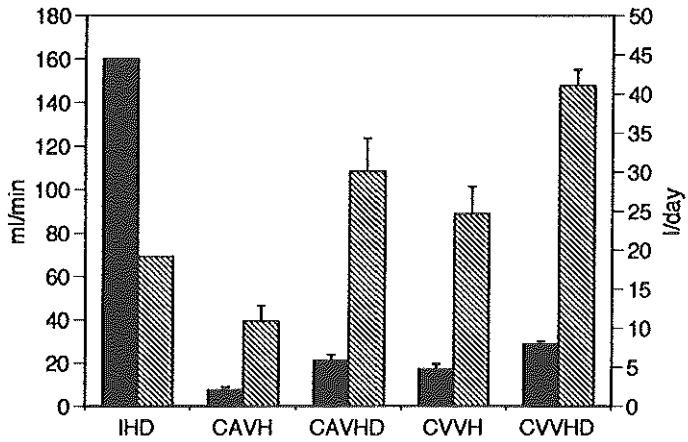


*Figure 2: Efficiency of different forms of acute renal replacement therapy. The mean (±SD) urea clearances of the various continuous treatment modalities (CAVH/CAVHD, CVVH/CVVHD) are calculated from 26 published studies [16,25,26,29,36,47-52,55-69]. Daily clearance of intermittent hemodialysis (urea clearance 160 ml/min) is calculated as the mean value of 4 hour every-other-day treatment. To allow comparison, clearances of all treatment modalities are expressed as ml/min (black bars) and L/day (hatched bars).*

In addition, blood-membrane exposure significantly aggrevated the negative hemodynamic response to endotoxemia [72]. Recently, Davenport *et al.* observed significant differences in cardiovascular stability during identical hemofiltration treatment with 2 different membranes in critically ill patients with combined hepatic and renal failure [73].

Several comparative studies evaluating filter effectiveness in terms of small-solute clearance during CRRT exist. Although low filter resistance may increase blood flow, it does not necessarily improve UF rate [39]. Olbricht *et al.* observed significant differences in UF rate, largely attributable to differences in hydraulic permeability of the membrane [40]. The UF rate declines during treatment due to partial clotting of the filter, resulting in reduced available membrane surface area [74]. Small-solute sieving coefficients do not decrease during CRRT [75,76]. With CAVHD and CVVHD, the UF rate becomes less important as small-solute clearance depends mainly on diffusive transfer. Yohai *et al.* observed superior performance characteristics of flat plate filters compared to hollow fiber filters, attributable to

greater diffusive urea clearances [77]. In contrast, Ifediora *et al.* observed no influence of dialyzer membrane type, surface area or geometry on small-solute clearance during CVVHD [50].

Clearance of large solutes (>500 Da) depends mainly on their convective removal and thus UF rate. Sieving properties of synthetic membranes for solutes up to 5,0 kDa remain constant during CRRT [75,76]. Sieving properties for larger solutes may decline because of protein adsorption ('secondary membrane formation') [78]. Membranes also differ in terms of adsorption and desorption capacity (*i.e.*,subsequent release)[75,76]. If the removal of large solutes is of primary concern (*e.g.*, inflammatory mediators such as TNF-$\alpha$, MW 16,8 kDa; see section '*non-renal effects*'), it may therefore be beneficial to change filters frequently [80].

Filter 'survival' in most centres averages 2-3 days [6,16,35]. Although some suggest that flat plate dialyzers with their low resistance to flow require less heparin to avoid clotting [74], no comparative data exist.

*Vascular access*

Vascular access is achieved either by means of femoral artery and vein catheters or alternatively a Scribner shunt [6,35]. Large-bore (8-10F) femoral arterial and venous catheters inserted percutaneously using the Seldinger technique are routinelly employed in most ICU's. Such catheters can be positioned quickly, requiring no special skill for their insertion, and are relatively simple to use. Higher blood flows are provided than that achieved with either Scribner shunts or arteriovenous fistulas [35,38,40]. Disadvantages associated with their use include an increased risk of infection, hemorrhage (either overt or concealed), arteriovenous fistula formation and limb ischemia distal to the catheter. Their use may be contra-indicated in patients with peripheral vascular disease or in cases of ARF complicating major vascular surgery because of the risk of limb ischemia [4,6,35]. Scribner shunts, inserted in the wrist or ankle, are an alternative to the use of femoral artery and vein catheters [36,38]. The risks of hemorrhage, infection and limb ischemia are less than with femoral catheters. The patients are more mobile which facilitates their nursing care and vascular access sight is more easily monitored. However, Scribner shunts 'consume' driving force and decrease blood flow at a given MAP [35,40]. In addition, this access may easily clot and render the vessels not suitable for future arteriovenous fistulas [6,35,38].

The dangers of arterial cannulation are avoided in CVVH(D), where vascular access can be obtained via a double-lumen catheter, inserted percutaneously with the Seldinger technique into the subclavian or femoral vein [26,81]. Indeed, fewer complications related to vascular access were noted with CVVHD ($n$ = 25) compared with CAVHD ($n$ = 28) in a recent prospective, comparative study (2 *vs* 10; $p <$ 0.025)[82].

**Table 1. Anticoagulant Regimes for Use in Continuous Renal Replacement Therapy**

| Agent | Activity | Dose | Monitoring | Other agents |
|---|---|---|---|---|
| Heparin | inhibition of thrombin, IXa, Xa, XIa, XIIa with AT III | 500 - 1000 U/h | APTT | protamin infusion postfilter |
| LMWH | anti - Xa activity | < 2.5 U/kg/h | anti - Xa activity | $PGI_2$ (-analogues) |
| $PGI_2$ | inhibition of platelet aggregation | 4 - 10 ng/kg/min | platelet aggregation after ADP stimulation | low-dose heparin or LMWH |
| $PGI_2$-analogues | inhibition of platelet aggregation (20% of $PGI_2$) | 25 - 35 ng/kg/min | platelet aggregation after ADP stimulation | low-dose heparin or LMWH |
| Protease-inhibitor | inhibition of thrombin, Xa, XIIa; prohibition of platelet aggregation | 0.1 mg/kg/h | APTT | |
| Sodium citrate | chelation of calcium prefilter | 4% trisodium citrate (170 ml/h prefilter) | APTT | calcium replacement via separate venous line (1mEq/10ml ~ 40 ml/h) |

Abbreviations: APTT, activated partial thromboplastin time; LMWH, low molecular weight heparin; $PGI_2$, prostacycline. From [27, 36, 86 - 93].

*Anticoagulation*

Anticoagulation, usually with heparin, is necessary to prevent blood from clotting and occluding the filter. The main determinant of filter clotting in CRRT is blood flow or the lack thereof. Interruption of flow by kinking of lines or catheters will promote clotting. Low Anti-thrombin III levels may also contribute to filter clotting [83,84]. Heparin is first introduced into the system when the filter is prepared for clinical use. The filter is primed with normal saline to which heparin is added (10.000 IU/2L). A systemic dose of 2000 IU is then given, followed by constant infusion of heparin at a rate of 10 IU/kg/hr (500-1500 IU/hr)(Table 1). Infusion of heparin is controlled by an infusion pump and is given pre-filter. Although convective clearance of heparin might be expected in view of its MW (13,0 kDa), it is barely detectable in the ultrafiltrate [84]. Heparin dosages as usually instituted may or may not alter the partial thromboplastin time. The purpose of measuring this parameter is *not* to achieve a given level of systemic anticoagulation but rather to determine if heparin is causing systemic anticoagulation in a patient who is bleeding [6]. With CVVH(D), less heparin is usually required because of the higher blood flow. Leslie *et al.* noted improved filter life with CVVHD compared with CAVHD in a prospective, comparative study [85]. In patients with a pre-existing bleeding tendency or low platelet counts (< 60 x $10^9$/L), effective filter function may be maintained without anticoagulation [35,82].

Several authors report the use of prostacyclin as an effective anticoagulant regime, either alone [27,44,86] or in combination with low-dose heparin [87](Table 1). Added beneficial effects of prostacyclin in MOSF patients may be improved tissue-oxygenation, cytoprotection and perhaps aiding recovery of renal function [88]. However, adverse effects of prostacyclin infusion prior to dialysis may include a deterioration in hemodynamics and oxygen transport, especially in ICU patients not adequately resuscitated [89]. Other approaches to anticoagulation include (Table 1): the use of sodium citrate, a rather complicated procedure with several potential technical problems [90]; regional heparinization via protamine infusion post-filter, a procedure which carries the risk of rebound anticoagulation because of difficult titration and differences in half-life [36]; the use of low molecular weight heparin [91,92]; and the use of protease-inhibitors [93].

The use of a heparin-coated CAVH circuit, avoiding the need for systemic heparinization, is currently under investigation and suggests enhanced safety and efficacy of the procedure [94].

*Replacement fluids*

Fluid replacement during CRRT is needed to maintain intravascular volume and serves to decrease the concentration of nitrogenous wastes and creatinine by a dilutional effect [6,35,39]. Administration of replacement fluid is adjusted to reach the desired negative fluid balance. By varying the electrolyte concentration and volume of replacement fluid administered, it is possible to regulate the electrolyte

balance of a patient independently of the total fluid balance [35,37].

Administration of filtration replacement fluid may be either prefilter ('predilutional') or postfilter ('postdilutional'). As discussed (see section *fluid and solute removal*), replacement of the filtration fluid in the predilutional mode will increase the urea clearance significantly compared with that in the postdilutional mode [42]. In addition, predilutional fluid replacement may decrease heparin requirements and prolong effective filter life [45]. However, as some of the filtration replacement fluid administered in the predilutional mode contributes to the ultrafiltrate volume, ultrafiltrate chemistries may not reflect true plasma-solute losses and an additional cost is associated with the increased need for replacement fluids.

Several (commercial) filtration replacement fluids are currently available (Table 2). They usually contain lactate or acetate as a buffering-anion. However, lactate as a buffer precursor must be metabolised to bicarbonate to achieve compensation of metabolic acidosis. In cases of impaired liver function, sepsis or hypoxemia in critically ill patients, lactate can accumulate [95] and metabolic acidosis may be additionally intensified [96]. Acetate may induce adverse hemodynamic effects [13]. For these reasons, bicarbonate-buffered substitution fluid may be preferable [97]. However, this requires a buffer-free solution to which bicarbonate is added just before use to avoid precipitation of calcium- and magnesium bicarbonate [97].

**Table 2. Typical Composition of Replacement/Dialysate Fluid for Use in Continuous Renal Replacement Therapy**

| | Ringer's solution | Replacement/dialysate fluid | CAPD fluid |
|---|---|---|---|
| $Na^+$ (mmol/l) | 130 | 135 - 142 | 134 |
| $K^+$ (mmol/l) | 5 | 2.0 - 4.0 | 0 - 2.0 |
| $Ca^+$ (mmol/l) | 2 | 1.0 - 3.5 | 1.75 |
| $Mg^{++}$ (mmol/l) | - | 0.75 - 1.5 | 0.5 |
| $Cl^-$ (mmol/l) | 112 | 110 - 118 | 103.5 |
| Buffer-anion: | | | |
| Lactate (mmol/l) | 27 | 24 - 55 | 35 |
| Acetate (mmol/l) | - | 10 - 35 | - |
| $HCO_3^-$ (mmol/l) | - | 31 - 34* | - |
| Glucose (g/dl) | - | 0 - 2.15 | 1.5 |
| Osmolality (mosmol/l) | 276 | 284 - 320 | 358 |

*: must be added prior to use to avoid precipitation of calcium- and magnesiumbicarbonate.

Other forms of replacement fluids may include standard mixtures such as Ringers lactate solution and NaCl (0,9%) with added buffer-anions or other electrolytes.
Since the replacement/dialysis fluid does not contain phosphate, it has to be substituted occasionally during prolonged continuous treatment [47,48]. In addition, with prolonged CAVHD potassium should usually be added to the dialysate at a concentration of 4 mmol/L to avoid hypokalemia [47,48].

*Complications*

Complications of the procedure have been found to be uncommon. Clotting of the filter may occur and is most often due to kinking of blood lines or the catheter or inadvertent discontinuation of heparin infusion [38,52]. In contrast to clotting within the hemofilter, some patients may paradoxically hemorrhage as a result of heparinization and/or the presence of severe underlying coagulopathy [9,38]. Other complications are mostly inherent to vascular access, *i.e.* infection and sepsis, limb ischemia and arterial thrombosis requiring surgical revision [7,38,52]. However, it should be noted that reported complication rates related to vascular access are relatively low [6,33,53,54]. Tominaga *et al.* reported 3.1% (2 of 64) and 1.6% (1 of 62) arterial and venous complication rates, respectively, during a total of 309 CAVHD days in 26 patients [54]. We noted 8 vascular access related complications (1 pseudoaneurysm, 3 thromboses of the venous limb of the Scribner shunt, 4 infections [3 femoral catheters, 1 Scribner shunt]) during a total of 531 CAVHD days in 60 patients (manuscript submitted). Although rare and easily detected, filter rupture with blood leakage into the circuit or from a communication between the blood and ultrafiltrate space is a problem intrinsic to the filter [38,52]. In addition, blood leaks from inadvertent tubing disconnections occur and may result in significant hemorrhage [9,38,52]. If not closely monitored, small errors in electrolyte and fluid balance, while easily correctable, may lead to significant iatrogenic morbidity [38]. In addition, with prolonged continuous treatment patients may develop a hypochloremic metabolic alkalosis [98].

*Drug removal*

Several recent reviews have described the principles and clinical findings regarding drug removal during CRRT [99-101]. As virtually all therapeutic agents have a MW less than 5,0 kDa, one can reasonable assume that drugs may permeate hemofiltration membranes [99,100]. Volume of distribution ($V_d$) and binding to non-ultrafiltrable plasma proteins play a dominant role in determining convective transport of drugs. The removal of a drug can be measured by multiplying the UF drug concentration by the UF rate. Alternatively, since plasma levels are usually required for clinical measurement, one may calculate the UF drug concentration as the product of the arterial concentration times the unbound fraction [99]. Protein-binding data for many drugs are available, usually from healthy people [102].

Many factors, however, may affect drug-protein binding including pH, molar concentration of drug and protein, bilirubin, uremic inhibitors, heparin, free fatty acids and the presence of displacing drugs [99,100]. Drug-membrane interactions may also affect the drug's sieving properties and thus clearance (*e.g.*, aminoglycosides) [99,100]. During CAVHD drug removal is more complicated and, depending on the drug's molecular size, occurs predominantly by convection or diffusion. Few data are available on drug clearance in CAVHD. Although clinical guidelines for calculating adjustments to drug dosages during CAVHD have been published [103,104]; as for CAVH, it is advisable that plasma levels of drugs are monitored frequently and that these levels are used to alter dose regimes accordingly.

The ability of CRRT to remove drugs may also be of therapeutic use. Because of its indefinite duration (*e.g.*, for drugs with large $V_d$) and/or ability to remove large molecules, CRRT has been used in several occasions of life-threatening drug-intoxication [105-108].

*Nutrient and hormone balance*

Distinct metabolic alterations occur in ARF, most notably excessive protein catabolism and sustained negative nitrogen (N) balance [109,110]. In contrast to IHD, CRRT facilitates the unrestricted supply of protein and energy sources without the risk of exacerbating azotemia or fluid overload. The technique, however, may have an impact on nutrient balance itself. Urea nitrogen (UN) losses with the ultrafiltrate represent 70-80% of the total eliminated N [109,110]. Non-UN losses occur as a result of convective removal of free amino acids (AA)(MW 75-240 Da). Their clearance is directly proportional to the serum concentration and UF rate and found to be in the range of 3-5% of nutritional input [109,112,113]. As expected from their MW, AA losses are greater during CAVHD and CVVHD, representing 9-12% (depending on dialysate flow rate) of daily protein input [111,114]. Urea kinetic modelling may be of value in determining nutritional needs of highly catabolic ARF patients [110,115-118]. In addition, identification and possibly modification of predictors of urea nitrogen appearance may help to reduce cumulative net N-deficit [110,118]. However, whether (positive) N-balance can actually be achieved in catabolic ARF patients undergoing CRRT is unclear [111,114,116,119] and the upper limit of N that should be administered has not been determined [114].

Convective loss of glucose relative to nutritional input is small (10% with UF rate 15 l/day) [109]. However, when using dextrose-based dialysate in CAVHD/CVVHD, one has to take into account significant glucose transfer from the dialysate to the patient to avoid the risk of 'overfeeding' hyperglycemia [48,111]. With a dialysate flow rate of 16.7 ml/min (1 l/h) and use of dialysate containing 1.5 g/dl dextrose, 550 kcal will be administered to the patient [48]. Although small amounts of insulin (MW 5,4 kDa) may be cleared during CRRT either by convection or adsorption [120,121], the influence of stimuli for hormonal secretion, e.g. glucose, has by far, greater importance than the effects resulting from hormonal elimination [109,120,121]. The same holds true for other hormones involved in nutrient utilization [109,120-122].

The patient's lipid status is not affected as triglycerides and cholesterol are not eliminated via the UF [36,111,113]. Although Davenport reported a case of functional carnitine deficiency following prolonged CAVH [123], there is no need for (routine) carnitine supplementation in patients undergoing continuous treatment [124]. Data regarding serum levels of vitamines and trace elements and their respective removal via the ultrafiltrate are scarce. Only Simpson *et al.* addressed this issue, observing no depletion in both trace elements and water-soluble vitamins in ARF patients treated with prolonged CRRT [125].

*Non-renal effects*

Recent observations have raised the potential for a beneficial effect of CRRT beyond that of simple renal replacement in critically ill patients. Several data suggest that CRRT may favourably influence the clinical course and possibly even outcome in these patients, even in the absence of renal failure (Table 3).

As CRRT allows the unlimited supply of energy and protein, it may eliminate the effect of malnutrition on mortality of these critically ill patients [126]. Lactic acidosis frequently occurs in critical illness and has deleterious effects on the cardiovascular system [137]. Experimental data suggest that hyperlactatemia, independent of acidosis, also exerts adverse effects on myocardial contractility [137]. In addition, acidosis significantly contributes to the catabolic state of the ARF patient [10,113]. Correction of (lactic) acidosis by CRRT may therefore be beneficial in the setting of critical illness [134,135].

**Table 3. Possible Influence of Continuous Renal Replacement Therapy on the Clinical Course in the Critically Ill Patient**

| Contributing factors | References |
|---|---|
| Allowance of adequate nutritional support | 16, 17, 27, 31, 51, 125, 126 |
| Titration of left ventricular filling pressure | 7, 32, 127, 128 |
| Reduction of extravascular lungwater | 128, 129, 130, 131, 132, 133 |
| Correction of lactic acidosis | 134, 135, 136, 137 |
| Convective clearance of inflammatory mediators | 31, 138, 139, 140, 141, 142, 143, 144, 145, 146 |

**Table 4. Outcome in ARF: Intermittent Hemodialysis vs Continuous Renal Replacement Therapy**

| First Author [ref] | Etiology | Treatment | *n* | Apache II | Mortality *n* (%) |
|---|---|---|---|---|---|
| Mauritz *et al.* [8] | Abdominal | IHD | 22 | -[a] | 20 (91) |
| | sepsis | CAVH/CVVH | 36 | - | 27 (75) |
| Simpson *et al.* [27][b] | Post-surgery, | IHD | 31 | 18 | 24 (77) |
| | medical | CUPID | 30 | 19 | 17 (57) |
| Paganini *et al.* [158][c] | Post-surgery, | IHD | 27 | 27 | 22 (81) |
| | medical | CAVH(D) | 47 | 36 | 38 (81) |
| Kierdorf *et al.* [156] | Post-surgery, | IHD[d] | 73 | - | 68 (93) |
| | medical | CVVH | 73 | - | 57 (78)* |
| Bastien *et al.* [61] | Post-cardiac | IHD | 32 | 20 | 24 (75) |
| | surgery | CVVHD | 34 | 25 | 17 (50) |
| Bellomo *et al.* [157] | Post-surgery, | IHD | 83 | 26 | 59 (70) |
| | medical | CAVHD | 84 | 28 | 49 (59) |
| | | IHD[e] | 24 | 24-29 | 21 (88) |
| | | CAVHD | 28 | 24-29 | 15 (54)** |
| van Bommel[f] | Post-surgery | IHD | 34 | 22 | 15 (44) |
| | | CAVHD | 60 | 27 | 37 (62) |

For abbreviations see text. [a]: both groups comparable in terms of age, sex, need for mechanical ventilation and inotropic support; [b]: prospective, randomized study; [c]: no statistical analysis performed; [d]: retrospectively randomized from original IHD group (n=243) without knowing of outcome so that both groups were comparable in terms of age, sex and organ system failures; [e]: stratified retrospectively from original groups without knowing of outcome into groups with similar Apache II scores; [f]: unpublished data, no statistical analysis performed. * CVVH vs IHD; $P < 0.05$; ** CAVHD vs IHD; $P < 0.025$.

Net fluid removal by CRRT in severely hypervolemic patients may improve cardiac performance by inducing changes in preload, thereby leading to a more optimal point on the Starling curve [32,128]. Likewise, negative balancing may have an influence on interstitial pulmonary edema and hydrostatic pressure in the pulmonary circulation, even in the case of ARDS, thereby enhancing gas exchange [131].

An additional beneficial effect is ascribed to the convective clearance of circulating mid- to high MW (0,5-20,0 kDa) inflammatory mediators (*i.e.*, cytokines, eicosanoids, anaphylatoxins etc.) involved in the pathogenesis of septic shock and vital organ system failures [38,138]. Uncontrolled, retrospective studies have shown an improvement of hemodynamics and gas exchange following the institution of CRRT in various clinical settings such as refractory cardiogenic and septic shock, ARDS and (non-renal) MOSF (Table 3). Beneficial results could not or only partially be explained by an impact on fluid balance. Removal of several inflammatory mediators with the ultrafiltrate, including TNF-α (MW 16,5 kDa) and a circulating cardiodepressant factor, was demonstrated [31,139,142,146]. Interim analysis of a prospective, randomized clinical trial evaluating the effect of isovolemic CAVH on the clinical course and outcome in septic ARDS patients revealed a non-significant trend towards improved survival in patients treated with CAVH compared to patients treated conventionally [147]. In animal models of septic shock, isovolemic hemofiltration improved hemodynamics, gas exchange and survival time [148-155]. Convective clearance of several mediators, including a circulating cardiodepressant factor (MW 10,0-30,0 kDa), was demonstrated [15,152]. In addition, infusion of ultrafiltrate from septic animals into healthy animals resulted in a deterioration of hemodynamics and gas exchange, similar to that observed in experimental septic shock [152,155]. Although these data support the hypothesis that convective blood purification *per se* improves hemodynamics and gas exchange in various shock states, little is known with respect to the exogeneous clearance of mediators in relation to their endogenous clearance, their binding to the filter and possible subsequent release during treatment [80].

## Outcome

CRRT has significant advantages when compared to conventional modes of treatment and has now been established as the treatment of choice in the management of ARF in critically ill patients. However, despite the provision of adequate metabolic control and greater flexibility and facility in the control of fluid and electrolyte balance, it is not yet clear whether these techniques will improve overall mortality.

In many earlier reported series of ARF patients treated with PD (<1980), similar outcome was observed compared to patients treated with IHD [20,22]. As PD is now rarely instituted in the ICU setting, no comparative studies exist.

Several recent studies have compared the outcome of ARF patients treated with IHD and CRRT (Table 4). Most studies show a (non-significant) trend towards improved survival in patients treated with one of the continuous techniques when compared to patients having similar severity of disease who are treated with IHD

[8,156,157]. Improved outcome in continuously treated patients was further suggested by the finding of a survival rate similar to that observed in patients treated with IHD, despite higher Apache II scores and more organ system failures [158]. We observed a higher mortality rate in surgical ARF patients treated with CAVHD compared to patients treated with IHD. However, actual comparison is made difficult because of treatment selection bias resulting in marked differences in the severity of disease between treatment groups (Table 4). It should be noted that in most retrospective studies, patients treated conventionally were usually historical controls. Therefore, factors other than the use of CRRT *per se*, such as improved overall medical care, newer drugs or hyperalimentation may have been (more) responsible for the observed decline in mortality. In the only prospective, randomized study to date, a clear, though not significant trend towards improved survival was found in patients treated continuously (*i.e.*, CUPID) when compared to patients treated with IHD [27].

Many studies reporting experience with one of the continuous techniques have now been published and show a wide variety in mortality rate (40-80%). This may partially be explained by differences in underlying diseases or differences in the severity of the disease that led to the development of ARF. Combining 32 published reports comprising more than 1600 patients, no significant difference is observed in the outcome of ARF patients treated with one of the continuous treatment modalities (Figure 3).

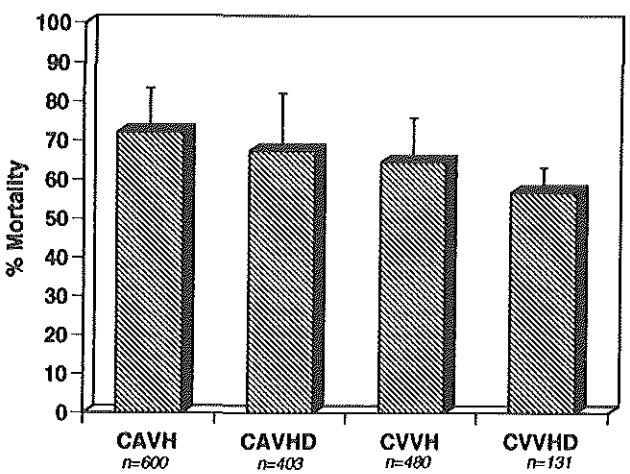


*Figure 3: Outcome (mean ± SD) in acute renal failure patients (n = 1614) treated with different forms of continuous renal replacement therapy (CAVH/CAVHD, CVVH/CVVHD), showing no significant difference in mortality rate. Pooled data from 32 studies [17,29,36,41,44,47,49,51,52,55-69,85,159-165].*

**Table 5. Outcome in ARF: Low-volume vs High-volume Hemofiltration**

| Author | Mode of treatment | UF (L/day) | Survival (%) | Recovery of renal function (%) |
|---|---|---|---|---|
| Storck *et al.* [166] | CAVH | 7.0 | 12.5 | - |
| | PDHF | 15.7* | 29.4*^ | - |
| Mauritz *et al.* [8] | CAVH | 14.6 | 11 | 11 |
| | PDHF | 38.4* | 29.6 | 48 |
| Journois *et al.* [167] | CAVH | 18.4 | - | correlation UF-recovery diuresis* |
| | PDHF | 22.3* | - | |
| Sieberth *et al.* [17] | CVVH | Survivors vs Non-survivors: 17.8 vs 10.7** | | - |

For abbreviations see text. *: $p < 0.05$; **: $p < 0.01$; ^: Correlation UF - survival, $p < 0.05$

Several data, however, suggest a positive correlation between the ultrafiltrate volume and survival as well as ultrafiltrate volume and recovery of renal function (Table 5). While some suggest that this represents greater clearance of circulating inflammatory mediators involved in the pathogenesis of septic shock and MOSF [166], others suggest that this may represent more adequate metabolic control [17].

However, as the severity of disease in critically ill patients who develop ARF is in the most part independent of the problems of acute uremia, correction of the uremia itself will not necessarily lead to any improvement.

## Which treatment is best?

During the last years, CRRT has been established as the preferred treatment modality in the management of the oliguric patient with hemodynamic instability and/or severe fluid overload. The distinct advantages of CRRT relative to conventional dialysis are illustrated in Table 6, which summarizes the major features of the various renal replacement therapies. CRRT creates space for the provision of early, aggressive nutritional support, antibiotics and inotropic drugs. Although limited clearances are obtained with CAVH, adequate metabolic control can now be achieved with its recent modifications (CAVHD, CVVH[D], CUPID). The choice of which form to use is mainly influenced by personal preference and the availability of equipment. There are no studies clearly demonstrating the superiority, in terms of improved outcome, of CRRT over conventional modes of treatment or the superiority of one continuous treatment modality over the other.

**Table 6. Major Features of Various Renal Replacement Therapies.**

| | IHD | PD | CRRT |
|---|---|---|---|
| Hemodynamic stability | - | + | ++ |
| Fluid removal | ++ | + | +++ |
| Correction of acidosis | ++ | + | +++ |
| Unlimited (par)enteral nutrition | - | - | ++ |
| Clearances | | | |
| small solutes (MW <500 Da) | ++ | + | +++ |
| large solutes (MW >500 Da) | - | + | ++(+)[a] |
| Access morbidity[b] | + | ++ | +(+)[c] |
| Anticoagulation needs | + | - | +(+)[d] |
| Simplicity | + | +++ | ++ |

Abbreviations: IHD, intermittent hemodialysis; PD, peritoneal dialysis; CRRT, continous renal replacement therapy; [a]: clearance of larger solutes may be augmented by increasing ultrafiltration rate; [b]: relates to angio (IHD, CRRT) and peritoneal cavity (PD) access; [c]: may be decreased by using veno-venous hemofiltration; [d]: may be decreased by using predilution hemofiltration or pump-driven hemofiltration.

However, several authors have recently propounded the view that CVVH(D) should be the preferred treatment modality [33,58,59,82,168,169]. The constant UF rate with CVVH(D) simplifies fluid and electrolyte management and the high blood flow rate contributes to the low heparin doses required to prevent clotting. The need for large-bore arterial access with its inherent complications is obviated. In addition, a high UF rate may lead to significant convective clearance of mid- to high MW inflammatory mediators, which may have a beneficial influence on the clinical course and possibly even outcome in critically ill patients. Although some suggest that use of a blood pump adds complexity to the procedure, it has been shown that with close supervision of the nephrologist, CVVH(D) is safe, easily implemented and managed efficiently by the ICU nursing staff [26,57,82,169,170]. However, although CRRT allows control of biochemistry and fluid balance in patients who were previously too unstable for satisfactory dialysis by conventional techniques, further studies are needed to assess long-term effects of CRRT on morbidity and mortality and to establish the preferred continuous treatment modality unequivocally. In addition, further research is warranted to provide a rationale for the use of CRRT in critically ill patients in the absence of conventional indications for dialytic support.

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Chapter III

# Use of APACHE II classification to evaluate outcome and response to therapy in acute renal failure patients in a surgical intensive care unit

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## Abstract

***Objective***: To determine the applicability of the Acute Physiology and Chronic Health Evaluation (APACHE) II score in surgical patients with acute renal failure (ARF) requiring dialytic support, and to assess its utility in evaluating data from this specific disease group.

***Design***: Retrospective, partly prospective follow-up study of patients who developed ARF during their course of stay on the surgical intensive care unit (ICU) of a Dutch university hospital from January 1, 1986 to January 31, 1994.

***Patients and methods***: A total of 111 patients were identified, of whom 104 patients were considered eligable for this study. Data for the individual APACHE II scores were calculated from the most deranged values during the initial 24 h of ICU admission (APACHE $II_1$) and on the day dialytic support was instituted (APACHE $II_2$). The ratio between both APACHE II scores was also calculated for each patient ($AP_2/AP_1$-ratio). Receiver operating characteristic curves (ROC) were constructed. Other variables evaluated included age, sex, serum creatinine, diagnostic category, time from ICU admission to start of dialytic support, and the type of dialytic support.

***Results***: Of these 104 patients (median age 64; range 23-85 yrs), 51 (50%) survived to leave the ICU, of whom 47 (46%) survived to leave hospital. The APACHE $II_2$ score (27.0 ± 4.4 *vs* 22.4 ± 3.5; $p < 0.001$) and $AP_2/AP_1$-ratio (1.12 ± 0.09 *vs* 0.97 ± 0.06; $p < 0.001$) were significantly higher for non-survivors as compared to survivors. The ROC curve was most discriminative for the $AP_2/AP_1$-ratio (area under the curve 0.92) and to a lesser extent for the APACHE $II_2$ score (area under the curve 0.78). Estimated risk of death with the APACHE II equation did not improve predictive power. Multivariate analysis of various variables revealed the $AP_2/AP_1$-ratio as the single most important factor predicting death (odds-ratio 13.8, $p < 0.001$). Adjusting for the $AP_2/AP_1$-ratio, no impact on outcome was observed for age, diagnostic category, time from ICU admission to start of dialytic support, and the type of dialytic support. Above a value of 1.0 of the $AP_2/AP_1$-ratio, logistic regression revealed a sharp increase in death probability with increasing $AP_2/AP_1$-ratio.

***Conclusions***: APACHE II, when used at the time of initiation of dialytic support, proved to be a valid way in our surgical ICU to stratify ARF patients by the severity of their illness. Moreover, use of the $AP_2/AP_1$-ratio further improved the usefullness of this severity-index and may help to identify patients who have little chance of survival. Estimating the risk of death with the APACHE II equation did not improve predictive power.

## Introduction

Despite continuous progress in intensive care medicine, the incidence and outcome of critically ill patients who develop acute renal failure (ARF) has changed little [1]. Some authors, however, suggest that progress has been made but is masked by a change in patient characteristics [1,2,3]. One major reason for our failure to show unequivocal evidence of progress in outcome of ARF patients on the intensive care unit (ICU) is the failure of most studies to provide information in a form that allows meaningful comparison [2,3]. While this problem is closely studied in the intensive care field, little is known in nephrological circles. Indeed, from most reports, it is difficult to determine if outcome variables were related to therapeutic efforts (*e.g.*, renal replacement therapy) or to a difference in case mix [2,3,4].

Recently, the need for a severity-of-disease scoring system for use in ARF patients was emphasised [1,4,5]. An accurate scoring system would allow us to risk-stratify patients, to compare patient risk from different units and to compare outcome of ARF patients subjected to different interventional strategies [6]. Although several risk models for use in ARF patients have been developed, none of these are widely adopted and most of them have not been formally validated [4,5]. Furthermore, recent data suggest that these risk models may be institution-specific [7]. In contrast, the Acute Physiology and Chronic Health Evaluation (APACHE) II scoring system is now used routinely in most ICU's and is familiar to most physicians involved in the care of critically ill patients [8,9,10]. However, while validated for use in the general and surgical ICU population [8-11], it is not clear whether use of APACHE II is valid in specific disease groups such as those with ARF.

The purpose of this study was to examine the APACHE II system as an outcome predictor in ICU patients with ARF receiving dialytic support. We also evaluated the lenght of time patients were in the ICU before renal replacement therapy was started, the type of dialytic support, the change in APACHE II scores between ICU admission and the start of dialytic support, and whether these variables are predictive for mortality.

## Patients and Methods

Records of patients admitted to the surgical ICU receiving dialytic support during the period January 1, 1986-August 31, 1992 were retrospectively reviewed. From September 1, 1992 untill January 31, 1994, patients receiving dialytic support were studied prospectively. Patients with pre-existing chronic renal failure treated with hemodialysis prior to ICU admission were excluded from this study. The University Hospital 'Dijkzigt' is a tertiary care, 800-bed teaching hospital with separated medical and surgical ICU's and as such, it receives patients referred from peripheral hospitals for specialized care. A total of 111 patients were identified for the study from dialysis and ICU records; however, insufficient data were available from 7 patients to calculate accurately the APACHE II score, either at the time of ICU admission or at the time dialytic support was instituted. Therefore, results of this

study were based on the records of the remaining 104 patients. The decision to initiate dialytic support was made conjointly by the critical care staff and consulting nephrologist. Indications for dialysis were azotemia (serum urea > 40 mmol/L), severe hyperkalemia, refractory acidosis and/or severe fluid overload. Patients received either intermittent hemodialysis (IHD) or continuous arteriovenous hemodiafiltration (CAVHD). IHD was performed approximately every-other-day using a high-flux cellulosic-triacetate membrane (CT 110-G, Baxter, USA) and bicarbonate as a buffering anion. Vascular access was achieved by inserting a single-lumen catheter (Medcomp, Harleysville, USA) into the femoral, jugular or subclavian veins or by the surgical creation of a Scribner shunt (Quinton instruments Co., Seattle WA, USA). Dialysate flow was 500 mL/min; mean blood flow 150-175 mL/min. CAVHD was performed using a hollow fiber polyacrilonitrile membrane (AN 69-HF, Hospal Ltd., France). Vascular access was by means of either large-bore catheters inserted into the femoral artery and vein (Medcomp, Harleysville, USA) or by means of a Scribner shunt. Bicarbonate-buffered dialysis fluid (Schiwa GmbH, Glandorf, Germany) was pumped counter-current to blood at a rate of 1L/h (16,6 mL/min). Mean ultrafiltration rate during CAVHD averaged 11 L/day (8 mL/min). During the study period, CAVHD was increasingly used in the more severely ill patients when compared to IHD. All patients who required continued renal support after discharge from the ICU were converted to, or maintained on, IHD. The APACHE II score was calculated as described in the original publication [8]. Briefly, the APACHE II system evaluates 3 aspects of health status: the patients' age, the patient's chronic health status, and a calculated acute physiology score (APS). The APS evaluates 11 routine physiologic measurements and assigns points for each based on the variations on the norm. In addition, points were added based on the Glasgow Coma Scale score to give the total APS. Finally, the points assigned because of the patient's age and health status were added to the APS to get the APACHE II score. The risk of death (%) for individual patients was calculated according to the equation: ln (R/1-R) = -3.517 + (APACHE II score x 0.146) + 0.603 (only if postemergency surgery done) + (diagnostic category weight), where R is the estimated risk of death (ERD)[8]. The predicted death rate for groups was calculated by summing the individual risks and dividing them by the total number of patients. Data for the individual patient APACHE II scores were calculated from the most deranged values during the initial 24 hours of admission to the ICU (APACHE $II_1$) and on the day dialytic support was instituted (APACHE $II_2$). The differences in the two scores were reviewed and an APACHE $II_2$/APACHE $II_1$ ($AP_2/AP_1$) ratio calculated [12]. Patients were divided into specific subgroups according to their underlying disease and/or according to the surgical procedure performed: polytrauma, major vascular surgery, gastrointestinal surgery, hepatobiliary surgery, pancreatitis, or miscellaneous. The following information was also obtained: age, sex, serum creatinine, duration of ICU stay, type and duration of renal replacement therapy, time interval from ICU admission to start of dialysis treatment and both ICU and final (alive on discharge from hospital) survival.

*Statistical analysis*

Percentages were compared using the Chi-square test or tested for trend where appropriate. Comparisons of continuous variables were done using Mann-Whitney's test. Correlation coefficients given are Pearson's. Logistic regression was used to evaluate various variables simultaneously regarding the probability of death. Receiver operating characteristic (ROC) curves, graphically depicting the sensitivity versus the specificity in predicting death of various cut-off levels, were constructed for each severity-index, death risk and the $AP_2/AP_1$-ratio [13]. The area under the curve, being a measure of the power of the predictive model, was also calculated [13]. *P*-values $\leq 0.05$ (two-sided) were considered statistically significant. Data are given as mean $\pm$ standard deviation (SD), or median and range if indicated otherwise. Analysis was done in duplicate (*i.e.*, ICU death and hospital death). As both analysis gave similar results, only the analysis of ICU death is presented.

## Results

Respiratory failure (46%) was the most common primary indication for ICU admission, followed by cardiac failure (22%) and intra-abdominal sepsis (20%). Other baseline characteristics of the patients are given in Table 1. Of the 104 patients, only 13 (13%) were dialysed immediately or on the day of ICU admission. In 38 (37%) patients, dialytic support was initiated more than 5 days after ICU admission. Overall, 51 (50%) patients survived to leave the ICU, of whom 47 (46%) survived to leave hospital. Table 2 represents the univariate analysis of different variables in comparing non-survivors and survivors. Non-survivors did not differ significantly from survivors with respect to age, gender, serum creatinine, APACHE $II_1$, $ERD_1$ or type of dialytic support. There were also no differences between non-survivors and survivors in terms of diagnostic categories ($p = 0.74$). The mean time-interval from ICU admission to start of dialytic support was significantly longer in those who died as compared to those who survived. Patients who were dialysed within 4 days after admission had a better survival as compared to those who were dialysed after this period (60% *vs* 38%; $p = 0.03$). The mean APACHE $II_2$ score, $ERD_2$ and $AP_2/AP_1$-ratio were significantly higher in those who died compared to those who survived (Table 2). Observed number of deaths did not differ significantly from the number of deaths predicted at the time of start of dialytic support, *i.e.*, $ERD_2$ (53 *vs* 48.9 patients; $p = 0.36$). The APACHE $II_1$ and APACHE $II_2$ score were strongly correlated (Fig 1). It is also evident from Figure 1 that most patients who had an increased APACHE II score at the time of initiation of dialytic support as compared to the score at admission, *i.e.*, the patients located above the line of identity, had died. In contrast, there were only a few deaths among those who had a decreased APACHE II score at that time. ROC curves were generated by using each severity-index and death risk as decision criteria to predict ICU mortality.

**Table 1. Baseline Characteristics of Study Population**

| Variable | Median (range) |
|---|---|
| Age (years) | 64 (23 - 85) |
| Sex ratio (M:F) | 83 (80%) : 21 (20%) |
| Diagnostic category | |
| polytrauma | 15 (14%) |
| gastrointestinal surgery | 21 (20%) |
| hepatobiliary surgery | 8 (8%) |
| acute pancreatitis | 7 (7%) |
| vascular surgery | 48 (46%) |
| miscellaneous[@] | 5 (5%) |
| Creatinine (μmol/l) | 578 (172-1086) |
| APACHE $II_1$[*] | 24 (14-35) |
| APACHE $II_2$[**] | 25 (14-37) |
| $AP_2$ / $AP_1$ - ratio | 1.04 (0.88-1.30) |
| Time-interval (days)[#] | 4.5 (0-25) |
| Dialytic support | |
| IHD | 36 (35%) |
| CAVHD | 68 (65%) |

Abbreviations: IHD, intermittent hemodialysis; CAVHD, continuous arteriovenous hemodiafiltration; [@]: urosepsis following nephrectomy ($n$ = 2), liver transplantation ($n$ = 1), pulmonary embolism ($n$ = 1), gastrointestinal bleeding ($n$ = 1); [*] APACHE II score at the time of ICU admission; [**]: APACHE II score at the start of dialytic support; [#]: time-interval from ICU admission to start of dialytic support.

These curves were in a discriminating position for APACHE $II_2$, $ERD_2$, and most pronounced for the $AP_2/AP_1$-ratio, but not for APACHE $II_1$ or $ERD_1$ (Fig 2). Observed mortality rates calculated within index intervals of the $AP_2/AP_1$-ratio are shown in Table 3. There was a significant increase of the mortality rates when the $AP_2/AP_1$-ratio was larger (test for trend; $p < 0.001$)).

**Table 2. Univariate Comparisons of Non-survivors and Survivors Regarding Various Characteristics**

| Variable | Non-survivors ($n$ = 53) | Survivors ($n$ = 51) | Significance |
|---|---|---|---|
| Age (years) | 62 ± 15 | 61 ± 16 | p = 0.77 |
| Male (%) | 43 (81) | 40 (78) | p = 0.56 |
| Creatinine (µmol/l) | 569 ± 207 | 641 ± 208 | p = 0.08 |
| APACHE $II_1$[@] | 24.2 ± 4.2 | 23.0 ± 3.3 | p = 0.26 |
| APACHE $II_2$[#] | 27.0 ± 4.4 | 22.4 ± 3.5 | p < 0.001 |
| $ERD_1$ (%)[@] | 47.2 ± 18.8 | 38.6 ± 20.2 | p = 0.09 |
| $ERD_2$ (%)[#] | 55.6 ± 20.3 | 36.9 ± 20.7 | p < 0.001 |
| $AP_2$ / $AP_1$ - ratio | 1.12 ± 0.09 | 0.97 ± 0.06 | p < 0.001 |
| Time-interval (days)[*] | 6.8 ± 5.6 | 4.5 ± 4.7 | p = 0.01 |
| Dialytic support | | | |
| IHD | 15 (28%) | 21 (41%) | - |
| CAVHD | 38 (72%) | 30 (59%) | p = 0.24 |

Abbreviations: IHD, intermittent hemodialysis; CAVHD, continuous arteriovenous hemodiafiltration. [*]: time from ICU admission to start of dialytic support; [@]: at the time of ICU admission; [#]: at start of dialytic support. Data are given as mean ± SD or percentage, where appropriate.

**Table 3. Relationship Between $AP_2$ / $AP_1$ - ratio and ICU Mortality**

| $AP_2$ / $AP_1$ - ratio | No of patients | Observed mortality rates (%) |
|---|---|---|
| ≤ 1.00 | 28 | 4[@] |
| 1.01 - 1.09 | 40 | 45 |
| ≥ 1.10 | 36 | 94 |

Abbreviations: see text. [#]: proportions of the number of patients who died to the total of numbers within each index interval; [@]: difference between the observed mortality rates in significant (test for trend, $p$ <0.001).

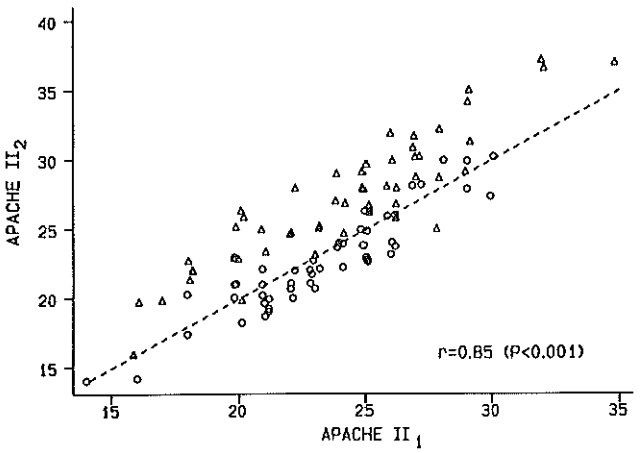


*Figure 1: Relationship between the APACHE $II_1$ and APACHE $II_2$ score. Dotted line represents the line of identity. Both variables are significantly correlated. In addition, most patients who had an increased score at the start of dialytic support, i.e., the patients located above the line of identity, died (◊), while most of the patients who survived (○) had a decreased score at that time, i.e., were located below the line of identity.*

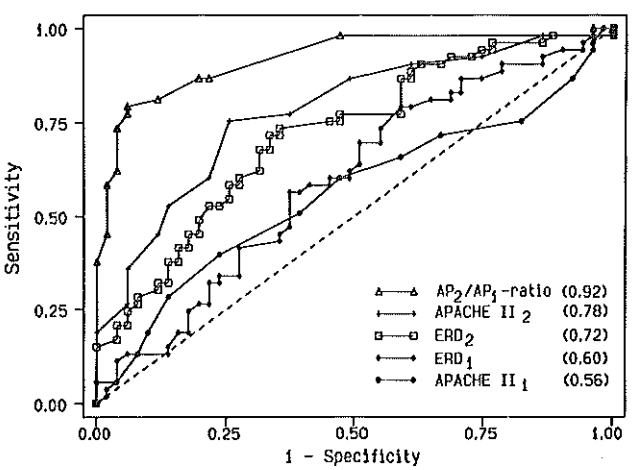


*Figure 2: Receiver operating characteristic curves plotting sensitivity (true positive) versus 1-specificity (false positive) for each severity-index, risk of death and $AP_2/AP_1$-ratio [13]. The diagonal line indicates an index that operates no better than chance. Numbers between parentheses indicate areas under the curve.*

Using multiple logistic regression analysis to evaluate variables which were found significant on univariate analysis, it appeared that the $AP_2/AP_1$-ratio was the most important factor predicting ICU mortality. Adjusting for the $AP_2/AP_1$-ratio, none of the other variables evaluated were of additional prognostic value. Results of multivariate analysis of the variables age, $AP_2/AP_1$-ratio, time-interval and type of dialytic support are shown in Table 4. The association between outcome and time-interval, found on univariate analysis (Table 2), could not be confirmed (Table 4). This could be explained by the observed correlation of time-interval with the $AP_2/AP_1$-ratio. Patients who were dialysed within 4 days after admission generally had lower $AP_2/AP_1$-ratios than those who were dialysed after this period: 1.03 ± 0.09 *vs* 1.08 ± 0.12 ($p$ = 0.04), respectively. Univariate analysis revealed no significant difference in outcome between patients receiving different types of dialytic support (CAVHD 56% death *vs* IHD 42% death; $p$ = 0.24), but significant differences were observed for each severity-index and risk of death between groups (Table 5).

**Table 4. Multivariate Analysis of Various Factors Regarding the Probability of ICU Death**

| Factor | No of patients | Odds-ratio | 95% CI | Significance |
|---|---|---|---|---|
| Age (yrs) | | | | |
| ≤ 50 | 23 | 1[#] | - | - |
| 51-70 | 46 | 0.4 | 0.1 - 2.0 | p = 0.25 |
| > 70 | 35 | 0.8 | 0.2 - 4.3 | p = 0.80 |
| $AP_2$ / $AP_1$-ratio | 104 | 13.8[@] | 4.7 - 40.2 | p < 0.001 |
| Time-interval (days)[*] | | | | |
| < 5 | 52 | 1[#] | - | - |
| ≥ 5 | 52 | 1.2 | 0.3 - 4.2 | p = 0.77 |
| Dialytic support | | | | |
| IHD | 36 | 1[#] | - | - |
| CAVHD | 68 | 0.9 | 0.2 - 3.9 | p = 0.94 |

Abbreviations: 95% CI, 95% confidence intervals; IHD, intermittent hemodialysis; CAVHD, continuous arterivenous hemodiafiltration; [#]: denotes the reference category; [@]: as compared to patients in whom the $AP_2$ / $AP_1$-ratio is 0.1 points smaller. [*]: time-interval from ICU admission to start of dialytic support. Data given are the ratios of the odds for ICU-death against survival (<1 indicates a decreased probability of death; >1 an increased probability).

**Table 5. Characteristics of Patients Receiving IHD or CAVHD**

| Variable | IHD ($n$ = 36) | CAVHD ($n$ = 68) | Significance |
|---|---|---|---|
| Age (years) | 63 ± 17 | 61 ± 15 | p = 0.71 |
| Male (%) | 29 (81) | 54 (79) | p = 0.52 |
| Creatinine (μmol/l) | 685 ± 186 | 557 ± 210 | p < 0.001 |
| APACHE $II_1$[@] | 21.4 ± 3.8 | 24.9 ± 3.3 | p < 0.001 |
| APACHE $II_2$[#] | 22.1 ± 3.8 | 26.5 ± 4.3 | p < 0.001 |
| $ERD_1$ (%)[@] | 30.9 ± 17.9 | 49.9 ± 17.6 | p < 0.001 |
| $ERD_2$ (%)[#] | 32.9 ± 18.9 | 54.4 ± 20.5 | p < 0.001 |
| $AP_2$ / $AP_1$ - ratio | 1.04 ± 0.13 | 1.06 ± 0.09 | p = 0.11 |
| Time-interval (days)[*] | 4.8 ± 4.2 | 6.2 ± 5.8 | p = 0.34 |

Abbreviations: IHD, intermittent hemodialysis; CAVHD, continuous arteriovenous hemodiafiltration. [@]: at the time of ICU admission; [#]: at start of dialytic support; [*]: time from ICU admission to start of dialytic support. Data given as mean ± SD, or percentage where appropriate.

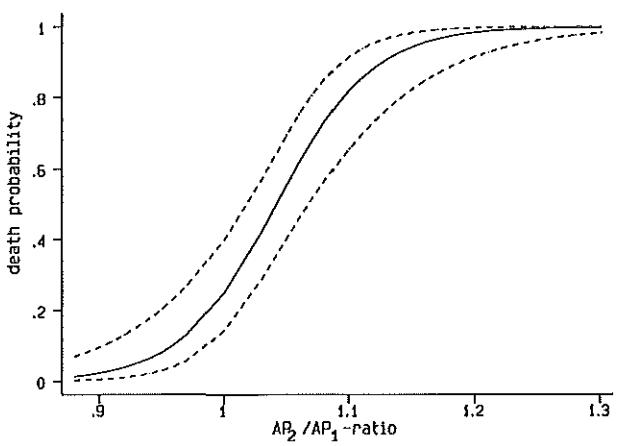


*Figure 3: The estimated probability of death, as found by logistic regression, according to the $AP_2/AP_1$-ratio. Below a value of 1.0, the estimated probability is less than about 20%. Above that value, there is a sharp increase in the probability of death with increasing $AP_2/AP_1$-ratio. Dotted curves indicate the 95 percent confidence limits of estimated probabilities.*

However, also after adjusting for these factors, no significant difference in outcome was observed between the CAVHD and IHD group. Outcome correlated with the $AP_2/AP_1$-ratio, independent from the type of dialytic support (Table 4). That the $AP_2/AP_1$-ratio strongly relates to outcome may also be demonstrated by plotting the estimated probability of death, as found by logistic regression, againsts the $AP_2/AP_1$-ratio (Fig 3). Below a value of 1.0 the estimated probability of death is less then about 20%. Above this value, there is a sharp increase in the probability of death with increasing $AP_2/AP_1$-ratio.

## Discussion

Since its introduction in 1981, the APACHE II scoring system system has gained general acceptance as a measure of disease severity and in outcome prediction of general ICU patients [8-11]. It has been used extensively in controlling for case mix in clinical studies and assessing quality of care among ICU's [12,14,15]. In recent years, use of APACHE II to describe disease severity or to risk stratify ICU patients with ARF to allow comparison of outcome among different centres or to compare different treatment strategies has been proposed by several authors [11,16-20]. However, the APACHE II system has been validated for large groups of patients with mixed diagnosis but as yet not for specific disease groups such as those with ARF [4,5,10]. In addition, APACHE II has been developed for use during the first 24 h following ICU admission and may not be automatically transferable for use in ARF patients receiving dialytic support at one particular time during their course of stay on the ICU [8].

Our results demonstrate that the APACHE II scoring system can be used without modification in surgical ARF patients. However, use of APACHE II at the time of initiation of dialytic support provided a more reliable index of severity of illness and likelihood of survival as compared to its use on ICU admission. It may be that the physiologic derangements observed within the first 24 hours of ICU admission do not accurately reflect the subsequent clinical course and outcome of patients who develop ARF. Today, many patients develop ARF as part of multiple organ systems failure [1,2,21]. As renal failure usually develops later than failure of other vital organs, particularly the cardiovascular and pulmonary system [21], calculation of APACHE II on ICU admission may lead to some bias. Indeed, in a prospective study it was shown that subsequent development of various organ failures in surgical patients could not be foreseen from scores calculated during the first 24 hrs of ICU admission [22]. This may also explain the findings of Maher *et al.* [16], who observed that patients with ARF had a lower chance of survival compared to general ICU patients at comparable admission APACHE II scores. Our findings contrast with those of Schaefer *et al.* [23], who found the system to be inaccurate in medical ICU patients with ARF receiving dialysis. They did not observe differences in median APACHE II scores between survivors and non-survivors. In addition, the overall accuracy at a death risk of 50% and 70% was only 57.5 and 53.7, respectively. As surgical patients have multiple, specific risk factors (*e.g.*, anesthesia, trauma, surgical complications)

that do not pertain to medical ICU patients, our results may not apply to this group of ARF patients.

Calculating the risk of death by combining the raw APACHE II score with a diagnostic weighing did not improve predictive power in our study. Paganini and co-workers [11] recently suggested use of the ratio between the APACHE II score at the time of renal consult and at the time of ICU admission (*i.e.*, $AP_2/AP_1$-ratio) to select the appropiate renal replacement therapy, *i.e.*, IHD or continuous renal replacement therapy (CRRT)[11]. If this ratio was greater than 1, patients were best served with CRRT. Our study showed that this ratio strongly correlated with ICU outcome and that its use significantly improved predicted power of the APACHE II system. The higher the ratio, *i.e.*, the greater the increase in APACHE II score, the lower was the chance of survival. This suggests that ultimate outcome is related to the degree of reversibility of physiologic derangements that led to the development of ARF. Use of the $AP_2/AP_1$-ratio may help to risk-stratify patients, by unabling us to classify patients within the group of ARF patients in which those who have stabilised but who have isolated renal failure and those who have developed renal failure as part of MOSF represent two sides of the spectrum.

Dobkin *et al.* [17] suggested use of APACHE II to identify patients who would not benefit from dialytic therapy. Using this system in ARF patients who received dialytic support from combined medical, surgical and pulmonary ICU's of 2 different hospitals ($n$ = 100), they reported a correct prediction of 100% specificity at a death risk of 70% regardless of what interventions were carried out. Sensitivity and predictive negative value were low in all cases, indicating a poor predictability of those who will survive. The authors suggested that if dialysis were withheld from those patients who were predicted to die, this would not change the overall outcome but would achieve considerable cost reduction [17]. Despite the accuracy of the APACHE II system, when used at the start of dialytic support, and the $AP_2/AP_1$-ratio in our study, we suggest that this approach be taken with great caution. Once undertaken this method becomes self-fulfilling: patients not expected to survive are not treated and therefore survival is precluded. In addition, an accurate estimate of the number of patients expected to die among a group of similar patients will not tell us which particular patient will actually die [3,9]. Furthermore, outcome is to some extent hospital specific and results from one hospital cannot be directly applied to other hospitals [10].

No consistency exist in the literature as to the impact of age on outcome in ICU patients with ARF [5,24]. We did not find age to be an independent predictive factor of death, suggesting that renal replacement therapy should not be withheld solely on the basis of advanced age. The same holds true for the different diagnostic categories. Irrespective of a patient's age or type of underlying disease and/or surgical procedure performed, outcome was determined by the patient's illness severity at the onset of dialytic support. Using the APACHE II system, we also evaluated whether the type of dialytic support affected patient survival. Several authors have recently propounded the view that CRRT is superior to IHD for the treatment of ARF on the ICU [1,16,24]. Comparative data, however, is scarce and potentionally confounding variables are present in these studies [25]. In our study, CAVHD treated patients had

a higher severity-index and death risk as compared to IHD treated patients, which probably resulted from treatment selection. However, outcome did not differ between groups. Although this may suggest a survival advantage in those treated with CAVHD, logistic regression could not confirm an influence of the type of dialytic support on outcome. The same was true for the moment of timing of dialytic support.

In conclusion, the APACHE II scoring system, when used at the time of initiation of dialytic support, proved to be a valid way in our surgical ICU to stratify ARF patients by the severity of their illness. Moreover, use of the $AP_2/AP_1$-ratio further improved the usefullness of this index of severity-of-disease and may help to identify patients who have little chance of survival. Using this index as described, we could not detect an influence of age, time-interval from ICU admission to start of dialytic support, or the type of dialytic support, on patient survival. Despite the accuracy of APACHE II, we do not recommend its use in individual decision making. As stated by Smithies and Cameron [3], 'one remembers - perhaps all to well - our exceptional patients who survived against the odds'.

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Chapter IV

# High-risk surgical acute renal failure treated by continuous arteriovenous hemodiafiltration: metabolic control and outcome in sixty patients

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## Abstract

***Objective***: The outcome and metabolic control was studied in 60 critically-ill patients with acute renal failure (ARF) treated by continuous arteriovenous hemodiafiltration (CAVHD) in a single surgical intensive care unit. In addition, the influence on outcome of various factors was determined.

***Results***: Mean age (± SEM) was 60 ± 2 years with a male predominance (80%). The majority of patients required mechanical ventilation (83%) and/or vasopressor support (70%) and suffered from multi-organ failure (mean number of organ system failures 3.3 ± 0.2 [range 1 - 6]). CAVHD resulted in a rapid decline of serum urea and creatinine levels during the first 72 hours (urea 47.4 ± 2.3 to 30.3 ± 1.4 mmol/l; $p < 0.05$, and creatinine 572 ± 27 to 361 ± 23 µmol/l; $p < 0.05$); thereafter, controlled steady-state levels were achieved with serum urea levels kept below 30 mmol/l with full protein alimentation and often despite hypotension, surgery and septicemia. Significant electrolyte derangements could be easily corrected and maintained within normal limits. Bicarbonate homeostasis could be restored within 48 hours in patients with severe metabolic acidosis ($HCO3^- < 20$ mmol/l) with use of bicarbonate as a buffering anion (17 ± 0.5 to 23.2 ± 0.6; $p < 0.05$). CAVHD allowed rapid removal of excess body and lung water (up to 5 l/day) without hemodynamic instability. Despite a mean pretreatment APACHE II score of 26.5, 26 patients (43%) survived until discharge from the ICU, of whom 23 (38%) survived to leave hospital. Requirement of mechanical ventilation or vasopressor support, higher APACHE II scores and septicemia were all associated with a poor prognosis. Although prognosis was inversely correlated with the number of organ system failures, 24% of patients with 3 or more organ system failures survived to leave hospital.

***Conclusions***: Data suggest that CAVHD represents a significant advance in the management of critically-ill patients with ARF and may have contributed to improved survival.

## Introduction

Despite many advances in the care of the critically-ill patient, acute renal failure (ARF) continues to be associated with a high mortality, attributed in part to a change in patient characteristics [1,2]. Today, ARF is often but one of several failing organs, leading to a complex and unstable patient population. As the traditional forms of hemodialysis treatment have characteristics which limit their use in these patients [3], continuous renal replacement therapy has been rapidly adopted as the treatment of choice [3,4]. Although the first to be introduced, continuous arteriovenous hemofiltration (CAVH), proved very useful in the management of these precarious patients, its capacity in terms of uremic control was limited and often insufficient. To overcome this shortcoming, continuous arteriovenous hemodiafiltration (CAVHD), combining the advantageous aspects of CAVH and intermittent hemodialysis (HD), was developed as a more versatile alternative [5,6].

We report herein our experience with CAVHD in 60 consecutive critically-ill patients with ARF treated in a single surgical intensive care unit, with emphasis on the efficacy of treatment and clinical outcome. In addition, the influence on outcome of various clinical and laboratory features present at the time of initiation of or during CAVHD treatment was determined.

## Material and methods

Records of patients admitted to the surgical intensive unit receiving CAVHD during the period January 1, 1986 - August 31, 1992 were retrospectively reviewed. From September 1992, patients receiving CAVHD were studied prospectively. The following information was obtained: age, sex, pre-existing medical conditions (chronic obstructive pulmonary disease, diabetes mellitus, cardiovascular disease, hypertension, chronic liver disease, chronic renal insufficiency, and malignancy), underlying disease and surgical procedures performed for each patient, need for vasopressor support or artificial ventilation, provision of total parenteral nutrition (TPN), systolic and diastolic blood pressure, heart rate, arterial blood gas, $FiO_2$ requirements, presence of suspected or proven sepsis, bleeding complications, renal and patient outcome and cause of death. Renal recovery was defined as return of renal function sufficient to discontinue dialytic support. To aid comparison with other studies, both ICU survival and final survival (alive on discharge from hospital) are discussed. The Acute Physiology and Chronic Health Evaluation (APACHE) II score at the start of dialysis treatment and the number of organ system failures (OSF's) at the time of initiation of or whilst on CAVHD were calculated according to the pertinent literature [7,8,9]. In a subgroup of 10 patients, cardiorespiratory parameters were reviewed prior to the initiation of CAVHD, and 1, 4 and 24 hrs, respectively, after the initiation of treatment.

**Table 1. Composition Of Dialysis Fluid [@]**

| Solute | mmol/L |
|---|---|
| $Na^+$ | 140.1 |
| $K^+$ | 2.01 |
| $Ca^{++}$ | 1.75 |
| $Mg^{++}$ | 0.60 |
| $Cl^-$ | 112.31 |
| lactate | 2.90 |
| $HCO_3^-$ | 31.40 |
| glucose | 5.80 (1.04 g/L) |

[@]: Composition of 4.5 L acidic solution and 160 mL sodium bicarbonate 8.4%; lactic acid is added to prevent precipitation of $Ca^{++}$ and $Mg^{++}$ carbonate.

*Continuous arteriovenous hemodiafiltration*

The decision to initiate CAVHD was made conjointly by the critical care staff and consulting nephrologist. CAVHD was performed using polyacrilonitrile hollow-fibre filters (AN-69HF, surface area 0,6 $m^2$, Hospal Ltd, France) connected to the arterial and venous vascular access devices in a pumpless circuit with the use of 1.25 mtr extracorporeal tubings with luer lock fittings. Vascular access was either by means of large bore catheters (MedComp, Harleysville PA, USA), introduced in the femoral vessels with the Seldinger technique, or the surgical creation of a Scribner shunt (Quinton Instrument Co., Seattle WA, USA) when cannulation of the femoral vessels was precluded because of severe atherosclerosis or the presence of a vascular prosthesis. Warmed bicarbonate-buffered dialysis fluid (Schiwa Combi-Pac, Schiwa GmbH, Glandorf, Germany), the composition of which is depicted in Table 1, was pumped counter-current to blood through the ultrafiltrate compartment of the filter (dialysate inflow rate, $Q_d$) at a rate of 1000 cc per hour (16,6 ml/min) with a calibrated, volumetric pump (3M, AVI inc., St Paul, USA). In severely catabolic patients, a $Q_d$ of 2 l/hr (33,2 ml/min) was used. The combined ultrafiltrate and dialysate was collected in a graded collection bag and the volume measured hourly. The ultrafiltration rate ($Q_{uf}$) was calculated by subtracting the hourly dialysate volume (typically 1000 cc) from the total volume of effluent in the collection device. Because the production of ultrafiltrate was typically much greater than the desired rate of volume contraction, replacement fluid (Ringer's lactate) was administered into the

arterial limb ("predilution") of the extracorporeal circuit. Standard anticoagulation consisted of 2000 U of heparin as a loading dose followed by continuous infusion of 500-700 U/hr into the arterial line. Low-dose (< 250-500 U/hr) or no heparin was used in the presence of severe underlying coagulopathy or severe thrombocytopenia (< $60 \cdot 10^9$/l). The filters were changed when there was objective evidence of inadequate filter function (*i.e.*, a sustained reduction in UF volume [< 300 ml/hr]) or evidence of filter clotting. Access devices were not routinely changed unless there were clinical signs of infectious (or other) complications. Routine investigations while on CAVHD included daily measurement of serum urea and creatinine, electrolytes, calcium and phosphate, magnesium, glucose, full blood cell count and the activated partial thromboplastin time (APTT). Technical data collected for analysis included ultrafiltrate volume (l/day), vascular access and vascular access-related complications, duration of CAVHD treatment and number of filters used for each patient.

*Biochemical analysis*

Serum urea and creatinine levels were recorded during the first 7 days on CAVHD. Other variables recorded for analysis were serum levels of sodium, potassium, calcium, phosphate and bicarbonate throughout CAVHD treatment. Urea and creatinine clearances (Cl) were calculated in 8 randomly selected patients studied prospectively by using the formula: $Cl = C_{do} \cdot Q_{do}/C_{pi}$, where $C_{do}$ = dialysate outlet solute (urea, creatinine) concentration, $Q_{do}$ = dialysate outflow rate, comprising dialysate inflow rate and net ultrafiltration flow rate ($Q_d + Q_{uf}$), and $C_{pi}$ = plasma inlet solute (urea, creatinine) concentration [5,6]. In addition, different variables were randomly measured at 6 different occasions in both serum and ultradiafiltrate to asses solute saturation of dialysis fluid at $Q_d$ 16,6 ml/min. Variables were measured by routine clinical laboratory methods.

*Statistical analysis*

Data are expressed as mean ± standard error (SEM) or percentage, where appropiate. For biochemical data, a two-factor mixed design ANOVA (group by repeated measures [time]) was used. For analysis of patient characteristics, a one-way between-subjects ANOVA (group) was used. When significant differences occurred between and/or within groups, these differences were further analyzed with a Student-Newman-Keuls test. Statistical significance was accepted at $p < 0.05$.

## Results

*Patient population*

Sixty patients were included in this study (Table 2). There were 12 female and 48 male patients, whose ages ranged from 17 to 83 years (mean 60 ± 2 yrs).

**Table 2. Characteristics of 60 Critically Ill Patients with Surgical ARF Treated by CAVHD**

| Etiology of ARF | No of patients | Age(yrs)/ Male | APACHE II | No of OSF's | Renal function recovery (%) | Survival (%) |
|---|---|---|---|---|---|---|
| Polytrauma | 8 | 48 ± 7/7 | 27.1 ± 2.1 | 3.8 ± 0.7 | 37 | 25 |
| Gastrointestinal surgery | 17 | 60 ± 4/10 | 25.6 ± 0.7 | 3.3 ± 0.3 | 53 | 35 |
| Hepatobiliary surgery | 6 | 47 ± 7/5 | 26.3 ± 1.4 | 3.3 ± 0.6 | 83 | 67 |
| Pancreatitis | 5 | 52 ± 4/4 | 26.6 ± 0.6 | 4.4 ± 0.5 | 60 | 40 |
| Vascular surgery | 22 | 71 ± 2/21 | 27.4 ± 1.0 | 2.6 ± 0.3 | 27 | 45 |
| Other[@] | 2 | 60 ± 22/1 | 22.0 ± 3.0 | 3.0 ± 1.0 | 100 | 100 |
| Total | 60 | 60 ± 2/48 | 26.5 ± 0.5 | 3.4 ± 0.2 | 48 | 43 |

Abbreviations: ARF, acute renal failure; No of OSF's, number of organ system failures (including ARF) as defined according to the pertinent literature [7,8,9]; [@]: Livertransplantation ($n$ = 1), urosepsis ($n$ = 1). Data expressed as mean ± SEM, or percentage where appropriate.

Thirty patients were aged 65 or older. Pre-existing chronic disease was present in 31 patients (52%). Four of these patients had pre-existent impaired renal function (serum creatinine > 180 µmol/l). Mean arterial pressure (MAP) at the initiation of CAVHD was 75 ± 3 mm Hg (range 45 - 144 mm Hg). The majority of patients required artificial ventilation (83%) and/or vasopressor support (70%) at the start of treatment. All but 4 patients (93%) were oligo-anuric (diuresis < 400 ml/day). The etiologies of ARF were varied and often multifactorial. The mean pretreatment APACHE II score was 26.5 ± 0.5 (range 19 - 32). The mean number of OSF's during CAVHD treatment was 3.3 ± 0.2 (range 1 - 6), with 27 patients (45%) having ≥ 4 failing organs. TPN was given in 76% of patients. In the majority of patients (71%), suspected or proven sepsis was present either at the start of (43%) or during CAVHD (28%), with several patients experiencing more than one septic episode.Indications for starting CAVHD included azotemia (91%), severe fluid overload (21%), hyperkalemia (8%) and/or severe metabolic acidosis (23%). CAVHD was performed via femoral cannulae in 44 (73%) and via a Scribner shunt in 16 (27%) patients (forearm, $n = 12$; ankle, $n = 4$).

*Hemodynamic tolerance*

Seven patients failed initial attempts at hemodialysis (defined as hypotension complicating volume removal necessitating discontinuation of dialysis) prior to the initiation of CAVHD. CAVHD was hemodynamically well tolerated. No significant differences in systolic blood pressure, MAP, heart rate and $PaO_2/FiO_2$-ratio were observed during treatment. During the first 24 hrs of CAVHD, no significant differences were observed in cardiorespiratory parameters when compared to pretreatment values. Significant *net* fluid loss (up to 5 L/day) could be obtained with no significant drop in MAP and in several patients with a concomittant decrease in oxygen requirements and vasopressor support.

*Metabolic control*

These 60 patients were treated with CAVHD for a total of 531 days (mean 8.9 ± 0.7; range 1 - 25 days). Mean UF volume was 11.5 ± 0.3 l/day (range 8.9 - 14.7). The mean serum urea and creatinine levels at the initiation of CAVHD were 47.4 ± 2.3 mmol/l (range 18.0 - 94.2 mmol/l) and 572 ± 27 µmol/l (range 172 - 1113 µmol/l) respectively. Overall, a significant decline of both parameters was observed during the first 72 h of treatment (urea 47.4 ± 2.3 to 30.3 ± 1.4 mmol/l; $p < 0.05$, and creatinine 572 ± 27 to 361 ± 23 µmol/l; $p < 0.05$); thereafter, controlled steady-state levels were achieved with serum urea levels kept below 30 mmol/l (Fig 1). Insufficient uremic control with Qd 1 l/hr was observed in 9 patients (15%), all of whom were hypercatabolic and suffering from refractory septic shock.

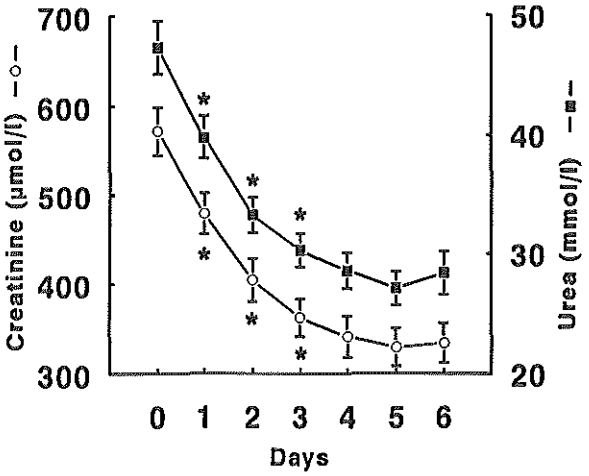


*Figure 1: Decline of serum urea and creatinine levels over time following the initiation of CAVHD in 60 patients. Data expressed as mean ± SEM; *: $p < 0.05$, ANOVA for repeated measurements.*

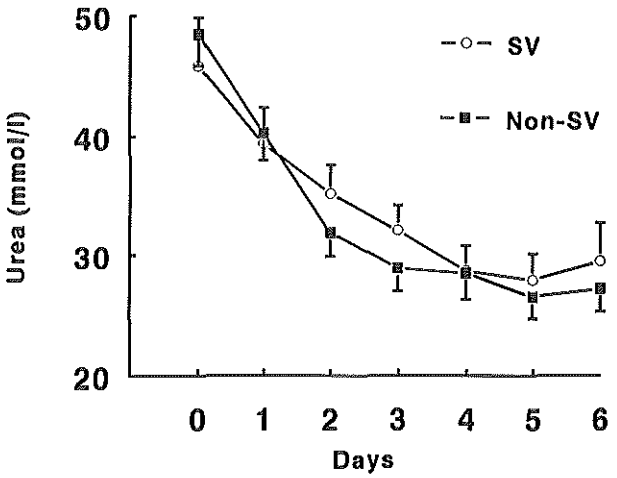


*Figure 2: Decline of serum urea level over time following the initiation of CAVHD in surviving (n = 26) and non-surviving (n = 34) patients. There was no significant difference between groups. Data expressed as mean ± SEM.*

Mean urea and creatinine clearances with $Q_d$ 1 l/hr amounted to 24.6 ± 0.4 and 24.3 ± 0.4 ml/min. Mean urea and creatinine ultradiafiltrate to plasma ratios were 0.95 ± 0.45 and 0.94 ± 0.51 respectively. There were no significant differences in serum urea and creatinine levels between surviving and non-surviving patients at the start of or during CAVHD treatment (Fig 2). No difference was observed in azotemic control between the 2 modes of vascular access. During treatment, serum sodium ($Na^+$) and potassium ($K^+$) were maintained within the normal range in most patients; however, supplemental potassium-chloride was required in some patients following prolonged CAVHD to prevent or correct hypokalemia. Serum calcium and magnesium were also maintained within the normal range throughout therapy. Serum phosphate fell below the normal range in several patients following prolonged CAVHD necessitating supplemental intravenous phosphate administration. Significant electrolyte derangements could be easily corrected and maintained within normal limits ($[K^+]$ 6.5 ± 0.1 to 4.2 ± 0.4 mmol/l; $n = 5$; $[Na^+]$ 130 ± 0.9 to 140 ± 0.5 mmol/l; $n = 5$; 155 ± 0.3 to 139 ± 1.7 mmol/l; $n = 2$). In patients with severe metabolic acidosis ($HCO3^-$ < 20 mmol, $n = 14$), bicarbonate homeostasis could be restored ($HCO3^-$ 17 ± 0.5 to 23.2 ± 0.6; $p < 0.05$) within 48 hours with use of bicarbonate as a buffering-anion. It was only occasionally necessary to administer additional intravenous supplementation of bicarbonate, this being mostly associated with an acute septic episode.

*Complications*

There were no complications related to the extracorporeal circuit itself apart from filter clotting. Overall, 261 filters were used during the total of 531 days of CAVHD treatment, *i.e.* a mean number of 4.4 ± 0.4 filters were used per patient. The mean life span of the filter per patient was 51.2 ± 1.2 hrs but there were marked inter-individual differences (mean filter life ranging from 16 to 96 hrs). Although the femoral catheters were removed 8 times because of bacteremia of unknown origin, documented infection (as evidenced by positive culture of the catheter) was present in only 5% (Table 3). One patient developed a false aneurysm at the site of the femoral arterial catheter insertion requiring surgical repair. Surgical revision of the Scribner shunt or the creation of a new one in the contra-lateral extremity, either because of (recurrent) thrombosis or infection was required 4 times in 3 patients. No distal ischaemic complications were seen with either access device. Overt bleeding complications requiring the temporary discontinuation of anticoagulation or subsequently CAVHD were seen in 6 patients, all of which were from the digestive tract. Three of these patients had severe concommitant thrombocytopenia ($< 60 \cdot 10^9$/l) (Table 3).

*Outcome*

Twenty-six patients (43%) survived until discharge from the ICU. Three of these patients subsequently died on the general ward a mean of 40 days (range 25-64) following discontinuation of CAVHD. Twenty-three patients (38%) ultimately survived and were discharged from the hospital.

**Table 3. Hemorrhagic And Vascular Access Related Complications Observed During CAVHD Treatment**

| Complication | No |
|---|---|
| Access Infection | |
| localized | 3 (*Klebsiella*, $n = 1$; *Serratia*, $n = 2$) |
| systemic | 1 (*Pseudomonas*, $n = 1$) |
| Shunt thrombosis | 3 (venous limb) |
| Pseudo-aneurysm | 1 (femoral artery) |
| Overt bleeding | 6[#] |

[#]: All from the digestive tract: oesophageal ulceration, $n = 1$; ulcus ventriculi, $n = 2$; bowel perforation, $n = 1$; unknown focus, $n = 2$. Mean platelet count in these 6 patients was 69 x $10^9$/l (range 31-110); mean heparin dosage was 533 U/hr (range 500-700 U/hr).

There was no difference in age or gender between survivors and non-survivors (Table 4). Similar survival (40% *vs* 37%) was observed in elderly patients (≥ 65 yrs) when compared to younger patients (< 65 yrs). There was no difference in the duration of CAVHD treatment between survivors and non-survivors as a group (8.7 ± 0.7 *vs* 9.3 ± 1.1 days; NS). Forty-two percent of patients receiving ≥ 10 days CAVHD survived to leave the ICU compared to 44% of those who received < 10 days CAVHD. There was no difference in the prevalence of pre-existing chronic disease between survivors and non-survivors (54% *vs* 50%). The non-surviving group had higher APACHE II scores, more additional OSF's, and a more frequent requirement for mechanical ventilation and/or inotropic support as compared to survivors. Of patients with an APACHE II score > 30, none survived. The incidence of sepsis was significantly higher in the non-surviving group (Table 4). All patients with non-oliguric ARF survived. Survival of patients who required mechanical ventilation was significantly lower when compared to those who did not (32% *vs* 70%; $p < 0.05$). Outcome was particularly poor in patients with ARF complicating polytrauma (Table 2). Prognosis was inversely related to the number of OSF's (Table 5). None of the patients with isolated ARF died. Of those patients with 3 or more OSF's (including ARF) 24% survived. Death was most often due to refractory septic shock and/or progression to irreversible multiple organ failure (70%). Other causes were myocardial infarction ($n = 4$), ventricular fibrillation ($n = 3$), massive pulmonary embolism ($n = 1$), coma vigil ($n = 1$), and stroke ($n = 2$). Seventy-six percent of those who survived had recovery of renal function, while this occurred in only 23% of those who died ($p < 0.05$). The mean serum creatinine level of these patients, either at the time of death or on discharge from the hospital, was 127 ± 13 μmol/l (range 44 - 269 μmol/l).

**Table 4. Characteristic Features of Survivors and Non-Survivors from Surgical ARF Treated by CAVHD**

| | Survivors ($n$ = 26) | Non-survivors ($n$ = 34) | Significance |
|---|---|---|---|
| Age (yrs) | 59 ± 3.5 | 61 ± 3 | NS |
| Male (%) | 20 (80) | 28 (80) | NS |
| APACHE II | 24.2 ± 0.7 | 28.1 ± 0.7 | $p < 0.05$ |
| No of OSF's | 2.2 ± 0.2 | 3.9 ± 0.2 | $p < 0.05$ |
| Sepsis (%) | 12 (48) | 30 (86) | $p < 0.05$ |
| Artificial ventilation (%) | 18 (72) | 32 (91) | $p < 0.05$ |
| Inotropics (%) | 11 (44) | 30 (86) | $p < 0.05$ |
| Pretreatment urea (mmol/L) | 45.8 ± 4.0 | 48.5 ± 2.6 | NS |
| Pretreatment creatinine (mmol/L) | 641 ± 46 | 523 ± 32 | NS |
| Duration CAVHD (days) | 8.7 ± 0.7 | 9.26 ± 1.1 | NS |

ARF, acute renal failure; CAVHD, continuous arteriovenous hemodiafiltration; No of OSF's, number of failed organ systems (including ARF) [7, 8, 9]. Values are expressed as mean ± SEM or percentage, where appropriate.

**Table 5. Mortality of High-Risk Surgical ARF Patients Treated by CAVHD**

| | No of organ systems failed [@] | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | ≥4 |
| No of patients | 7 | 11 | 15 | 27 |
| Died | 0 | 3 | 8 | 23 |
| Mortality (%) | 0 | 27 | 53 | 85 |

ARF, acute renal failure; CAVHD, continuous arteriovenous hemodiafiltration; [@]: number of organ system failures (including ARF) as defined according to the pertinent literature [7,8,9].

None of the patients with pre-existing chronic renal failure (serum creatinine > 180 μmol/l; $n$ = 4) recovered renal function and required continued renal support. The chance of renal recovery was particularly low (27%) in patients who underwent major vascular surgery (Table 2).

## Discussion

Present data demonstrate that CAVHD provides efficient renal support for critically ill patients. The majority of our patients (85%) reached consistent and controlled steady-state urea and creatinine levels within 72 hrs, with no protein restriction and often despite surgery, hypotension and septicemia. In addition, satisfactory correction of acidosis and plasma electrolyte concentration was obtained. The urea and creatinine clearances corresponded to the ultrafiltrate/dialysate flow rate, being approximately 24 ml/min, because of almost complete (> 94%) dialysate solute saturation. Even in severely hypotensive, inotropic-dependent patients excellent tolerance to fluid removal was observed, thereby enabling aggresive nutritional support together with intravenous infusions, yet still attaining an overall negative fluid balance if needed. The complication rate was relatively low. Access-related complications occurred 8 times. Gastrointestinal bleeding occurred in 6 patients, in which the continuous heparinization may be assumed to be a contributing factor. However, some cases of overt bleeding will always occur in polytrauma and postoperative patients, and this incidence of gastrointestinal bleeding is not different from that reported in ARF patients treated with intermittent hemodialysis (IHD) [9,10]. Nevertheless, reducing the dose or even avoiding heparin in patients at risk of bleeding is of utmost importance.

As noted by others [4], prolonged duration of renal support was not associated with a poor prognosis. No difference was observed in metabolic control between surviving and non-surviving patients, suggesting that the outcome is in the most part determined by the underlying disease process and not by uremia *per se*. This is further supported by the marked differences in severity of illness between non-survivors and survivors (Table 4). Like Maher *et al* [4], we noted an increased risk of dying with higher APACHE II scores. A patient's age or sex did not affect outcome. No consistency exists as to the impact of age on prognosis. Some related age to increasing mortality [1], while others did not [4,10,12]. As in others studies [11,12], premorbid conditions did not seem to have an important impact on acute outcome. However, it may exert deleterious effects on long-term survival [12].

Present data underline [1,12] the importance of sepsis as being the major cause of death in surgical ARF patients. Overall patient survival in the present series was 38%, the majority of which with recovery of renal function. Direct comparison with mortality data from other reports is hampered by the fact that each series contains patients of varying qualifications (usually a case-mix of medical, surgical and/or obstetrical ARF), not all of whom required dialysis or stay on the ICU. In addition, many studies lack validated and objective illness severity scores (*e.g.*, APACHE II [13]). However, our data do compare favourably with several studies specifically

dealing with ARF patients on the surgical ICU treated by conventional dialysis (mortality ranging from 81% to 94%)[1,10,11,12,14]. When analyzing subgroups of patients considered to have an unfavourable prognosis, CAVHD treated patient outcomes also compares favourable to other reports. Recently, Spiegel *et al.* [10] reported a 100% mortality of ARF patients treated with intermittent hemodialysis, who also required artificial ventilation. In our series, mortality rate of ventilated patients was 70%. Similar results of ventilated ARF patients treated by CAVHD were reported by others [15,16]. We also [1,4] noted an inverse correlation between survival and the number of OSF's. However, 24% of patients with 3 or more OSF's still survived to leave the hospital. Outcome of our multiple organ failure patients compared favourably with those of Fry *et al.* [16], who reported mortality rates of 79 and 100% for 3 and 4 OSF's, respectively, in postoperative patients, and those of Pine *et al.* [18], who found a 100% mortality in patients with 3 or more OSF's.

While this apparent increase in survival may at least in part be explained by advances in general intensive care medicine (*e.g.*, more potent antibiotics, vasopressor agents, improved monitoring and ventilation techniques etc), the use of CAVHD *per se* may have also contributed to a better prognosis of these critically ill patients. As illustrated, CAVHD avoids dialysis-related complications such as (aggrevation of) hypotension, cardiac arrhythmias, and an increase in oxygen consumption [4,19]. Commonly observed cardiac and/or pulmonary system failure may be exarcerbated (or provoked) by overhydration. In one study [14], all but one postoperative patients were grossly overhydrated. In the present study, severe fluid overload was present in 21% of patients. In this complex and unstable patient population, CAVHD offers the potential of continuous fine tuning of intravascular volume and left ventricular filling pressure. Indeed, Lauer *et al.* [20] observed a significant rise in cardiac index after gradual volume reduction during CAVH, attributed to changes in preload thereby leading to an improved position on the Starling curve. In addition, while use of IHD usually leads to a tendency to restrict fluids and protein, CAVHD enables the provision of unlimited amounts of energy and proteins without the risk of exacerbating azotemia or fluid overload. In our study, serum urea levels were consistently below 30 mmol/l in a population of which the majority (76%) received TPN. Prolonged protein-calorie malnutrition can precipitate or worsen ventilatory failure [21]. There is some evidence to suggest that high calorie feeding results in better outcome than low caloric feeding in surgical ARF [19]. With CAVHD, unlike IHD, it may be possible to counter-act excessive catabolism and, at least in some patients, to establish positive nitrogen balance [22]. Of note, however, one should take into account an aminoacid loss with the ultradiafiltrate of approximately 9% of daily protein load and the upper limit of nitrogen that should be administered to these patients has not been determined [23]. In addition, when using high-dextrose containing CAPD fluid as dialysate, significant glucose uptake occurs which must be taken into account when prescribing nutritional support to avoid the risk of 'overfeeding' hyperglycemia with its detrimental effects on metabolism and respiratory function [15,24].

As shown in this study, beneficial effects may also result from the adequate correction of metabolic acidosis. We routinely use bicarbonate-buffered dialysis fluid

as the use of lactate as a buffering anion in the critically ill may lead to hyperlactatemia and worsening acidosis, probably because of impaired lactate conversion by the reduced liver flow [25]. Severe acidosis may result in decreased cardiac contractility, vasodilation and hypotension, decreased hepatic and renal flow and increased susceptibility to ventricular arhythmias [26]. In addition, acidosis significantly contributes to the catabolic state of the ARF patient [27]. Recent experimental and uncontrolled clinical data suggest that the initiation of continuous hemo(dia)filtration in septic shock and (non-renal) multi-organ failure may result in improved hemodynamics and gas exchange, independent of the fluid balance, attributed to the convective removal of inflammatory mediators (*e.g.*, cytokines) from the circulation [28]. However, this proposed beneficial effect awaits further investigation.

In summary, CAVHD proved to be a safe and efficient mode of renal replacement therapy in our critically-ill patients with surgical ARF. In addition, a comparatively favourable outcome was observed. However, it does not yet seem possible to identify with any degree of certainty those patients most likely to benefit from prolonged intensive care treatment (including renal support) nor those in whom additional organ failure will adversely determine the outcome of ARF. There has been a tendency to be pretty grim as to the treatment and outcome of ARF in the ICU setting [2,11]. Present data, however, suggest that CAVHD represents a significant advance in the management of these patients and may have contributed to improved survival.

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Chapter V

# Acute dialytic support for the critically ill: intermittent hemodialysis versus continuous arteriovenous hemodiafiltration

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## Abstract

***Objective and design***: There is still debate about whether continuous renal replacement therapy is superior to intermittent hemodialysis (IHD) as dialytic support for the critically ill patient with acute renal failure (ARF), mainly because of lack of comparative data. We sought to address this issue by reviewing the medical records of such patients admitted to a single surgical intensive care unit (ICU) treated with either continuous arteriovenous hemodiafiltration (CAVHD) or IHD between january 1, 1986 and august 31, 1993.

***Results***: Of 94 consecutive patients who received dialytic support for severe ARF, 34 (36%) patients were treated with IHD and 60 (64%) patients with CAVHD. Patients were comparable in terms of age or gender and represented a similar case-mix. Patients treated with CAVHD were more severely ill as manifested by a lower mean arterial pressure (75 ± 3 *vs* 86 ± 5 mm Hg; $p < 0.05$), higher APACHE II score (26.5 ± 0.5 *vs* 22.2 ± 0.3; $p < 0.05$), and a higher number of organ system failures (3.4 ± 0.2 *vs* 2.6 ± 0.3; $p < 0.05$). Despite greater illness severity and a higher probability of death (55 ± 2.6% *vs* 33 ± 2.5%; $p < 0.0001$) in those treated with CAVHD, no difference in outcome was observed between groups (CAVHD 26/60 [43%] *vs* IHD 20/34 [59]%; NS). The mean APACHE II score of patients treated with CAVHD who survived was similar to that of patients treated with IHD who died (24.5 ± 0.3 *vs* 24.2 ± 0.4; NS). CAVHD was associated with improved hemodynamic stability, better control of fluid balance and biochemistry, increased nutritional intake, and a shorter duration of ARF ($p < 0.05$).

***Conclusion***: Data suggest that CAVHD offers several distinct advantages over IHD, which may translate in improved survival, particularly in the more severely ill patient.

## Introduction

Despite impressive advances in the field of intensive care medicine, the mortality rate of critically ill patients who develop acute renal failure (ARF) is still uniformly high [1]. As traditional forms of hemodialysis treatment have characteristics which limit their use in these patients, continuous renal replacement therapy (CRRT) has been rapidly adopted as the preferred treatment modality [2,3]. However, there is still debate about whether CRRT is superior to intermittent hemodialysis (IHD), especially in terms of metabolic control and clinical outcome [4,5,6,7]. While many publications exist concerning the technique of CRRT, relative advantages offered by the various systems, and mortality rates of critically ill patients with ARF on the intensive care unit (ICU) [3,8,9], few studies have directly compared CRRT and IHD [10,11].

The purpose of this study was to compare the efficacy of metabolic control and clinical outcome in critically ill ARF patients treated with either continuous arteriovenous hemodiafiltration (CAVHD) or IHD in the same surgical ICU.

## Material and methods

The medical records of 94 consecutive patients admitted to the surgical ICU between January 1, 1986 and August 31, 1993 who had severe ARF requiring dialytic support were reviewed. Patients with pre-existing chronic renal failure treated with hemodialysis prior to ICU admission were excluded from this study. Mean age was 61 ± 2 years (range 17 -85 yrs) and 46 patients (49%) were aged 65 or older. There was a male (83%) predominance. The etiologies of ARF were varied and often multifactorial. Sixty-seven (71%) patients required mechanical ventilation, 55 (59%) patients received vasopressor drugs at the start of dialysis treatment. All but 9 patients (90%) were oligo-anuric (diuresis < 400 ml/day). Forty-six patients (49%) survived until discharge from the ICU, of whom 42 (45%) could be discharged from the hospital. Indications for dialysis were azotemia (serum urea > 40 mmol/l), severe hyperkalemia, refractory acidosis and/or severe fluid overload. Patients received either IHD ($n$ = 34) or CAVHD ($n$ = 60). During the study period, CAVHD was increasingly used in the more severely ill patients when compared to IHD. All patients who required continued renal replacement therapy after discharge from the ICU were converted to, or maintained on, IHD. The following information was obtained: age, sex, pre-existing medical conditions (chronic obstructive pulmonary disease, diabetes mellitus, cardiovascular disease, hypertension, chronic liver disease, chronic renal insufficiency, and malignancy), underlying disease and surgical procedures performed for each patient, need for vasopressor support or artificial ventilation, provision of full (par)enteral nutrition, systolic and diastolic blood pressure, heart rate, arterial blood gas, $FiO_2$ requirements, $PaO_2/FiO_2$-ratio [12], presence of suspected or proven sepsis, bleeding complications, renal and patient outcome and cause of death. Renal recovery was defined as return of renal function sufficient to discontinue dialytic support, either during the course of stay on the ICU or on the general ward. To aid comparison with other studies, both ICU survival and

final survival (alive on discharge from hospital) are discussed. Serum urea, creatinine and bicarbonate levels were recorded during the first 7 days on dialytic support. Other biochemical and hematological variables recorded for analysis were serum levels of potassium, albumin, the white blood cell count and platelet count at the time of initiation of dialytic support. Technical data collected for analysis included ultrafiltration rate, type of vascular access and vascular access-related complications, duration of treatment and number of filters used for each patient. The urea and creatinine clearance with CAVHD were assessed according to standard formulas [13]. To assess severity of illness and to establish whether the IHD and CAVHD groups were truly comparable, the Acute Physiology and Chronic Health Evaluation (APACHE) II score at the start of treatment and the number of organ system failures at the time of initiation of or whilst on dialytic support were calculated according to the pertinent literature [14,15,16]. For each individual the probability of death (%) was calculated according to the APACHE II equation [14], which incorperates a weighing factor for the diagnostic category or major organ system failure leading to ICU admission. This is important as death rate varies according to the principal underlying disease [14]. The mean predicted values were then assessed for both the CAVHD and IHD group. In a subgroup of inotropic-dependent and ventilated patients (IHD, $n$ = 10; CAVHD, $n$ = 10) cardiorespiratory parameters were reviewed prior to the initiation of dialytic support, and 1, 4 and 24 h, respectively, after the initiation of treatment. The costs of both IHD and CAVHD were also estimated for providing one week of dialytic support, using standard accounting techniques.

*Intermittent hemodialysis*

IHD was performed using high-flux cellulose-triacetate hollow-fiber membranes (CT-110G, surface area 1.1 $m^2$, Baxter Healthcare, USA) and standard dialysis machines with volumetric controlled ultrafiltration (Fresenius A 2008 C, Bad Homburg, Germany). Vascular access was achieved by inserting a single-lumen acute dialysis catheter (MedComp, Harleysville, USA) into the femoral, subclavian or jugular veins with the Seldinger technique ($n$ = 31), or by the surgical creation of a Scribner shunt (Quinton instruments Co., Seattle WA, USA)($n$ = 3). Dialysate sodium content varied from 140-145 mmol/L and potassium content from 1-2 mmol/L; bicarbonate was used as a buffering-anion (BC-F 8.4%, Fresenius AG, Bad Hoburg, Germany). Dialysate flow was set at 500 mL/min, mean blood flow at 150-175 mL/min. Using these flow rates, the *in vitro* urea clearance with the CT-110G dialyser is 160 mL/min (Manufacturer's data; Baxter healthcare, USA) . Where neccesary, sequential ultrafiltration and isovolemic dialysis was performed. Albumin, saline, and dopamine infusions were used for hemodynamic support during dialysis as clinically required. Standard anticoagulation consisted of a heparin loading dose (1000-1500 U) followed by continuous infusion of heparin (1000-1500 U/h). In case of a bleeding diathesis, regional heparinisation was instituted (1000-1500 U/h heparin prefilter *vs* 500-1000 U/h protamine postfilter).

*Continuous arteriovenous hemodiafiltration*

CAVHD was performed using polyacrilonitrile (PAN) hollow-fiber filters (AN-69HF, surface area 0,6 $m^2$, Hospal Ltd, France) connected to the arterial and venous vascular access devices in a pumpless circuit with the use of 1.25 m extracorporeal tubings with luer lock fittings. Vascular access was either by means of large bore catheters (MedComp, Harleysville PA, USA), introduced in the femoral vessels with the Seldinger technique ($n$ = 44), or by the surgical creation of a Scribner shunt ($n$ = 16) when cannulation of the femoral vessels was precluded because of severe atherosclerosis or the presence of a vascular prosthesis. Warmed bicarbonate-buffered dialysis fluid (SH 44-HEP, Combi-Pac, Schiwa GmbH, Glandorf, Germany) was pumped counter-current to blood flow through the ultrafiltrate compartment of the filter (dialysate inflow rate, $Q_d$) at a rate of 1000 mL per hour (16,6 mL/min) with a calibrated, volumetric pump (3M, AVI inc., St Paul, USA). In severely catabolic patients, a $Q_d$ of 2 L/h (33,2 mL/min) was used. The ultradiafiltrate was collected in a graded collection bag and the volume measured hourly. The ultrafiltration rate ($Q_{uf}$) was calculated by subtracting the hourly dialysate volume (typically 1000 mL) from the total volume of effluent in the collection device. Replacement fluid (Ringers lactate) was given as clinically indicated, administered into the arterial limb ('predilution') of the extracorporeal circuit. Standard anticoagulation consisted of 2000 U of heparin as a loading dose followed by continuous infusion of 500-700 U/h into the arterial line. Low-dose (< 250-500 U/h) or no heparin was used in the presence of severe underlying coagulopathy or severe thrombocytopenia (< $60 \cdot 10^9$/L). The filters were changed when there was objective evidence of inadequate filter function (*i.e.*, a sustained reduction in UF volume [< 300 mL/h]) or evidence of filter clotting. Access devices were not routinely changed unless there were clinical signs of infectious (or other) complications.

*Statistical analysis*

Data are expressed as mean ± standard error (SEM) or percentage, where appropiate. The Wilcoxon signed-rank test and Kruskal-Wallis test were used to analyse nonparametric data. Repeated measures ANOVA test and the unpaired $t$-test were used to analyse normally distributed data. The Chi-square test, including Yates' continuity correction where appropiate, was used to assess nominal differences between two groups. Statistical significance was accepted at a $p < 0.05$ level.

## Results

*Patient population*

Thirty-four patients (36%) treated with IHD were compared with 60 patients (64%) treated with CAVHD. All patients were treated in the same surgical ICU. Groups were comparable in terms of age or gender and represented a similar case-mix.

**Table 1. Characteristics of High-Risk ARF Patients Upon Initiation of Dialytic Support**

| | IHD ($n$ = 34) | CAVHD ($n$ = 60) | Significance |
|---|---|---|---|
| Age (yrs) | 62 ± 3 | 60 ± 2 | NS |
| Male (%) | 82 | 80 | NS |
| MAP (mmHg) | 86 ± 5 | 75 ± 3 | $p < 0.05$ |
| APACHE II | 22.2 ± 0.7 | 26.5 ± 0.5 | $p < 0.05$ |
| No of OSF's | 2.6 ± 0.3 | 3.4 ± 0.2 | $p < 0.05$ |
| Sepsis (%) | 67 | 71 | NS |
| Arteficial ventilation (%) | 50 | 83 | $p < 0.05$ |
| Inotropic support (%) | 41 | 70 | $p < 0.05$ |

ARF, acute renal failure; IHD, intermittent hemodialysis; CAVHD, continuous arteriovenous hemodiafiltration; No of OSF's, number of failed organ systems (including ARF) [14,15,16]. Values are given as mean ± SEM or percentage, where appropriate.

**Table 2. Biochemical and Hematological Variables of High-Risk ARF Patients Upon Initiation of Dialytic Support**

| | IHD ($n$ = 34) | CAVHD ($n$ = 60) | Significance |
|---|---|---|---|
| Urea (mmol/l) | 39.1 ± 1.9 | 47.4 ± 2.3 | $p < 0.05$ |
| Creatinine (μmol/l) | 695 ± 36 | 572 ± 27 | $p < 0.05$ |
| Potassium (mmol/l) | 4.8 ± 0.1 | 4.9 ± 0.1 | NS |
| Bicarbonate (mmol/l) | 23.2 ± 0.6 | 21.8 ± 0.6 | NS |
| Albumin (g/l) | 24.6 ± 0.8 | 25.2 ± 1.0 | NS |
| Platelet count (x $10^9$/l) | 140 ± 12 | 105 ± 9 | $p < 0.05$ |
| WBC (x $10^9$/l) | 13.3 ± 1.3 | 17.2 ± 1.4 | $p < 0.05$ |

ARF, acute renal failure; IHD, intermittent hemodialysis; CAVHD, continuous arteriovenous hemodiafiltration; WBC, white blood cell count. Values expressed as mean ± SEM.

There were significant differences in the severity of illness between groups (Table 1). Patients treated with CAVHD had a lower MAP, higher APACHE II score, more additional organ system failures and a more frequent requirement of mechanical ventilation and vasopressor support as compared to patients treated with IHD. The prevalence of ARF as the only vital organ dysfunction differed significantly between groups (CAVHD 6/60 [10%] *vs* IHD 14/34 [41%]; $p < 0.05$). In addition, there was a significant difference in the white blood cell and platelet count between groups (Table 2). There was no significant difference in the prevalence of pre-existing chronic disease (CAVHD 52% *vs* IHD 56%), including the presence of pre-existing impaired renal function (CAVHD 7% *vs* IHD 18%). Four patients (7%) in the CAVHD-group had non-oliguric ARF compared to 5 patients (15%) in the IHD group. Forty-six patients (76%) in the CAVHD-group received full (par)enteral nutrition compared to only 10 patients (34%) in the IHD-group ($p < 0.05$).

*Hemodynamic tolerance*

Severe hypotension occurred in 25 of 130 (19%) HD-procedures. Thirteen of 130 (10%) HD-procedures were complicated by cardiac arythmias (rapid supraventricular tachycardia, $n = 12$; ventricular fibrilation, $n = 1$). When patients with isolated ARF were excluded, the frequency of severe hypotension was 26% (22 of 84 HD-procedures) and the frequency of cardiac arrythmias 14% (12 of 84 HD-procedures). Hemodynamic instability often led to premature termination of IHD and/or inability of effective fluid removal. Subgroup analysis of inotropic-dependent and ventilated patients (Fig 1) showed a significant decrease in MAP (77.3 ± 5.2 to 63.2 ± 4.7 mm Hg; $p < 0.05$) and a trend towards a concomittant decrease in the $PaO_2/FiO_2$-ratio (2.2 ± 0.2 to 1.7 ± 0.2; NS) during the first hour of IHD when compared to pretreatment values. No differences were observed in these parameters 4 h and 24 h, respectively, after the initiation of IHD compared to pretreatment values (Fig 1). CAVHD was hemodynamically well tolerated. No significant differences in heart rate, systolic blood pressure, MAP (Fig 1) and $PaO_2/FiO_2$-ratio were observed during treatment. Significant net fluid loss (up to 5 L/day) could be obtained with no significant drop in MAP and in several patients ($n = 9$) with a concomittant decrease in oxygen requirements and vasopressor support.

*Metabolic control*

There was no significant difference in the duration of dialytic support during the course of stay on the ICU (CAVHD 8.9 ± 0.7 [range 1 - 25] *vs* IHD 8.1 ± 1.0 [range 2 - 27] days; NS). During a total of 531 days of CAVHD, the mean life span of the filter was 51.2 ± 1.2 h. A mean of 3.8 ± 0.5 IHD-procedures were performed during this period of 8.1 ± 1.0 days, giving an average of alternate-day treatment (1:2.1 days). Average duration of a dialysis session was 4 h (range 1-5 h). The mean serum urea level was higher and creatinine level lower upon initiation of dialytic support in patients receiving CAVHD as compared to those receiving IHD (urea 47 ± 2.3 *vs* 39.1 ± 1.9 mmol/L; $p < 0.05$, and creatinine 572 ± 27 *vs* 695 ± 36 μmol/L; $p < 0.05$).

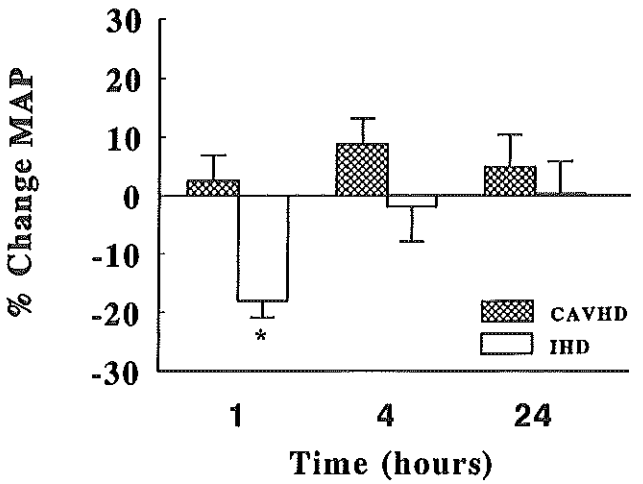


*Figure 1: Effects of intermittent hemodialysis (IHD) and continuous arteriovenous hemodiafiltration (CAVHD) on mean arterial pressure (MAP) in inotropic-dependent and ventilated patients with acute renal failure (CAVHD, n = 10; IHD, n = 10). There was a significant decline of MAP during the first hour of IHD. Ultrafiltration volume during IHD was 1.1 ± 0.4 L (mean ± SEM); net ultrafiltration volume during CAVHD was 3.7 ± 0.3 L/day. Values of MAP are expressed as percent change from pretreatment values. *: $p < 0.05$ vs previous time point.*

Overall, no significant changes in serum urea or creatinine levels were observed during treatment with IHD (Fig 2a,b). In patients receiving CAVHD, a significant decline of both parameters was observed during the first 72 h of treatment (urea 47.4 ± 2.3 to 30.3 ± 1.4 mmol/L; $p < 0.05$, and creatinine 572 ± 27 to 361 ± 23 µmol/L; $p < 0.05$, respectively). Thereafter, controlled steady-state levels were achieved with serum urea levels kept below 30 mmol/L (Fig 2a,b). Mean urea and creatinine clearances with CAVHD ($Q_d$ 1 L/h) were 24.6 ± 0.4 and 24.3 ± 0.4 mL/min respectively. Mean UF volume during CAVHD was 11.5 ± 0.3 L/day (range 8.0 - 14.7 L/day). In patients with severe metabolic acidosis ($HCO3^- < 20$ mmol/L), bicarbonate homeostasis was restored more adequately with CAVHD when compared to IHD (Fig 3).

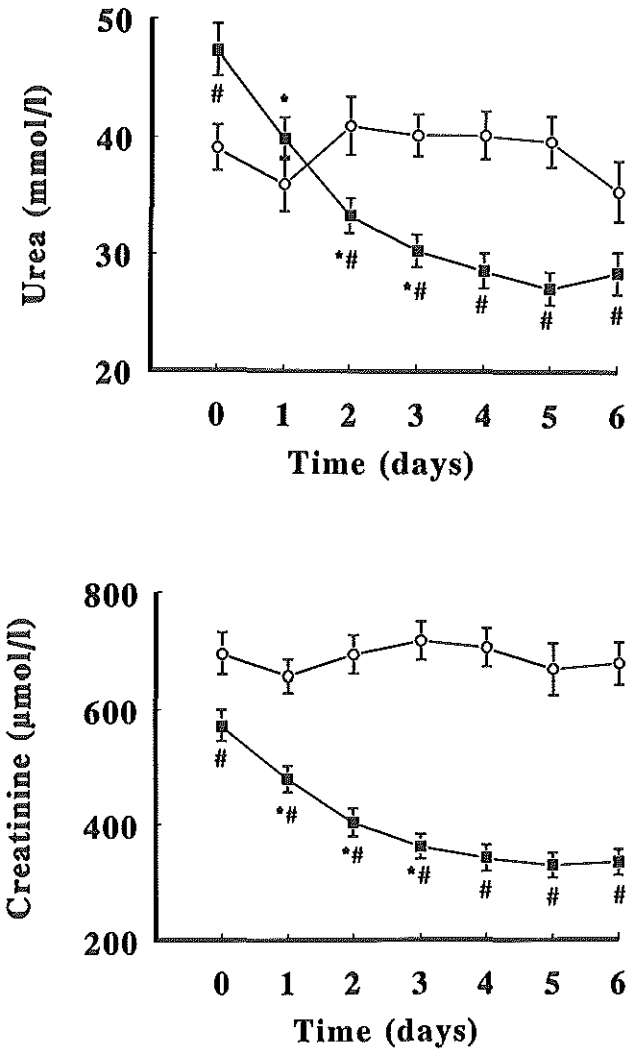


*Figure 2a,b: Course of serum urea (a) and creatinine (b) levels (CAVHD,■; IHD,○) following the institution of dialytic support. In patients receiving CAVHD (n = 60), a significant decline of serum urea and creatinine levels was observed during the first 72 h of treatment; thereafter, steady-state levels were achieved. No changes in these levels were seen in patients treated with IHD (n = 34). The peak/trough levels that are normally seen with IHD are smoothed out by the graph. Values are expressed as mean ± SEM. *: $p < 0.05$ vs previous time points; #: $p < 0.05$ vs IHD.*

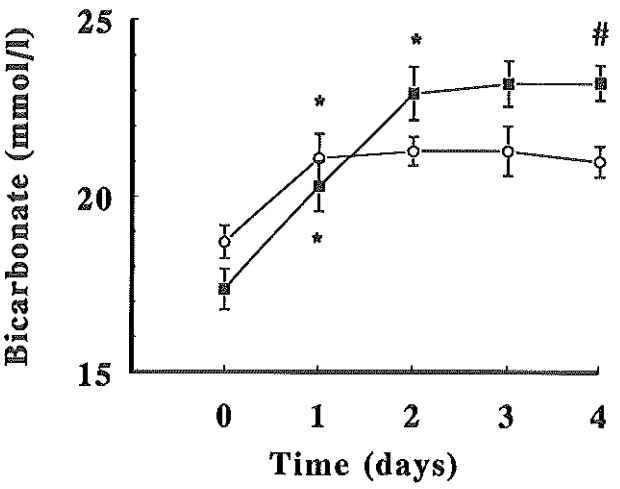


*Figure 3: Serum bicarbonate levels (CAVHD,■; IHD,○) following the initiation of dialytic support in patients with severe metabolic acidosis ($HCO3^-$ < 20 mmol/l). Bicarbonate homeostasis was restored more adequately in patients treated with CAVHD (n = 14) when compared to those treated with IHD (n = 8). Values are expressed as mean±SEM. *: p< 0.05 vs previous time points; #: p < 0.05 vs IHD.*

*Complications*

Apart from hemodynamic deterioration as observed during IHD, no difference in the (hemorrhagic- or vascular access related) complication rate was observed between groups (Table 3). No distal ischemic complications were seen with either femoral cannulation or Scribner shunt insertion. Despite continuous heparinization during CAVHD, no difference in the incidence of overt bleeding complications (all of which were from the digestive tract) were observed (Table 3).

*Outcome*

Twenty-six patients (43%) treated with CAVHD survived to leave the ICU, of whom 23 (38%) could be discharged from the hospital, compared to 20 (59%) and 19 (55%) patients, respectively, treated with IHD. These differences were not statistically significant. The calculated probability of death (%), however, was significantly higher for the CAVHD group compared to the IHD group (55 ± 2.6 *vs* 33 ± 2.5; $p < 0.001$). In addition, the mean APACHE II score of patients treated with CAVHD who survived was similar to that of patients treated with IHD who died (Fig 4). None of the patients with ARF as the only vital organ dysfunction (CAVHD, $n$ = 6/60 [10%]; IHD, $n$ = 14/34 [41%]) died.

**Table 3. Complications of Different Forms of Dialytic Support**

| Complication | IHD ($n$ = 34) | CAVHD ($n$ = 60) |
|---|---|---|
| Hypotension | 25 (19)[#] | 0 |
| Cardiac arrythmias | 13 (10)[#] | 0 |
| Vascular access-related: | 4 (12) | 8 (13) |
| shunt thrombosis | 1 | 3 |
| infected shunt site | 0 | 1 |
| pneumothorax | 1 | - |
| infected dialysis catheter | 2 | 3 |
| false aneurysm femoral artery | - | 1 |
| Overt bleeding | 2 ( 6) | 6 (10) |

[#]: given as number of hemodialysis procedures ($n$ = 130). Values between parentheses are percentages.

For the group as a whole, duration of stay on the ICU was longer for patients treated with CAVHD compared to patients treated with IHD (22.1 ± 2.0 *vs* 15.5 ± 1.8 days; $p < 0.05$). Time-interval from ICU admission to start of dialysis treatment did not differ between survivors and non-survivors for patients treated with IHD (Fig 5). In patients treated with CAVHD, however, this interval was significantly shorter for those who survived compared to those who died (Fig 5). There was no difference in the pretreatment creatinine levels between survivors and non-survivors treated with CAVHD (641 ± 46 *vs* 523 ± 32; NS). In both groups, death was most often due to refractory septic shock and/or progression to irreversible multiple organ system failure (MOSF), followed by cardiovascular causes. Forty-seven percent of patients receiving CAVHD regained renal function compared to 53% of patients receiving IHD. Mean serum creatinine levels of these patients, either at the time of death or on discharge from the hospital, differed significantly between groups (CAVHD 127 ± 13 *vs* IHD 185 ± 12 μmol/L; $p < 0.05$). In addition, the time from start of dialytic support to dialysis independency was significantly shorter in patients treated with CAVHD compared to patients treated with IHD (10.9 ± 1.6 [range 3 - 52] *vs* 17.6 ± 3.4 [range 5 - 73] days; $p < 0.05$).

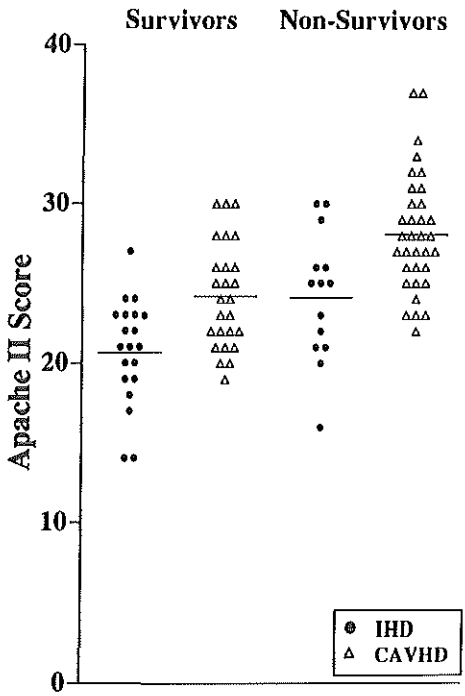


*Figure 4: Mean APACHE II score of surviving (IHD, n = 20; CAVHD, n = 26) and non-surviving patients (IHD, n = 14; CAVHD, n = 34). The mean APACHE II score of non-surviving patients treated with IHD was similar to that of surviving patients treated with CAVHD. There were significant differences between all other groups in the mean APACHE II score ($p < 0.05$).*

*Costs*

The weekly costs of IHD were calculated by assuming a dialysis frequency of 1:2.1 days (*i.e.*, 3.3 treatments/wk), with an average duration of 4 h each. The costs of dialysis machines, water treatment systems and physicians were not included. The weekly costs of CAVHD were calculated by assuming a $Q_d$ of 16.6 mL/min (1 L/h) and a mean life span of the filter of 51.2 h (*i.e.*, 7 x 24 h/51.2 = 3.3 filters/wk).
No requirement to change access was assumed for both treatments. There was a difference in apparent costs of approximately $400 per week in favour of IHD (Table 4).

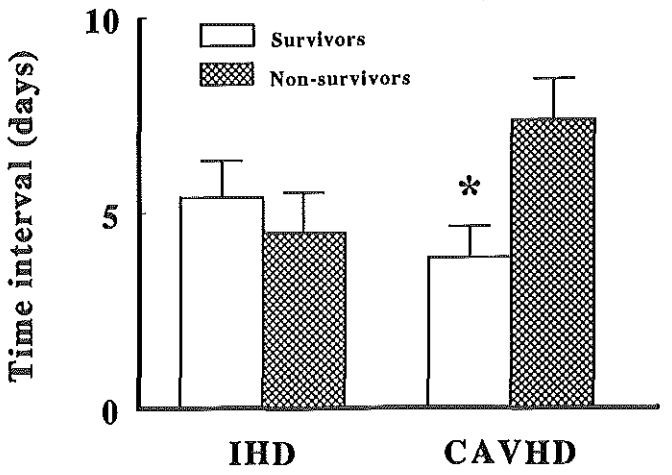


*Figure 5: Time interval (days) between admission to the intensive care unit (ICU) and initiation of dialytic support. In patients treated with CAVHD, survival was more likely when treatment was started earlier during the course of stay on the ICU. *: $p < 0.05$ vs non-survivors.*

## Discussion

In recent years, CRRT has been rapidly adopted as a viable alternative to IHD for the treatment of ARF in the critically ill patient. However, whether continuous treatment modalities are superior to IHD is still debated, mainly because of lack of comparative data [6,7]. In addition, because of its high efficiency (urea clearance 120 - 180 ml/min), single-vessel access and less risk of bleeding, several authors have stated that IHD should still be considered as first line therapy in ARF [4,5,6]. We sought to address this important issue by comparing the continuous treatment modality as employed in our hospital, *i.e.*, CAVHD, with IHD, not only in terms of control of biochemistry and fluid balance, but also in terms of morbidity, mortality and costs. We are aware that the current study suffers in being retrospective and non-randomized, and that treatment selection bias became evident during the study period. However, carefull assessment of disease severity with use of clinical and laboratory data, including calculation of the APACHE II score and the number of failed organ systems, allowed a meaningfull comparison between both groups.

**Table 4. Weekly Cost of Therapy[a]**

| | |
|---|---|
| CAVHD costs (7 days) | |
| Dialysate[b] | $ 454 |
| Catheters | 87 |
| Replacement (8 l/day) | 112 |
| Hemofilter (3.3 @ $78 each)[c] | 257 |
| Renal nurse time ($20/hr x 30 min. x 3.3)[d] | 32 |
| Total | $ 932 |
| IHD costs[e] (3.3 treatments, 4 hrs each) | |
| Dialysate ($12 x 3.3) | $ 40 |
| Catheters | 42 |
| Lines ($3 x 3.3) | 10 |
| Dialyzer (3.3 @ $26 each) | 86 |
| Renal nurse time ($20/hr x 5 hrs x 3.3) | 330 |
| Total | $ 508 |

[a] Costs of dialysis machines, water treatment systems, and physicians not included; [b] $Q_d$ 16.6 ml/min (1 l/hr); [c] assuming filterlife of 51.2 hrs; [d] renal nurse time involved in priming of the filter and set-up CAVHD system; [e] assuming dialysis frequency 1:2.1 days (= 3.3 treatment/wk), average duration 4 hrs each.

One of the major findings of our study was the superior metabolic control obtained with CAVHD. We observed a significant decline of serum urea levels with CAVHD, achieving controlled steady-state levels within 72 h, whereas no significant changes were seen in serum urea levels with (alternate-day) HD. Others have also found more effective control of azotemia with CRRT when compared to IHD [10,11]. The peak/trough urea concentrations as seen with IHD are avoided and the 'steady-state' urea achieved may well be a more appropriate measure of the uremic status [7]. CAVHD was also associated with more adequate correction of bicarbonate homeostasis. This may be of importance as acidosis significantly contributes to the catabolic state [17], attenuates the response to (exogenous) catecholamines [18], and exerts deleterious effects on hemodynamics and cardiac performance [19].

Using acetate-buffered dialysate and cellulosic membranes, Mauritz *et al.* [10] observed severe hypotension in 31.9% of dialysis procedures performed in patients with ARF secondary to abdominal sepsis. Despite the performance of more 'contemporary' IHD with often sequential ultrafiltration/isovolemic dialysis [20], use of bicarbonate-buffered [21], high sodium [22] dialysate and use of a modified

cellulosic membrane, hypotension and the inability of effective fluid removal was still a major problem. It may be that circulating vaso-active mediators, the presence of 'leaky capillaries' and the presence of low serum albumin levels (Table 2), as frequently observed in critically ill patients with MOSF [23], contributed to a diminished plasma refilling rate and the prohibition of adequate compensatory peripheral venoconstriction during (rapid) ultrafiltration. By contrast, CAVHD afforded great ease in volume control and improved hemodynamic stability was noted. In addition, subgroup analysis of mechanically ventilated patients revealed a trend towards a decrease in the $PaO_2/FiO_2$-ratio [12] concomittant with a fall of MAP following 1 h of IHD, whereas no changes were seen in these parameters during the first 24 h of CAVHD. Impaired gas exchange may be explained by a decrease in venous oxygen tension as a result of a decrease in cardiac output, an increase in oxygen consumption ($VO_2$), or both. An increase in $VO_2$ during IHD, independent of the membrane or buffer-anion used, has been demonstrated in ventilated ARF patients on the ICU [24]. During CRRT, $VO_2$ is unchanged or even reduced [25,26] and an increase in cardiac performance may occur as a result of gradual volume removal [27] or by the removal of circulating mediators with cardiodepressant properties [28].

The ample water and solute removal with CAVHD facilitated the administration of full parenteral nutrition without the risk of exacerbating azotemia (steady-state urea levels < 30 mmol/L) or fluid overload. Attempts at full parenteral nutrition in patients treated with IHD, however, were frequently thwarted by the problems of fluid overload or severe hypotension induced by rapid ultrafiltration. Excessive catabolism is frequently present in the critically ill patient with ARF and adversely affects prognosis [17,25]. It is associated with impaired healing rate and depressed immune response [25]. In addition, prolonged protein-calorie malnutrition may precipitate or worsen respiratory failure [29]. With CAVHD, unlike IHD, it is possible to reduce the protein catabolic rate and to achieve, at least in some patients, positive nitrogen balance [9].

There was no difference in the number of patients who recovered renal function between groups. However, serum creatinine levels of patients treated with CAVHD, either at the time of death or upon discharge from the hospital, were lower compared to those of patients treated with IHD. In addition, the duration of ARF was significantly longer in patients who were treated with IHD when compared to patients who were treated with CAVHD. One effect of ischemic ARF may be to impair renal autoregulation [30,31]. It is possible that recurrent episodes of hypotension, as occurred during IHD, may be accompanied by a proportionate fall in renal perfusion pressure, thus potentially prolonging renal failure by inducing repeated ischemic insults [31].

Several findings suggest that CAVHD contributed to improved survival. Despite significantly greater illness severity and a higher probability of death in those treated with CAVHD, no difference in outcome was observed between groups. The finding of a similar APACHE II score of surviving patients treated with CAVHD and non-surviving patients treated with IHD further suggest an improved outcome in continuously treated patients. Others have also noted improved survival for patients treated with CRRT compared to patients, matched for the severity of disease, treated

with IHD [11,32].

However, differences in the type of membrane used (*i.e.*, modified cellulosic membrane [IHD] *vs* synthetic membrane [CAVHD]) may have been confounding variables in the present comparative study. Experimentally, cellulosic membrane, but not synthetic (PAN) membrane, exposed blood delayed resolution of ischemic ARF in rats [33]. In addition, preliminary data from a randomized, clinical study comparing cellulosic membranes and synthetic (polymethylmethacrylate) membranes in the treatment of ARF suggested enhanced recovery of renal function and improved outcome in patients dialyzed with the biocompatible synthetic membrane [34]. Therefore, use of the (more) biocompatible PAN membrane in the CAVHD group may have contributed to the observed difference in the duration of ARF and outcome between groups, independent of the mode of dialysis.

In the present study, survival was more likely when CAVHD was instituted earlier during the course of stay on the ICU. This difference was not observed in patients treated with IHD. There was no difference in serum creatinine levels between survivors and non-survivors upon initiation of CAVHD. It may be that patients treated later developed ARF with a more protracted course or developed ARF as part of MOSF. Otherwise, one might speculate that earlier intervention with CRRT may have a favourable impact on outcome. Commonly observed cardiac and/or pulmonary system failure accompanying postoperative ARF may be exacerbated (or provoked) by overhydration [35] and increases the risk of dying [36]. Therefore, prevention or the rapid reversal of any existing overhydration with the early institution of CRRT may lead to a diminution of additional vital organ dysfunctions. In addition, it gives the opportunity for early and aggressive nutritional support, thereby counter-acting the often excessive catabolism with its adverse effects [16]. Yet another beneficial effect of (early) CRRT may be a down-modulation of the body's exaggerated response to septicemia by the removal of soluble inflammatory mediators with vasoactive and cardiodepressant properties [28].

Finally, the cost of ARF support was also considered. There was an apparent difference in cost of approximately $400 per week in favour of IHD. The actual difference is reduced somewhat as the costs of dialysis machines and water treatment systems were not considered. Moreover, to achieve azotemic control similar to that achieved with CAVHD, the frequency of IHD would have to be increased, thus increasing its costs. The apparent prolongation of ARF with IHD represents a further increase in total costs. However, had equal cost been attained with more frequent hemodialysis, survival might have been different, *i.e.*, higher in the IHD group. The costs of CAVHD were largely dependent upon the use of large amounts of sterile dialysate, which is inevitable, and the use of synthetic hemofilters. Maximizing filter life may thus be an important issue pertaining to these costs. One factor may be that a more appropiate timing of investigations or procedures that require discontinuation of CRRT is performed.

In conclusion, the present comparative study suggests that CAVHD offers several distinct advantages relative to IHD. It is associated with superior control of biochemistry and fluid balance; avoids hemodynamic instability and deterioration of gas exchange, as often observed with IHD; enables the provision of full (par)enteral

nutrition; and reduces the duration of ARF. All of these factors may have contributed to the apparent improved outcome in patients treated with CAVHD. Although CAVHD may be more expensive, effectiveness rather than costs should determine the technique employed. With all the limitations of a retrospective study, we think the present data add weight to the contention that CRRT is superior to IHD as dialytic support for the critically ill patient with ARF and may contribute to improved survival.

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Chapter VI

# Infusion of ultrafiltrate from endotoxemic pigs depresses myocardial performance in normal pigs

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## Abstract

***Objective and design:*** A beneficial effect of hemofiltration on the hemodynamics of endotoxic shock pigs has recently been shown (*see chapter I.4*). To test the hypothesis that this effect of hemofiltration is caused by convective removal of factors that adversely affect hemodynamics during endotoxemia, we infused ultrafiltrate from endotoxic shock and normal pigs into healthy pigs. Twelve anesthetized and ventilated pigs were hemodynamically monitored for 150 minutes following the infusion of 2 liters of ultrafiltrate from 12 donor pigs. The acceptor pigs were randomly divided into two groups; group 1 received ultrafiltrate from pigs who were hemofiltered after the infusion of 0.5 mg/kg endotoxin over 30 minutes; group 2 served as a control group, receiving ultrafiltrate from healthy donor pigs.

***Results:*** Group 1 showed a decrease in mean arterial pressure of 28 ± 7 mmHg [mean ± SEM] versus an increase of 17 ± 3 mmHg in group 2 ($p < 0.04$). Mean pulmonary artery pressure increased in group 1 compared to group 2 (9 ± 2 mmHg *vs* 1 ± 1 mmHg; $p < 0.04$). The decrease in cardiac output in group 1 was greater than in group 2 (3.3 ± 0.2 l/min *vs* 0.3 ± 0.3 l/min; $p < 0.02$) and was due to a fall in stroke volume. The fall in right ventricular ejection fraction was also greater (0.15 ± 0.02 *vs* 0.01 ± 0.00; $p < 0.01$). Systemic vascular resistance, right atrial pressure, right ventricular end diastolic volume, pulmonary wedge pressure and heart rate did not differ between groups.

***Conclusion:*** In contrast to ultrafiltrate from healthy pigs, ultrafiltrate from endotoxic shock pigs contains soluble, filtrable factors that increase pulmonary artery pressure and depress cardiac performance.

## Introduction

Septic shock and multiple organ system failure (MOSF) carry a high mortality rate [1]. The availability of new antibiotics, inotropic agents and techniques to replace the function of failing organ systems does not prevent the high mortality of these patients. Novel approaches in the treatment of these patients include optimization of oxygen delivery and the administration of monoclonal antibodies against endotoxins and tumor necrosis factor (TNFα) [2].

Another approach is the convective elimination of mediators of sepsis by hemofiltration (HF) [3-5]. In intensive care unit (ICU) patients with acute renal failure treated by HF, a relation between ultrafiltrate volume and survival has been observed [6], suggesting that toxic substances are removed from the circulation with this technique. Animal studies revealed only minimal effects of low volume (600 ml/h) HF on cardiac performance [7-9]. We recently reported that high volume HF (ultrafiltrate flow 6 liters/h) had a beneficial effect on left [10] and right [11] ventricular performance in porcine endotoxic shock. The discrepancy between our results and those obtained by others suggests a relationship between the ultrafiltrate volume and hemodynamics. This may indicate that the beneficial effect of HF is based on convective elimination of factors responsible for myocardial dysfunction via the ultrafiltrate.

To further test this hypothesis, we infused ultrafiltrate, obtained from endotoxic shock pigs, into healthy acceptor pigs and compared the hemodynamic response to that after infusion of ultrafiltrate from healthy pigs.

## Materials and methods

The protocol was approved by the local ethical committee for animal experiments. Twenty-four pathogen-free pigs from our own herd were used. Average age was 12 weeks and weight varied from 28 to 32 kg. All pigs were fasted overnight and allowed free access to water. The pigs were randomly assigned to serve as donor or acceptor. Thereafter, the donor was randomly assigned to a controle group or a group receiving endotoxin (*E.coli* O.111:B4, Sigma, St.Louis, USA).

### *Donor pigs*

The pigs were premedicated with 300 mg ketamine intramuscularly. They were intubated and mechanically ventilated, using a volume-controlled ventilator (Oxylog, Draeger, Luebeck, Germany) with $FiO_2$ 0.40, ventilator minute volume 4.0 liters and frequency 12 breath/min. A double-lumen catheter (DL6K, Impra, Inc., Tempe, AZ) was introduced into the superior caval vein, using the Seldinger technique. Thereafter, the pigs received 180 mg pentobarbital i.v., followed by a continuous infusion of pancuronium bromide (0.2 mg/kg/h) and pentobarbital (6.0 mg/kg/h). After a stabilization period of 30 min, endotoxin (0.5 mg/kg in 60 ml Ringer's

lactate), or 60 ml Ringer's lactate was infused over 30 min. Thereafter, pigs were subjected to zero-balanced hemofiltration, exchanging 2.0 liters ultrafiltrate over 30 min. The ultrafiltrate was collected under sterile conditions. The hemofiltration set-up consisted of a roller pump, air detector and pressure limiter (Gambro AK 10, Lund, Sweden). The pump flow was set at 250 ml/min, the pressure limiter was set at 250 mmHg. A 0.6 $m^2$ polysulphon hollow fiber filter with a cut-off point of 30,000 Dalton (Diafilter 30, Amicon Corp., Lexington, USA) was used. Prior to experiments, the filter was rinsed with 2 liters Ringer's lactate containing 5000 U heparin. Zero-balanced HF was achieved using a balance (BS 1.Gambro, Sweden). The substitution fluid (HF 21 hemofiltration solution, Fresenius, Bad Homburg, Germany) was warmed and infused before the filter. After collection of ultrafiltrate, the pigs were sacrificed.

*Acceptor pigs*

The pigs were premedicated with 300 mg ketamine i.m. After 15 min, they were orally intubated and ventilated ($FiO_2$ 0.40; 12 breath/min), using a blender (SJO1, Ohio medical products, Minneapolis, USA) and a volume-controlled ventilator (Siemens 900A, Elema, Sweden). The minute volume was adjusted to obtain an arterial $pCO_2$ of 38-42 mm Hg. Thereafter, ventilation was kept constant during the experiment. Anesthesia was maintained with 6 mg/kg/h phenobarbital and 0.2 mg/kg/h pancuronium bromide, via a continuous intravenous infusion. A 30 cm F5 cannula (Cavafix, 417375/9, Braun, Melsungen, Germany) was advanced into the femoral artery after cutdown and connected to a pressure transducer (P/N 966025/07, Baxter, Irvine, USA), positioned at the level of the left atrium. Arterial blood pressure was measured by connecting the transducer to a monitor (Hewlett Packard, 78342A), after calibration and zeroing to atmospheric pressure. A 7F rapid response, balloon-tipped thermodilution catheter (TD) (type 93A-431H-7, Baxter Healthcare Corp., Irvine, USA) was introduced into the superior caval vein via a percutaneous puncture using the Seldinger technique. Under monitoring of pressure wave forms, the catheter was advanced into the pulmonary artery until the inflated balloon wedged, and the injectate port positioned 3 cm above the tricuspid valve. This position was checked by pressure tracing before each set of cardiac output measurements. The catheter was connected to a cardiac output monitor (REF-1, Baxter Healthcare Corp., Irvine, USA) and to a pressure transducer (type P/N 966025-07, Baxter Healthcare Corp., Irvine, USA) connected to a Hewlett-Packard monitor (type 78342A). The transducer was positioned at the level of the left atrium and pressures were measured after calibration and zeroing to atmospheric pressure. Right atrial pressure (RAP) and pulmonary artery wedge pressure (PAWP) were measured intermitttently. Cardiac output (CO) and right ventricular ejection fraction (RVEF) were measured by the thermodilution technique. The injectate was cooled using an injectate coil (type 93-500, Baxter Healthcare Corp.). The injectate temperature was measured on line. Each injection was started at the end of a ventilatory cycle and for each variable the average of 3 measurements was taken. The

arterial pressure and pulmonary artery pressures were recorded continuously on a multichannel recorder (WS-682G, Nihon Kohden Co. Tokyo, Japan). RAP and PAWP were recorded before the start of ultrafiltrate infusion and subsequently every 15 min. Values were calculated from pressure tracings. After instrumentation, the pigs were allowed to stabilize for 75 min, during which they received 500 ml Ringers lactate. In this period, the donor pigs were instrumented. Thereafter, baseline measurements were made, followed by the infusion of 2 liters of ultrafiltrate over 2 h. After baseline measurements, hemodynamic measurements were repeated every 15 min during 150 min. At each hemodynamic measurement, arterial and mixed venous blood samples were taken simultaneously for measurement of pH, blood gases, hemoglobin (Hb) concentration and white blood cell count (WBC). Blood gases ($pO_2$, $pCO_2$) were measured with an IL-1306 analyser (Instrumentation Laboratories, Milan, Italy). A Contraves 8016 Analyzer (Contraves AG, Zurich, Switserland) was used to determine WBC and Hb concentration.

*Calculations*

Stroke volume:
SV=CO/HR, *ml*
Systemic vascular resistance:
SVR=(MAP-RAP)x80/CO, *dynes.sec.cm*$^{-5}$
Left ventricular stroke work:
LVSW=(MAP-PAWP)xSVx0.0136, *gm*
Right ventricular stroke work:
RVSW-(MPAP-RAP)xSVx0.0136, *gm*
Right ventricular end diastolic volume:
RVEDV=SV/RVEF, *ml*
Right ventricular end systolic volume:
RVESV=RVEDV-SV, *ml*

*Statistical analysis*

To compare data of groups at different time points, statistical analyses were performed on all variables. We used the ante-dependence method for repeated measurements, as described by Kenward [12,13]. This method can decompose observations into independent components, so that it is possible to identify the first moment at which a new significant difference between the groups occurs. In addition, this method provides a cumulative overall test for comparison of hemodynamic profiles. Moreover, Fisher's least significant difference (LSD) was performed, comparing the values for each parameter at the start of the experiments to those at the end of the experiments. This test shows the least difference between two effects that is significant as a measure of precision of the estimated difference [13]. Results are given as mean ± SEM; $p < 0.05$ is considered statistically significant.

**Table I. Values of Variables at Different Time Points in Group 1 and 2[a]**

| | Time (min) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 15 | 30 | 45 | 60 | 75 | 90 | 105 | 120 | 135 | 150 |
| HR (bpm) | | | | | | | | | | | |
| Group 1 | 152 ± 3.2 | 151 ± 12.3 | 150 ± 15.2 | 133 ± 11.0 | 139 ± 12.8 | 134 ± 9.9 | 128 ± 9.3 | 125 ± 9.3 | 114 ± 7.7 | 112 ± 7.4 | 113 ± 9.6 |
| Group 2 | 151 ± 4.0 | 149 ± 4.5 | 156 ± 4.9 | 147 ± 6.8 | 141 ± 7.8 | 141 ± 7.8 | 141 ± 6.7 | 132 ± 9.5 | 124 ± 10.5 | 125 ± 12.5 | 124 ± 11.1 |
| SVR (dynes.s.cm$^{-5}$) | | | | | | | | | | | |
| Group 1 | 1483 ± 31 | 1618 ± 128 | 1967 ± 308 | 2041 ± 236 | 2114 ± 142 | 2390 ± 298 | 2108 ± 168 | 2020 ± 257 | 2233 ± 269 | 2413 ± 274 | 2415 ± 325 |
| Group 2 | 1709 ± 74 | 1562 ± 91 | 1523 ± 79 | 1707 ± 90 | 1726 ± 103 | 1741 ± 72 | 1798 ± 70 | 1943 ± 65 | 2203 ± 200 | 2191 ± 252 | 2158 ± 182 |
| PAWP (mmHg) | | | | | | | | | | | |
| Group 1 | 5 ± 0.7 | 10 ± 1.6 | 9 ± 1.3 | 8 ± 1.6 | 7 ± 1.9 | 6 ± 1.2 | 5 ± 1.4 | 4 ± 1.0 | 5 ± 1.4 | 5 ± 1.4 | 5 ± 1.8 |
| Group 2 | 5 ± 0.6 | 8 ± 1.5 | 8 ± 1.1 | 7 ± 0.4 | 7 ± 0.7 | 6 ± 0.8 | 5 ± 0.9 | 6 ± 1.0 | 6 ± 1.1 | 6 ± 0.8 | 5 ± 0.8 |
| RAP (mmHg) | | | | | | | | | | | |
| Group 1 | 2 ± 0.5 | 3 ± 0.8 | 3 ± 1.2 | 2 ± 1.1 | 3 ± 1.2 | 2 ± 0.8 | 2 ± 0.9 | 2 ± 1.1 | 2 ± 1.0 | 2 ± 0.8 | 2 ± 1.0 |
| Group 2 | 1 ± 0.3 | 3 ± 1.0 | 3 ± 0.7 | 3 ± 0.4 | 1 ± 0.5 | 1 ± 0.3 | 1 ± 0.3 | 1 ± 0.5 | 2 ± 0.8 | 1 ± 0.4 | 1 ± 0.3 |
| RVSW (g) | | | | | | | | | | | |
| Group 1 | 8 ± 0.3 | 14 ± 1.1 | 13 ± 0.8 | 13 ± 1.4 | 11 ± 1.4 | 9 ± 0.7 | 9 ± 0.9 | 13 ± 1.9 | 10 ± 0.5 | 10 ± 1.2 | 9 ± 1.0 |
| Group 2 | 6 ± 0.6 | 10 ± 1.9 | 10 ± 1.5 | 9 ± 1.5 | 10 ± 1.8 | 6 ± 1.2 | 9 ± 0.9 | 8 ± 0.8 | 8 ± 1.1 | 9 ± 0.9 | 8 ± 0.6 |
| RVEDV (mL) | | | | | | | | | | | |
| Group 1 | 80 ± 4.0 | 79 ± 3.1 | 76 ± 2.5 | 77 ± 4.4 | 69 ± 4.8 | 73 ± 5.8 | 71 ± 6.1 | 76 ± 8.8 | 77 ± 6.4 | 79 ± 8.9 | 78 ± 9.8 |
| Group 2 | 86 ± 3.4 | 86 ± 3.3 | 86 ± 3.4 | 86 ± 3.6 | 83 ± 3.6 | 86 ± 3.6 | 86 ± 3.8 | 85 ± 4.1 | 84 ± 4.4 | 83 ± 4.8 | 80 ± 4.5 |
| RVESV/RVESP | | | | | | | | | | | |
| Group 1 | 1.6 ± 0.6 | 0.7 ± 0.9 | 0.7 ± 0.9 | 1.1 ± 0.3 | 1.1 ± 0.2 | 1.2 ± 0.2 | 1.2 ± 0.5 | 1.1 ± 0.2 | 1.5 ± 0.7 | 1.4 ± 0.4 | 1.5 ± 0.6 |
| Group 2 | 1.9 ± 0.5 | 1.7 ± 0.5 | 1.7 ± 0.6 | 1.8 ± 0.5 | 1.9 ± 0.6 | 1.7 ± 0.2 | 1.8 ± 0.3 | 1.8 ± 0.4 | 1.9 ± 0.6 | 1.9 ± 0.5 | 2.1 ± 0.3 |
| Hb (mmol/L) | | | | | | | | | | | |
| Group 1 | 5.6 ± 0.2 | 6.3 ± 0.3 | 6.4 ± 0.3 | 6.5 ± 0.4 | 6.8 ± 0.4 | 7.0 ± 0.4 | 7.3 ± 0.3 | 7.3 ± 0.3 | 7.2 ± 0.4 | 7.2 ± 0.4 | 6.9 ± 0.4 |
| Group 2 | 6.1 ± 0.3 | 6.0 ± 0.4 | 5.9 ± 0.3 | 5.8 ± 0.2 | 5.8 ± 0.3 | 6.0 ± 0.2 | 6.0 ± 0.3 | 5.7 ± 0.3 | 5.9 ± 0.2 | 5.9 ± 0.3 | 5.7 ± 0.3 |
| WBC (x10$^9$/L) | | | | | | | | | | | |
| Group 1 | 8.1 ± 1.3 | 7.4 ± 1.0 | 9.8 ± 1.4 | 10.8 ± 1.8 | 8.9 ± 1.5 | 7.6 ± 1.8 | 8.1 ± 2.1 | 8.4 ± 2.2 | 8.5 ± 2.4 | 7.7 ± 2.3 | 7.8 ± 2.6 |
| Group 2 | 7.8 ± 0.6 | 8.0 ± 0.9 | 7.0 ± 0.7 | 6.6 ± 0.7 | 6.8 ± 0.6 | 6.4 ± 0.8 | 6.8 ± 1.0 | 6.9 ± 0.9 | 6.9 ± 1.0 | 7.0 ± 1.1 | 6.0 ± 1.6 |
| Arterial pH | | | | | | | | | | | |
| Group 1 | 7.41 ± 0.01 | 7.37 ± 0.02 | 7.35 ± 0.01 | 7.36 ± 0.01 | 7.36 ± 0.01 | 7.36 ± 0.02 | 7.36 ± 0.02 | 7.40 ± 0.02 | 7.38 ± 0.02 | 7.38 ± 0.02 | 7.38 ± 0.02 |
| Group 2 | 7.43 ± 0.02 | 7.42 ± 0.02 | 7.41 ± 0.01 | 7.39 ± 0.02 | 7.38 ± 0.01 | 7.38 ± 0.02 | 7.37 ± 0.02 | 7.36 ± 0.02 | 7.35 ± 0.02 | 7.35 ± 0.01 | 7.36 ± 0.02 |

For abbreviations see text. [a]: Values not significantly different over time (Antedependence method).

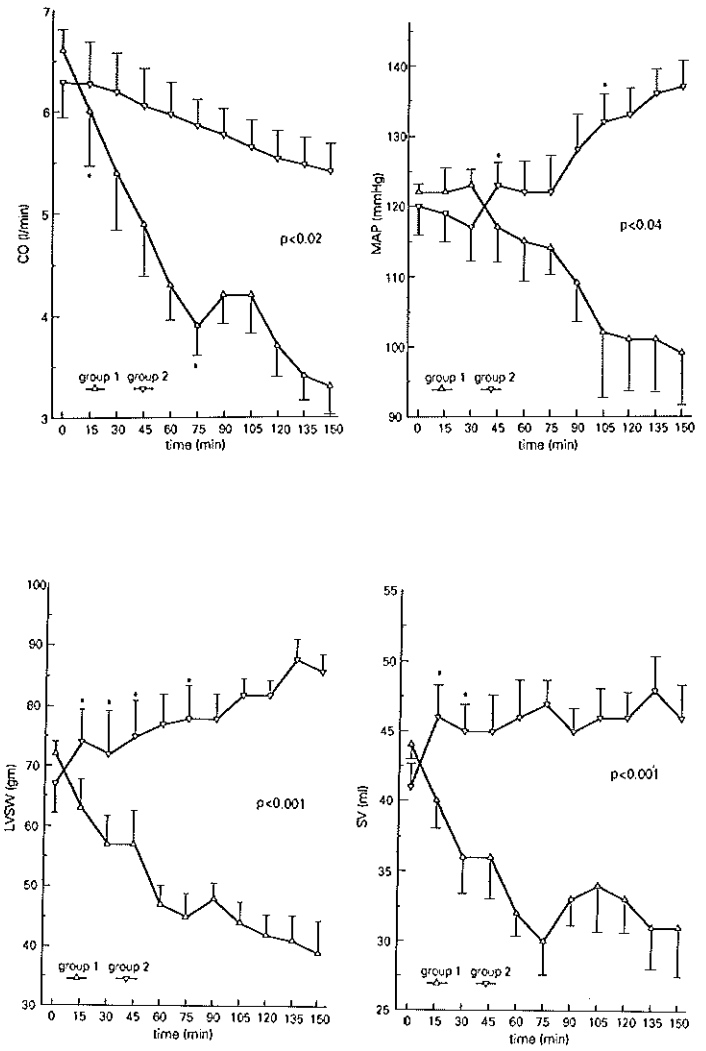


*Figure 1: The course of cardiac output (CO), mean arterial pressure (MAP), left ventricular stroke work (LVSW) and stroke volume (SV) after the infusion of 2 liters of ultrafiltrate from endotoxic shock pigs (Group 1; n = 6) or healthy pigs (Group 2; n = 6). The mean ± SEM values are shown. The probability value results from the overall tests of profiles. The asterisks indicate the occurrence of a new significant difference between groups (p < 0.05), using the antedependence method.*

## Results

All pigs survived till the end of the experiment. No filter clotting occurred, in all pigs a blood flow of 250 ml/min through the filter was achieved and venous pressure of 200 mmHg was never exceeded. In all donor pigs 2 liters of ultrafiltrate could be obtained over 30 min. The hemodynamic and blood gas data are shown in Table 1 and depicted in Figures 1-3.

**Table 2. Fisher's Least Significant Difference Test**

| | Group 2-1 | LSD 2-1 |
|---|---|---|
| HR | 12.3 | 41.6 |
| Cardiac output | 3.01* | 0.987 |
| SV | 18.0* | 9.90 |
| MAP | 47.4* | 21.9 |
| PCWP | 0.50 | 3.50 |
| SVR | 1029 | 1602 |
| MPAP | 8.0* | 5.17 |
| RAP | 0.67 | 1.63 |
| LVSW | 54.8* | 17.81 |
| RVSW | 0.6 | 3.19 |
| RVEF | 1.33* | 0.072 |
| RVEDV | 15.1 | 22.5 |
| RVESV/RVESP | 0.188 | 0.307 |
| Hb | 1.8* | 1.18 |
| WBC | 1.6 | 8.99 |
| Arterial $PO_2$ | 53* | 51.5 |
| Arterial $PCO_2$ | 2.5 | 5.59 |
| Arterial pH | 0.038 | 0.08 |

Note: The decrease or increase between baseline values and values at 150 minutes for each variable in group 2 is compared with the change in that variable in group 1. Considering $P < .05$ significant, the value under 'Group 2-1' that should be exceeded to reach significance was calculated (least significant difference, 2-1). For abbreviations see text. *$P < .05$.

*Global hemodynamics*

Cardiac output decreased more in Group 1 than in Group 2 due to a fall in SV and not in HR. This difference occurred immediately after the start of ultrafiltrate infusion (Fig 1). MAP increased in Group 2 and decreased in Group 1, a significant difference occurring at 45 min. LVSW increased in Group 2 and decreased in Group 1, a significant difference occurring at 15 minutes. Overall, cardiac output, SV, MAP and LVSW were significantly lower in Group 1 than in Group 2 (Fig 1), as were their values at 150 min compared to those at the start of the experiments (Table 2). MPAP increased significantly more in Group 1 than in Group 2. This difference occurred at 15 min. PAWP, RAP, HR and SVR did not differ between the groups.

*Right ventricular volumes and performance*

RVEF gradually fell in Group 1, in contrast to a very small change in Group 2. At 15 min, a significant difference in this variable occurred, while a concomitant increase in MPAP was observed (Fig 2). Overall, RVEF was lower and MPAP was higher in Group 1 than in group 2, as were their values at 150 min compared to those at 0 min. No overall difference was found in the RVESV/peak systolic pulmonary pressure ratio between both groups.

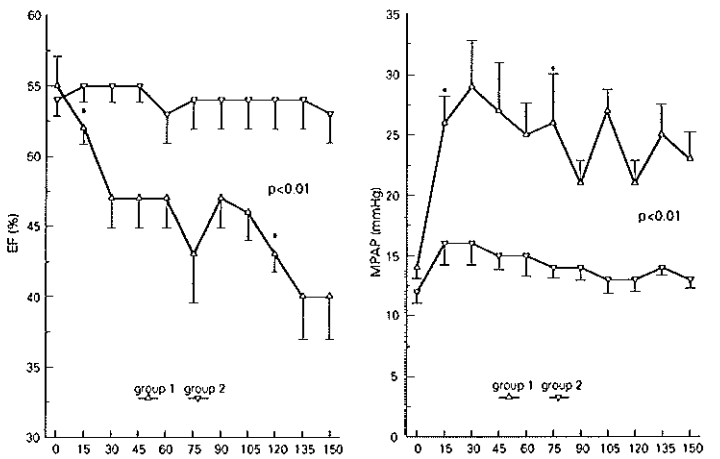


*Figure 2: The course of right ventricular ejection fraction (EF) and mean pulmonary arterial pressure (MPAP) after the infusion of 2 liters of ultrafiltrate from endotoxic shock pigs (Group 1; n = 6) or healthy pigs (Group 2; n = 6). The mean ± SEM values of RVEF and MPAP are shown. The probability value results from the overall tests of profiles. The asterisks indicate the occurrence of a new significant difference (p < 0.05) between groups, using the antedependence method.*

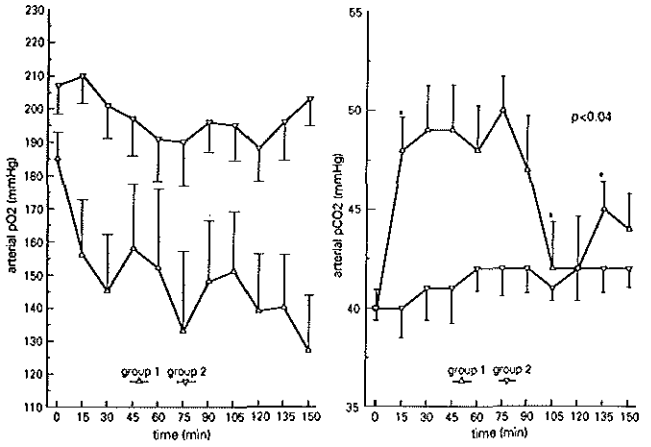


*Figure 3: The course of arterial $pCO_2$ and $pO_2$ after infusion of 2 liters of ultrafiltrate from endotoxic shock pigs (Group 1; n = 6) or healthy pigs (Group 2; n = 6). The mean ± SEM values are shown. The probability value results from the overall tests of profiles. The asterisks indicate the occurrence of a new significant difference (p < 0.05) between groups, using the antedependence method.*

*Biochemistry*

At 15 min, arterial $pCO_2$ was higher in Group 1 than in Group 2; this difference disappeared at 105 minutes (Fig 3). Comparing arterial $pCO_2$ at 150 minutes to the baseline values, no difference was found between the groups; overall arterial $pCO_2$ was higher in Group 1 than in Group 2. Comparing Hb concentration and arterial $pO_2$ of Group 1 with Group 2 at 150 minutes, Hb concentration was higher, while arterial $pO_2$ was lower; no overall differences in these variables between the groups were seen. WBC and pH did not differ between the groups.

## Discussion

Our results show that ultrafiltrate of endotoxic shock pigs induces pulmonary hypertension and decreases cardiac performance in healthy pigs. These findings suggest that ultrafiltrate of endotoxic shock pigs contains filtrable factors, responsible for these deleterious effects. The cause of the fall in cardiac output is probably multifactorial. We measured RVEF and derived right ventricular end systolic volume using the rapid response thermodilution technique [14]. This technique has been shown to correlate well with gated blood pool techniques. The difference in RVEF between the groups should be interpreted with care. The decrease in RVEF in Group 1 needs not reflect a decrease in right ventricular function, but may be caused at least

partially by the increase in pulmonary artery pressure, as supported by the absence of differences in the right ventricular end-systolic volume/peak pulmonary pressure relation [15]. In Group 1 an increase in RVEDV would be expected in response to the increase in MPAP [16]. The absence of right ventricular dilatation in this group indirectly suggests a fall in venous return. An increase of the venous capacitance is consistent with a septic circulation [2] and may have contributed to the drop in cardiac output in Group 1. The difference in LVSW in the absence of significant differences in PAWP between the groups suggests an adverse effect of ultrafiltrate infusion on LV function. However, as we did not measure LV end-diastolic volume, differences in LVSW between the groups may also be caused by a decreased LV compliance in Group 1. However, RVEDV did not differ between the groups, so that a fall in LV compliance due RV distension is unlikely. Therefore, the fall in cardiac output may result from both a decreased venous return and decreased left ventricular function.

The cause of the transient difference in arterial $pCO_2$ is unclear. It may either reflect increased $CO_2$ production by the action of infused mediators of sepsis or a deterioration of pulmonary function. This latter is further suggested by the lower $pO_2$ in this group at the end of the experiment. It was previously demonstrated [17] that continuous arteriovenous hemofiltration improved survival time and arterial $pO_2$ of pigs infused with *S. aureus*. Infusion of ultrafiltrate of endotoxic shock pigs into healthy pigs induced lung injury, similar to that seen after *S. aureus* infusion.

The cause of the increase in pulmonary and systemic pressure in the control group is unclear. Contributing factors may be volume infusion, the presence in the ultrafiltrate of vasoactive mediators resulting from extracorporeal circulation [18] and the presence in the ultrafiltrate of ketamine or catecholamines, released by the donor pig as a result of the instrumentation. As we did not study the effect of volume infusion alone, no data are available to substantiate this point.

Myocardial depression during septic and endotoxic shock is well-documented. Decreased or uneven myocardial perfusion [19,20] and myocardial edema [21] have all been suggested to play a role in its pathogenesis. The role of circulating substances that depress myocardial performance during sepsis has been studied for many years [22-27]. Attempts to reveal the identity of myocardial depressant factor(s) (MDF) have focused on identification of production site and molecular weight [22-24,28]. TNFα induces myocardial depression in *in vitro* assays of rat myocardial cells [29]. In human experiments, interleukin-2 [30] and endotoxin [31] administration resulted in cardiovascular abnormalities analogeous to the hemodynamics of human septic shock. Therefore, the (inter-)action of many mediators may be involved in producing cardiac depression during sepsis. We did not measure levels of important mediators of sepsis, such as TNF-α and interleukins, in serum or ultrafiltrate, because no reliable, quantitive tests for assaying these mediators in pigs are available in our area. Nevertheless, our findings do support the hypothesis [10,11] that the improvement in cardiac performance during HF is caused by the removal of factors, responsible for cardiac depression after endotoxin infusion, via the ultrafiltrate. Therefore, it can be expected that the positive effect of HF on cardiac performance of endotoxic shock pigs is related to the ultrafiltrate volume. This may explain our

previous findings [10,11] of a more pronounced effect of high volume HF (6 liters/h) than was seen in other studies on the effect of low volume HF (600 ml ultrafiltrate/h) on cardiac performance of endotoxic shock pigs [7,9].

Several other investigators have addressed the question if hemofiltration could reduce the cardiac depression during septic shock by elimination of the causative substances. Gomez *et al.* [8] demonstrated that *E. Coli* infusion resulted in myocardial dysfunction, as measured by myocardial contraction velocity and end-systolic pressure-volume relation. Hemofiltration using an Amicon filter (molecular cut-off point 30.000 dalton) resulted in an improvement of these parameters. In addition, plasma of septic dogs reduced isometric tension of isolated right ventricular trabeculae. This effect was not seen when plasma of dogs after HF was used. This study indicates that circulating factor(s), responsible for cardiac dysfunction during sepsis, can be removed by ultrafiltration. In patients with refractory cardiogenic shock [32] or acute respiratory failure following open heart surgery [33], hemofiltration (Amicon diafilter 20; molecular cutoff point 50.000 Da) has been shown to improve cardiac output and MAP. Subsequent *in vitro* experiments showed that ultrafiltrate from these patients reduced isometric tension of isolated papillary muscle. Parrillo *et al.* [28] demonstrated that serum of septic shock patients depresses contractility of isolated rat myocytes. The quantity of depression of the *in vitro* myocyte was shown to correlate with the reduction in the left ventricular ejection fraction in septic shock patients. Molecular filtration experiments with Amicon filters by this group of investigators produced somewhat contradictory results as to the molecular weight of MDF, some experiments suggesting a molecular weight between 500 and 5000 Da, others a molecular weight of greater than 10,000 Da [28,34,35]. These studies confirm that both plasma of septic animals and ultrafiltrate of septic patients are capable of reducing the contractile properties of isolated papillary muscle and myocytes.

Concerning the clinical relevance of these findings, many questions remain to be answered. Most animal studies are short term studies on the effect of HF on hemodynamics of pigs in the acute phase of endotoxic shock. The potential role of hemofiltration in the treatment of septic shock lies in its ability to remove mediators, known to play a causative role in its development. Several studies demonstrated that filters with a cut-off point of 30.000 are able to remove $PGE_2$ [4], Thromboxane $B_2$ [4,9,36], ß-endorphin [4] and TNFα [36,37]. Other mediators, for instance 6keto PGF1α, were shown to be bound to the filter. We previously showed that high volume hemofiltration improves hemodynamics of endotoxic shock pigs [10,11]. Our present study shows that ultrafiltrate from these pigs contains factors that adversely affects hemodynamics. Therefore, convective blood purification by hemofiltration seems to be at least partially responsible for the improvement in hemodynamics during endotoxemia in pigs.

Translation of these experimental results into the clinical setting of septic shock, however, is difficult as we performed a short term study using ultrafiltrate volumes that may be difficult to achieve on a continuous basis. Given the low clearance of some key mediators of sepsis in man, such as TNFα [37], and the progressive decline in sieving properties of hemofilters over time, it is therefore unclear whether

clinically achieveable ultrafiltrate volumes are capable of clearing adequate amounts of mediators to improve hemodynamics or survival of septic shock patients. Only prospective, clinical trials might answer the question if high volume HF is of any use in the management of septic shock patients.

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Chapter VII

# Cytokine kinetics (TNFα, IL-1ß, IL-6) during continuous hemofiltration: a laboratory and clinical study

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## Abstract

***Objective***: To determine whether the clinical improvement noted in some critically ill patients undergoing continuous renal repacement therapy (CRRT) is in part due to the removal of inflammatory mediators, we assessed the impact of hemofiltration membranes on cytokine kinetics (TNFα, IL-1ß, IL-6) during both *in vitro* and *in vivo* hemofiltration (HF).

***Design***: *In vitro* HF was performed using a closed-loop recirculation model containing Ringers lactate with human albumin in which recombinant human cytokines were added in consecutive experiments. Cytokine kinetics in humans were assessed in 20 patients suffering from the systemic inflammatory response syndrome and acute renal failure undergoing CAVH-D. To assess sieving characteristics, the dialysate pump was stopped 15 min prior to sample collection so as to obtain 'pure' ultrafiltrate (UF).

***Results***: Appreciable sieving of TNFα was observed *in vitro* only for the AN69 membrane. In addition, initial sieving of TNFα was masked by its rapid adsorption onto the AN69 membrane. Significant sieving of IL-1ß was observed for all membranes tested. Significant sieving of IL-6 occurred with the AN69 membrane but less than that for TNFα and IL-1ß. No appreciable adsorption was noted for IL-1ß and IL-6. All patients had detectable TNFα and IL-6 levels; none of the patients had detectable IL-1ß levels. In contast to our *in vitro* experiments, we noted no appreciable sieving of TNFα *in vivo*; this cytokine being detected in only 17 of 60 UF specimens (8.9 ± 0.8 pg/mL [mean ± SEM]). Mean ultrafiltrate clearance ($K_{uf}$) was 0.1 ± 0.02 L/day. No significant change over time was observed in plasma TNFα levels during CAVH-D. Mass transfer of TNFα from blood was greater than that appearing in the UF suggesting membrane adsorption. Clearance from blood ($K_b$) of TNFα differed significantly with filter duration (17.7 ± 4.6 [1-2h]; 3.0 ± 3.8 [4-6h]; -30.6 ± 11.8 mL/min; $p < 0.05$). Significant amounts of IL-6 were detected in all 60 UF specimens (304 ± 28.6 pg/mL). The mean sieving coefficient of IL-6 was 0.26 ± 0.04. Mean $K_{uf}$ was 3.4 ± 2.2 L/day. Plasma IL-6 levels decreased over time (796 ± 163.2 [pre] to 548 ± 82.2 [24h] pg/mL; $p < 0.05$). $K_b$ of IL-6 with filters used for for ≤ 6 h was significant (5.3 ± 3.4 [1-2h]; 2.6 ± 2.68 [4-6h] mL/min), but became negative over time (-4.7 ± 4.4 [20-24h] mL/min). Mass transfer of IL-6 from blood did not differ from that appearing in the UF for any given filter duration.

***Conclusions***: Cytokines can be removed from the circulation with CRRT, either by their adsorption or by their removal via the UF. Differing sieving properties of TNFα *in vitro* and *in vivo* may be explained by the fact that this cytokine exists in the circulation as a trimer or that circulating TNFα is rapidly bound to soluble TNF receptors. Prolonged blood-membrane interaction seemingly affects adversely cytokine clearances, possibly by desorption and/or by increased generation. If removal of cytokines is of primary concern, high UF volumes and frequent filter change are needed to extract significant amounts of cytokines from the circulation.

## Introduction

The development of acute renal failure (ARF) in intensive care unit (ICU) patients, usually as part of multiple organ systems failure (MOSF), carries a poor prognosis [1,2]. Although continuous hemo(dia)filtration is now increasingly accepted as the preferred treatment modality for the critically ill patient with ARF, it is not clear whether its use has an impact on outcome of these patients [2].

Both experimental [3,4] and uncontrolled clinical data [2,5,6] suggest that CHF may improve hemodynamics and gas exchange in patients with septic shock and (non-renal) MOSF, independent of an impact on fluid balance. These beneficial effects are ascribed to the removal from the circulation of middle- and large molecular weigth (>500 Dalton [Da]) inflammatory mediators, particularly cytokines, responsible for the cardiorespiratory and metabolic alterations leading to MOSF [7-9]. Indeed, (persistently) elevated levels of TNFα and IL-6 have been associated with progressive inflammatory illness and poor outcome in both septic and non-septic shock [7,8]. However, few and controversial data exist concerning the removal of cytokines from the circulation with continuous renal replacement therapy (CRRT) [10,11].

The aim of the present study was to investigate whether cytokines are removed from the circulation with CRRT both under in vitro conditions and in vivo, *i.e.*, in patients with ARF suffering from the 'systemic inflammatory response syndrome' (SIRS)[12]. In addition, it was investigated whether these cytokines were sieved through or adsorbed to the hemofiltration membrane.

## Material and methods

### *In vitro*

Continuous hemofiltration was conducted in vitro using an experimental set-up, consisting of a 'blood' reservoir containing Ringers lactate with human albumin (15 g/L), a synthetic hemofilter with standard arterial, venous and ultrafiltrate tubings, and roller pumps (Rhone Phoulenc, France) to regulate blood and ultrafiltrate rates. The venous outflow and ultrafiltrate were returned to the blood reservoir, thus minimizing changes in blood volume during the experiment. Polyacrilonitrile (AN 69-HF, Hospal Ltd, France [0.60m2]), polyamide (PAM)(FH66-D, Gambro BV, Sweden [0.60 m2]) and polysulphone (PS)(BL-624, Sorin biomedica, Germany [1.0 $m^2$]) hollow-fibre hemofilters were used. In consecutive experiments using a single mediator, recombinant human tumor necrosis factor-α (TNFα, 16,5 kDa) and interleukin-1ß (IL-1ß, 16,5 kDa), respectively, were added to the blood reservoir and allowed to equilibrate for 15 min. The pumps were calibrated to deliver a blood flow ($Q_b$) of 150 mL/min and an ultrafiltrate flow ($Q_{uf}$) of 30 mL/min. During initial experiments, samples (2 mL) were taken from the arterial, venous and ultrafiltrate line at t = 15, t = 60, and t = 120 min. At t = 0 min and t = 150 min, samples were taken from the reservoir. Because these results suggested that the sieving properties

of cytokines were masked by their initial adsorption and that the binding capacity of the AN69 membrane was not saturated for TNFα, we subsequently performed continuous hemofiltration with the AN69 membrane during a 24-hrs period, again using a single mediator (TNFα, IL-1ß, and IL-6 [22,0 kDa], respectively) in each experiment. Samples were taken immediately prior to and at 5, 10, 15, 30, 60, 120, 240, 360, 480, 720 and 1440 min, respectively, after the start of continuous hemofiltration. The amount of cytokine left unbound was calculated from the 'blood' volume (corrected for sample collection) and final cytokine concentration. The amount of cytokine bound is equal to the amount added initially minus the amount remaining unbound. Samples were drawn in ethylenediamine (EDTA) tubes and immediately stored at -70°C until assays were performed.

*in vivo*

*Patients*

Twenty critically ill patients with ARF who were treated by continuous arteriovenous hemodiafiltration (CAVH-D) in a single surgical ICU were included in a prospective study during the period August 1, 1992 - January 31, 1994. All patients suffered from SIRS, as manifested by 2 or more of the following conditions: temperature > 38°C or < 36°C; heart rate > 90 beats/min; respiratory rate > 20 breaths/min or $PaO_2$ < 4.3 kPa (< 32 torr); WBC >1 2,000 cells/$mm^3$, < 4000 cells/$mm^3$, or > 10% immature (band)forms [12]. All patients required mechanical ventilation and inotropic support prior to the institution of CAVH-D. The following information was obtained: age, gender, underlying disease(s) and surgical procedures performed, presence of systemic infection, severity of illness as calculated from the Acute Physiology and Chronic Health Evaluation (APACHE II) score [13] and the number of failed organ systems [12,13], outcome and cause of death. Cardiorespiratory and acid-base variables were monitored prior to the start of CAVH-D and 1, 4, and 24 h, respectively, after the start of treatment.

*Continuous arteriovenous hemodiafiltration*

CAVH-D was performed using a hollow-fibre polyacrilonitrile hemofilter (AN 69-HF) connected to the arterial and venous vascular access devices in a pumpless circuit. Vascular access was by means of large-bore femoral catheters (Medcomp, Harleysville, USA)($n$ = 17) or by means of a scribner shunt (Quinton, USA; $n$ = 3). Warmed bicarbonate-buffered dialysis fluid (SH 44-HEP, Schiwa GmbH, Glandorf, Germany) was pumped counter-current to blood through the ultrafiltrate compartment of the filter at a rate of 1 L/h with a calibrated, volumetric pump (3M, AVI inc., St Paul, USA). Lactate-based replacement fluid was given as clinically indicated, administered into the arterial limb of the extracorporeal circuit. The extracorporeal circuit was anticoagulated with heparin (500-700 U/h) unless there was severe coagulopathy or thrombocytopenia (< 60 · $10^9$/L). The filters were changed when there was objective evidence of inadequate filter function (*i.e.*, a sustained reduction in ultrafiltrate volume [< 300 mL/h] or evidence of filter clotting. Net ultrafiltration

rate at each time point was measured from timed volumetric collections ($Q_{uf}$ [mL/min]).

*Sample collection*

Both blood and ultrafiltrate levels of the cytokines TNFα, IL-1ß, and IL-6 were measured in these patients ($n$ = 20). Blood samples were taken from a port on the arterial tubing prior to the infusion of predilution fluid and, as such, represent the patient's systemic levels. Simultaneously, samples were drawn from the ultrafiltrate port. To assess cytokine sieving properties (*i.e.*, no dilution of ultrafiltrate by dialysis fluid), the dialysate line was clamped and dialysate pump stopped 15 min prior to collection so as to obtain 'pure' ultrafiltrate, *i.e.*, convective solute transfer occurs only (CAVH). To assess cytokine mass transfer across the membrane, clearances of cytokines from blood and the impact of prolonged blood-membrane interaction on these characteristics, blood samples were also taken from a port immediately postfilter in 10 of these patients. To calculate the blood flow pre- ($Qb_{in}$) and postfilter ($Qb_{out}$), hematocrit (Hct) levels were measured simultaneously at the filter inlet and outlet ($Hct_{in}$,$Hct_{out}$) in these patients ($n$ = 10). For each patient, samples were taken immediately prior to and 1, 4 and 24 h, respectively, after the initiation of CAVH-D. Postfilter values were corrected for hemoconcentration as a result of ultrafiltration. The 'age' of the filter was recorded at each sampling time point because filter replacement was required within 24 h in some patients as a result of filter clotting. Samples were placed in EDTA tubes and held on ice until centrifugation. The plasma was removed and stored at -70°C until assays were performed. Ultrafiltrate samples were drawn in EDTA tubes and held on ice until storage at -70°C.

***Calculations [14]:***

Blood flow:

$Qb_{in} = Q_{uf} \cdot Hct_{out}/(Hct_{out} - Hct_{in})$, *ml/min*

$Qb_{out} = Qb_{in} - Q_{uf}$, *ml/min*

Sieving coefficient:

$S = 2 \cdot C_{uf}/C_{in + Cout}$

Clearance (filtrate):

$K_{uf} = C_{uf} \cdot Q_{uf}/ C_{in}$, *ml/min*

Clearance (blood):

$K_b = ([Qb_{in} \cdot C_{in}] - [Qb_{out} \cdot C_{out}])/C_{in}$, *ml/min*

Mass transfer (J) across the membrane from blood:

$J_b = (Qb_{in} \cdot C_{in}) - (Qb_{out} \cdot C_{out})$, *pg/min*

Mass transfer into ultrafiltrate:

$J_{uf} = Q_{uf} \cdot C_{uf}$, *pg/min*

Mass balance:

$J_{bin} - J_{bout} = J_{uf}$

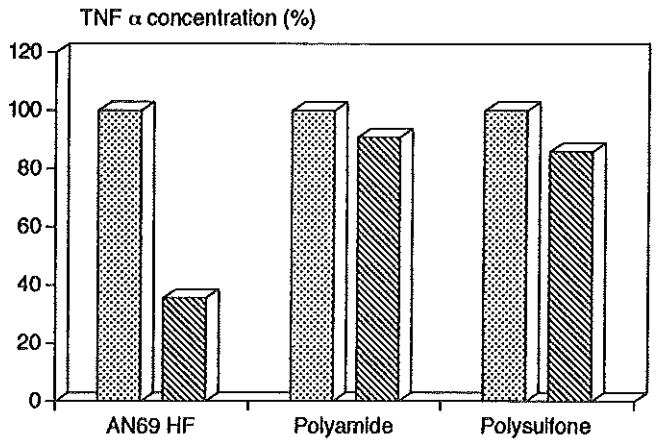


*Fig 1: TNFα elimination (monomeric form; 16,5 kDa) during in vitro hemofiltration (HF) over 150 min with 3 different membranes. Both the ultrafiltrate and venous outflow were returned to the 'blood' reservoir; therefore, mass lost from 'blood' could only be due to adsorption. Results are expressed as percent of total TNFα measured in the blood reservoir before the start of recirculation. Only the AN69 membrane exhibited appreciable adsorption.*

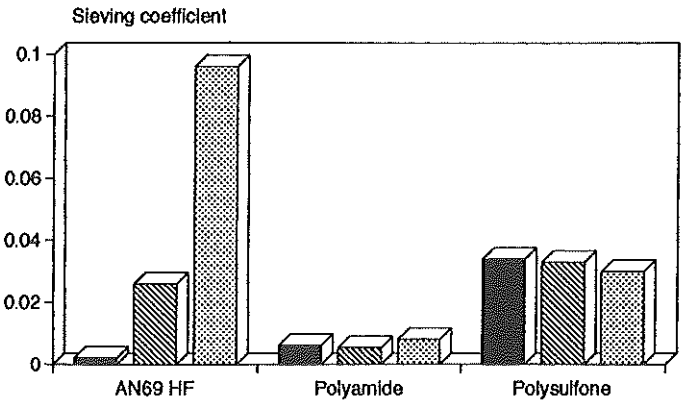


*Fig 2: Sieving coefficient of TNFα (16,5 kDa) during in vitro HF with 3 different membranes at 15 min (black bars), 60 min (hatched bars), and 120 min (dotted bars), respectively. No appreciable sieving of TNFα was observed during the first 60 min of HF; thereafter, sieving properties of the AN69 membrane increased with the sieving coefficient of TNFα approaching 0,1 (10%).*

### *Assay procedures*

Blood and ultrafiltrate concentration of cytokines were measured by commercially available enzyme-linked immunosorbent assays (ELISA) and performed according to the manufacturers instructions. TNFα concentrations were measured with a one-step "sandwich" type immunoassay (Immunotech S.A., Marseille, France). The lower detection limit of TNFα was 7.8 pg/mL. The coëfficient of variation was less than 10% in the range of 115-1000 pg/mL. No cross reactivity appears with TNFß, IL-1ß, IL-2, IL-6, or the p55 and p75 forms of the TNF receptor. IL-1ß concentrations were measured using a two-step immuno-assay (Immunotech S.A., Marseille, France). Analytical sensitivity of the assay was 5 pg/mL. Coëfficient of variation was less than 8% in the range of 50-1000 pg/mL. No cross reactivity occurs with IL-α, IL-6, or TNFα. IL-6 concentrations were measured with a three-step immuno-assay, using the human (hu) IL-6 ELISA compact kit (C.L.B., Amsterdam, The Netherlands). Analytical sensitivity of the assay was 5 pg/mL. Coëfficient of variation was less than 10% in the range of 6.5 - 400 pg/mL. No cross reactivity occurs with either IL-1ß or TNFα. Samples were assayed in duplicate and all cytokine levels assayed in the same run. Cytokine concentrations, where necessary, were corrected for dilution. The mean of the duplicate measurements is reported at each time period.

### *Statistical analysis*

Data are expressed as mean ± standard error of the mean (SEM) or percentage, where appropriate. The Wilcoxon signed-rank test was used to analyse non-parametric data. Repeated measures ANOVA test was used to analyse normally distributed data. Statistical significance was accepted at a $p < 0.05$ level.

## Results

### *In vitro*

*Different membranes*

Significants amounts of TNFα (3.5 µg) disappeared from the blood compartment with the AN69 membrane (Fig 1) with only minimal amounts detectable in the ultrafiltrate. The only plausible explanation for the observed mass balance error in the closed-loop recirculation model is that TNFα is bound to the membrane. No appreciable adsorption of TNFα was noted for the polysulfone (0.15 µg) and polyamide (0.3 µg) membrane (Fig 1), steady-state blood levels occurring after 15 min. There was no appreciable sieving of TNFα during these short-term hemofiltration experiments (Fig 2). However, sieving properties of TNFα with the AN69 membrane seemed to increase over time with a concomittant increase of convective clearance ($K_{uf}$ 0 mL/min [15 min]; 0.8 mL/min [60 min]; 2.9 mL/min [120 min]). Only minimal convective clearance occurred with the 2 other membranes

($K_{uf}$ [PS] 0.96 mL/min; [PAM] 0.24 mL/min at 120 min). The adsorption capacity of all 3 membranes for IL-1ß was less compared to that seen for TNFα (AN 69 1.0 µg; PAM 0.03 µg; PS 0.06 µg). However, significant sieving of IL-1ß was seen with all 3 membranes, again with increasing sieving properties over time with the AN69 membrane (*S* [AN69] 0.96; [PS] 0.67; [PAM] 0.62 at 120 min). This resulted in significant convective clearances of IL-1ß ($K_{uf}$ [AN 69] 28.8 mL/min; [PS] 20.1 mL/min; [PAM] 16.5 mL/min at 120 min) with all 3 membranes.

*Twenty-four hours hemofiltration with the AN69 membrane*
During the 24-hrs hemofiltration experiments with the AN69 membrane, the adsorption capacity of the membrane became saturated for all 3 cytokines, as indicated by steady-state arterial (*i.e.*, prefilter) cytokine levels (Fig 3). Calculated adsorption capacity of the membrane for TNFα was 4.5 µg, IL-1ß 1.6 µg, and for IL-6 1.9 µg. Sieving capacities of the different cytokines were masked by their initial adsorption. When the binding capacity of the membrane became saturated, the sieving coefficient of all cytokines increased significantly (TNFα 0.01 ± 0.003 to 1.0 ± 0.01; IL-1ß 0.12 ± 0.01 to 1.0 ± 0.14; IL-6 0.01 ± 0.004 to 0.32 ± 0.031; $p < 0.05$ [$n$ = 3]).

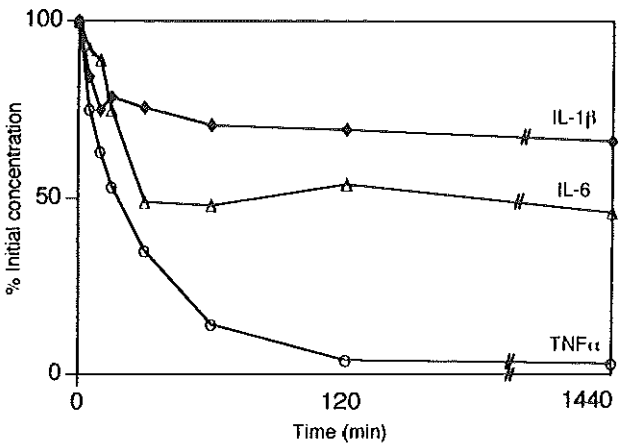


*Fig 3: Arterial (i.e., prefilter) cytokine levels (TNFα, IL-1ß, IL-6) over time during continuous hemofiltration. Both the ultrafiltrate and venous outflow were returned to the 'blood' reservoir; therefore, mass lost from 'blood' could only be due to adsorption. A single mediator was added in each experiment. Results are expressed as percent of total cytokine measured in the 'blood' before the start of recirculation. For the purpose of clarity, steady-state cytokine values between 240 and 1440 min are not shown.*

*In vivo*

*Patients*

Mean age of the patients was 54 ± 3.8 yrs (range 17-83 yrs) with a male predominance (75%). The mean pretreatment APACHE II score was 27 ± 0.7 (range 19-34) and the mean number of OSFs was 3.3 ± 0.3 (range 1-6). MAP upon initiation of CAVH-D was 73 ± 1.8 mm Hg (range 55-86 mm Hg). Eight patients (40%) survived to leave the ICU, of whom 7 (35%) survived to leave hospital. Nine patients (69%) died in refractory septic shock complicated by MOSF, 3 patients (23%) died from irreversible MOSF following multitrauma, and 1 patient (8%) died from myocardial infarction. All patients had detectable TNFα and IL-6 plasma levels. The plasma TNFα levels in non-survivors were higher than in survivors (Fig 4a). No difference in plasma IL-6 levels was observed between survivors and non-survivors (Fig 4b). None of the patients had detectable IL-1ß plasma levels. Hemodynamic, gas exchange, and acid-base variables prior to and during 24 h of CAVH-D treatment are shown in Table 1. There was a non-significant trend to improved hemodynamics and gas exchange after 4 h of treatment, which could at least in part be explained by fluid removal. In addition, a significant increase in serum bicarbonate levels was observed after 24 h of treatment.

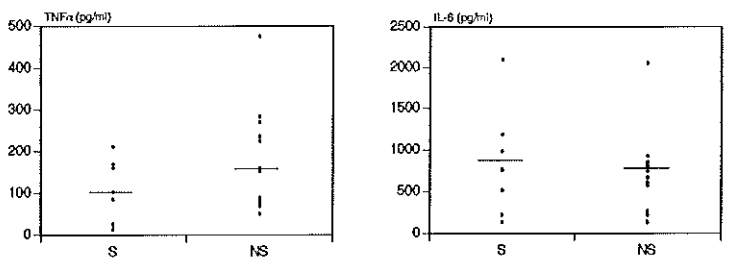


*Fig 4 a,b: Individual plasma TNFα (a) and IL-6 (b) concentrations in surviving (S) and non-surviving (NS) patients. TNFα levels were higher in non-surviving patients ($p < 0.05$).*

**Table 1. Cardiorespiratory And Acid-Base Variables Prior To And During CAVH-D Treatment**

| Variable | Time (h) | | | |
|---|---|---|---|---|
| | Pre | 1 | 4 | 24 |
| MAP (mmHg) | 73 ± 1.8 | 76 ± 2.0 | 84 ± 2.1 | 78 ± 1.8 |
| CO (L/min) | 5.8 ± 0.5 | 6.1 ± 0.4 | 6.5 ± 0.4 | 6.0 ± 0.3 |
| HR (beats/min) | 108 ± 2.3 | 106 ± 2.1 | 101 ± 1.8 | 104 ± 1.7 |
| SVR (dynes.sec.cm$^{-5}$) | 724 ± 82.1 | 732 ± 61.2 | 884 ± 121.1 | 801 ± 112.3 |
| MPAP (mmHg) | 27 ± 2.5 | 29 ± 2.1 | 26 ± 2.0 | 28 ± 0.4 |
| PCWP (mmHg) | 15 ± 1.1 | 13 ± 0.8 | 15 ± 1.1 | 14 ± 0.8 |
| $PaO_2/FiO_2$-ratio | 2.3 ± 0.3 | 2.4 ± 0.4 | 2.6 ± 0.3 | 2.6 ± 0.4 |
| pH | 7.36 ± 0.3 | 7.38 ± 0.3 | 7.40 ± 0.4 | 7.39 ± 0.3 |
| Bicarbonate (mmol/L) | 16.2 ± 0.7 | 17.4 ± 1.6 | 17.5 ± 0.9 | 18.9 ± 0.4* |

Abbreviations: MAP, mean arterial pressure; CO, cardiac output; HR, heart rate; SVR, systemic vascular resistance; MPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure. All patients required artificial ventilation and inotropic support (n=20). Daily ultrafiltrate volume 12.6 ± 0.42 L/day; *Net* ultrafiltration was 3.2 ± 0.1 L/day. Net 24 hours fluid balance was plus 1208 ± 564 mL. Results are expressed as mean ± SEM. *: $p < 0.05$ vs pretreatment value.

**Table 2. Ultrafiltrate Clearances of Cytokines During CAVH-D**

| Variable | TNFα | IL-6 |
|---|---|---|
| Plasma concentration (pg/ml) | 153 ± 7.3 (26-475) | 796 ± 163.2 (265-2097) |
| Ultrafiltrate concentration (pg/ml) | 8.9 ± 0.8 (2.1-48) ($n$ = 17 [28%]) | 304 ± 128.6 (34-1294) ($n$ = 60 [100%]) |
| Daily UF Clearance (L/day) | 0.1 ± 0.02 | 3.9 ± 1.8 |
| Daily mass transfer UF (μg/day) | 0.03 ± 0.01 | 3.4 ± 0.3 |

Abbreviations: CAVH-D, continuous arteriovenous hemo(dia)filtration; UF, ultrafiltrate. Mean UF volume during CAVH-D was 12.6 L/day (range 7.8-14.8 L/day); mean blood flow through the filter was 92 ± 3.8 mL/min. Data expressed as mean ± SEM ($n$ = 20).

*Ultrafiltrate clearances (Table 2)*
Mean ultrafiltrate volume during CAVH-D was 12,6 L/day (range 7.8-14.8 L/day). Mean blood flow through the filter was 92 ± 3.8 mL/min. Overall, the mean plasma TNFα level upon initiation of CAVH-D was 153 ± 7.3 pg/mL. TNFα could be detected in only 17 of 60 (28%) ultrafiltrate specimens, resulting in only minimal daily mass transfer of TNFα into the ultrafiltrate (Table 2). Mean daily ultrafiltrate clearance of TNFα was 0.1 ± 0.02 L/day. No significant change in the plasma TNFα level was observed over time following the initiation of CAVH-D (pretreatment TNFα 153 ± 7.3 *vs* 24h TNFα 170 ± 41.7 pg/mL; NS). The mean IL-6 concentration upon initiation of CAVH-D was 795 ± 163.2 pg/mL. Significant amounts of IL-6 were detected in all 60 ultrafiltrate specimens with significant daily mass transfer of IL-6 into the ultrafiltrate (Table 2). Mean daily ultrafiltrate clearance was 3.9 ± 1.8 L/day. There was a significant decrease of plasma IL-6 level over time following the initiation of CAVH-D (pretreatment IL-6 level 796 ± 163.2 *vs* 24h 548 ± 82.2 pg/mL; $p < 0.05$).

*Filter duration*
No differences were found between the mean sieving coefficient of TNFα, when correlated to the age of the filter (SC 0.02 ± 0.01 [1-2h], 0.01 ± 0.01 [4-6h], 0.02 ± 0.01 [20-24h]; NS). Postfilter TNFα levels, corrected for hemoconcentration, were significantly lower with filters used for 1-2h (prefilter TNFα 152 ± 43.2 *vs* postfilter TNFα 126 ± 36.7 pg/mL; $p < 0.05$). No difference between pre- and postfilter levels of TNFα were observed with filters used for 4-6h (178 ± 47.8 *vs* 184 ± 51.2 pg/mL; NS). Significant clearance of TNFα from blood occurred with filters used for ≤ 6 h (Fig 5a). Mass transfer of TNFα from blood with filter duration ≤ 6 h was greater than that appearing in the ultrafiltrate ($J_b$ 2.7 ± 0.8 *vs* $J_{uf}$ 0.03 ± 0.01 ng/min [1-2h]; $J_b$ 0.5 ± 0.7 *vs* $J_{uf}$ 0.02 ± 0.01 ng/min [4-6h]; $p < 0.001$), suggesting that membrane adsorption occurs. However, with prolonged filter use, postfilter values were significantly higher than prefilter values (prefilter TNFα 159 ± 22.1 *vs* postfilter TNFα 233 ± 58.6 pg/mL [20-24h]; $p<0.05$). Negative mass balance (-4.3 ± 1.6 ng/min) and blood clearance of TNFα with filters used for ≥ 20 h (Fig 5a), suggest that either desorption of increased generation of TNFα occurs. No differences in the mean sieving coefficient of IL-6 were found, when correlated to filter duration (*S* 0.28 ± 0.06 [1-2h], 0.30 ± 0.08 [4-6h], 0.24 ± 0.02 [20-24h]; NS). Postfilter levels of IL-6, corrected for hemoconcentration, were lower with filters used for 1-2h (prefilter IL-6 level 733 ± 160 *vs* 628 ± 100 pg/mL; $p < 0.05$). Pre- and postfilter levels of IL-6 did not differ significantly with filters used for ≥ 4 h (699 ± 114 *vs* 692 ± 153 pg/mL [4-6h], and 665 ± 89 *vs* 735 ± 106 pg/mL [20-24h]; NS). Significant blood clearance of IL-6 occurred with filters used for ≤ 6 h, but became negative with prolonged filter use (Fig 5b). Mass transfer of IL-6 from blood did not differ significantly from that appearing in the ultrafiltrate for any given filter duration.

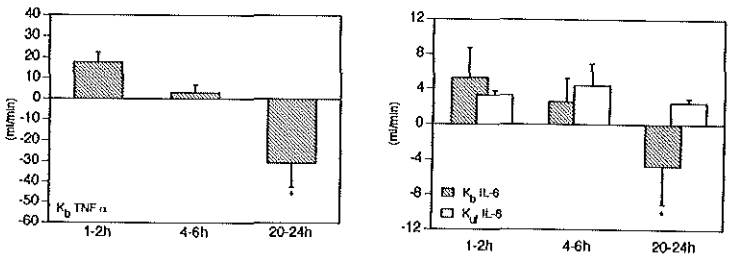


*Fig 5 a,b: Clearance of TNFα (a) and IL-6 (b) from blood ($K_b$) and ultrafiltrate ($K_{uf}$), correlated to filter duration, during continuous hemofiltration with the AN69 membrane. $K_b$ of TNFα and IL-6 declined following prolonged filter use and became negative over time. No appreciable ultrafiltration of TNFα ($K_{uf}$ < 0.2 mL/min) occurred. *: $p < 0.05$ vs 1-2h.*

## Discussion

The present study demonstrates that circulating cytokines can be removed during continuous hemofiltration. During the first period of *in vitro* hemofiltration, significant amounts of TNFα disappeared from the blood compartment with only minimal amounts detectable in the ultrafiltrate. The only plausible explanation for the observed mass balance error in the closed-loop recirculation model is that TNFα is bound to the membrane. Results also suggested that the sieving property of the monomeric form of TNFα was masked by the large capacity of the AN69 membrane to bind TNFα. When the membrane was saturated, mass transfer of TNFα into the ultrafiltrate was maximal (*i.e.*, the SC of TNFα was 1.0). These findings are in accordance with those of Leypoldt *et al.*, who found that initial sieving of model macromolecules (*i.e.*, polydisperse DEAE dextran) during hemofiltration were masked by their rapid adsorption to the AN69 membrane [15]. We also noted significant adsorption of this cytokine to the AN69 membrane *in vivo*. However, the sieving capacity of TNFα *in vivo* was low, irrespective of filter duration. Other investigators also detected no [10,16] or only small amounts of TNFα [17,18] in ultradiafiltrate samples during CHF. One explanation for the low sieving capacity of TNFα *in vivo* may be that it exists in its bioactive form as a trimer (52 kDa) [19],

thereby exceeding the molecular cut-off point of the membrane. Another explanation may be that TNFα is rapidly bound to the soluble TNF receptor (sTNFR)[20]. When plasma levels of TNFα are less than 500 pg/ml, there is a positive correlation between sTNFR and TNFα levels. However, when plasma levels of TNFα exceed 500 pg/ml, levels of sTNFR may not rise proportionally [20]. With very high TNFα levels, therefore, it may be that a greater proportion of TNFα circulates unbound, thus being potentionally removed via the ultrafiltrate. This might also explain the difference in sieving characteristics of TNFα between this and other studies (serum TNFα levels varying from 60-153 pg/ml), in which little or no sieving of TNFα was observed [10,16,18], and the study of Bellomo *et al.* (mean serum TNFα level 765 pg/ml), in which significant amounts of TNFα were detected in 69.5% of ultradiafiltrate samples during continuous venovenous hemodiafiltration (CVVHD) in septic patients [11]. In the present study, significant removal of IL-6 via the ultrafiltrate was demonstrated in all patients. In addition, serum IL-6 levels decreased over time during CAVH-D. Gueugniaud *et al.* also detected significant amounts of IL-6 in ultradiafiltrate samples of 4 severely burned patients and decreasing serum levels of this cytokine during CVVHD [16]. Our *in vitro* data suggest that significant removal of IL-1ß via the ultrafiltrate can be expected. Although we could not confirm our *in vitro* data because of lack of elevated serum IL-1ß levels in our patients, others have noted significant amounts of this cytokine in the ultradiafiltrate of septic patients [11]. However, because of its transient appearance [7,8], significant IL-1ß clearance will probably occur only when hemofiltration is instituted during the early phase of (non-)septic shock.

The binding capacity of the AN69 membrane for IL-1ß and IL-6 was significantly less compared to that for TNFα. In addition to these cytokine-dependent differences, our *in vitro* data suggest that synthetic membranes differ in adsorption capacity. This might explain why Byrick *et al.* did not find removal of TNFα from the circulation during CAVH-D without ultrafiltration with the polysulfone membrane, irrespective of filter duration, in a patient with rhabdomyolysis [10]. The affinity of synthetic membranes for cytokines may reside in their hydrofobic surfaces [21]. One important factor explaining the comparatively high adsorption capacity of the AN69 membrane may be its electrical charge. For example, the anaphylatoxins C3a (9,0 kDa) and C5a (11,2 kDa) have shown to display high affinity for the AN69 membrane, presumably because of electrostatic interactions [21].

Adsorption of cytokines as well as other proinflammatory peptides may be beneficial because of their removal from the circulation. Conversely, however, a high concentration of these proteins locally on the membrane surface may elicit an inflammatory response by stimulating adherent neutrophils and monocytes. We and others [18] observed higher postfilter TNFα values, corrected for hemoconcentration, following prolonged filter use. An increase in IL-1ß levels, although not corrected for hemoconcentration, was also observed after 4 h of CVVHD treatment in septic patients [11]. In addition, Kaplan *et al.* observed significantly higher postfilter values of another important proinflammatory peptide, *i.e.* C5a, corrected for hemoconcentration, during CAVH in ARF patients [22]. These results may be explained either by desorption of these peptides from the membrane [15] or by

increased generation. Recent data indicate that blood-membrane interaction in chronic hemodialysis patients does not directly lead to increased cytokine production, but results in priming of mononuclear cells for enhanced release of cytokines following secondary stimulation, *e.g.* LPS-fragments from contaminated dialysate [23]. Therefore, it is possible that the immunologic response to (prolonged) blood-membrane interaction during continuous hemofiltration in critically ill patients suffering from sepsis or SIRS is significantly different compared to that resulting from short-term blood-membrane interaction in uremic but otherwise healthy patients. However, despite this potentially adverse effect of prolonged blood-membrane interaction in critically ill patients, it does not seem to have any clinical significance. On the contrary, (improved) hemodynamic stability (Table 1) is uniformly found during continuous hemofiltration [1,2]. It may be that the positive effect of an unselective removal of both identified (*e.g.*, cytokines, anaphylatoxins) and as-yet-to-be-identified vasoactive mediators from the circulation outweighs the possible negative effect of prolonged blood-membrane interaction during continuous hemofiltration. This would also explain the correlation between the ultrafiltrate volume and hemodynamic changes, recovery time of diuresis and survival, which has been found by some investigators in animal and retrospective, clinical studies [1,2,24].

In conclusion, the present study suggest that cytokines can be removed from the circulation with continuous hemofiltration, either by their adsorption to the membrane (*i.e.*, TNFα) or by their convective removal (*i.e.*, IL-1ß and IL-6, unbound TNFα ?) into the ultrafiltrate. In addition to these cytokine-dependent differences, synthetic membranes seem to differ in adsorption and sieving capacities, which may be of clinical relevance. However, prolonged blood-membrane interaction seemingly affects adversely cytokine clearances, possibly by desorption and/or increased generation. If removal of cytokines is of primary concern, high ultrafiltrate volumes and frequent change of filters are needed to extract significant amounts of cytokines from the circulation. However, further research is warranted to establish whether this will have an impact on the outcome of human septic and non-septic shock. Untill such studies are performed, the rational for the use of CRRT in critically ill patients in the absence of conventional indications for dialytic support remains unproven.

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Chapter VIII

# Summary and Conclusions

Over the last decade, significant advances have been made in the techniques available for the treatment of acute renal failure (ARF) in critically ill patients on the intensive care unit (ICU). First introduced by Kramer *et al.* [1] as continuous arteriovenous hemofiltration (CAVH), there are now various forms of continuous renal replacement therapy (CRRT) which are touted as having major advantages relative to conventional dialysis treatment (*i.e.*, intermittent hemodialysis, peritoneal dialysis) [2]. However, while abundant (and often confusing) data is available upon the efficacy of CRRT, comparative data is scanty. This has led to considerable controversy as to which specific form of dialytic support should be preferred in this group of patients [3,4]. This thesis contains a series of studies examining the efficacy of CRRT as renal support for critically ill patients and its proposed superiority over intermittent hemodialysis (IHD). In addition, it was studied by which mechanisms CRRT, as opposed to IHD, could have an beneficial influence on the clinical course in these patients.

**Chapter I** gives relevant background information on the incidence and outcome of ARF, different dialytic treatment modalities and on severity-of-illness scoring systems, which use is of great importance in risk-stratification and in comparing outcome data. In addition, inflammatory mediators thought to play an important role in the development of the 'systemic inflammatory response syndrome' (SIRS) and ARF are discussed.

In **chapter II** a comprehensive review is given of the various continuous renal replacement techniques and an attempt is made to clarify the possible beneficial role of CRRT in reducing patient morbidity and mortality. Available data suggest distinct advantages of CRRT relative to conventional dialysis treatment but no clear survival advantage of patients treated with CRRT has yet been shown. In addition, no data clearly illustrate the superiority of one specific form of CRRT over the other forms. All, except CAVH, are effective in controlling biochemistry and fluid balance in hemodynamically unstable patients. Pump-driven forms have the advantages of obviating the need for arterial cannulation and its inherent complications and by providing high ultrafiltrate volumes (*i.e.*, a high convective blood purification rate) which may be of particular value. However, no survival advantage of patients treated with pump-driven forms has yet been shown.

**Chapter III** describes the use of the 'Acute Physiology And Chronic Health Evaluation' (APACHE) II scoring system on the day of ICU admission and on the day dialytic support was initiated. Using logistic regression analysis, use of the APACHE II system at the time of initiation of dialytic support (APACHE $II_2$), as opposed to the use of APACHE II at the time of ICU admission (APACHE $II_1$), proved to be a valid way to risk-stratify ARF patients by the severity of their illness and to compare outcome data. Estimating the risk of death with the APACHE II equation did not improve the usefullness of this system. However, reliability of this index of severity-of-disease was improved significantly by using the ratio between the APACHE $II_2$ and APACHE $II_1$ score. The higher the ratio, *i.e.*, the greater the change in APACHE II score, the lower was the chance of survival. This suggests that ultimate outcome is related to the degree of reversibility of physiologic derangements that led to the development of ARF. Using multivariate analysis, no impact of age,

diagnostic category, time from ICU admission to start of dialytic support, or specific form of dialytic support was observed.

In **chapter IV** the efficacy of the continuous treatment modality as employed in our hospital, *i.e.*, continuous arteriovenous hemodiafiltration (CAVHD), was examined. In addition, a detailed description of the patient population was provided, including APACHE II scoring and factors (other than uremia *per se*) influencing survival, to allow a meaningfull comparison with other reports. It was shown that the majority of patients required mechanical ventilation and/or inotropic support and suffered from multiple organ systems failure (MOSF). In this group of hemodynamically unstable patients, CAVHD proved efficient in controlling fluid balance and azotemia and in correcting acid-base and electrolyte disturbances. Despite the fact that most patients were severely ill (mean APACHE II score 26.5) and suffered from MOSF, 26 patients (43%) survived until discharge from the ICU, of whom 23 (38%) survived to leave hospital. These results compared favourably to other reports in the literature. The need for mechanical ventilation and the presence of sepsis were both associated with a poor prognosis. Another important finding was the inverse correlation of prognosis with the number of (additional) organ system failures.

In **chapter V** a direct comparison of CAVHD and IHD was made in ARF patients treated in the same ICU. A detailed description of the patient population, including the APACHE II score and relevant biochemical and hematological data, was provided. Although patients treated continuously were more severely ill as compared to patients treated with alternate-day IHD, CAVHD proved superior in controlling biochemistry and fluid balance. There was no difference in the incidence of hemorrhagic complications between groups, despite continuous anticoagulation in CAVHD treated patients. Severe hypotension and cardiac arythmias were frequent complications during IHD, which was not observed in patients treated with CAVHD. In addition, CAVHD was associated with increased nutritional intake and a shorter duration of oliguria. This latter is possibly related to the observed differences in hemodynamic stability between groups in favor of CAVHD treated patients. Despite greater illness severity in those treated with CAVHD, no significant difference in ICU outcome was observed between groups.

**Chapter VI** describes the results of a controlled animal study, in which ultrafiltrate, obtained (under sterile conditions) during hemofiltration of endotoxemic pigs, was infused into healthy pigs and their hemodynamics compared with those of pigs who were infused with ultrafiltrate from normal pigs. It was shown that infusion of ultrafiltrate from endotoxemic pigs, in contrast to ultrafiltrate from normal pigs, into healthy pigs induced pulmonary hypertension and decreased cardiac performance, suggesting that ultrafiltrate of endotoxemic pigs contains soluble, filtrable factors that are responsible for these deleterious effects. This study supports the hypothesis that convective blood purification *per se* is at least in part responsible for the observed beneficial hemodynamic effects of CRRT in some patients with MOSF.

**Chapter VII** describes the results of a study in which the impact of hemofiltration membranes on the kinetics of some key mediators of SIRS (*i.e.*, TNFα, IL-1ß, IL-6) was investigated during both *in vitro* and *in vivo* CRRT, with emphasis on the

possible mechanisms involved in mediator clearance and the effects hereon of prolonged filter use. Although significant sieving of the monomeric form of TNFα (16,5 kDa) was observed *in vitro* with the AN69 membrane, no appreciable sieving occurred *in vivo* with this membrane. This may be explained either by the fact that TNFα circulates in its bio-active form as a trimer (52 kDa) or that circulating TNFα is rapidly bound to soluble TNF receptors, in both ways thereby exceeding the molecular cut-off point of the membrane. However, significant adsorption of TNFα onto the membrane surface was noted. In contrast to TNFα and despite its higher molecular weight (22 kDa), appreciable ultrafiltrate clearance of IL-6 was observed during both *in vitro* and *in vivo* CRRT with the AN69 membrane. Significant ultrafiltrate clearance of IL-1ß occurred with different synthetic membranes during *in vitro* CRRT. However, IL-1ß was not detectable in any patient, thereby precluding calculation of *in vivo* clearance rates of this cytokine. Of importance, prolonged blood-membrane interaction seemingly affected adversely cytokine clearances, possibly by desorption or increased generation. Results suggested that if removal of cytokines is of primary concern, high ultrafiltrate volumes and frequent change of filters are needed to extract significant amounts of cytokines from the circulation. In addition, synthetic membranes seem to differ in adsorption and sieving capacities, which may be of clinical relevance.

From these studies it can be concluded that final proof that CRRT improves outcome in ARF on the ICU has still to be provided. It may be that renal failure as such does not contribute sufficiently important to death in MOSF for there to be a demonstrable difference in outcome between patients treated with CRRT and conventional dialysis treatment. However, ease of implementation, the facility of full nutritional support, superior metabolic control, improved hemodynamic stability and perhaps a shorter duration of oliguria afforded by CRRT, would appear to justify its use as the treatment of choice in the ICU setting. Although no particular form of CRRT has yet been shown to be superior in terms of survival, experimental and clinical data suggest that a high convective blood purification rate (*i.e.*, a high ultrafiltrate volume) may be of value, not only by providing efficient renal support, but also by counter-acting the exaggerated inflammatory response in patients with SIRS by the removal of mediators with vasoactive and cardiodepressant properties into the ultrafiltrate. If this were to be true, than the early initiation of pump-driven CRRT in critically ill patients with SIRS (*i.e.*, before the occurence of ARF) might have a (more) beneficial effect on the clinical course, thereby perhaps preventing ARF/MOSF. However, one must recognize that CRRT is an invasive procedure with substantial risks (*e.g.*, due to continuous anticoagulation, prolonged vascular access, errors in fluid balance), which requires continuous vigilence. In addition, recent data indicate that pump-driven CRRT may induce platelet dysfunction, thereby aggrevating coagulopathy [5]. Future research should focus on the impact of the early initiation of CRRT, independent of the presence of ARF, on the clinical course of patients with SIRS and on the importance of using high ultrafiltrate volumes. In addition, more research is warranted to identify the charactistics of mediators, and their clearance (either by convection or adsorption) in relation to observed clinical

effects of CRRT to substantiate a possible 'cause-and-effect' relationship.

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Chapter IX

# Samenvatting en Conclusies

Gedurende de laatste 10 jaar zijn er belangrijke vorderingen gemaakt in de beschikbare nierfunctievervangende technieken voor de behandeling van acute nierinsufficiëntie op de intensive care. Sinds de introductie van de eerste continue techniek door Kramer en anderen [1] als continue arterioveneuze hemofiltratie (CAVH), zijn hiervan verschillende modificaties ontwikkeld die belangrijke voordelen zouden bieden ten opzichte van conventionele dialyse (intermitterende hemodialyse, peritoneaal dialyse)[2]. Hoewel nu vele, soms verwarrende, gegevens voorhanden zijn over de efficiëntie van continue nierfunctievervangende technieken zijn er nauwelijks vergelijkende data beschikbaar, hetgeen heeft geleid tot een belangrijke controverse omtrent welke therapie de voorkeur zou moeten krijgen [3,4]. Dit proefschrift omvat verschillende studies waarin de efficiëntie van continue nierfunctievervangende technieken en de vermeende superioriteit ten opzichte van conventionele dialyse werden onderzocht. Daarnaast werd onderzocht door welke mechanismen deze continue nierfunctievervangende technieken, in tegenstelling tot intermitterende hemodialyse (IHD), een gunstige invloed zouden kunnen hebben op het klinisch beloop bij kritisch zieke patiënten.

In **hoofdstuk I** werd relevante achtergrond informatie gegeven omtrent de incidentie en uiteindelijke uitkomst van acute nierinsufficiëntie, de verschillende beschikbare nierfunctievervangende technieken en scoringssystemen om adeqaat de ernst van de ziekte uit te kunnen drukken. Dit laatste is van groot belang voor risico-stratificatie en om het zinvol te kunnen vergelijken van mortaliteitscijfers. Tevens werd beschreven welke ontstekingsmediatoren een rol spelen bij de gegeneraliseerde onstekingsreactie en acute nierinsufficiëntie, welke gezien worden bij patiënten met shock als gevolg van bijvoorbeeld trauma, pancreatitis en sepsis.

In **hoofdstuk II** werd een uitgebreid overzicht gegeven van de literatuur over de verschillende continue nierfunctievervangende technieken en werd op grond van de beschikbare gegevens geanalyseerd op welke manier deze technieken mogelijk een gunstige invloed zouden kunnen hebben op de morbiditeit en mortaliteit van patiënten met acute nierinsufficiëntie op de intensive care. Hoewel hieruit blijkt dat continue technieken belangrijke voordelen bieden ten opzichte van conventionele dialyse, is (nog) niet duidelijk aangetoond dat dit leidt tot een verbetering van de overleving. Ook is nog niet duidelijk welke specifieke continue techniek de voorkeur zou moeten verdienen. Allen, behalve CAVH, zijn effectief in termen van metabole controle en regulering van de vloeistofbalans in hemodynamisch instabiele patiënten. Pompgedreven vormen hebben het voordeel dat geen arteriële canulatie nodig is en dat hoge ultrafiltraat volumina (= hoge convectieve bloedzuiveringssnelheid) bereikt kunnen worden. Dit laatste is mogelijk van specifiek belang.

In **hoofdstuk III** werd het gebruik van het 'Acute Physiology And Chronic Health Evaluation' (APACHE) II scoringssysteem zowel op de dag van opname op de intensive care, als op de dag dat nierfunctievervangende therapie werd gestart, geanalyseerd. Logistische regressie analyse liet zien dat het gebruik van het APACHE II systeem op de dag dat nierfunctievervangende therapie werd gestart (APACHE $II_2$), in tegenstelling tot het gebruik van dit systeem op de dag van opname op de intensive care (APACHE $II_1$), valide was om patiënten te stratificeren naar de ernst van hun ziekte en om overlevingscijfers te vergelijken. Gebruik van de 'APACHE II

vergelijking' om het risico (%) om te overlijden te voorspellen leidde niet tot een verbetering van het scoringssysteem. De betrouwbaarheid van het scoringssysteem nam echter significant toe wanneer gebruik gemaakt werd van de ratio tussen de APACHE $II_2$ en APACHE $II_1$. Hoe hoger de ratio, ofwel hoe groter de verandering in APACHE score, hoe kleiner de kans op overleving. Dit suggereert dat de uiteindelijke overleving bepaald wordt door de reversibiliteit van de fysiologische ontregeling welke heeft geleid tot het ontstaan van acute nierinsufficiëntie. Multivariaat analyse liet geen invloed zien van leeftijd, diagnostische categorie, tijdsinterval tussen opname op de intensive care en start van nierfunctievervangende therapie of specifieke nierfunctievervangende therapie op de overleving.

In **hoofdstuk IV** werd de efficientie van de continue nierfunctievervangende techniek zoals die wordt toegepast in het 'Dijkzigt' ziekenhuis, continue arterioveneuze hemodiafiltratie (CAVHD), onderzocht. Tevens werd de patiëntenpopulatie nauwkeurig beschreven in termen van de ernst van hun ziekte, waaronder de APACHE II score en factoren (anders dan het nierfalen per sé) welke een invloed op de overleving hadden, om een zinvolle vergelijking met andere studies mogelijk te maken. Het bleek dat de meerderheid van patiënten werd beademd en inotrope ondersteuning nodig hadden; de meesten hiervan leden aan het 'multipel orgaanfalen syndroom'(MOF). In deze groep van hemodynamisch instabiele patiënten bleek CAVHD een effectieve methode voor het reguleren van de vloeistof balans en uremie en voor het corrigeren van electroliet alswel zuur-base evenwichts verstoringen. Ondanks het feit dat de meeste patiënten kritisch ziek waren (gemiddelde APACHE II score 26.5) en leden aan MOF, konden 26 patiënten (43%) de intensive care verlaten, waarvan 23 patiënten (38%) uiteindelijk uit het ziekenhuis konden worden ontslagen. Deze getallen zijn relatief gunstig in vergelijking met andere mortaliteitsstudies in de literatuur. Noodzaak tot mechanische beademing en de aanwezigheid van sepsis waren beiden geassocieerd met een slechte prognose. Een andere belangrijke bevinding was de correlatie tussen het aantal uitgevallen orgaansystemen en overleving.

In **hoofdstuk V** werd een vergelijkende studie beschreven tussen intensive care patiënten met acute nierinsufficiëntie welke werden behandeld met CAVHD of IHD. Beide patiëntengroepen werden gedetaileerd beschreven, waaronder de APACHE II score en relevante biochemische en hematologische data, om een zinvolle vergelijking mogelijk te maken. Hoewel patiënten welke continue behandeld werden veel zieker waren dan die welke werden behandeld met IHD bleek CAVHD superieur in het reguleren van het 'milieu-interieur' en de vloeistofbalans. Ondanks continue antistolling in patiënten welke werden behandeld met CAVHD was er geen verschil in de incidentie van ernstige bloedingscomplicaties. Ernstige hypotensie en cardiale aritmieën waren frequent optredende complicaties tijdens IHD, hetgeen niet werd gezien tijdens behandeling met CAVHD. Patiënten welke werden behandeld met CAVHD hadden bovendien een hogere voedingsintake en een kortere oligurische periode. Dit laatste lijkt samen te hangen met de verbeterde hemodynamische stabiliteit van patiënten welke worden behandeld met CAVHD in vergelijking tot met IHD behandelde patiënten. Ondanks het feit dat de met CAVHD behandelde patiënten veel zieker waren was er geen significant verschil in overleving tussen beide groepen.

In **hoofdstuk VI** werden de resultaten beschreven van een gecontroleerde studie waarin ultrafiltraat, verkregen (onder steriele omstandigheden) tijdens hemofiltratie van endotoxemische varkens, werd geinfundeerd in gezonde varkens en hun hemodynamiek vergeleken met die van varkens welke waren geinfundeerd met ultrafiltraat van gezonde varkens. In tegenstelling tot ultrafiltraat van gezonde varkens, leidde infusie van ultrafiltraat van endotoxemische varkens tot pulmonale hypertensie en verminderde cardiale prestatie, hetgeen suggereert dat dit ultrafiltraat oplosbare, filtreerbare factoren bevat welke verantwoordelijk waren voor de waargenomen negatieve hemodynamische effecten. Deze studie steunt de hypothese dat convectieve bloedzuivering *per sé* in ieder geval voor een deel verantwoordelijk is voor de soms waargenomen gunstige effecten van continue technieken op het klinisch beloop bij patienten met MOF.

**Hoofdstuk VII** beschrijft de resultaten van een studie waarin de impact van hemofilters op de kinetiek van enkele mediatoren welke een belangrijke rol spelen bij het ontstaan van de systemische ontstekingsreactie en MOF (TNFα, IL-1ß, IL-6) werd onderzocht tijdens zowel *in vitro* als *in vivo* hemofiltratie, met de nadruk op het klaringsmechanisme en op het effect van langdurig filtergebruik hierop. Hoewel tijdens *in vitro* hemofiltratie met de AN69 membraan een redelijke convectieve klaring van de monomere vorm van TNFα (16.5 kDa) werd gezien, werd tijdens *in vivo* hemofiltratie met ditzelfde membraan geen convectief transport van TNFα gevonden. Dit kan mogelijk worden verklaard door het feit dat de bio-actieve vorm van TNFα circuleert als een trimeer (52 kDa) of dat circulerend TNFα snel word gebonden aan oplosbare TNF receptoren, waardoor in beide gevallen het moleculaire cut-off punt van de membraan word overschreden. Er werd echter wel significante adsorptie van TNFα aan het membraanoppervlak waargenomen. In tegenstelling tot TNFα en ondanks het hogere molecuulgewicht (22 kDa), werd een redelijke convectieve klaring van IL-6 waargenomen tijdens zowel *in vitro* als *in vivo* hemofiltratie met de AN69 membraan. Tijdens *in vitro* hemofiltratie met verschillende synthetische membranen werd significant convectief transport gevonden van IL-1ß. Bij geen enkele patiënt werd echter een detecteerbare IL-ß concentratie gevonden zodat geen *in vivo* klaringen konden worden berekend. Van belang was de observatie dat langere bloed-membraan interactie een schijnbaar negatief effect had op de klaringskarakteristieken, waarschijnlijk door desorptie en/of (grotere) generatie van deze cytokinen. Deze gegevens suggereren dat wanneer de verwijdering van circulerende cytokinen (en mogelijk ook andere mediatoren) van primair belang is, grote ultrafiltraat volumina en frequente filter wisseling noodzakelijk zijn om significante hoeveelheden circulerende cytokines te kunnen verwijderen. De verschillen in adsorptie en convectie eigenschappen van synthetische membranen zijn hierbij mogelijk van klinisch belang.

Vanuit bovenstaande studies kan geconcludeerd worden dat het definitieve bewijs dat continue nierfunctievervangende technieken de overleving van patiënten met acute nierinsufficiëntie op de intensive care verbetert nog steeds moet worden geleverd. Het is mogelijk dat acute nierinsufficiëntie op zich te weinig bijdraagt aan de uiteindelijke prognose van patiënten met MOF om een verschil in overleving tussen patiënten

welke worden behandeld met continue technieken en IHD te kunnen aantonen. De duidelijke voordelen van continue nierfunctievervangende technieken ten opzichte van conventionele dialyse, zoals superieure metabole controle, verbeterde hemodynamische stabiliteit, het mogelijk maken van adequate (par)enterale voeding, het relatieve gemak waarmee de techniek kan worden geimplementeerd en mogelijk de kortere oligurische periode rechtvaardigen het gebruik van deze technieken als de therapie van keuze voor acuut nierfalen op de intensive care. Hoewel nog niet is aangetoond dat een specifieke vorm van continue nierfunctievervangende techniek superieur is in termen van overleving, suggereren zowel experimentele als klinische gegevens dat een hoge convectieve bloedzuiveringssnelheid (ofwel een groot ultrafiltraatvolume), naast het garanderen van efficiënte nierfunctievervanging, ook van specifieke waarde is door het onderdrukken van de gegeneraliseerde ontstekingsreactie in patiënten met shock (t.g.v. trauma, sepsis, pancreatitis) door verwijdering van circulerende mediatoren met vasoactieve en cardiodepressieve eigenschappen. Indien dit het geval zou zijn, betekent dit dat het vroegtijdig, m.a.w. vóór het onstaan van acute nierinsufficiëntie, initiëren van pompgedreven continue nierfunctievervangende therapie een (meer) geprononceerde invloed op het klinische beloop kan hebben, waardoor het onstaan van acuut nierfalen/MOF mogelijk wordt voorkomen. Men moet zich echter realiseren dat deze techniek een invasieve procedure is met potentiëel belangrijke complicaties (bijv. als gevolg van continue antistolling, langdurige canulatie grote vaten, fouten in vloeistof balans), hetgeen continue surveillance vereist. Bovendien werd recentelijk aangetoond dat deze pompgedreven techniek plaatjes dysfunctie kan induceren waardoor bestaande coagulopathie kan worden verergerd [5]. Toekomstig onderzoek moet worden gericht op de impact van het vroegtijdig initiëren van continue nierfunctievervangende therapie op het klinisch beloop van kritisch zieke patiënten met een gegeneraliseerde ontstekingsreactie (bijv. ten gevolge van trauma, sepsis) en op de rol van het ultrafiltraat volume hierbij. Bovendien is meer onderzoek nodig om de eigenschappen te identificeren van oplosbare mediatoren en hun klaring (door convectie en/of adsorptie aan het filtermembraan) in relatie tot waargenomen klinische effecten van continue technieken om een 'oorzaak en gevolg'- relatie te kunnen onderbouwen.

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# Curriculum Vitae

The author was born on the 16th of March 1958 in Oisterwijk. From 1970 he received secondary education at the Jacob Roeland Lyceum in Boxtel, where he graduated ('Atheneum ß') in 1977. It was not untill 1980 that he was able to commence studies in medicine at the University of Utrecht, from which he graduated in may 1987. After having worked as a resident (AGNIO) at the departments of internal medicine of the 'Medisch Centrum Alkmaar' and the St. Clara Hospital in Rotterdam (july, 1987 - may, 1988), he was formally trained in internal medicine at the departments of internal medicine of the St. Clara Hospital (Dr. J. Bruins Slot) and the University Hospital 'Dijkzigt' (Prof. Dr. M.A.D.H. Schalekamp) in Rotterdam, respectively. In 1993 he was recorded in the register of recognized specialists of the Netherlands Medical Association for the specialism of Internal Medicine. After having received special training in the field of nephrology at the department of internal medicine I, division of nephrology, University Hospital 'Dijkzigt' (Prof. Dr. W. Weimar), he was entered in february 1994 in the register of the Dutch Internists Association for the area of specialisation of Nephrology. From may 1994 he is working at the department of internal medicine of the Drechtsteden Hospital in Dordrecht.