CONTINUOUS ARTERIOVENOUS HEMODIAFILTRATION

CONTINUOUS ARTERIOVENOUS HEMODIAFILTRATION

continue arterioveneuze hemodiafiltratie

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

Ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de Rector Magnificus Prof. Dr. C.J. Rijnvos
en volgens het besluit van het College van Dekanen.

De openbare verdediging zal plaatsvinden
op woensdag 19 mei 1993 om 15.45 uur

door

MARGREET CORNELIA VOS

geboren te Bergen op Zoom

PROMOTIECOMMISSIE

Promotor:	Prof.Dr. M.A.D.H. Schalekamp
Overige leden:	Dr.Ir. W.A. van Duyl
	Prof.Dr. W. Weimar
	Dr. R. Krediet
Deskundige:	Dr. H.H. Vincent

Things just happen in the right way, at the right time. At least they do when you let them, when you work with circumstances instead of saying, "This isn't supposed to be happening this way," and trying hard to make it happen some other way. [...]

Later on, you can look back and say, "Oh, now I understand [...]". Then you realize that even if you'd tried to make it all turn out perfectly, you couldn't have done better, and if you'd really tried, you would have made a mess of the whole thing.

(Benjamin Hoff,
The Tao of Pooh)

This study was financially supported by the Dutch Kidney Foundation (Grants nr C88.821 and C89.0873), Hospal, MSD, Glaxo and Bayer.
The printing of this thesis was financed by Roussel, which is gratefully acknowledged.

Cover: D.J. Vos

Uitgeverij Eburon
Postbus 2867
2611 CW Delft
The Netherlands

ISBN 90-5166-324-2

CONTENTS

ABBREVIATIONS

α	volume fraction of proteins	[L/g]
ω	blood channel width	[cm]
μ	viscosity	[mmHg · min]
A1	integration constant	[]
A2	a constant	[]
C_d	solute concentration in dialysate	[mmol/L]
C_f	solute concentration in ultrafiltrate	[mmol/L]
C_m	solute concentration in membrane	[mmol/L]
C_p	solute concentration in plasma	[mmol/L]
C_{prot}	plasma protein concentration	[mmol/L]
COP	colloid osmotic pressure	[mmHg]
b	blood channel half-height	[]
Cl	clearance rate	[ml/min]
Cl_{cavh}	clearance rate by CAVH	[ml/min]
Cl_{cavhd}	clearance rate by CAVHD	[ml/min]
C_p	plasma protein concentration	[g/dl]
C_{p0}	initial plasma concentration	[mmol/L]
C_{prot-a}	plasma protein concentration at filter inlet	[g/dl]
C_{pt}	plasma concentration after a time span t	[mmol/L]
C_{prot-v}	plasma protein concentration at filter outlet	[g/dl]
C_w	solute concentration in plasma water	[mmol/L]
f	fractional volume distribution of solute in blood cells	[]
F	free fraction of a drug	[]
h	height of the fluid column in the UF-line	[cm]
Ht	hematocrit	[]
π_i	at filter inlet	[]

J_s	solute flux	[µm/min]
J_v	volume flux	[µm/min]
K_d	mass transfer coefficient of diffusion	[µm/min]
K_{dc}	mass transfer coefficient of diffusion of creatinine	[µm/min]
K_{dp}	mass transfer coefficient of diffusion of phosphate	[µm/min]
K_{du}	mass transfer coefficient of diffusion of urea	[µm/min]
K_{dmax}	maximal Kd at infinite dialysate flow rate	[µm/min]
L	fiber length	[cm]
L_p	hydraulic membrane permeability	[cm/min · mmHg]
MAP	mean arterial pressure	[mmHg]
MI	hydraulic permeability index of the membrane, or filter membrane index	[ml/h · mmHg]
MW	molecular weight	[Daltons]
Mw	total solute mass in plasma water	[mmol]
N	number of fibers or blood channels of the filter	[]
n	K_d/J_v	[]
^-_o	at filter outlet	[]
P_b	hydraulic pressure in blood compartment	[mmHg]
P_d	hydraulic pressure in dialysate compartment	[mmHg]
P_{ia}	hydraulic pressure in the artery	[mmHg]
P_{iv}	hydraulic pressure in the vein	[mmHg]
P_a	hydraulic pressure in the arterial line	[mmHg]
P_v	hydraulic pressure in the venous line	[mmHg]
Q_b	blood flow rate	[ml/min]
Q_f	ultrafiltration flow rate	[ml/min]
Q_d	dialysate flow rate	[ml/min]
Q_w	plasma water flow rate	[ml/min]
Q_{pa}	arterial plasma flow rate	[ml/min]

Q_{pred}	predilution flow rate	[ml/min]
r	radius of the fiber of the filter	[μm]
R	total resistance to diffusion	[min/μm]
R_{aa}	resistances to flow of the arterial access	[mmHg · min/ml]
R_b	resistance to diffusion in blood compartment	[min/μm]
R_d	resistance to diffusion in dialysate compartment	[min/μm]
R_f	resistance to blood flow of the filter	[mmHg · min/ml]
R_{fn}	Rf corrected for blood viscosity (R_f/μ)	[10^5/ml]
R_m	resistance to diffusion in membrane	[min/μm]
R_{va}	resistances to flow of venous access	[mmHg · min/ml]
s	sieving coefficient	[]
S	membrane surface area	[m^2]
t	time	[hr]
TMP	transmembrane pressure	[mmHg]
$T_{½}ß$	drug half life	[hrs]
V_z	volume of distribution	[L/kg]
w	width (S/L)	[m]

CHAPTER 1

INTRODUCTION

THE DEVELOPMENT OF BLOOD PURIFICATION TECHNIQUES

History

The history of blood purification started with the judgement of different body fluids by color and consistency. Blood letting, as popularized by Hippocrates (460-377 B.C.), was one of the most common therapeutic tools in antique medicine. History tells us that too much blood letting was weakening the Spartan army and may very well have contributed to its defeat by the Athenians. In the 17th and 18th century, blood purification was achieved by adequate purgation every week, application of a strong emetic once a month, and blood letting twice a year, in spring and fall. In 1854, Graham demonstrated that a vegetable parchment, sealed with albumin, acted as a semipermeable membrane. When he placed a fluid, containing crystalloids and colloids, on one side of this membrane, he found that only cristalloids diffused through the membrane. He named this phenomenon dialysis [1].

In 1911, Haas in Giessen, Germany, who was confronted with numerous cases of 'field nephritis', first tried to perform dialysis of the blood in uremic patients. In 1913, Abel reported the first successful dialysis on a live animal. In 1924, Haas performed a 15 minute dialysis in a uremic patient, by using a celloidin membrane. Two further developments were very important for the development of dialysis, i.e. the discovery of heparin in 1918 and the manufacturing of cellophane membranes in the 1930's, which were used as package material for sausages. Using this material, Kolff, in 1943, treated his first patient in Kampen, the Netherlands, with his rotating drum dialyzer. Blood access was obtained by arteriotomies and venesections, which limited the number of dialysis treatments in one patient. His 17th patient was the first that survived. This patient was the first human being whose life was saved by dialysis [2].

During World War II, the hundreds of patients with renal failure from crush injuries instigated further developments. Alwall, in Sweden, stressed the importance of fluid overload. He devised a 'dialyzer-ultrafilter' in order to perform ultrafiltration. In 1947, Malinow, in the USA, in an experimental study of dogs, produced ultrafiltrate from blood and replaced it with Ringers solution [3], thereby cleaning the blood. This was the first description of hemofiltration. In 1948, Kolff was invited to New York to continue his work in the United States in cooperation with Merrill. By

1952, Merrill reported that about 45 rotating drum dialyzers were in use in the United States, mostly for the treatment of acute renal failure. A few years later, the Baxter company started the commercial manufacturing of dialysis equipment. In 1960, Quinton and Scribner described a method for the chronic cannulation of blood vessels by the use of a teflon tubing by-pass of the artery and vein [1]. Both these developments made an enormous contribution to the spreading of the dialysis technique.

Mechanisms of solute transport and terminology

Nowadays, hemodialysis and hemofiltration are commonly used blood purification techniques. With both techniques, blood is led through a flat sheet or a capillary dialyzer. The dialyzer consists of a blood and an ultrafiltrate/dialysate compartment, separated by a membrane. The membrane is permeable to solutes of up to several thousand Daltons, depending on the membrane pore size, but not to proteins and blood cells. By virtue of the difference in hydrostatic pressure on both sides of the membrane, plasma water leaks through the membrane (*ultrafiltration*) (see Figure 1). If solutes have a molecular weight far below the 'cut-off' point of the membrane, they can pass the membrane together with the plasma water, so their concentration in the ultrafiltrate will be equal to that in plasma water. This transport is called *convection*. Therefore, for these solutes, the convective transport rate is determined by the rate of ultrafiltration alone. Ultrafiltration does not affect the concentration of the solute in plasma water. Only if the ultrafiltration fluid is replaced with a clean substitution fluid, the solute concentration in the plasma water falls. This technique is called *hemofiltration* (see Figure 2) and is performed either intermittent or continuous. Another way to clean the blood is by running a clean fluid through the dialysate compartment so as to cause *diffusion* of solutes from plasma water to the dialysate compartment. This technique is called *hemodialysis* (see Figure 3). The diffusive transport rate is largely determined by the molecular size. Thus, the transport of small molecules is favored by hemodialysis whereas that of large molecules is favored by hemofiltration. With intermittent hemodialysis, it is now common practice to use a high dialysate flow rate (500 ml/min) and it is possible to realize a fixed ultrafiltration flow rate, adjusted to the patient' overweight. Therefore, a relatively small convective transport occurs too, which can largely be neglected when compared to the large diffusive transport. The combination of hemodialysis and hemofiltration, in which both modalities function as major transport mechanisms, is called *hemodiafiltration* (see Figure 4), also performed either in the intermittent or continuous mode.

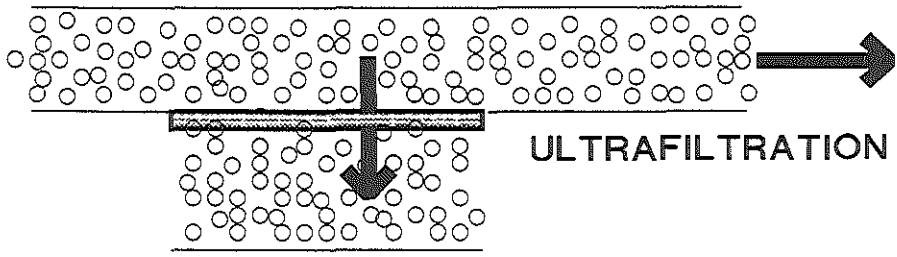

Figure 1. A schematic drawing of ultrafiltration. No clearance of solutes passing the membranes will occur as solute concentration in plasma water does not decrease. This method is used to withdraw an excess of body fluid.

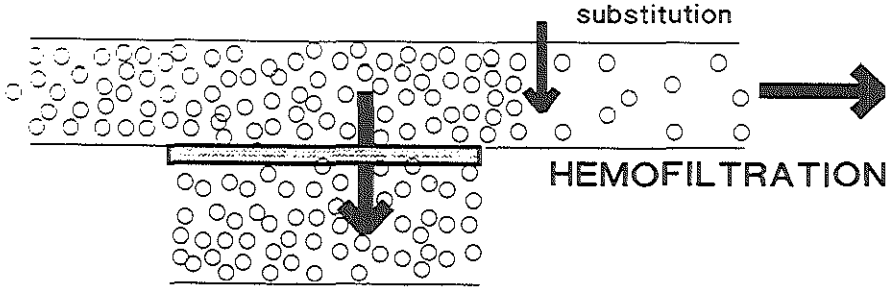

Figure 2. A schematic drawing of hemofiltration. Solutes drawn here, have a molecular weight far below the cut-off point of the membrane. Therefore, solute concentration in the ultrafiltrate compartment will be the same as that in plasma water. Transport of solutes is by convection. Substitution fluid is used to decrease the solute concentration in blood and to impede too much fluid withdrawal.

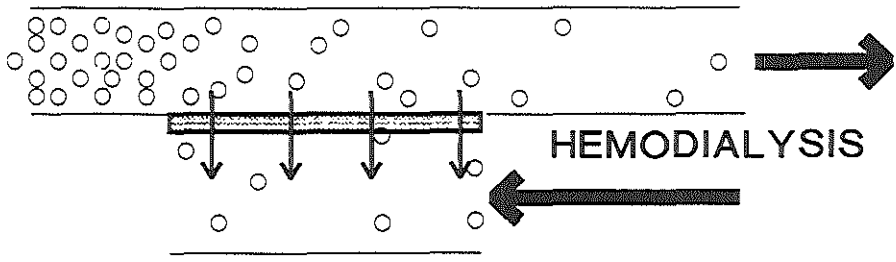

Figure 3. A schematic drawing of hemodialysis. Dialysate flows countercurrently through the dialysate compartment, which causes a solute concentration difference over the membrane. Transport is by diffusion.

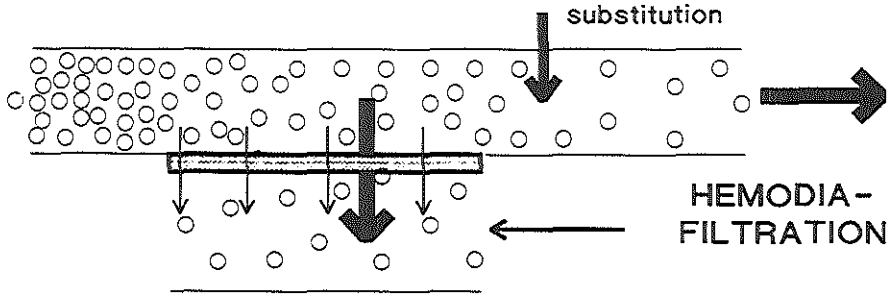

*Figure 4. A schematic drawing of hemodiafiltration. Both by convection, by a high ultrafiltration flow rate, and by diffusion, by using dialysate, solutes are removed from blood. Both convection and diffusion contribute significantly to solute transport.**

* Figures 1-4 reprinted with permission from NTVG 1992, 136: 561-565 (see list of publications nr. 8)

Further refinement of the blood purification techniques

In the early years of dialysis, patients were treated for 8 to 12 hours, two to three times a week. Understandably, the developments in those days were aimed at improving the efficiency of the treatment so as to reduce treatment time. Accordingly, dialysis membranes became thinner and larger and blood and dialysate flow rates were increased. In 1964, however, the drawback of this development became clear when Peterson described acute encephalopathy during dialysis treatment. This was explained by the rapid fall in the concentration of solutes in plasma due to diffusion, leading to an osmotic 'disequilibrium' between plasma water and the brain tissue [4]. Dialysis induced hypotension was another frequent complication. In 1967, Henderson promoted hemofiltration [5]. With hemofiltration the efficiency of the removal of urea was lower but disequilibrium was seldom seen and blood pressure was more stable. Moreover, as Babb [6] pointed out, so called 'middle molecules', which were believed to contribute to the uremic syndrome, were removed more efficiently with this technique. This middle molecule hypothesis also led to the development of peritoneal dialysis techniques.

For hemofiltration, new membranes were developed, which allowed passage of water and solutes of up to several thousand Daltons at very low pressures. At the same time, hemodialysis was refined by controlled ultrafiltration, by the use of bicarbonate rather than acetate as a buffer substitute and by the use of high or variable sodium concentrations in dialysate. By virtue of these developments, most patients with chronic renal failure can now adequately be treated by intermittent hemodialysis in two or three sessions of 4 to 5 hours a week. In case of acute renal failure, however, many problems remained to be solved.

Continuous arteriovenous hemodiafiltration

Acute renal failure often results from sepsis, a clinical syndrome that is accompanied also by massive edema and circulatory insufficiency, respiratory failure and sometimes neurological damage [7, 8]. Patients with acute renal failure are characterized by a high catabolic rate and therefore need intensive dialysis treatment. The combination of low or unstable blood pressure and edema makes it quite difficult to judge how much fluid should be withdrawn. The combination of ultrafiltration and hemodialysis frequently leads to hypotension and neurological deterioration and may further jeopardize kidney function [9]. Furthermore, rapid

correction of the acidosis together with the rise of inflammatory mediators that results from the blood-membrane interaction may aggravate respiratory failure [10-15]. Consequently, in many patients with acute renal failure, 'conventional' hemodialysis is contraindicated. Therefore, this group of patients demands a different approach [16]. The prerequisites that must be met by the treatment can be summarized as follows:

1. It must be possible to start treatment at any time;
2. It must be a very gradual treatment, so as to avoid sudden disturbances in the delicate equilibrium and fluid status of the patient;
3. It must be very efficient in order to treat the uremic syndrome.

In 1977 Kramer published a method to treat massive overhydration. He used a small dialyzer and connected it to catheters in the femoral artery and vein to obtain a spontaneous blood flow driven by the blood pressure of the patient [17]. No substitution fluid was given. This technique is now known as *slow continuous ultrafiltration* (SCUF). Later, in order to control the rate of fluid loss, the technique was modified by the addition of fluid substitution [18]. In this way, the blood is also cleaned. This treatment is called *continuous arteriovenous hemofiltration* (CAVH). When small highly permeable dialyzers became generally available, an increasing number of doctors relied on CAVH for the treatment of critically ill patients with acute renal failure. In spite of very low blood pressures, the gradual fluid withdrawal was very well tolerated by these patients [19]. As far as the treatment of uremia was concerned, the treatment proved to have its limitations. For these highly catabolic patients, the rate of ultrafiltration was seldom enough to provide adequate clearance of uremic solutes. Indeed, it was common practice for patients on CAVH to have intermittent machine dialysis treatment as well. Several adaptations of the technique were suggested. Some advocated the application of a suction pump to the ultrafiltrate compartment to increase the ultrafiltration rate [20] while others relied on pumped venovenous hemofiltration [21]. Kaplan demonstrated the enhancement of the efficiency of CAVH by infusing the substitution fluid in the arterial line (predilution), rather than in the venous line (postdilution) [22]. Ronco suggested additional dialysis with the same dialyzer. He first used a dialysate flow rate of 20 L/hr for 2 hrs a day [23] and reasoned that, at a high dialysate pressure, no ultrafiltration would take place. The method was, of course, soon abandoned because of the considerable risk of 'backfiltration'. At the same time Geronemus suggested continuous hemodialysis rather than hemofiltration. At a dialysate flow rate of 1-2 L/hr adequate clearance of urea was easily obtained. Unfortunately, with the dialyzer he used (a low hydraulic permeability of the membrane) the ultrafiltration flow rate was very low [24]. Later he suggested

the use of highly permeable membranes [25]. In 1987, Vincent and van Geelen presented their first experience in the University Hospital in Rotterdam with *continuous arteriovenous hemodiafiltration* (CAVHD) [26, 27]. They stressed the importance of both convection and diffusion [27]. This remarkably simple method, which does not require complicated equipment or specially trained personnel, proved both safe and very effective. It was soon to become the first choice treatment of acute renal failure in the intensive care setting [27-30].

Clinical examples

The following case histories give a picture of the clinical setting in which CAVHD treatment is used and show the impact of CAVHD on the treatment of the patient.

Case 1:
The patient is a 67 year old man, who had undergone an aneurysmectomy of the thoracic aorta. The operative procedure had been technically difficult and had lasted for 8 hours. During the operation the blood pressure had been very low. In the immediate postoperative period, he required ventilatory support and despite inotropic treatment his blood pressure remained unstable. Urine output decreased to zero. On the third postoperative day, the plasma level of urea was 56 mmol/L, that of creatinine was 760 µmol/L, and that of potassium was 6.2 mmol/L. There was severe peripheral edema and the patient was judged to be overhydrated. The mean arterial pressure was 60 mmHg. Treatment of the acute renal failure was needed. Because of his circulatory instability the patient was considered to be a poor candidate for intermittent hemodialysis and he was treated with CAVHD. Catheters were introduced into the femoral artery and vein. Treatment was started at a dialysate flow rate of 2 L/hr (1 L/hr is recommended in the standard protocol), because of hyperkalemia. On the first day, a negative fluid balance of 1.5 liter was obtained. Urea levels decreased to 38 mmol/L, creatinine to 450 µmol/L and potassium to 4.1 mmol/L. Dialysate flow rate could be adjusted to 1 L/hr. The following days, urea levels stabilized at 20 mmol/L, creatinine at 210 µmol/L and potassium levels were maintained at 4-5 mmol/L. The mean arterial pressure increases to 70 mmHg and less vasopressor support was needed. After two weeks the patient could be weaned from the ventilator. Finally, on the 16th day of treatment, the filter was disconnected because renal function had recovered. The patient could then be mobilized. He was eventually dismissed from the hospital after five weeks.

Case 2:
This patient was a 59 year old man, who was admitted to the intensive care unit, because of respiratory failure and progressive loss of consciousness. A sepsis syndrome was diagnosed but the cause was unknown. Blood pressure was 100/50. Ventilator support was needed. The hemodynamic and respiratory conditions deteriorated rapidly and his condition was further complicated by acute oliguric renal failure. The patient was treated with tobramycin and cefotaxime and large amounts of intravenous fluid were administered to maintain adequate blood pressure levels and the patients developed massive edema. At the second day, CAVHD treatment was started. Catheters were introduced in the femoral vessels. Dialysate flow rate was 1 L/hr. A net zero fluid balance was aimed for. The dose of tobramycin was increased to accommodate for the clearance by the dialyzer. To eliminate a possible source of infection, the femoral catheters were replaced after a week. The condition of the patient did not improve. Because the arterial oxygen pressure remained low, possibly due to pulmonary edema it was decided to withdraw as much as fluid as possible. A total of 21 liters were withdrawn over three days. The arterial oxygen pressure rose. CAVHD treatment was continued with an average fluid withdrawal of 1-2 liters per day for 25 days. Overall, the dialyzer was replaced 4 times. Then the patient began to pass urine, his renal function recovered. CAVHD treatment was stopped. Ventilatory support was still needed. Three days later, symptoms of sepsis reappeared. There were signs of pulmonary infection and Pseudomonas aeruginosa was isolated from blood cultures. Despite all possible medical support the infection could not be eradicated and on the 29th day of his illness the patient died.

AIMS OF THE STUDY

As demonstrated by the above examples, in CAVHD blood access is usually obtained through femoral catheters, the blood flow rate is not routinely measured and the dialysate flow rate is arbitrarily set to 1 to 2 L/hr. In this way, the treatment proved generally effective. However, sometimes problems were encountered. In some patients frequent clotting of dialyzers occurred, probably because blood flow rate was too low. Sometimes plasma urea levels did not come down as quickly as we had expected or levels of phosphate were found to become too low. There was virtually no insight in the determinants of transport rates and the dialysate flow rate that is necessary. It was not known to what extent CAVHD treatment had influence on the disappearance rate of drugs. Therefore, in 1989 a study was begun of the

determinants of blood flow rate, ultrafiltration and solute transport rate in CAVHD, so as to be able to optimize CAVHD treatment. The aims of this study can be summarized as follows:

1. Analysis of the determinants of blood flow rate.
   The resistance to flow rate of catheters and dialyzers was studied and the influence of blood viscosity was analyzed. A method was investigated for the determination of blood flow rate by using a probe outside the blood line.
2. Analysis of the determinants of ultrafiltration and convective transport rate.
   The transmembrane pressure difference and the hydraulic permeability of dialyzers were determined as well as the change in hydraulic permeability over time. Furthermore, the 'sieving coefficients' were determined for a number of clinically relevant solutes.
3. Analysis of the determinants of the diffusive transport rate.
   A mathematical model of combined convection and diffusion was developed and used to determine the diffusive mass transfer coefficient of a number of solutes as a function of solute characteristics and operational conditions.
4. Application of the new knowledge in mathematical models in order to predict blood flow, ultrafiltration and solute clearance rates.
5. Development of guidelines for the performance of CAVHD therapy with respect to equipment, operational conditions and adjustment of drug dosage and additional therapy.
6. Description of the outcome of patients with acute renal failure, treated with CAVHD.

REFERENCES

1. Drukker WA. Haemodialysis, a historical review. In: Replacement of renal function by dialysis. Sec ed. 1986 Martinus Nijhoff Publishers Dordrecht. Ed. Drukker WA. Chapter 2, page 3-52.
2. Klinkmann H. Historical overview of renal failure therapy- A homage to Nils Alwall. Contrib Nephrol 1990; 78: 1-23.
3. Malinow MR, Korzon W. An experimental method for obtaining an ultrafiltrate of the blood. J of Lab Clin Med 1947; 32: 461-471.
4. Peterson HdeC, Swanson AG. Acute encephalopathy occurring during hemodialysis. Archives in internal Medicine 1964; 113:877-880.
5. Henderson LW, Besarab A, Michaels, Bluemle LW. Blood purification by ultrafiltration and fluid replacement (diafiltration). Trans Am Soc Artif Intern Organs 1967; 13: 216-226.
6. Babb AL, Popovich RP, Cristopher TG, Scribner BH. The genesis of the square meter-hour hypothesis. Trans Am Soc Artif Intern Organs 1971; 17: 81.
7. Steinhausen M, Parekh N. Principles of acute renal failure. Proceedings of 9th international congress of nephrology. Ed. Robinson RR. Springer Verlag New York 1984 page 702-710.
8. Cameron JS. Acute renal failure in the intensive care unit today. Intensive Care Medicine 1986; 12: 64-70.
9. Myers BD, Moran SM. Mechanism of disease. Hemodynamically mediated acute renal failure. New England Journal of Medicine 1986; 314: 97-105.
10. Sherman RA. The pathophysiologic basis for hemodialysis-related hypotension. Seminars in dialysis 1988; 1: 136-142.
11. Port FK, Johnson WJ, Klass DW. Prevention of dialysis disequilibrium syndrome by using of high sodium concentration in the dialysate. Kidney International 1973; 3: 327-333.
12. Keshaviah P, Shapiro FL, A critical examination of dialysis-induced hypotension. Am J Kidney Dis 1982; 2: 58.
13. Henderson LW. Symptomatic hypotension during hemodialysis. Kidney International 1980; 17: 571-576.
14. Henrich WL, Woodard TD, Blachley JD, Gomez-Sanchez C, Pettinger W, Cronin RE. Role of plasma osmolality in blood pressure stability after dialysis and ultrafiltration. Kidney International 1980; 18: 480-488
15. de Broe MA, Heyrman RM, De Backer WA, Verpooten GA, Vermeire PA. Pathogenesis of dialysis-induced hypoxemia: A short overview. Kidney Int 1988; 33 (supp 24): S 57-61.

16. Lauer A, Saccagi A, Ronco C, Belledonne M, Glabman S, Bosch J. Continuous arteriovenous hemofiltration in the critically ill patient. Annals of internal medicine 1983; 99: 455-460.
17. Kramer P, Wigger W, Rieger J, Matthaei D, Scheler F. Arteriovenous haemofiltration: A new and simple method for treatment of over-hydrated patients resistant to diuretics. Klin Wschr 1977; 55: 1121-1122.
18. Kramer P, Seegers A, De Vivie D, Trautmann M, Scheler F. Therapeutic potential of hemofiltration. Clinical Nephrology 1979; 11: 145-149.
19. Kaplan AA, Longnecker RE, Folkert VW. Continuous arteriovenous hemofiltration. A report of six months' experience. Annals of Internal Medicine 1984; 100: 358-367.
20. Kaplan AA, Longnecker RE, Folkert VW. Suction-assisted continuous arteriovenous hemofiltration. Trans Am Soc Artif Intern Organs 1983; 29: 408-413.
21. Wendon J, Smithies M, Sheppard M, Bullen K, Tinker J, Bihari D. Continuous high volume veno-venous haemofiltration in acute renal failure. Intensive Care Med 1989; 15; 358-363.
22. Kaplan AA. Predilution versus postdilution for continuous arteriovenous hemofiltration. Trans Am Soc Artif Intern Organs 1985; 31: 28-32.
23. Ronco C, Brendolan A, Braganti L, Chiaramonte S, Fabris A, Ferriani M, Dell'Aquila R, Milan M, La Greca G. Arteriovenous hemodiafiltration associated with continuous arteriovenous hemofiltration: A combined therapy for acute renal failure in the hypercatabolic patient. Blood Purification 1987: 5: 33-40.
24. Geronemus R, Schneider N. Continuous arteriovenous hemodialysis: A new modality for treatment of acute renal failure. Trans Am Soc Artif Intern Organs 1984; 30: 610-613.
25. Geronemus R, Schneider N. Further studies with continuous arteriovenous hemodialysis (CAVHD) in acute renal failure (ARF). Abstract Trans Am Soc Artif Intern Organs 1985; 14: 54.
26. Vincent HH, van Geelen JA. Continuous arteriovenous hemofiltration (CAVH) and hemodiafiltration (CAVHD) in the critically ill. Experience with the AN-69 plate filter. Int Symposium on Acute Renal Replacement Therapy, Boca Raton, Florida, March 1987 (Abstract).
27. van Geelen JA, Vincent HH, Schalekamp MADH. Continuous arteriovenous haemofiltration and haemodiafiltration in acute renal failure. Nephrol Dial transplant 1988; 2: 181-186.

28. Raja R, Kramer M, Goldstein S, Caruana R, Lerner A. Comparison of continuous arteriovenous hemofiltration and continuous arteriovenous dialysis in critically ill patients. Trans Am Soc Artif Intern Organs 1986; 32: 435-436.
29. Stevens PE, Riley B, Davies SP, Gower PE, Brown EA, Kox W. Continuous arteriovenous haemodialysis in critically ill patients. The Lancet 1988; 16: 150-152.
30. Golper TA. Continuous arteriovenous hemofiltration in acute renal failure. Am J Kidney Dis 1985; 6: 373-386.

CHAPTER 2

PROBLEMS ASSOCIATED WITH INTERMITTENT HEMODIALYSIS IN ACUTE RENAL FAILURE

The term *acute renal failure* is used to indicate the total loss of kidney function within hours or days. This is usually caused by acute tubular necrosis, which is in fact a misnomer, resulting from ischemic or toxic damage to the tubular cells. It is encountered after a period of shock, often associated with sepsis, after aortic surgery and after rhabdomyolysis, administration of large doses of X-ray contrast material or nephrotoxic antibiotics. Sometimes, acute renal failure is caused by immune complex mediated glomerulonephritis, resulting from an infection with Staphylococcus or Streptococcus species. Most patients in whom acute renal failure occurs are critically ill and their condition is frequently complicated by multiple organ failure with hemodynamic, respiratory or neurological instability. Acute renal failure is a potentially reversible condition. After acute tubular necrosis, if the patient's general condition improves, recovery of kidney function may be expected after a period of two to six weeks [1].

In acute renal failure patients, intermittent machine hemodialysis is relatively contraindicated because of the clinical instability of the patient. In this chapter a short overview is given of clinical problems encountered with intermittent hemodialysis, with emphasis on the possible consequences for critically ill patients.

Intermittent hemodialysis is a form of renal replacement therapy, that was further developed for the treatment of patients with chronic renal failure. Patients are now dialyzed 2 or 3 times a week, for 3 to 6 hours per session. In these few hours, clearance rates have to be very high to tide over the interdialytic time interval. The high clearance rates are obtained by using a large membrane surface area, a blood flow rate of 200 to 300 ml/min and a dialysate flow rate of 500 ml/min. During dialysis, fluid is withdrawn to an amount adjusted to the interdialytic weight-gain of the patient. Dialysis treatment is supplemented by dietary treatment, which at least implies restriction of protein and fluid intake. Thus, every means is used to enable the removal of uremic solutes and water as fast as possible in the shortest possible time. However, there is another side of the coin.

Over-efficient dialysis is fraught with clinical complications. The most frequent complication is dialysis-induced hypotension [2]. It is known from clinical studies that rapid fluid removal during dialysis often leads to arterial hypotension. In the

early years of hemodialysis, this was attributed to hypovolemia caused by a fluid removal rate that exceeds the rate of fluid mobilization from the interstitial space [3]. However, in 1978, Bergström et al showed that rapid fluid removal was better tolerated if performed without simultaneous dialysis [4]. Also, during simultaneous hemodialysis and hemofiltration, removal of water was easier to perform than during hemodialysis alone [5, 6]. Furthermore, it was demonstrated that even with isovolemic hemodialysis a reduction in blood pressure could be observed [7]. This suggested that solute transport during dialysis interferes with blood pressure control and therefore contributes to the side effects of the dialysis treatment. Although this phenomenon is still not fully explained, a number of explanations have been put forward. It has been stated that the rapid fall in plasma osmolality causes a fluid shift from the extracellular compartment into the intracellular compartment, the so called disequilibrium syndrome [4, 8, 9]. This internal fluid shift together with external fluid removal by ultrafiltration results in a decreased intravascular volume and hypotension [10]. Another possible explanation of hypotension during hemodialysis is an altered response of the autonomic nervous system [11, 12], either because of autonomic neuropathy or because of the fall in plasma osmolality. Schultze et al [13] have demonstrated that when using a dialysate containing a sodium concentration of 126 mmol/L, mean arterial blood pressure dropped 30 mmHg and plasma levels of PGE_2, $PGF_{2\alpha}$ and plasma renin activity rose significantly in comparison with a dialysate containing 140 mmol/L. By using the latter dialysate, blood pressure drop was only 13 mmHg [13]. Also, the blood-membrane interaction leads to complement activation, which, probably through the production of arachidonic acid metabolites, causes vasodilatation [13, 14-16]. In general, the risk of dialysis-induced hypotension poses no severe restrictions to the treatment of patients with chronic renal failure. In hemodynamically unstable patients, however, the risk of hypotension with intermittent hemodialysis is often unacceptable. Even with a relatively slow dialysis, at a blood flow rate of 180 ml/min, recirculating dialysate and an ultrafiltration rate of only 200-300 ml/hr, hypotension frequently occurs in these patients [17].

Another side effect of hemodialysis is hypoxemia. This can be explained by several causes. First, in the case of acetate-buffered dialysate, CO_2 loss into the dialysate and a decreased respiratory quotient that results from acetate metabolism will lead to both an insufficient respiratory drive and hypoventilation [18, 19]. Second, hypoventilation may also occur with bicarbonate-buffered dialysate, because of a rapid increase in blood pH [18]. Third, membrane bio-incompatibility gives rise to the secretion of inflammatory mediators that may lead to pulmonary vasoconstriction [16, 20-22]. By using bicarbonate-containing dialysate and more biocompatible membranes (AN-69,

polysulfone) rather than cuprophane, these ventilatory problems may largely be prevented [20, 22].

Hemodialysis may cause neurological deterioration. Patients may become unconscious as a result of uremic encephalopathy itself. Also, the uremic state predisposes to the development of seizures [23]. Hemodialysis may, paradoxically, impair the neurological condition as a result of sudden changes in pH and osmolality. Kennedy et al and La Greca et al have shown that during hemodialysis urea levels in cerebrospinal fluid decreased more slowly than plasma levels [24, 25]. Arieff et al have shown that in uremic dogs rapid dialysis causes brain edema and seizures. Slow dialysis, although resulting in a similar reduction in urea concentration, was not associated with brain edema. The brain edema was caused by a fluid shift resulting from an osmotic disequilibrium between plasma and cerebrospinal fluid. Interestingly, it could be shown that the change in osmolality did not result from changes in urea concentration alone. The authors suggested that another, as yet undefined, osmotically active solute ('idiogenic osmoles') is present in the brain, creating an osmotic gradient between brain tissue and plasma [26]. In a clinical study Port et al demonstrated that the first dialysis treatment caused disturbances in the electroencephalogram in virtually all patients and subjective symptoms of disequilibrium in most of them. They compared two group of patients, one with a normal dialysate sodium concentration and one in which dialysate sodium concentration had been increased in order to prevent the fall in plasma osmolality. They found that by this intervention, neurological problems could be prevented [27]. Davenport et al showed that, in case of hepatic encephalopathy, cerebral perfusion pressure fell during intermittent hemofiltration treatment but not during continuous arteriovenous hemofiltration (CAVH) [28]. These are indications that, in order to prevent neurological complications of dialysis, one should aim for slower solute transport rates. Therefore, in patients with neurological problems, continuous treatment methods are preferable.

In conclusion, rapid removal of solutes and fluids in intermittent hemodialysis has some disadvantages. In general, these problems do not impede the treatment of chronic renal failure patients. With acute renal failure patients, however, we are faced with hemodynamic, neurologic and/or respiratory instability, which is inherent to the cause of the renal failure. These problems call for a more restrained approach, i.e. by continuous methods, such as continuous arteriovenous hemofiltration (CAVH), continuous arteriovenous hemodiafiltration (CAVHD) or continuous peritoneal dialysis (CPD). With these methods, solute clearance rate is low, which prevent osmotic disequilibrium and fluid removal occurs more gradually.

REFERENCES

1. Vincent HH, Vos MC The use of continuous arteriovenous hemodiafiltration in multiple organ failure patients Applied Cardiopulmonary Pathophysiology 1991; 4: 109-116.
2. Rosa AA, Fryd DS, Kjellstrand CM. Dialysis symptoms and stabilization in long-term dialysis. Arch Int Med 1980; 140: 804-807.
3. Maher JF, Schreiner GE. Hazards and complications of dialysis. The New England Journal of Medicine 1965; 12: 370-377.
4. Bergström J. Ultrafiltration without dialysis fir removal of fluid and solutes in uremia. Clinical Nephrology 1978; 4: 156-164.
5. Leber HW, Wizemann V, Goubeaud G, Rawer P, Schutterle G. Hemodiafiltration: A new alternative to hemofiltration and conventional hemodialysis. Artificial Organs 1987; 2: 150-153.
6. Leber HW, Wizemann V, Goubeaud G, Rawer P, Schutterle G. Simultaneous hemofiltration/hemodialysis an effective alternative to hemofiltration and conventional hemodialysis in the treatment of uremic patients. Clinical Nephrology 1978; 9: 115-121.
7. Wehle B, Asaba H, Castenfors J, Fürst P, Gunnarsson B, Shaldon S, Bergström J. Hemodynamic changes during sequential ultrafiltration and dialysis. Kidney International 1979; 15: 411-418.
8. Henrich WL, Woodard TD, Blachley JD, Gomez-Sanchez C, Pettinger W, Cronin RE. Role of plasma osmolality in blood pressure stability after dialysis and ultrafiltration. Kidney International 1980; 18: 480-488.
9. Sherman RA. The pathophysiologic basis for hemodialysis-related hypotension. Seminars in dialysis 1988; 1: 136-142.
10. van Stone, Bauer J, Carey J. The effect of dialysate sodium concentration on body fluid distribution during hemodialysis. Trans Am Soc Artif Intern Organs 1980; 26: 383-386.
11. Baldamus CA, Ernst W, Koch KM. Sympathetic and hemodynamic response to volume removal during different forms of renal replacement therapy. Nephron 1982; 31: 324-332.
12. Maeda K, Fujita Y, Shinzato T, Morita H, Kobayakawa H, Takai I. Mechanism of dialysis-induced hypotension. Trans Am Soc Artif Intern Organs 1989; 35: 245-247.
13. Schultze G, Maiga M, Neumayer HH, Wagner K, Keller F, Molzahn M, Nigam S. Prostaglandin E_2 promotes hypotension on low-sodium hemodialysis. Nephron 1984; 37: 250-256.

14. Shaldon S, Deschodt G, Branger B, Granolleras C, Baldamus CA, Koch KM, Lysaght MJ, Dinarello CA. Haemodialysis hypotension: The interleukin hypothesis restated. Proceedings EDTA-ERA 1985; 22: 229-243.
15. Basile C, Drüecke T. Dialysis membrane biocompatibility. Nephron 1989; 52: 113-118.
16. Hakim RM, Breilatt J, Lazarus M, Port F. Complement activation and hypersensitivity reactions to dialysis membranes. N Engl J Med 1984; 311: 878-882.
17. van Geelen JA, Woittiez AJJ, Schalekamp MADH. Bicarbonate versus acetate hemodialysis in ventilated patients. Clin Nephrol 1987; 28: 130-133.
18. De Broe MA, Heyrman RM, De Backer WA, Verpooten GA, Vermeire PA. Pathogenesis of dialysis-induced hypoxemia: A short overview. Kidney Int 1988; 33 (supp 24): S 57-61.
19. Blanchet F, Kanfer A, Cramer E. Benyahia A, Georges R, Mery JP, Amiel C. Relative contribution of intrinsic lung dysfunction and hypoventilation to hypoxemia during hemodialysis. Kidney Int 1984; 26: 430-435.
20. Kolb G, Fischer W, Schoenemann H, Bathke K, Hoeffken H, Mueller T, Lange H, Joseph K, Havemann K. Effects of cuprophan, hemophan, and polysulfone membranes on the oxidative metabolism, degranulation reaction enzyme release and pulmonary sequestration of granulocytes. Contrib Nephrol (Basel) 1989; 74: 10-21.
21. Henderson LW, Chenoweth D. Biocompatibility of artificial organs: an overview. Blood Purif 1987; 5: 100-111.
22. De Backer WA, Verpooten GA, Borgonjon DJ, Vermeire PJ, Lins RR, De Broe ME. Hypoxemia during hemodialysis: effects of different membranes and dialysate compositions. Kidney Int 1983; 23: 738-743.
23. Tyler H. Neurologic disorders in renal failure. American Journal of medicine. 1968; 44: 734-748.
24. Kennedy AC, Linton AL, Eaton JC. Urea levels in cerebrospinal fluid after haemodialysis. The Lancet 1962; 24: 410-411.
25. La Greca G, Biasioli S, Borin D, Brendolam A, Chiaramonte S, Fabris A, Feriani M, Ronco C. Dialytic encephalopathy. Contrib. Nephrol. 1985; 45: 9-28.
26. Arieff AI, Massry SG, Barrientos A, Kleeman CR. Brain water and electrolyte metabolism in uremia: Effects of slow and rapid dialysis. Kidney International 1973; 4: 177-187.

27. Port FK, Johnson WJ, Klass DW. Prevention of dialysis disequilibrium syndrome by use of high sodium concentration in the dialysate. Kidney International 1973; 3: 327-333.
28. Davenport A, Will EJ, Davison AM. Early changes in intracranial pressure during haemofiltration treatment in patients with grade 4 hepatic encephalopathy and acute oliguric renal failure. Nephrol Dial Transplant 1990; 5: 192-198.

CHAPTER 3

THE CLINICAL PRACTICE OF CONTINUOUS ARTERIOVENOUS HEMODIAFILTRATION

INDICATIONS FOR CAVHD

In Chapter two the possible problems with intermittent hemodialysis in acute renal failure were discussed. It was concluded that problems encountered with intermittent dialysis treatment of patients with acute renal failure and hemodynamic, neurologic and/or respiratory instability call for less vigorous, continuous methods of dialysis. Examples of these methods are continuous arteriovenous hemofiltration (CAVH), continuous arteriovenous hemodiafiltration (CAVHD) and continuous peritoneal dialysis (CPD). Treatment by CPD will not be discussed in this thesis. As treatment with CAVHD provides higher clearance rates than with CAVH, optimal treatment is by using CAVHD. In the University Hospital Rotterdam, indications for CAVHD are cases of renal failure, complicated by circulatory, respiratory or neurological instability, and cases of renal failure for which daily dialysis treatment would be needed. In general, patients treated by CAVHD are patients who have had major surgery or patients with sepsis and multiple organ failure, including renal failure.

The combination of renal failure and circulatory instability is the single most important reason for treatment with CAVHD. The combination of low or unstable blood pressure and edema makes it quite difficult to judge how much fluid can be withdrawn safely. In cases of compromised myocardial function, vascular refilling rate during ultrafiltration is very slow. If such patients were to be treated with intermittent hemodialysis, this would lead to osmotic disequilibrium with further impairment of vascular refilling. With CAVHD, the low clearance rates prevent the occurrence of osmotic disequilibrium [1] and fluid removal occurs more gradually. Indeed several studies have shown improved vascular stability during treatment with CAVHD [2-6].

Respiratory failure or threatening respiratory failure due to fluid overload alone are not necessarily indications to use continuous instead of intermittent techniques. These patients are best treated with intermittent ultrafiltration. However, if a patient with renal failure is weaned from the ventilator with difficulty, CAVHD is preferably to intermittent hemodialysis. The latter may lead to a diminished respiratory drive and pulmonary vasoconstriction. This phenomenon is attributed to bio-incompatibility of the membrane [7, 8]. In CAVHD only the more bio-compatible synthetic membranes are used. Moreover, with the longer duration of use, protein adsorption to the membrane minimizes any bioincompatibility effects [9-11].

Neurological instability is another indication for CAVHD. Neurological disturbances during intermittent hemodialysis arise from an osmotic disequilibrium between blood and cerebrospinal fluid [12-14]. Again, with CAVHD, the lower solute clearance rates prevent osmotic disequilibrium. This has been borne out by the study of Davenport et al, who showed that in patients with hepatic encephalopathy cerebral perfusion pressure fell after intermittent hemofiltration but was preserved during treatment with CAVH [15].

The indications for continuous treatment mentioned thus far stem from a contraindication to intermittent treatment. Another reason to choose continuous rather than intermittent treatments is the need for daily dialysis treatment. Acute renal failure patients, especially those with sepsis, are in a hypermetabolic state with fever, increased cardiac output and increased resting energy expenditure [16]. Therefore, there is an increased demand for both energy and proteins. It has been shown that a positive cumulative caloric balance is associated with improved overall survival [16-18]. In order to achieve a positive caloric balance, patients often receive total parenteral nutrition, which may be complicated by very high rates of urea production and fluid overload. Until recently, this necessitated daily hemodialysis and ultrafiltration. Today these problems are easily managed by CAVHD [19-22]. Indeed, Bartlett et al have demonstrated that patients with multiple organ failure who were treated by CAVH showed a more positive energy balance and higher survival rates than patients, who were treated by intermittent methods [23]. Compared to intermittent hemodialysis, the *rate* of uremic solute removal is lower in CAVHD, but at usual dialysate flow rates the *total* removal per day is similar. Furthermore, intermittent therapies carry the risk of fluid overload in the period between successive treatments. This risk is avoided by CAVHD. It must be realized that with both treatment modalities amino acids are removed to a certain extent [24-28] but the rate of removal is small when compared to the rate of administration. Another example of a situation, which used to be managed by daily intense dialysis treatment, is kidney transplantation in a patient with primary hyperoxaluria. In these patients plasma oxalate levels should be kept below 20 µmol/L [29] until the graft functions well. This is virtually impossible with intermittent treatment. However, with CAVHD, at a dialysate flow rate of approximately 4-5 L/hr, a constant plasma oxalate clearance rate of 40-50 ml/min can be achieved, which suffices to control hyperoxalemia.

Logistic indications for treatment with CAVHD are especially justified if frequent dialysis treatment would interfere with other aspects of patient care and if the arterial blood access poses no particular problem. Frequent and prolonged investigations or operations can proceed without disconnecting the filter.

It has been hypothesized that continuous techniques can effectively remove inflammatory mediators associated with sepsis, the adult respiratory distress syndrome (ARDS) and multiple organ failure [30, 31]. This prompted Cosentino et al to study the effect of CAVH in patients with ARDS, who had no renal failure. In this study, a beneficial effect on the course of ARDS could not be demonstrated [32]. It is likely, however, that, for most peptides, endogenous clearance rates are much faster than their removal by CAVH or CAVHD. Therefore, current research still focuses on the precise pathophysiological mechanisms involved in the multiple organ failure syndrome. The trend is to look for ways to more selectively remove or neutralize the key pathogenetic factors by affinity columns or specific antibodies or drugs.

CONTRAINDICATIONS FOR CAVHD

If a patient has a vascular prothesis of the femoral artery located less than 20 cm above the groin, the use of the femoral artery can be hazardous. Sometimes, due to extensive arteriosclerosis, cannulation of the femoral artery is impossible. In such cases, the axillary or brachial artery or, if blood pressure is high enough, a Scribner shunt may be used as an alternative vascular access. If none of these possibilities remains, then the use of pumped veno-venous hemodiafiltration should be considered. The main disadvantage of the pumped technique is that more specialized personnel are needed to watch this system. Moreover, if the pump is equipped with all the necessary alarms and safeguards, this implies that the pump can be interrupted which may lead to clotting of the system.

In our view, CAVHD (or CVVHD) is contraindicated only if the extracorporeal circuit interferes with the mobilization of the patient. Thus, when a patient who has been treated with CAVHD, recovers, we tend to continue the treatment by intermittent hemodialysis.

EQUIPMENT AND INSTRUCTIONS FOR USE

A list of the necessary equipment for CAVHD is given below:

1. Catheters for arterial and venous access (and the disposables used for their introduction).
2. Small surface high-flux dialyzer.
3. Arterial/venous blood tubing set with at least an entrance port in the arterial blood line for heparin administration and preferably an additional arterial and/or venous port for administration of substitution fluid.

4. Ultrafiltration line.
5. Graduated ultrafiltration collection bag or urometer.
6. Heparin pump.
7. Substitution pump, which can deliver up to 1000 ml/hr and infusion line.
8. Dialysate pump, which can deliver up to approximately 5 L/hr, and corresponding infusion line.
9. Weighing device.
10. Dialysate heater.
11. Heparin, substitution fluid and dialysate fluid.
12. Two liters of rinsing fluid: NaCl 0.9%, containing heparin 5000 U/L.

Priming and installation

The purpose of priming a hemofilter is to eliminate air and, with some hemofilters, glycerine, which is used to prevent dehydration of the membrane.

To prime the system, attach the blood lines and the ultrafiltrate line to the hemofilter. The ultrafiltrate outlet should be situated on the arterial site of the hemofilter to achieve a countercurrently dialysate flow. Place the hemofilter in a holder in the upright position, with the venous port at the top. Connect the proximal end of the arterial line to the rinsing fluid bag and the distal end of the venous line to an empty sterile bag. Clamp the ultrafiltrate line and run 1 to 1½ liter of rinsing fluid through the blood lines and filter under gravity forces. Make sure that side ports have been rinsed as well and that all air has been eliminated. Then unclamp the ultrafiltrate line and clamp the venous line. Run ½ liter of rinsing fluid through the system. In this way, forced ultrafiltration will occur and glycerine will be rinsed out of the pores of the membrane. Finally unclamp the venous line and rinse the rest of the fluid through the system.

After priming, the pumps, heater, urimeter, heparin, substitution fluid and dialysate fluid are connected to the system and the hemofilter, filled with rinsing fluid, is connected to the catheters. Figure 1 shows a schematic drawing of the hemofilter and the requirements. It is customary to position the filter with the ultrafiltrate/dialysate outlet up (not shown in the Figure), in order to ensure that any air in the dialysate compartment leaves the compartment immediately. The ultrafiltrate/dialysate container is positioned below the level of the filter in order to create a negative pressure in the dialysate compartment and thereby enhance the rate of ultrafiltration. There must be no direct contact between the sterile dialysate exit port and the container in which ultrafiltrate and dialysate are collected. The filter is

left in place as long as it functions well. If the ultrafiltration rate falls below 200 ml/hr, and kinking of the catheters or blood lines has been excluded, the filter is replaced. When the patient must be transported, it is easiest to temporarily disconnect the dialysate infusion line and fix the filter onto the patient's leg.

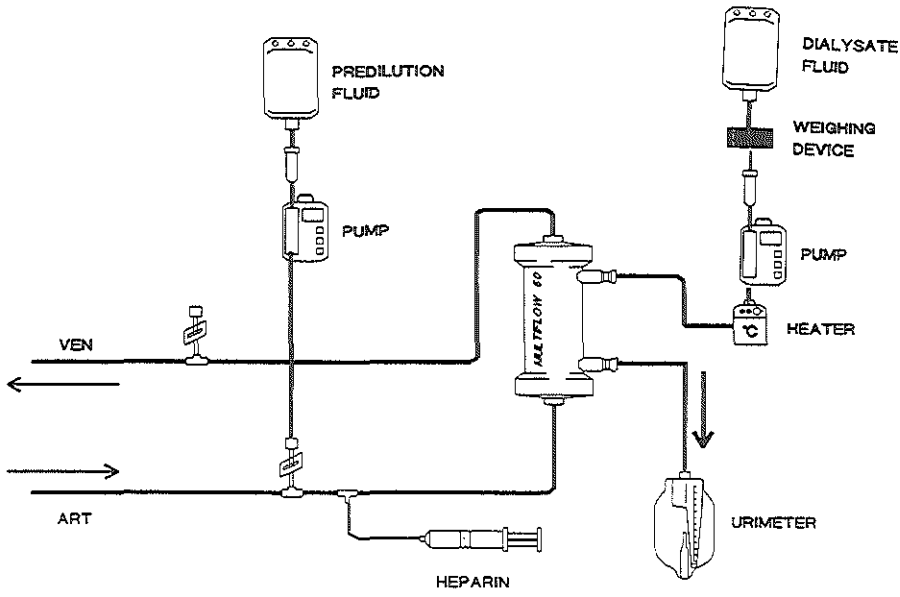

Figure 1. Schematic drawing of CAVHD system

Blood Access

In CAVHD, blood flows spontaneously. Low blood flow rates may lead to excessive hemoconcentration and to early clotting of the filter. Therefore, high blood flow rates are desirable. Blood flow rate (Q_b, [ml/min]) is a function of arterial and venous blood pressure and the total extracorporeal system resistance to flow:

$$Q_b = \frac{(P_{ia} - P_{iv})}{R_{aa} + R_f + R_{va}} \qquad (1)$$

where P_{ia} and P_{iv} [mmHg] are the pressures in the femoral artery and vein respectively and where R_f, R_{aa}, and R_{va} [mmHg · min/ml] are the resistances to flow of the filter, the arterial access and the venous access. Usually, the arterial and

venous access constitute approximately one half of the total resistance to blood flow. For straight catheters and for capillary hemofilters the resistance to flow is determined largely by the internal radius of the lumen as given by Poiseuille's law:

$$R_f = \frac{8 \cdot L \cdot \mu}{N \cdot \pi \cdot r^4} \qquad (2)$$

Here L is the length, N is the number of the capillaries, r is the radius of the catheter or capillary, and μ is the viscosity of the medium [mmHg · min].

The best results have been obtained with special short wide bore CAVH-catheters. Our experience is with L=11.4 cm catheters (M8CAVH4, Medcomp) with an internal diameter of 2.7 mm. With these catheters the average resistance to blood flow is 0.10 mmHg · min · ml^{-1} per catheter. Limited experience with 15 cm 'Shaldon catheters' (MCY306PS, Medcomp) with an internal diameter of 2.3 mm (8F) indicates an average resistance to flow of 0.16 mmHg · min · ml^{-1}. With Scribner shunts, the average resistance to flow was 0.36 mmHg · min · ml^{-1}, i.e. 3 to 4 times higher than with CAVH-catheters (see Chapter 4). It should be noted that the contribution to the total resistance to flow of the tubings from the catheters to the hemofilter need not be considered. With 180 cm of tubing with an internal diameter of 4.36 mm, it can be calculated that the resistance to flow exerted by the tubing alone is 0.07 mmHg · min · ml^{-1}. Shortening of the tubing will have a negligible influence on the overall resistance to flow of the extracorporeal circuit. With CAVH-catheters, blood flow rates are typically in the range of 100 to 250 ml/min. Ideally, blood flow rate should be measured continuously. It is now technically feasible to measure blood flow rate by means of echo transit time measurement, using a flow probe around the blood line [33]. As an alternative, blood flow rate may be determined by injecting a 0.3 ml air bubble into the blood line and measuring the transit time of the air bubble over a known distance of the blood line [34, 35]. Calculation of blood flow from arterial and venous hematocrit and ultrafiltration rate is unreliable.

CAVH-catheters are best placed in the femoral artery and vein. These vessels are usually wide enough to accommodate the catheters and the introduction procedure is simple. If the femoral vessels cannot be used, one may consider using the axillary or brachial artery and the jugular or subclavian vein for access. Scribner shunts may be placed in the lower leg or in the forearm.

Reported complications of arterial cannulation include dissection, thrombosis, false aneurysm formation, fistula formation, infection, and superficial or retroperitoneal bleeding. Although this sounds alarming, Kramer et al have demonstrated that these complications were considerably reduced once specially

designed short catheters were used exclusively [36]. In recent series, with the use of special CAVH-catheters, the incidence of damage to the femoral artery was reported to be 2% [37-39]. Furthermore, in a retrospective analysis, Swann et al found no evidence for either sepsis or increased morbidity related to catheter infections [40].

The hemofilter

For CAVHD one needs a small surface highly permeable hemofilter with a low resistance to blood flow. Using a high surface hemofilter is not desirable. First, because it leads to an excessive ultrafiltrate production and thereby necessitates substitution infusion rates that are above the range of the intravenous infusion pumps that are generally available. Second, because a larger membrane surface area implies more extensive contact between blood and membrane material and, hence, a greater risk of clotting. High flux characteristics usually coincide with good biocompatibility [41]. For optimal function, a high diffusive permeability is also required. Protein adsorption to the membrane causes a decrease of membrane permeability over time. In view of the long duration of use, obviously, protein adsorption is undesirable. The typical hemofilter used for CAVH or CAVHD has short capillaries with a diameter of between 200 and 280 μm and a membrane surface area of between 0.2 and 0.6 m^2.

Knowledge of the resistance to flow is important, as in CAVH(D) blood flow is spontaneous generated by the pressure difference between the arterial and venous access. Especially because it is no common practice to measure blood flow rate continuously, one should aim for a hemofilter with a low resistance to flow to prevent early clotting and therapy failure. If one uses a blood pump, the resistance to flow is of minor concern. Table 1 provides manufacturer data of several filters for CAVH(D) that are available. From these data, the resistance to flow for capillary hemofilters is calculated by using Poiseuille's law (Eq. 2). The resistance to flow for plate filters is calculated according to:

$$R_f = \frac{3 \cdot L \cdot \mu}{2 \cdot N \cdot \omega \cdot b^3} \qquad (3)$$

where N is the number of blood channels, ω is the blood channel width and b is the blood channel half-height [42]. The viscosity used to calculate resistance to flow as given in Table 1, is calculated as described by Pallone et al [43] and by using a correction factor (see Chapter 4), with a hematocrit of 0.30, a protein concentration of 50 mg/L and a temperature of blood of 36°C. When the resistance to flow is calculated from the manufacturer data, most of these have a resistance to flow below

0.30 mmHg · min/ml, which is suitable for CAVH(D). However, from in vivo as well as laboratory studies it is known that, very often, the actual resistance to flow is higher than the value that was calculated from the official specifications [44, Chapter 4]. Therefore, before a filter is used for CAVHD, one should best rely on precise determination of the resistance to flow in a laboratory setting [45]. The resistance to flow of a hemofilter has been found to be constant over time. Figure 2 shows a recording of mean arterial pressure and blood flow rate within the CAVHD-circuit over 5 days. Fluctuations in blood flow rate reflect those in mean arterial pressure (MAP, [mmHg]). Only after four days a precipitous drop in blood flow is seen. A few hours later the filter had become clotted completely.

The ultrafiltration rate (Q_f, [ml/min]) is determined by the hydraulic permeability of the membrane (L_p, [ml/mmHg · min · m^2]), the membrane surface area (S, [m^2]) and the transmembrane pressure (TMP, [mmHg]):

$$Q_f = L_p \cdot S \cdot MP \tag{4}$$

or

$$Q_f = MI \cdot TMP \tag{5}$$

where MI [ml/min · mmHg] is the more commonly used hydraulic permeability index of the membrane. A recording over time of ultrafiltration rate is shown in Figure 3. The data shown in Figures 2 and 3 were obtained from the same patient. It is apparent from Figure 3 that, while mean pressure and blood flow rate remained constant, ultrafiltration rate decreased over time. This indicates that MI and, presumably, Lp decreased over time. This phenomenon has also been demonstrated by others [46-48]. It has been shown that during continued use of a membrane, a decline in the hydraulic permeability occurs as a result of protein adhesion [49, 50]. We have described the average rate of decline of MI with three different hemofilters (Chapter 4). The data showed that the decline of MI was least apparent with a small polysulfone capillary hemofilter. The influence of hemofilter geometry and membrane material in this respect has not been studied in detail so far.

In CAVH, high-flux membranes are used in order to obtain adequate convective clearance rates. In CAVHD, clearance occurs more by diffusion than by convection. The rate of ultrafiltration must still be high enough to be able to withdraw several liters of fluid per day. When using a high flux membrane, a total membrane surface area of 0.6 m^2 is enough to obtain an ultrafiltration rate of 300 to 1000 ml/hr.

Both hydraulic and diffusive permeability have been found to decrease over time (Chapter 4, 6). Thus, a very low hydraulic permeability is associated with a low diffusive permeability. Generally, if clearance rates are inadequate, they may be effectively increased by increasing dialysate flow rate (Chapter 6). However, when membrane permeability has become poor, as reflected by an ultrafiltration rate of less than 200 ml/hr, the filter is best replaced. Changing of the filter can nearly always be postponed so as to take place during working hours.

Table 1. Manufacturer data of CAVH(D) filters and calculated resistance to flow. Fres.= Fresenius, AN-69=Acrylonitrile-69, PS=Polysulfone, PA=Polyamide, PAN=Polyacrylonitrile. $\mu = 3.5 \cdot 10^{-7}$ *mmHg · min.*
[1] : Channel height, [2] : Channel length,
[3] : Channel width, [4] : Number of blood channels, [5] : TMP = 55 mmHg,
[6] : Wet condition, [7] : Calculated from membrane surfae area.

filter	membrane	membrane wall thickness µm	fiber diameter µm	fiber length cm	number of fibers	effective membrane surface area. m^2	R_f calc
Hospal plate	AN-69	23	200+ 0.26 · TMP[1]	26.8[2] 6.7[3]	15[4]	0.43	0.11[5]
Hospal Multiflow-60	AN-69	50[6]	240[6]	15	6000	0.60	0.11
Amicon D-20	PS	75	250	12.7	5000	0.40	0.09
Amicon D-30	PS	75	250	21.2	5000	0.70	0.15
Gambro FH 22	PA	60	215	14.1	2100	0.16	0.44
Gambro FH 66	PA	60	215	17.2	6200	0.59	0.18
Fres. A-V 400	PS	35	220	25.5	4500	0.70	0.34
Sorin HFT 02	PS	40	200	12.0	4600	0.24	0.23
Renaflo HF250	PS	40	280	14.0	2800[7]	0.25	0.11
Renaflo HF500	PS	40	280	21.5	3350[7]	0.50	0.15
Asahi APF-03	PAN	35	250	18.5	3400	0.30	0.20
Asahi APF-06	PAN	35	250	18.5	6400	0.60	0.11

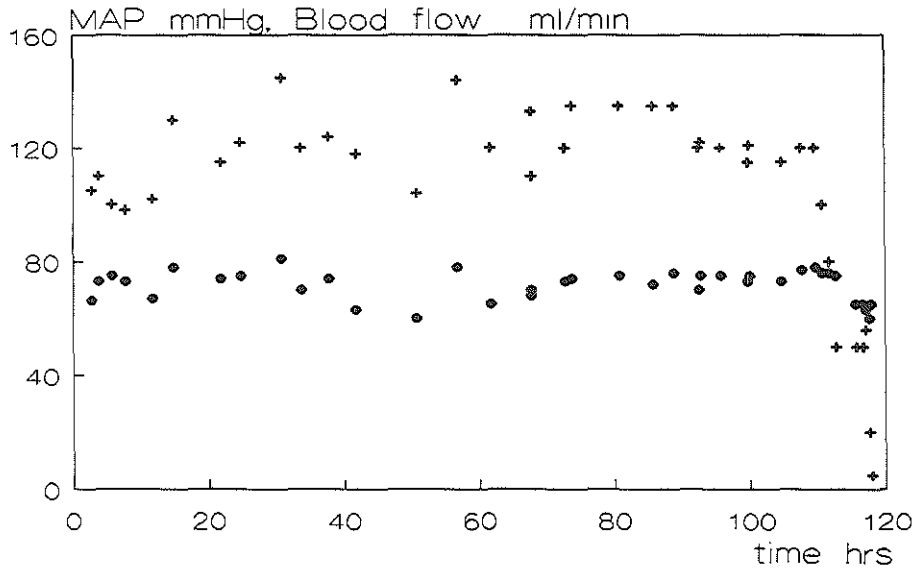

Figure 2. Blood flow rate over time using the AN-69 capillary dialyzer (in vivo data). + :Blood flow, • :MAP

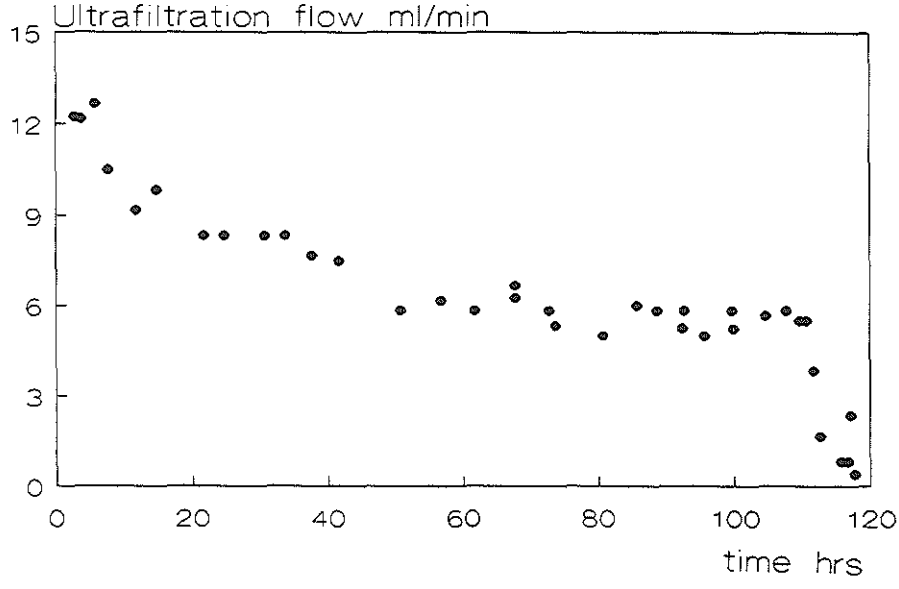

Figure 3. Ultrafiltration flow rate over time using the AN-69 capillary dialyzer (in vivo data)

Fluids and flow rates

In CAVHD, dialysate must be sterile in order to prevent back-transport of products of possible contaminants, such as pyrogens, from dialysate to blood [51-53]. It is easiest to use a commercially available hemofiltration substitution fluid for dialysate. These fluids come in bags of up to 5 liters. In Table 2, several solutions are mentioned that can be used as dialysate fluid. Dialysate fluid for peritoneal dialysis is less suitable for use in CAVHD, mainly because of its low sodium content and high content of glucose. After a few days of treatment with CAVHD, at a dialysate flow rate of 1 L/hr, we frequently encountered hypokalemia, hypophosphatemia and alkalosis. In our view therefore, the ideal dialysate solution should be composed so as to prevent electrolyte derangements during the stable phase of CAVHD treatment. At the start of treatment, when serum potassium and phosphate are high and bicarbonate is low, the same dialysate fluid may still be used albeit at a higher dialysate flow rate. We do not advocate the use of a range of different dialysate solutions, because it is impractical and because individual modifications or supplementations may still be needed. Therefore, it is recommended to measure serum levels of phosphate, potassium and sodium at least once a day. Until recently, all solutions contained either lactate or acetate as a buffer substitute, since the addition of bicarbonate would be precluded because of precipitation with calcium and magnesium. Presently, we use for dialysate a fluid to which bicarbonate is added just before use (Schiwa). When used within 24 hours, precipitation of calciumcarbonate is negligible. With bicarbonate containing fluids, the possible harmful effects of acetate and the inconvenience of spurious elevation of blood lactate is eliminated. Furthermore, Jenkins et al have demonstrated that in children on CAVHD who have persistent metabolic acidosis, changing from lactate containing dialysate to bicarbonate containing dialysate considerably improves the metabolic acidosis [54].

Blood and dialysate run in opposite directions. This countercurrent flow increases the concentration gradient between blood and dialysate. In most cases a dialysate flow rate of 1 L/hr is enough to control the uremic state. The influence of dialysate flow rate on diffusion is extensively discussed in Chapter 6.

As substitution fluid one may use simple Ringer's lactate. In case of hyponatremia, the addition of 1 gr NaCl to 500 ml of Ringer's lactate so as to increase its sodium concentration to 180 mmol/L, will lead to gradually correction of the hyponatremia. Alternatively, if the patient is no longer acidotic, one might consider the use of isotonic saline for substitution fluid. Substitution can be given either by infusing the fluid on the arterial line (predilution) or on the venous line of the filter (postdilution). Predilution has several advantages [55, 56]. By predilution

the hematocrit and the plasma protein concentration are decreased, which leads to a decrease of the blood viscosity and an increase of blood flow rate. Also, at least theoretically, by lowering colloid osmotic pressure ultrafiltration rate will be increased. The flow rate of the substitution fluid must be adjusted hourly to the rate of ultrafiltration so as to achieve the desired fluid balance. It is recommended not to decrease the rate of ultrafiltration, as this would decrease clearance rates, especially of solutes with a high molecular weight.

Table 2. Composition of fluids which can be used for dialysate fluid in CAVHD (mmol/L).

Dialysate	Na^+	K^+	Ca^{2+}	Mg^{2+}	Cl^-	Lact	Ac^-	HCO_3^-	Gluc
Fres. HF11	140	1	1.63	0.75	101	45.0	0	0	10.9
Fres. HF21	135	2	1.88	0.75	109	33.8	0	0	8.3
Fres. HF02	140	0	2.00	1.00	111	0	35	0	0
Schiwa SH-44 HEP	140	2	1.75	0.50	112	2.9	0	31.4	5.6
Schiwa SH-35 HEP	140	0	1.75	0.50	110	2.9	0	31.4	5.6
Schiwa SH-36 HEP	140	4	1.75	0.50	114	2.9	0	39.7	5.6
Schiwa SH-41 HEP	141	0	0	0.72	108	0	0	34.3	5.6
Hospal L0	140	0	1.75	0.75	100	45.0	0	0	0
Hospal L2	142	2	2.00	0.75	110	40.0	0	0	0
Hospal LG4D	140	4	2.00	0.75	110	40.0	0	0	6.1
Gambro Hemofiltrasol 21	140	1	1.60	0.75	100	45.0	0	0	11.1
Gambro Hemofiltrasol 22	140	0	1.60	0.75	100	45.0	0	0	11.1
Gambro Hemofiltrasol 23	140	1	1.80	0.75	100	45.0	0	0	11.1

Pumps and weighing devices

For safety reasons, we advise against the use of a pump in the blood line. If one were to use a pump in the blood line, this would at least necessitate the use of a bubble trap and monitoring of the pressures in the arterial blood line, immediately after the pump (in order to detect clotting of the filter) and preferably also in the venous blood line. One might also argue that the extracorporeal system ought to be supervised by a renal nurse.

For pumping dialysate fluid, a special pump that may deliver up to 3-5 L/hr, is useful but a simple screw clamp will also do. As dialysis fluid comes in big bags, it is necessary to use a weighing device to check the amount of dialysate delivered every hour. The total amount of ultrafiltrate plus spent dialysate may be measured either by weighing or by using a calibrated container.

When substitution fluid is given into the arterial line ('predilution'), an infusion pump must be used because of the high pressure. In view of the high ultrafiltration flow rate that occurs in the first few hours, this pump must be able to deliver up to 1000 ml/hr.

Anticoagulation

Our practice is to start with a heparin dose of 500 U/hr, administered just before the hemofilter in the arterial line. No loading dose is given. The dose may be changed to between 250 and 750 U/hr as clinically indicated. In case platelets counts are below $20 \cdot 10^9$/L we give no heparin at all.

One might consider regional heparinization, i.e. heparin in the arterial line and protamine in the venous line [57]. Recently, Mehta et al have published a scheme for citrate anticoagulation in CAVHD [58, 59].

REFERENCES

1. Twardowski ZJ, Nolph KD. Blood purification in acute renal failure. Annals of Internal Medicine 1984; 100: 447-449.
2. Kohen JA, Whitley KY, Kjellstrand CM. Continuous arteriovenous hemofiltration: A comparison with hemodialysis in acute renal failure. Trans Am Soc Artif Intern Organs 1985; 31: 196-173.
3. Tam PYW, Huraib S, Mahan B, LeBlanc D, Lunski CA, Holtzer C, Doyle CE, Vas SI, Uldall PR. Slow continuous hemodialysis for the management of complicated acute renal failure in an intensive care unit. Clinical Nephrology 1988; 30: 79-85.
4. Paganini EP, Suhoza K, Swann S, Golding L, Nakamoto S. Continuous renal replacement therapy in patients with acute renal dysfunction undergoing intraaortic balloon pump and/or left ventricular device support. Trans Am Soc Artif Intern Organs 1986; 32; 414-417.
5. Kaplan AA, Longnecker RE, Folkert VW. Continuous arteriovenous hemofiltration. A report of six months' experience. Annals of Internal Medicine 1984; 100: 358-367.
6. Paganini EP, O'Hara P, Nakamoto S. Slow continuous ultrafiltration in hemodialysis resistant oliguric acute renal failure patients. Trans Am Soc Artif Intern Organs 1984; 30: 173-177.
7. Hakim RM, Breilatt J, Lazarus M, Port F. Complement activation and hypersensitivity reactions to dialysis membranes. N Engl J Med 1984; 311: 878-882.
8. De Backer WA, Verpooten GA, Borgonjon DJ, Vermeire PJ, Lins RR, De Broe ME. Hypoxemia during hemodialysis: effects of different membranes and dialysate compositions. Kidney Int 1983; 23: 738-743.
9. Kuwahara T, Markert M, Wauters JP. Protein adsorption on dialyzer membranes influences their biocompatibility properties. Contrib Nephrol (Basel) 1989; 74: 53-57.
10. Kuwahara T, Markert M, Wauters JP. Modulations of leukopenia, thrombocytopenia and protein adsorption of 3 hemodialyzer membranes. A comparison of dialyzer reprocessing techniques. Kidney Int. 1987; 32: 434-435.
11. Chenoweth DE, Cheung AK, Ward DM, Henderson L. Anaphylatoxin formation during hemodialysis: Comparison of new and re-used dialyzers. Kidney International 1983: 24: 770-774.

12. Port KF, Johnson WJ, Klass DW. Prevention of dialysis disequilibrium syndrome by use of high sodium concentration in the dialysate. Kidney Int 1973; 3: 327-333.
13. Peterson HC, Swanson AG. Acute encephalopathy occurring during hemodialysis. Archives of internal medicine 1964; 113: 877-880.
14. La Greca G, Biasioli S, Borin D, Brendolam A, Chiaramonte S, Fabris A, Feriani M, Ronco C. Dialytic encephalopathy. Contrib. Nephrol. 1985; 45: 9-28.
15. Davenport A, Will EJ, Davison AM. Early changes in intracranial pressure during haemofiltration treatment in patients with grade 4 hepatic encephalopathy and acute oliguric renal failure. Nephrol Dial Transplant 1990; 5: 192-198.
16. Shizgal HM, Martin MF. Caloric requirement of the critically ill septic patient. Critical Care Medicine. 1988; 16: 312-317.
17. Mault JR, Bartlett RH, Dechert RE, Clark SF, Swartz RD. Starvation: a major contribution to mortality in acute renal failure? Trans Am Soc Artif Organs 1983; 29: 390-393.
18. Mault JR, Kresowik TF, Dechert RE, Arnoldi DK, Swartz RD, Bartlett RH. Continuous arteriovenous hemofiltration: The answer to starvation in acute renal failure? Trans Am Soc Artif Organs 1984; 30: 203-205.
19. Raja R, Kramer M, Goldstein S, Caruana R, Lerner A. Comparison of continuous arteriovenous hemofiltration and continuous arteriovenous dialysis in critically ill patients. Trans Am Soc Artif Intern Organs 1986; 32: 435-436.
20. Stevens PE, Riley B, Davies SP, Gower PE, Brown EA, Kox W. Continuous arteriovenous haemodialysis in critically ill patients. The Lancet 1988; 16: 150-152.
21. Maher ER, Hart L, Levy D, Scoble JE, Baillod RA, Sweny P, Varghese Z, Moorhead JF. Comparison of continuous arteriovenous haemofiltration and haemodialysis in acute renal failure. The Lancet 1988; 16: 129.
22. Keshaviah PR. Technical aspects of continuous and intermittent therapies. Trans Am Soc Artif Intern Organs 1988; 34: 61-62.
23. Bartlett RH, Mault JR, Dechert RE, Palmer J, Swartz D, Port FK. Continuous arteriovenous hemofiltration: Improved survival in surgical acute renal failure? Surgery 1986; 100: 400-408.
24. Chanard J, Toupance O, Gillery P, Lavaud S. Evaluation of protein loss during hemofiltration. Kidney International. 1988; 33 suppl.24: 114-116.
25. Wolfson M, Jones MR, Kopple JD. Amino acid loss during hemodialysis with infusion of amino acids and glucose. Kidney International 1982; 21: 500-506.

26. Paganini EP, Flaque J, Whitman G, Nakamoto S. Amino acid balance in patients with oliguric acute renal failure undergoing slow continuous ultrafiltration (SCUF). Trans Am Soc Artif Intern Organs 1982; 28: 615-620.
27. Davenport A, Roberts NB. Amino acid losses during haemofiltration. Blood Purif 1989; 7: 192-196.
28. Davenport A, Roberts NB. Amino acid losses during continuous high-flux hemofiltration in the critically ill patient. Critical Care Medicine. 1989; 17: 1010-1014.
29. Scheinman JI. Therapy for primary hyperoxaluria. Kidney International 1991; 40: 389-399.
30. Wolner E. Continuous arteriovenous hemofiltration. Applications other than for renal failure. In: Paganini E, ed. Acute continuous renal replacement therapy, Martinus Nijhoff Publishing. 1986: 283-292.
31. Coraim FJ Coraim HP, Ebermann R, Stellwag FM. Acute respiratory failure after cardiac failure: Clinical experience with the application of continuous arteriovenous hemofiltration. Critical Care Medicine 1986; 14: 714-718.
32. Cosentino F, Paganini E, Lockrem J, Bosworth C, Stoller J, Wiedemann H. Continuous arteriovenous hemofiltration (CAVH) in the adult respiratory distress syndrome (ARDS): a randomized controlled trial. Intensivbehandlung 1990; 15: 103-104 (Abstract).
33. Burton RG, Gorewit RC. Ultrasonic flowmeter. Uses Wide-beam transit-time technique. Medical Electronics 1984; 15: 68-73.
34. Hoenich NA, Kerr FL. Dialysers. Replacement of renal function by dialysis. sec edition. 1986. Ed. Drukker W. page 121-122.
35. Keshaviah PR, Shaldon S. Haemodialysis monitors and monitoring Replacement of renal function by dialysis. sec edition. 1986. Ed. Drukker W. page 226.
36. Kramer P, Bohler J, Kehr A, Grone HJ, Schrader J, Matthaei D, Scheler F. Intensive care potential of continuous arteriovenous hemofiltration. Trans Am Soc Artif Intern Organs 1982; 28: 28-32.
37. Vos MC, Vincent HH. Continue arterioveneuze hemodiafiltratie: een nieuwe nierfunctie vervangende therapie. Nederlands Tijdschrift voor Geneeskunde 1992; 136: 561-565.
38. Olbricht CJ. Continuous arteriovenous hemofiltration. The control of azotemia in acute renal failure. In: acute continuous renal replacement therapy. 1986, Martinus Nijhoff Publishing. Ed. E. Paganini.
39. Vincent HH, Vos MC. The use of continuous arteriovenous hemodiafiltration in multiple organ failure patients. Applied Cardiopulmonary Pathophysiology 1991; 4: 109-116.

40. Swann S. Paganini E. The practical technical aspects of slow continuous ultrafiltration (SCUF) and continuous arteriovenous hemofiltration (CAVH). Developments in Nephrology, Acute continuous renal replacement therapy. Ed. Paganini EP, Martinus Nijhoff Publishing, Boston 1986; 13: 51-77.
41. Lysaght MJ. Hemodialysis membranes in transition. Contr. Nephrol. 1988: 61; 1-17.
42. Min-Shing Lih M. Transport phenomena in medicine and biology. J Wiley & Sons, New York 1975 (Ed.)
43. Pallone TL, Hyver S, Petersen J. The simulation of continuous arteriovenous hemodialysis with a mathematical model. Kidney International 1989; 35: 125-133.
44. Olbricht CJ, Haubitz M, Habel U, Frei U, Koch K. Continuous arteriovenous hemofiltration: In vivo functional characteristics and its dependence on vascular access and filter design. Nephron 1990; 55: 49-57.
45. Vincent HH e.a. on behalf of the Kwaliteits-kommissie DGN. Adviezen t.a.v. CAVH(D). DGN Nieuwsbrief 1992.
46. van Geelen JA, Vincent HH, Schalekamp MADH. Continuous arteriovenous haemofiltration and haemodiafiltration in acute renal failure. Nephrol Dial Transplant 1988; 2: 181-186.
47. Sigler MH, Teehan BP. Solute transport in continuous hemodialysis: A new treatment for acute renal failure. Kidney International. 1987; 32: 562-571.
48. Jenkins RD, Kuhn RJ, Funk JE. Permeability decay in CAVH hemofilters. Trans Am Soc Artif Intern Organs 1988; 34: 590-593.
49. Colton CK, Henderson LW, Ford CA, Lysaght MJ. Kinetics of hemodiafiltration. I. In vitro transport characteristics of a hollow-fiber blood ultrafilter. Journal of Laboratory and Clinical Medicine 1975; 3: 355-371.
50. Bosch T, Schmidt B, Santleben W, Gurland HJ. Effect of protein adsorption on diffusive and convective transport through polysulphon membranes. Contrib Nephrol 1985; 46: 14-22.
51. Golper TA, Leone M. Backtransport of dialysate solutes during in vitro continuous arteriovenous hemodialysis. Blood Purif 1989; 7: 223-229.
52. Baurmeister U, Vienken J, Daum V. High-flux dialysis membranes: Endotoxin transfer by backfiltration can be a problem. Nephrol Dial Transplant 1989; 4 Suppl: 89-93.
53. Kolmos HJ. Hygienic problems in dialysis. Danish medical bulletin 1985; 32: 338-361.
54. Jenkins RD, Jackson E, Kuhn R, Funk J. Benefit of bicarbonate dialysis during CAVHD. Trans Am Soc Artif Intern Organs 1990; 36: M465-466.

55. Kaplan AA. The predilution mode for continuous arteriovenous hemofiltration. In: Developments in Nephrology, Acute continuous renal replacement therapy. Ed. Paganini EP, Martinus Nijhoff Publishing, Boston 1986 (Chapter 9, page 143-172).
56. Kaplan AA. Predilution versus postdilution for continuous arteriovenous hemofiltration. Trans Am Soc Artif Intern Organs 1985; 31: 28-32.
57. Kaplan AA, Petrillo R. Regional heparinization for continuous arterio-venous hemofiltration. Trans Am Soc Artif Intern Organs 1987; 33: 312-315.
58. Mehta RL, McDonald BR, Aguilar M, Ward DM. Regional citrate anticoagulation for continuous arteriovenous hemodialysis in critically ill patients. Kidney International 1990; 38: 976-981.
59. Mehta R, McDonald BR. Regional citrate anticoagulation for continuous arteriovenous hemodiafiltration. Contrib Nephrol 1991; 93: 210-214.

CHAPTER 4

DETERMINANTS OF BLOOD FLOW AND ULTRAFILTRATION: THEORETICAL PREDICTIONS AND LABORATORY AND CLINICAL OBSERVATIONS*

INTRODUCTION

Continuous arteriovenous hemofiltration (CAVH) and hemodiafiltration (CAVHD) are based on spontaneous blood flow and spontaneous ultrafiltration [1]. Failure of the technique may occur due to an inadequate blood flow rate, leading to excessive hemoconcentration and clotting.

Theoretically, blood flow rate and ultrafiltration rate may be predicted on the basis of filter geometry, membrane characteristics and blood viscosity. Pallone and Petersen developed a mathematical model by which they were able to predict filter performance in a laboratory setting [2]. In their study the resistance to blood flow was in good agreement with model predictions. On the other hand, Olbricht et al in a clinical study found that the resistance to blood flow was 3 times higher than expected [3]. The aim of the present study was to examine the feasibility of predicting filter performance under clinical conditions. In patients who were treated with CAVHD we performed serial measurements of blood flow rate, blood pressures and ultrafiltration rate, so as to estimate the filter resistance to blood flow and its hydraulic permeability. We also measured filter resistance to flow in a laboratory setting. Clinical and laboratory data were then compared with theoretical predictions.

METHODS

Clinical protocol

Twenty patients were treated with CAVHD for acute renal failure and sepsis and/or circulatory or neurological instability. A hemofiltration substitution solution (HF-11, Fresenius, Germany) was used for dialysate. The CAVHD circuit was installed as depicted in Figure 1 (for details, see Chapter 3). For vascular access we used special 11 cm CAVH-catheters (Medcomp, 8 F) in the femoral vessels, or Scribner shunts. Three types of hemofilters were used (all specifications according to manufacturers):

* Reprinted in revised form with permission from Nephrol Dial Transplant 1990, 5: 1031-1037

- the AN-69 plate filter (15 compartments, length 26.8 cm, width 6.7 cm, channel height 200+0.26 · TMP µm, membrane surface 0.43 m^2; SCU/CAVHD, Hospal, France),
- the AN-69 capillary filter (6000 fibers, length 15 cm, including 2 cm within potting, internal diameter of fibers 240 µm, and 220 µm within potting, membrane surface 0.6 m^2; Multiflow-60, Hospal, France)
- a polysulfone capillary filter (4600 fibers, fiber length 8.5 cm, internal diameter of fibers 200 µm, membrane surface 0.24 m^2; Spiraflo HFT02, Sorin Biomedica, Italy).

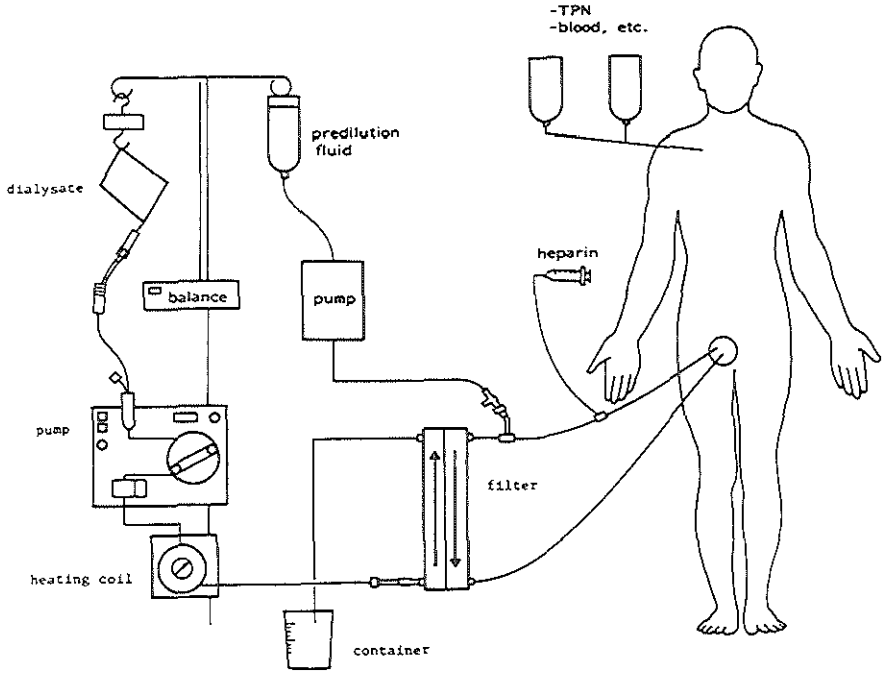

Figure 1. CAVHD system

Filters were prepared by rinsing the blood compartment with 2 L of saline, containing heparin 5000 U/L, allowing filtration to take place (see Chapter 3 for rinsing procedure). Filters were placed in the upright position, with the ultrafiltrate outlet up. Ultrafiltrate column height was about 60 cm. Standard anticoagulation consisted of heparin 500 U/hr into the arterial line of the filter. No loading dose of heparin was given. No protamine was used. Three patients received no heparin

because of excessive bleeding, thrombocytopenia or hepatic failure and coagulation disorders. Substitution fluid (Ringers lactate) was infused into the arterial line (predilution). The amount of substitution fluid was adjusted hourly to the net ultrafiltration (UF) rate. Reasons for filter replacement were clotting of the filter or a UF rate < 200 ml/hr. Furthermore, filters were removed when dialysis was no longer necessary or when clinical improvement allowed mobilization of the patient, in which case patients were treated further with conventional intermittent hemodialysis. Thus, average filter 'survival' time was 3 days.

In a separate study we took blood for viscosity measurements from 10 patients, aged 38 to 66 years, who had been treated in the intensive care department for at least three days.

Laboratory protocol

The 0.6 m^2 AN-69 capillary hemofilter was studied in the laboratory. Filters were prepared by rinsing the blood compartment with 2 l of saline, containing heparin 5000 U/L, allowing filtration to take place. After that, the dialysate compartment was closed. Blood tubing, with an inner diameter of 4.3 mm, containing side ports was used and adjusted so we could measure the pressure in the perfusion fluid 2 cm before and after the hemofilter. An electromagnetic flow probe was inserted into the tubing so that mean flow rate could be measured continuously.

The experiments were performed at room temperature. Filters were in the horizontal position. Eight filters were used. They were all first perfused with saline, then two filters were perfused with a sucrose solution and three filters were perfused with pig blood. A Rhodial^R blood pump was used to generate pulsatile flow rates from 50 to 600 ml/min in case of saline perfusion and from 50 to 300 ml/min in case of blood or sucrose perfusion. The filter resistance to flow was thus determined at different flow rates. Furthermore, with all three solutions we once changed the set up so as to create an open circuit with a container at a variable height, in which a constant flow through the filter was generated by gravity and the pump was used to return the fluid to the container.

We also measured the resistance to flow over 223 cm of standard polyvinylchloride (PVC) blood tubing with an inner diameter of 4.36 mm, using saline as the perfusion fluid.

Measurements

Electronic pressure transducers were connected to the arterial and the venous lines to measure the pre- and postfilter hydraulic pressures (P_i and P_o respectively). Both pressures were measured using the same pressure transducer. In the patients, we also measured intra-arterial and intra-venous (P_{ia} and P_{iv}) pressures by the same pressure transducers after clamping the line for 10 seconds. The pressure midway in the ultrafiltrate-compartment (P_d, [mmHg]) was calculated from the height of the fluid column in the UF-line (h, [cm]) according to:

$$P_d = \frac{h}{1.36} \tag{1}$$

where the value 1.36 is needed for the conversion from cmH_2O to mmHg. Effective transmembrane pressure (TMP) in the filter was calculated according to:

$$TMP = \frac{P_i + P_o}{2} - P_d - COP \tag{2}$$

where COP [mmHg] is the colloid osmotic pressure caused by the protein in the blood compartment. (Bernouilli effects were thus neglected, see Discussion). Colloid osmotic pressure was calculated according to the equation of Landis and Pappenheimer:

$$COP = 2.1 \cdot C_{prot} + 0.16 \cdot C_{prot}^{\ 2} + 0.009 \cdot C_{prot}^{\ 3} \tag{3}$$

where C_{prot} is the mean plasma protein concentration (g/dl) in the filter. This equation had previously been found to fit experimental data closely over the range 0 to 25 % of protein [4]. When we compared measured and calculated values, the difference was always less than 5 mmHg (n=12).
C_{prot} is calculated according to:

$$C_{prot} = \frac{C_{prot\text{-}a} + C_{prot\text{-}v}}{2} = \frac{C_{prot\text{-}a} \cdot (2\,Q_{pa} + 2\,Q_{pred} - Q_f)}{2 \cdot (Q_{pa} + Q_{pred} - Q_f)} \tag{4}$$

where $C_{prot\text{-}a}$ and $C_{prot\text{-}v}$ are the plasma protein concentrations at the filter inlet and outlet respectively; Q_{pa} [ml/min] is the plasma flow rate through the arterial catheter before addition of predilution fluid, which is calculated as:

$$Q_{pa} = Q_b \cdot (1 - Ht) \tag{5}$$

where Ht is the blood hematocrit, Q_{pred} is the predilution fluid infusion rate; Q_f the ultrafiltration flow rate and Ht the hematocrit. In the patients, blood flow through the filter was determined in duplicate by measuring the time required for air bubble displacement over 13.0 ml of tubing. In the laboratory blood flow was measured with an electromagnetic flow probe (see laboratory protocol). Ultrafiltration rate was determined by timed collection of fluid from the ultrafiltrate line over five minutes after switching off the dialysate pump. Filter membrane index (MI, [ml/h · mmHg]) was defined as:

$$MI = \frac{Q_f \cdot 60}{TMP} \tag{6}$$

Hydraulic membrane permeability of the membrane (L_p, [cm/min · mmHg]) was calculated from:

$$L_p = \frac{MI}{S} = \frac{Q_f}{TMP \cdot S} \tag{7}$$

where S [cm^2] is the membrane surface area of the filter.
The resistance of the filters to blood flow [R_f, mmHg · min/ml] was calculated according to:

$$R_f = \frac{P_i - P_o}{Q_b} \tag{8}$$

and resistances of the arterial and venous access were likewise derived from the pressure drop P_{in} - P_i and P_o - P_{iv} respectively. Resistances were normalized for blood viscosity according to:

$$R_{fn} = \frac{R_f}{\mu} \tag{9}$$

where, for blood, viscosity (μ, [mmHg · min]) is calculated as described by Pallone et al [5], assuming a blood temperature of 37 °C in the patient for calculating the resistance of the arterial access and of 34 °C in the filter for calculating the resistance of the filter and the venous access and taking the effect of ultrafiltration on hematocrit and protein concentration into account. In narrow tubes blood viscosity may be decreased according to the Fahreus Lindqvist effect. With a diameter of 200

to 240 µm, however, the decrease is less than 5 % and may therefore be neglected [6]. Values of viscosity for the saline and sucrose solutions were taken from published tables [7].

Under the conditions of our study, with shear rates of 150 to 400 sec^{-1}, blood may be regarded as a Newtonian fluid [8]. Furthermore, within the fibers, blood flow is laminar. Therefore, R_{fn} may also be predicted according to Poiseuille's Law:

$$R_{fn}\,pred = \frac{8 \cdot L}{N \cdot \pi \cdot r^4} \qquad (10)$$

where L is the fiber length; N is the number of fibers and r is the internal radius of the fibers of the hemofilter.

For the flat plate filter, R_{fn} was predicted according to:

$$R_{fn}\,pred = \frac{3 \cdot L}{2 \cdot N \cdot \omega \cdot b^3} \qquad (11)$$

where N is the number of blood channels; ω is the blood channel width and b is the blood channel half-height [9].

Viscosity measurements were performed using an apparatus that measures the flow rate of blood at 37 °C through a glass capillary with a known resistance. The internal diameter of the capillary is 1.05 mm and the velocity is approximately 30 mm/sec, resulting in shear rates similar to those within the fibers of the hemofilters.

Statistics

The clinical data are presented as means ± 1 S.D. The time dependent decrease of hydraulic membrane permeability was analyzed by regression analysis. Previous experiments showed that a good fit was obtained by linear regression of the filter membrane index or hydraulic membrane permeability as a function of the logarithm of time (Ln t). This regression analysis was performed for each individual filter. An approximately equal number of data points were obtained before and after 12 h of use (for number of data, see Table 4). Slopes and extrapolated values at 12 h of use were compared by Wilcoxon's Rank test.

Filter resistance, measured in the laboratory, was plotted against flow rate and linear regression analyses were used to calculate the resistance at zero flow rate and to determine the slopes.

RESULTS

Blood path resistance and blood flow rate

On starting CAVHD treatment, mean arterial pressure was below 70 mmHg in a third of the patients. The CAVH-catheters had a resistance to blood flow of only 0.10 mmHg per ml/min, while for the Scribner shunt this value was fourfold higher (Table 1). The average filter resistance to blood flow was between 0.24 and 0.35 mmHg per ml/min. Generally, there was no appreciable change in filter resistance with time. In a few cases, a sudden increase in the resistance to blood flow heralded clotting of the filter. Using CAVH-catheters, overall blood path resistance during CAVHD treatment was approximately 0.45 to 0.55 mmHg per ml/min. This resulted in blood flow rates of 164 ± 59 ml/min (range 63-284 ml/min).

The normalised resistance, R_m, of the hemofilters we observed was two to three times higher than the predicted value (Table 1). This was partly explained by underestimation of blood viscosity. Blood viscosity proved to be 1.4 times higher than the value calculated according to Pallone et al [5] (Table 2).

Results of laboratory experiments are given in Table 3 and Figures 2 and 3. For the PVC tube, the resistance to flow was in accordance with that predicted according to Poiseuille's law. For the hemofilter, both with saline and with the sucrose solution, the resistance was 40 % higher than the calculated value. Similar values were obtained with either pulsatile or constant flows. The resistance rose with increasing flow rate. With blood, the resistance to flow was 160 % higher than the calculated value, and it did not significantly increase with flow rate.

Table 1. Resistance to blood flow (clinical data). PS= polysulfone

		R_f [mmHg · min/ml]	R_{fn} [10^5/ml]	n
CAVHD catheter	art	0.10 ± 0.04	3.8 ± 1.3	39
	ven	0.10 ± 0.04	3.7 ± 1.3	39
Scribner shunt	art	0.36 ± 0.07	14.8 ± 3.1	6
	ven	0.36 ± 0.13	14.7 ± 5.4	6
AN-69 plate filter:				
calculated			3.0 ± 0.2	
observed		0.25 ± 0.06	8.8 ± 2.2	16
AN-69 cap. filter:				
calculated			3.0	
observed		0.24 ± 0.11	9.0 ± 4.0	17
PS cap. filter:				
calculated			4.7	
observed		0.35 ± 0.14	11.4 ± 2.3	17

Table 2. Whole Blood Viscosity Measurements. [1] *See ref. [5]*

No.	Ht	C_{prot}	μ 10^{-7} mmHg · min	obs/pred[1]
1	21	55	2.84	1.33
2	31	49	3.55	1.49
3	25	55	2.66	1.17
4	21	53	3.23	1.54
5	26	36	3.06	1.53
6	33	45	3.69	1.55
7	30	75	3.93	1.41
8	34	54	3.96	1.54
9	26	54	3.05	1.33
10	24	56	3.11	1.38
			-------	-------
		mean ± SD:	3.31 ± 0.43	1.43 ± 0.12

Table 3. Resistance to Blood Flow (Laboratory Data)

	R_{fn} predicted 10^5 ml^{-1}	R_{fn} measured 10^5 ml^{-1}	Slope % per 100 ml/min
BLOOD TUBING			
saline $\mu=1.2\cdot10^{-7}$	2.41	2.15	0.00
HEMOFILTER	3.24	4.58	8.8
saline $\mu=1.2\cdot10^{-7}$		5.17	8.8
		5.83	6.0
		2.92	10.0
		5.00	8.1
		4.69	4.1
		3.88	6.0
		4.60	6.1
	mean ± SD:	4.58 ± 0.82	7.2 ± 1.8
HEMOFILTER	3.24	5.43	5.1
sucrose $\mu=2.8\cdot10^{-7}$		3.98	4.9
	mean ± SD:	4.71 ± 0.72	5.0 ± 0.1
HEMOFILTER	3.24	7.93	1.5
Pig blood Ht= 0.23-0.26 $\mu=2.8\cdot10^{-7}$		8.11	-0.4
		8.93	0.5
	mean ± SD:	8.33 ± 0.44	0.5 ± 0.8

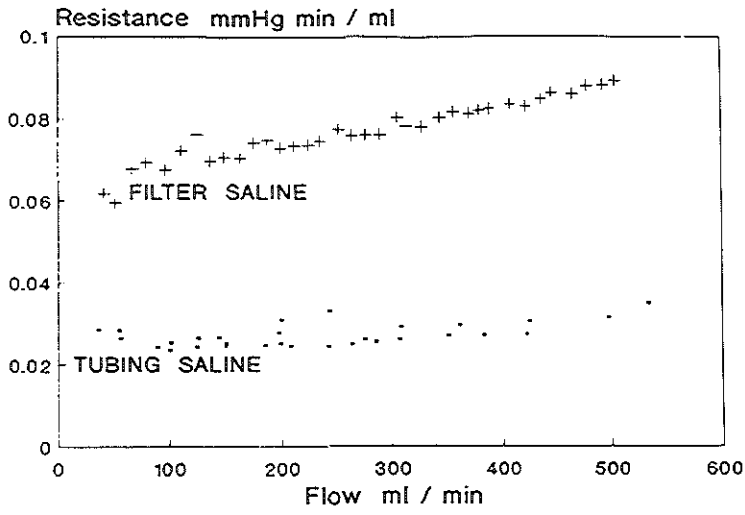

Figure 2. Resistance to flow of tubing and of AN-69 capillary filter, using saline. (R_f predicted tubing = 0.03, R_f predicted filter = 0.04).

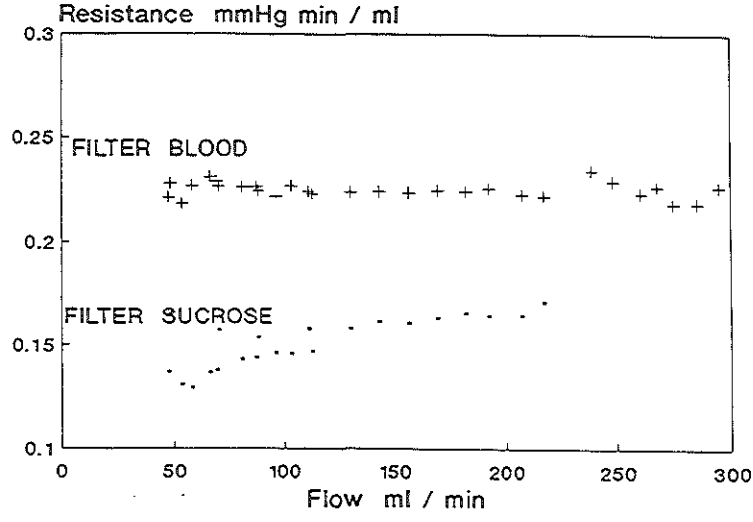

Figure 3. Resistance to flow of AN-69 capillary filter, using sucrose and blood. (R_f predicted = 0.09).

Table 4: Hydraulic membrane permeability. The average L_p-values of 2.77 and 2.58 for the AN-69 filters were both lower than the value of 5.03 for the polysulfone filter ($p<0.01$) The slopes 0.72 and 0.69 for the capillary filters were both lower than the slope of 1.35 for the plate filter ($p<0.05$).
[1] Value obtained by interpolation
[2] Slope b in the formula $L_p = a - b\ ln(time)$

	AN-69 capillary		AN-69 plate		PS capillary	
	L_p[1] after 12 hr	slope[2]	L_p[1] after 12 hr	slope[2]	L_p[1] after 12 hr	slope[2]
	2.69	0.39	2.81	0.67	6.47	0.55
	3.66	1.55	0.56	1.62	5.94	1.30
	2.57	0.60	5.70	1.79	4.11	0.05
	2.14	0.34	2.34	0.84	6.27	0.70
	2.90	0.73	2.26	1.05	4.50	1.27
	2.60	0.98	2.87	2.01	6.53	0.53
	2.81	0.87	2.02	1.53		
			2.97	1.26		
			3.35	1.05		
			2.85	1.10		
			3.23	1.08		
			0.92	1.03		
			1.71	2.53		
	-----	-----	-------	-----	------	-----
average:	2.77	0.72	2.58	1.35	5.03	0.69

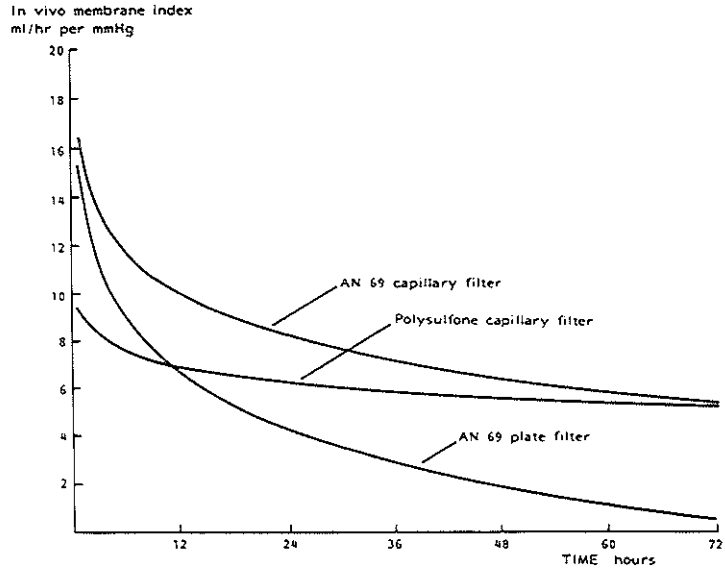

Figure 4. Decrease of filter membrane index with time.

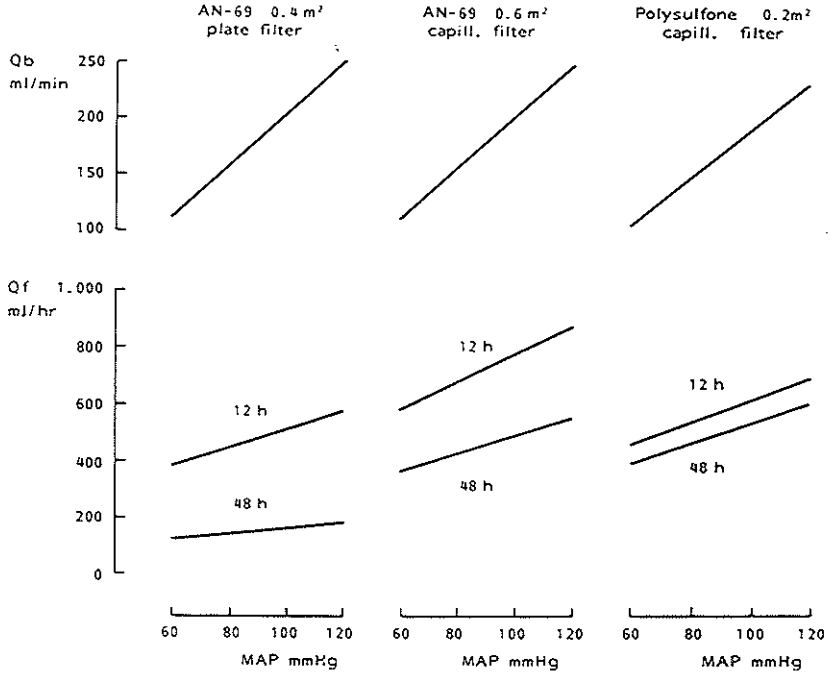

Figure 5. Estimated average extracorporeal blood flow and ultrafiltration rate as a function of mean arterial pressure.

Hydraulic membrane permeability

Hydraulic membrane permeability of the AN-69 membrane was less than that of the polysulfone membrane (Table 4). This difference was largely made up for by the difference in membrane surface area of the hemofilters. Hydraulic membrane permeability decreased with time. The rate of the decrease was faster with the plate filter than with the capillary filters (see also Figures 4 and 5).

DISCUSSION

Blood flow

Pallone and Petersen have shown that, for capillary and flat plate hemofilters, the resistance to flow may be predicted from the filter geometry [2, 5]. Their prediction was based on Poiseuille's law. In their calculations it was assumed that blood behaves as a Newtonian fluid and that flow through the filter is laminar. In addition, they used data from the literature which allow the calculation of blood viscosity from hematocrit, protein concentration and temperature. In our study we used the same calculation methods. We found that the filter resistance to flow was two to three times higher than the predicted value. A similar finding has recently been reported for a number of other hemofilters [3]. To explain this discrepancy we considered clotting of fibers, underestimation of blood viscosity, turbulent flow and/or additional pressure losses due to the sudden changes in the blood path diameter and deviations of the internal diameter of the fibers.

Laboratory measurements showed that the resistance of a length of tubing was in accordance with the calculated value, which argues against gross methodological mistakes. The resistance of the hemofilter, perfused with saline or a sucrose solution, was 40 % higher than expected. Furthermore, it was to some extent flow dependent, suggesting that turbulence does occur, most likely at the filter inlet. However, this can hardly explain why the extrapolated resistance at zero flow rate was 40 % higher than calculated. Also, when we applied Bernouilli's law to estimate the pressure drop that results from the sudden change in diameter at the filter inlet [7], we calculated a pressure drop of far less than 1 mmHg. On the other hand, a 40 % increase in resistance would be explained if the fiber diameter would be a mere 8 % lower than the given value. When filters were perfused with blood, the viscosity-corrected filter resistance was higher than with saline or sucrose. With blood, a similar filter resistance was found both in laboratory experiments, where clotting was prevented

by a high dose of heparin, and in the clinic. This argues against a significant contribution of clotting of fibers to filter resistance. Furthermore, in Chapter 3 it was observed that filter resistance was constant over time. On the other hand, comparison of actual blood viscosity with the calculated value confirmed our suspicion that we had grossly underestimated blood viscosity. With blood, filter resistance no longer seemed flow dependent, probably indicating that turbulence is diminished by the higher viscosity of blood. If blood flow rate was predicted on the basis of our laboratory data on filter resistance during saline perfusion and on the basis of a more accurate estimation of blood viscosity, flow rate would be overestimated by only 25%.

Ultrafiltration

The fall in ultrafiltration rate with time may be explained both by changes in the hydraulic membrane permeability, presumably resulting from protein adsorption to the membrane, and by a fall in the available membrane surface area, e.g. due to inadvertent clotting of fibers. For reasons given above, under clinical conditions inadvertent clotting of fibers is unlikely to occur. Therefore, the decrease in hydraulic membrane permeability with time is more likely to be due to ongoing protein adsorption. It should be noted that according to Jenkins et al [10] the hemofilter hydraulic membrane permeability may fall even after contact with water alone. To our knowledge, however, this finding has not been reproduced by others. For the AN-69 capillary filter we did not observe a fall in hydraulic membrane permeability between 1 and 48 hours of saline perfusion, but we do observe a fall in hydraulic membrane permeability with plasma and blood (data not shown).

Clinical Implications

In critically ill patients, in whom CAVH(D) is indicated, blood pressure tends to be low. A low resistance to flow of the extracorporeal circuit is therefore mandatory. In this respect CAVH catheters are clearly to be preferred to Scribner shunts. The use of a Scribner shunt instead of catheters doubled the overall resistance of the extracorporeal system. In our view Scribner shunts should be regarded as unsuitable for CAVH(D).

The resistance to flow of the hemofilters studied was low enough to ensure an adequate blood flow rate in most cases. By using laboratory data on filter resistance

and a more accurate estimation of blood viscosity, a reasonably accurate prediction of blood flow rate under clinical conditions can be obtained.

With the three filters studied, ultrafiltration rate is always high enough for correction of overhydration. On the other hand, due to the time-dependent fall in hydraulic membrane permeability, ultrafiltration rate will soon become too low for adequate solute removal through convection alone. In case of CAVH this necessitates frequent changes of the filter. In case of CAVHD the fall in filtration rate is less important, as solute removal then occurs largely by diffusion.

ACKOWLEDGEMENTS

We are grateful to Dr. G.C.D. Kuiken from the Technical University, Delft, for his advice and to Dr. C. Slager from the department of Thoracic Technology of the Erasmus University, Rotterdam, for his help in performing viscosity measurements.

REFERENCES

1. van Geelen JA, Vincent HH, Schalekamp MADH. Continuous arterio-venous haemofiltration and haemodiafiltration in acute renal failure. Nephr Dial Transpl 1988; 2: 181-186.
2. Pallone TL, Petersen J. Continuous arteriovenous hemofiltration: An in vitro simulation and mathematical model. Kidney Int 1988; 33: 685-698.
3. Olbricht CJ, Haubitz M, Häbel U, Frei U, Koch K-M. Continuous arteriovenous hemofiltration: In vivo functional characteristics and its dependence on vascular access and filter design. Nephron 1990; 55: 49-57.
4. Landis EM, Pappenheimer JR. Exchange of substances through the capillary wall. In: Handbook of Physiology. Circulation, (vol II Chapter 29). Washington, D.C., Am Physiol Soc, 1963, page 962-1034.
5. Pallone TL, Hyver S, Petersen J. The simulation of continuous arteriovenous hemodialysis with a mathematical model. Kidney International 1989; 35: 125-133.
6. Gaehtgens P. Flow of blood through narrow capillaries: Rheological mechanisms determining capillary hematocrit and apparent viscosity. Biorheology 1980; 17: 183-189.
7. Handbook of biochemistry. Selected data for molecular biology. Eds. Soben HA, Harte RA. The Chemical Rubber Co. Cleveland, Ohio, 1968.
8. Merrill EW, Pelletier GA. Viscosity of human blood: Transition from Newtonian to non-Newtonian. J Appl Physiol 1967; 23: 178-182.
9. Min-Shing Lih M. Transport phenomena in medicine and biology. J Wiley & Sons, New York 1975 (Ed.)
10. Jenkins RD, Kuhn RJ, Funk JE. Permeability decay in CAVH hemofilters. Trans Am Soc Artif Intern Organs 1988; 34: 590-593.

CHAPTER 5

A MATHEMATICAL MODEL OF SOLUTE TRANSPORT IN CONTINUOUS ARTERIOVENOUS HEMODIAFILTRATION

INTRODUCTION

Continuous arteriovenous hemofiltration (CAVH) is characterized by the use of a small surface highly permeable hemofilter, spontaneous blood flow and spontaneous ultrafiltration. Solutes are removed solely by convection, i.e. plasma water is removed together with all dissolved molecules that are able to pass through the membrane pores. The driving force is the trans membrane pressure difference. Solute clearance is limited by the amount of ultrafiltrate produced. It is technically feasible to increase ultrafiltration rate by the use of a pump, either in the blood circuit or in the filtrate line, but the inherent hazards of such techniques necessitate the use of sophisticated safety measures and supervision by specially trained personnel. An easier way to increase solute clearance is by continuous arteriovenous hemodiafiltration (CAVHD), a technique in which CAVH is combined with continuous slow dialysis [1, 2]. In this technique, transport occurs by combined convection and diffusion. Both processes have an influence on one another [3]. Ultrafiltration leads to an increased solute concentration in the dialysate side of the dialyzer and thereby decreases diffusion. Dialysis lowers the solute concentration in plasma water and thereby decreases the amount of solute that is removed by ultrafiltration.

CAVHD is a new renal replacement technique. Insight into the determinants of solute clearance is needed to determine the optimal flow rates. Also, data on drug clearance are needed. For some drugs dose adaptations may be necessary. For this, we needed a mathematical model that could be used to analyze solute transport by CAVHD. We must realize that CAVHD differs from conventional intermittent hemodialysis and hemodiafiltration in several respects. First, solute transport occurs by simultaneous convection and diffusion. Second, dialysate flow rates (10-30 ml/min) are very low compared to blood flow rate (100-250 ml/min) and as a consequence the change in dialysate solute concentration over the length of the filter cannot be taken to be linear, as in conventional models of dialysis [4]. The dialysate flow rates that are used in CAVHD might be too low for optimal distribution of dialysate over the dialysate compartment. Consequently, by low dialysate flow rates, the resistance to diffusion exerted by the dialysate compartment may be much higher than in conventional hemodialysis. Third, CAVHD is a continuous technique. With prolonged use of the filter, deterioration of the membrane is likely not only to

decrease the rate of ultrafiltration but also to impair diffusive transport. For the above reasons, existing models of hemodialysis are not likely to be useful for the analysis of solute transport in CAVHD.

Previous models of solute transport by hemodialysis

In the model of hemodialysis, as published by Sargent and Gotch [4], a linear change in solute concentration over the length of the dialyzer is assumed. Convective transport is neglected. Thus the rate of transport depends on the difference between the concentration in blood and that in dialysate and the mass transfer coefficient of diffusion (K_d). By using this model, the length-averaged K_d may be calculated from the total solute transport and the log-mean concentration difference over the membrane [4]. In CAVHD, the contribution of convective transport is relatively great. Also, because of the ratio of blood and dialysate flow rates, a curvilinear decrease of solute concentration over the length of the dialyzer is to be expected.

The mass transfer coefficient of diffusion is the inverse of the total resistance to diffusion, which consists of the resistance to diffusion of the blood compartment, that of the membrane and that of the dialysate compartment [5]. In conventional dialysis the greater part of the resistance to diffusion is exerted by the blood compartment and the membrane. According to Grimsrud and Babb [6], at a fast and turbulent dialysate flow, the resistance to diffusion in the dialysate compartment approaches zero. Accordingly, they developed a model of solute transport in which the resistance to diffusion of the dialysate compartment was neglected. Also, in their model ultrafiltration rate was taken to be zero. In CAVHD, this approach is not valid because of the low dialysate flow rate and the relatively high rate of ultrafiltration.

Sigler and Teehan first described solute clearance by CAVHD in patients [7]. They did not discern between convective and diffusive clearance and the study does not provide any insight into the determinants of diffusive transport.

Pallone et al studied solute transport by CAVHD in a laboratory setting. They presented a model in which they defined the solute flux by convection and by diffusion. These fluxes were then integrated over the length of the dialyzer [8]. With their model, they were able to calculate the curvilinear change in solute concentration along the dialyzer. Their model does not provide an analytical expression of K_d. They did not recognize the influence of differences in dialysate flow rate on K_d (Chapter 6).

Jaffrin published a mathematical model of combined convection and diffusion, to be applied to intermittent hemodiafiltration [9]. He expressed K_d as a function of

the resistance of diffusion in blood, in the membrane and in dialysate. These values are, however, not readily available. Furthermore, in order to derive K_d, experiments had to be done at zero ultrafiltration rate. The model can therefore not be applied to data obtained from patients treated with CAVHD.

In view of the shortcomings of the above models, we developed a new model of CAVHD. In the present chapter, we first define a model of hemodiafiltration that can be easily implemented in any spread sheet program. Then, with some simplifications, the model equations are analytically solved, so as to provide an expression of K_d as a function of blood, filtrate and dialysate flow rates and solute concentrations. By virtue of this expression of K_d, the model is well suited for the analysis of diffusive transport in CAVHD.

Mathematical model of CAVHD

The model describes the flux of a solute from plasma water to dialysate by simultaneous convection and diffusion during countercurrent hemodiafiltration. The solute concentration at the dialysate inlet is taken to be zero.

Three important assumptions are made. First, blood and dialysate flows are assumed to be homogeneously distributed over their respective compartments. Second, the membrane permeabilities for ultrafiltration and for diffusion are assumed to be constant over the entire membrane length. Third, within both the blood and dialysate compartments, the solute concentration varies in the axial direction but not in the radial direction, i.e. calculations are based on local "mixing cup" concentrations. In reality, the so called 'concentration polarisation' occurs on both sides of the membrane. Thus, in our model, diffusive solute transport results from a difference between mixed concentrations in plasma water and dialysate only. The influence of solute concentration polarization on the resistance to diffusion is thereby neglected. The validity of the latter assumption was experimentally studied (see next chapter).

Input variables of the model are:

- blood flow rate at the inlet of the dialyzer (Q_{bi}),
- hematocrit (Ht),
- plasma protein concentration (C_{prot}),
- dialysate flow rate (Q_{di}),
- ultrafiltration rate (Q_f),
- infusion rate of predilution fluid (Q_{pred}),
- solute concentration in the arterial blood plasma (C_{pi}),

- total membrane surface area (S),
- the length of the membrane (L) and
- the mass transfer coefficient of diffusion (K_d).

Also the non-protein-bound fraction of the solute (F) and the sieving coefficient (s) are required. The sieving coefficient is the fraction of the solute mass that passes through the membrane during ultrafiltration, defined as the solute concentration in ultrafiltrate divided by its concentration in plasma water. From these input values, we calculate the changes in solute concentration in blood and dialysate over the length of the dialyzer and, thereby, solute clearance.

Model equations

The flow rate of plasma water at the blood inlet (Q_{wi}) is calculated by:

$$Q_{wi} = Q_{bi} \cdot (1 - Ht) \cdot (1 - \alpha \cdot C_{prot}) + Q_{bi} \cdot Ht \cdot f + Q_{pred} \qquad (1)$$

where f is the fractional solute distribution in red blood cells. For urea f is 0.8 [10]. For most other solutes f may be taken to be zero. C_{prot} is the plasma protein concentration in g/L and α, the volume fraction of proteins, is 0.00107 L/g [11]. The solute concentration in plasma water at the inlet of the dialyzer (C_{wi}) is calculated by:

$$C_{wi} = \frac{C_{pi}}{(1 - \alpha \cdot C_{prot})} \cdot \frac{(Q_{wi} - Q_{pred})}{Q_{wi}} \qquad (2)$$

The plasma water flow rate at the blood outlet (Q_{wo}) is calculated by:

$$Q_{wo} = Q_{wi} - Q_f \qquad (3)$$

and the dialysate flow rate at the dialysate side outlet (Q_{do}) is:

$$Q_{do} = Q_{di} + Q_f \qquad (4)$$

The trans membrane pressure difference is the sum of the hydraulic pressure in blood and dialysate (P_b and P_d respectively) and the colloid osmotic pressure in blood (COP):

$$TMP = P_b - P_d - COP \tag{5}$$

The value of COP may be estimated from the blood protein concentration by using the Landis-Pappenheimer equation [12]. The hydraulic permeability coefficient of the membrane (L_p) is calculated from the rate of ultrafiltration, the length-averaged trans membrane pressure difference (TMP) and the membrane surface area according to:

$$L_p = \frac{Q_f}{TMP \cdot S} \tag{6}$$

The volume flux ($J_v = Q_f / S$) is a function of the trans membrane pressure difference (TMP) and the hydraulic permeability:

$$J_v = TMP \cdot L_p \tag{7}$$

Solute flux through the membrane (J_s) occurs by convection and diffusion. The most rigorous expression of J_s during combined convection and diffusion is:

$$J_s = \frac{J_v \cdot s \cdot [C_w - C_d \cdot e^{\left(-J_v \cdot \frac{s}{K_d}\right)}]}{1 - e^{\left(-J_v \cdot \frac{s}{K_d}\right)}} \tag{8}$$

This equation is equivalent with the one derived by Levitt [13]. In case of high values of $J_v \cdot s$ and low values of K_d, the above equation reduces to:

$$J_s = J_v \cdot s \cdot C_w + K_d \cdot (C_w - C_d) \quad \text{for} \quad \frac{J_v \cdot s}{K_d} >> 1 \tag{9}$$

In case of low values of $J_v \cdot s$ relative to the value of K_d, equation 8 reduces to:

$$J_s = J_v \cdot s \cdot \frac{C_w + C_d}{2} + K_d \cdot (C_w - C_d) \quad \text{for} \quad \frac{J_v \cdot s}{K_d} << 1 \tag{10}$$

In case of uremic solutes, protein-binding does not usually occur. With drugs, on the other hand, very often part of the solute is bound to plasma proteins and only the free fraction (F) is available for convection and diffusion. To take the effect of protein binding into account, in Eq. 9 and 10 the value of C_w must be substituted by

	A	*B*	*C*	*D*	*E*	*F*	*G*	*H*
1	x/L	Qw	Qd	Mw	Md	Cw	Cd	Js
2	0.00	Qwi	Qdo	Qwi·Cwi	Qdo·Cdo	*D2/B2*	*E2/C2*	Jv·*F2*·F+Kd·(*F2*·F-*G2*)
3	0.01	Qwi-0.01·Qf	Qdo-0.01·Qf	*D2*-0.01·S·*H2*	*E2*-0.01·S·*H2*	*D3/B3*	*E3/C3*	Jv·*F3*·F+Kd·(*F3*·F-*G3*)
4	0.02	Qwi-0.02·Qf	Qdo-0.02·Qf	*D3*-0.01·S·*H3*	*E3*-0.01·S·*H3*	*D4/B4*	*E4/C4*	Jv·*F4*·F+Kd·(*F4*·F-*G4*)
101	0.99	Qwi-0.99·Qf	Qdo-0.99·Qf	*D100*-0.01·S·*H100*	*E100*-0.01·S·*H100*	*D101/B101*	*E101/C101*	Jv·*F101*·F+Kd·(*F101*·F-*G101*)
102	1.00	Qwo	Qdi	*D101*-0.01·S·*H101*	*E101*-0.01·S·*H101*	*D102/B102*	*E102/C102*	Jv·*F102*·F+Kd·(*F102*·F-*G102*)

Figure 1. Stepwise numerical integration in a spreadsheet program. Note that, an approximation procedure must be used to find the value of C_{do} at which the value of cell G102 approaches zero.

$C_w \cdot F$. This implies immediate re-equilibration between bound and free fractions as solute is removed from the blood. Thus, Eq. 9 becomes:

$$J_s = J_v \cdot s \cdot C_w \cdot F + K_d \cdot (C_w \cdot F - C_d) \quad \text{for} \quad \frac{J_v \cdot s}{K_d} >> 1 \qquad (11)$$

and Eq. 10 becomes:

$$J_s = J_v \cdot s \cdot \frac{C_w \cdot F + C_d}{2} + K_d \cdot (C_w \cdot F - C_d) \quad \text{for} \quad \frac{J_v \cdot s}{K_d} << 1 \qquad (12)$$

For the calculation of total solute transport, Eq. 11 or Eq. 12 is integrated along the length of the dialyzer.

Implementation of the model in a spread sheet program

The above model is implemented in a spread sheet program as follows (see Figure 1).

The length of the dialyzer is divided into sections. At each section, d(x), $P_b(x)$ is defined as a linear function of P_{bi} and P_{bo}; TMP(x) is defined as a function of $P_b(x)$, P_d and COP. Since, in CAVHD, the ultrafiltration rate is small in relation to blood flow rate, one may use a single length-averaged value of the blood protein concentration and of COP. Also, at a low dialysate flow rate one may use a single value of P_d. $J_v(x)$ is then defined as a function of TMP(x). $Q_w(x)$ and $Q_d(x)$ are expressed as a function of Q_{wi} and $J_v(x)$ and of Q_{do} and $J_v(x)$ respectively. The total solute mass in plasma water, Mw(x), is defined as a function of MW_i, which is the product of Q_{wi} and C_{wi}, and $J_s(x)$. Likewise the total solute mass in dialysate is defined as a function of MW_o and $J_s(x)$. Thus, to start the procedure, an estimated value of C_{do} is required (see below). $C_w(x)$ and $C_d(x)$ are defined as a function of mass and flow rate. Finally, at each section, J_s is defined according to Eq. 11 or 12. An iterative approximation procedure is used to find the input value of C_{do} at which C_{di} becomes zero.

If C_{do} is known and K_d must be determined, then an initial estimation of K_d is required and the approximation procedure is followed to find the value of K_d at which C_{di} becomes zero.

Simplification of the model and analytical solutions

In the case that the free fraction, F, and the sieving coefficient, s, of the solute equal one, as is true for urea, creatinine and phosphate, the transport equation (Eq. 11) becomes:

$$J_s = J_v \cdot C_w + K_d \cdot (C_w - C_d) \quad \text{for} \quad \frac{J_v \cdot s}{K_d} >> 1 \tag{13}$$

If, for simplicity, we assume that J_v is constant along the length of the filter, it is possible to obtain an analytical expression of $C_w(x)$ and $C_d(x)$ as follows [14, 15]: From the condition of continuity over a differential length d(x) of the hemofilter it follows that:

$$\frac{dQ_w(x)}{dx} = -\frac{dQ_d(x)}{dx} = -w \cdot J_v \tag{14}$$

where w is the width, defined as S/L. Integration of Eq. 14 yields:

$$Q_w(x) = Q_{wi} - w \cdot J_v \cdot x \tag{15}$$

and

$$Q_d(x) = w \cdot J_v \cdot x - Q_{do} \tag{16}$$

Mass transfer of the solute in the blood compartment is given by:

$$\frac{d[Q_w(x) \cdot C_w(x)]}{dx} = -w \cdot J_s(x) \tag{17}$$

and in the dialysate compartment by:

$$\frac{d[Q_d(x) \cdot C_d(x)]}{dx} = w \cdot J_s(x) \tag{18}$$

where the solute flux is:

$$J_s = J_v \cdot C_w(x) + K_d \cdot (C_w(x) - C_d(x)) \tag{19}$$

By combining Eqs. 14, 17 and 18 we get:

$$\frac{dC_w(x)}{dx} = -w\frac{K_d \cdot (C_w(x) - C_d(x))}{Q_w(x)} \tag{20}$$

and

$$\frac{dC_d(x)}{dx} = w\frac{(J_v + K_d) \cdot (C_w(x) - C_d(x))}{Q_d(x)} \tag{21}$$

On substracting Eq. 21 from Eq. 20 and eliminating d(x) by Eq. 14 we obtain:

$$\frac{d\delta C(x)}{\delta C(x)} = n\frac{dQ_w(x)}{Q_w(x)} - (n+1)\frac{dQ_d(x)}{Q_d(x)} \tag{22}$$

where $n = K_d/J_v$. Integration of Eq. 22 along the length of the filter yields:

$$(C_w(x) - C_d(x)) = [Q_w(x)]^n \cdot [-Q_d(x)]^{-(n+1)} \cdot (-A1) \tag{23}$$

where A1 is an integration constant. The condition of conservation of solute, both in blood and dialysate side, implies:

$$Q_w(x) \cdot C_w(x) + Q_d(x) \cdot C_d(x) = A2 \tag{24}$$

where A2 is a constant. Multiplying Eq. 23 by $Q_w(x)$ we find

$$Q_w(x) \cdot (C_w(x) - C_d(x)) = -A1\,[Q_w(x)]^{n+1} \cdot [-Q_d(x)]^{-(n+1)} \tag{25}$$

and multiplying Eq. 23 by $Q_d(x)$ we find:

$$Q_d(x) \cdot (C_w(x) - C_d(x)) = A1\,[Q_w(x)]^n \cdot [-Q_d(x)]^{-n} \tag{26}$$

Substracting Eq. 25 from Eq. 24 and adding Eq. 26 to Eq. 24 we find:

$$C_d(x) = \frac{1}{Q_{wi} - Q_{do}} A2 + A1\,[Q_w(x)]^{n+1} \cdot [-Q_d(x)]^{-(n+1)} \tag{27}$$

and

$$C_w(x) = \frac{1}{Q_{wi} - Q_{do}} A2 + A1\,[Q_w(x)]^n \cdot [-Q_d(x)]^{-n} \tag{28}$$

From the boundary conditions at x = 0 we find:

$$A1 = (C_{do} - C_{wi})(Q_{do})^{n+1} \cdot (Q_{wi})^{-n} \tag{29}$$

and

$$A2 = Q_{wi} \cdot C_{wi} - Q_{do} \cdot C_{do} \tag{30}$$

Substitution of A1 and A2 in Eqs. 27 and 28 and their further elaboration gives the concentration profile on the dialysate side:

$$C_d(x) = \frac{Q_{wi} \cdot C_{wi} - Q_{do} \cdot C_{do}}{Q_{wi} - Q_{do}} + \frac{Q_{wi}(C_{do} - C_{wi})}{Q_{wi} - Q_{do}} \cdot \frac{(1 - \frac{Q_f \cdot x}{Q_{wi} \cdot L})^{n+1}}{(1 - \frac{Q_f \cdot x}{Q_{do} \cdot L})^{n+1}} \tag{31}$$

and the concentration profile at the blood side by:

$$C_w(x) = \frac{Q_{wi} \cdot C_{wi} - Q_{do} \cdot C_{do}}{Q_{wi} - Q_{do}} + \frac{Q_{do}(C_{do} - C_{wi})}{Q_{wi} - Q_{do}} \cdot \frac{(1 - \frac{Q_f \cdot x}{Q_{wi} \cdot L})^{n}}{(1 - \frac{Q_f \cdot x}{Q_{do} \cdot L})^{n}} \tag{32}$$

Because of the boundary condition $C_{di} = 0$, Eq. 31 gives us an expression for the ratio of the diffusive mass transfer coefficient to the volume flux:

$$n = \frac{K_d}{J_v} = \frac{\ln[\frac{Q_{do} \cdot C_{do} - Q_{wi} \cdot C_{wi}}{Q_{wi}(C_{do} - C_{wi})}]}{\ln[\frac{(Q_{wi} - Q_f)Q_{do}}{Q_{wi} \cdot Q_{di}}]} - 1 \tag{33}$$

When membrane total surface area, flow rates and solute concentrations are known, Eq. 33 may be used to calculate the value of n and of K_d. By substituting the value of n in Eqs. 31 and 32 one may calculate the solute concentration profiles.
Alternatively, for the case that both the sieving coefficient of the solute and the free fraction equal one. Convective solute flux may also be regarded as the volume flux times the solute concentration in the membrane (C_m) approximated by $(C_w + C_d)/2$, rather than that in plasma water (C_w). Now starting from Eq. 12, by substituting Eq. 12 in Eqs. 17 and 18, we get another expression for the concentration in dialysate:

$$C_d(x) = \frac{Q_{wi} \cdot C_{wi} - Q_{do} \cdot C_{do}}{Q_{wi} - Q_{do}} + \frac{Q_{wi}(C_{do} - C_{wi})}{Q_{wi} - Q_{do}} \cdot \frac{(1 - \frac{Q_f \cdot x}{Q_{wi} \cdot L})^{n+1/2}}{(1 - \frac{Q_f \cdot x}{Q_{do} \cdot L})^{n+1/2}} \qquad (34)$$

and for the concentration in plasma water:

$$C_w(x) = \frac{Q_{wi} \cdot C_{wi} - Q_{do} \cdot C_{do}}{Q_{wi} - Q_{do}} + \frac{Q_{do}(C_{do} - C_{wi})}{Q_{wi} - Q_{do}} \cdot \frac{(1 - \frac{Q_f \cdot x}{Q_{wi} \cdot L})^{n-1/2}}{(1 - \frac{Q_f \cdot x}{Q_{do} \cdot L})^{n-1/2}} \qquad (35)$$

The ratio of the diffusive mass transfer coefficient to the volume flux is obtained from Eq. 34, using $C_{di} = 0$:

$$n = \frac{K_d}{J_v} = \frac{1/2 \ln[\frac{(Q_{wi} - Q_f)Q_{wi}}{Q_{di} \cdot Q_{do}}] - \ln[\frac{Q_{do} \cdot C_{do} - Q_{wi} \cdot C_{wi}}{Q_{wi}(C_{do} - C_{wi})}]}{\ln[\frac{(Q_{wi} - Q_f)Q_{do}}{Q_{wi} \cdot Q_{di}}]} \qquad (36)$$

K_d values calculated by using Eq. 36 are slightly higher than those calculated by using Eq. 33.
If K_d is known and C_{do} must be calculated, we use the formula derived by van Geelen [16]:

$$C_{do} = C_{wi} \cdot \frac{(Q_{wi}/Q_{do})^{n+1} - (Q_{wo}/Q_{di})^{n+1}}{(Q_{wi}/Q_{do})^{n} - (Q_{wo}/Q_{di})^{n+1}} \qquad (37)$$

COMMENTS

Two models have been described, the numerical and the analytical model. The numerical model describes the process more clear. However, use of the numerical model is more time-consuming. It may best be combined with the analytically derived expression of K_d as an initial estimation to start the approximation procedure.

The analytical model has a few limitations. It is only applicable for s=1 and F=1. This poses no problems when the model is used to study the transport of uremic toxins. Analysis of the consequences of the assumption that J_v is constant rather than decreasing along the length of the dialyzer on the calculated value of K_d, turns out to be not significantly different [17]. The analytical model presented here, cannot be used to calculate backfiltration from dialysate to blood. It is not applicable to protein-bound solutes, unless it is assumed that protein binding is irreversible, i.e. C_w can be substituted by $C_w \cdot F$.

A possible source of error in both the numerical and the analytical model is that 'unstirred layer effects', which would lead to an influence of the axial flow rates on the concentration gradient, are not taken into account.

In the next chapter, data are presented showing that, with low and variable dialysate flow rates, there is an appreciable effect of dialysate flow rate on the calculated value of K_d. A correction for this effect will be suggested in the following chapter.

REFERENCES

1. van Geelen JA, Vincent HH, Schalekamp MADH. Continuous arteriovenous haemofiltration and haemodiafiltration in acute renal failure. Nephrol Dial Transpl 1988; 2: 181-186.
2. Geronemus R, Schneider N. Continuous arteriovenous hemodialysis: A new modality for treatment of acute renal failure. Trans Am Soc Artif Intern Organs 1984; 30: 610-613.
3. Husted FC, Nolph KD, Vitale FC, Maher JF. Detrimental effects of ultrafiltration on diffusion in coils. J. Lab. Clin. Med. 1976; 3: 435-442.
4. Sargent JA, Gotch FA. Principles and biophysics of dialysis. In: Drukker W, Parsons FM, Maher JF. Replacement of renal function by dialysis. Martinus Nijhoff Medical Division Publ, The Hague, 1978.
5. Colton CK, Lowrie EG. Hemodialysis,: Physical principles and technical considerations, in: The Kidney, second edition 1981; 2: 2425-2489.
6. Grimsrud L, Babb AL. Velocity and concentration profiles for laminar flow of a newtonian fluid in a dialyzer. Chem Eng Progr Symp Ser no 66 1966; 62: 20-31.
7. Sigler MH, Teehan BP. Solute transport in continuous hemodialysis: A new treatment for acute renal failure. Kidney International 1987; 32: 562-571.
8. Pallone TL, Hyver S, Peterson J. The simulation of continuous arteriovenous hemodialysis with a mathematical model. Kidney Int 1989; 35: 125-33.
9. Jaffrin MY, Ding L, Laurent JM. Simultaneous convective and diffusive mass transfer in a hemodialyser. Trans of the ASME. 1990; 212: 212-219.
10. Colton CK, Smith KA, Merrill EW, Reece JM. Diffusion of organic solutes in stagnant plasma and red cell suspensions. Chem Eng Progr Symp Ser no 66, 1970; 99: 85-100.
11. Colton CK, Henderson LW, Ford CA, Lysaght MJ. Kinetics of hemodiafiltration I. In vitro transport characteristics of a hollow-fiber blood ultrafilter. J Lab Clin Invest 1975; 85: 355-371.
12. Landis EM, Pappenheimer JR. Exchange of substances through the capillary wall, in: Handbook of Physiology. Circulation. Washington, Am Physiol Soc 1963, sect 2, vol II, chapt 29, p 962-1034.
13. Levitt DG. General continuum analysis of transport through pores. I. Proof of Onsager's reciprocity postulate for uniform pores. Biophys J 1975; 15: 533-51.
14. Akcahuseyin E, Vincent HH, van Ittersum FJ, van Duyl WA, Schalekamp MADH. A mathematical model of continuous arterio-venous hemodiafiltration (CAVHD). Computer Methods and Programs in Biomedicine 1990; 31 215-224.

15. Vincent HH, van Ittersum FJ, Akçahuseyin E, Vos MC, van Duyl WA. Schalekamp MADH. Solute transport in continuous arteriovenous hemodiafiltration: A new mathematical model applied to clinical data. Blood Purif 1990; 8: 149-159.
16. van Geelen JA. Hemodiafiltration, simultaneous application of hemodialysis and hemofiltration. Thesis, 1983. University of Limburg, Maastricht, the Netherlands.
17. Akçahuseyin E, Vos MC, Vincent HH, van Duyl WA. A mathematical model on solute transport in continuous arteriovenous hemodiafiltration (CAVHD): The influence of taking into account the decrease in volume flux over the length of the dialyzer (in preparation).

CHAPTER 6

VALIDATION OF THE MATHEMATICAL MODEL OF CONTINUOUS ARTERIOVENOUS HEMODIAFILTRATION: THE ASSUMPTION OF MIXING CUP CONCENTRATIONS

INTRODUCTION

In the previous chapter, a mathematical model of solute transport in CAVHD was presented. In this model a number of assumptions were made. The most important assumption was the so called 'mixing cup' concentrations within both the blood and dialysate compartment. Assuming mixing cup concentrations is valid when compartments are well stirred, a condition which could be approached if flows are turbulent, but at least in the blood compartment, flow is laminar.

The true driving force for diffusion is the solute concentration gradient over the membrane, which may be equated with the difference between the solute concentration in blood and dialysate close to the membrane. In both the numerical and analytical model, these concentrations are approached by taking the bulk or 'mixing cup' concentrations in blood and dialysate (Figure 1a). This assumption implies that possible radial concentration profiles within either of the respective compartments are not taken into account. However, solute concentrations close to the membrane may be different from mixing cup concentrations, thereby inducing a radial concentration profile. It is evident that a concentration difference between the area close to the membrane and anywhere else in the blood or dialysate compartment will be generated by solute diffusion from blood to dialysate (Figure 1b) [6]. With assuming mixing cup concentrations, the concentration gradient over the membrane will be overestimated and K_d may be underestimated. Also, the solute concentration in the blood compartment can be higher near the membrane, as will be described below. Then, with assuming mixing cup concentrations, the concentration gradient over the membrane will be underestimated and K_d values may be overestimated.

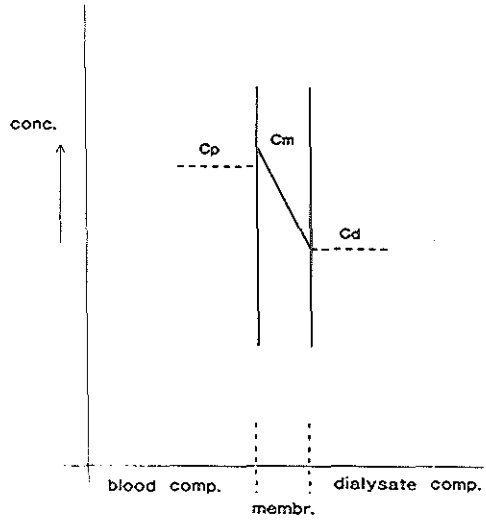

Figure 1a. Illustration of mixing cup concentrations on both sides of the membranes. In both the blood and dialysate compartment, no gradient of concentration is regarded. Concentration difference over the membrane is calculated from concentrations in blood (C_p) and dialysate (C_d). C_m: concentration in the membrane.

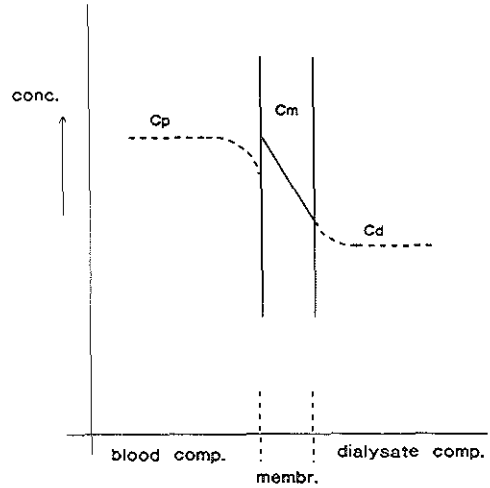

Figure 1b. Illustration of a possible concentration profile in both the blood (C_p) and dialysate compartment (C_d) due to diffusion from the blood to the dialysate compartment and due to concentration boundary layer formation. C_m: concentration in the membrane.

Factors influencing the radial concentration profiles

A radial concentration gradient can be influenced by blood and dialysate flow rates. In the blood compartment, as blood flow in the fiber is laminar, the distribution of solutes over the fiber is not homogeneous (i.e. concentration boundary layer formation) [6]. Accordingly, the difference between the concentration in the middle of the stream and that near the membrane may be expected to depend on the blood flow rate. Furthermore, with low blood flow rates, an inhomogeneous blood flow distribution might occur. Within the dialysate compartment, due to diffusive transport, the concentration near the membrane is higher than that more distant from the membrane. Furthermore, with low dialysate flow rates, a 'stagnant' fluid layer surrounds the fiber, which is not mixed with fresh dialysate. Within this layer, solute concentration is higher than more distant from the membrane. Therefore, this layer adds to the resistance to diffusion. At higher dialysate flow rates, the stagnant layer will diminish and the solute concentration in dialysate near the membrane will decrease until, at an infinitely high dialysate flow rate, no stagnant layers exist.

Thus, the axial flow rates may be expected to have an influence on the radial concentration gradient and thereby on the driving force for diffusion. As a result, when axial flow rates are changed, the calculated value of the mass transfer coefficient of diffusion (K_d) may also be changed [1, 2].

The influence of ultrafiltration rate on the solute concentration gradient during CAVHD has not been previously studied. It is, however, conceivable that, in case of ultrafiltration, dragging leads to a higher blood solute concentration near the membrane [4, 7], which would enhance diffusive transport (Figure 1c). On the other hand, ultrafiltration leads to an increased concentration of proteins near the membrane. This 'protein boundary layer formation' (protein concentration polarization) may lead to diminished membrane permeability and may thereby diminish transport by diffusion and convection.

By the assumption of mixing cup concentrations the possible influences of axial flows and of ultrafiltration on diffusion gradients are neglected. We are, therefore, faced with the question whether changes in blood- or dialysate flow rate and changes in ultrafiltration flow rate have an influence on the calculated value of K_d, based on the simplified model. In the present study we therefore measured solute clearance and calculated K_d values at different blood, ultrafiltration and dialysate flow rates.

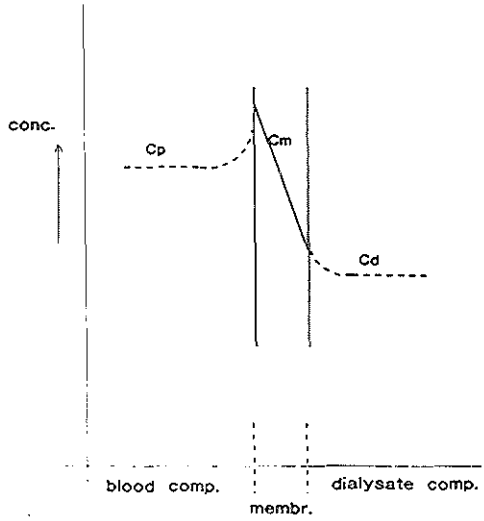

Figure 1c. Illustration of a possible influence of ultrafiltration on the solute concentration gradient in the blood compartment. Solutes are dragged along with the ultrafiltrate and near the membrane a concentration build up will occur.

PROTOCOLS

Studies were performed during CAVHD in the Intensive Care Unit. Some additional studies were performed in the laboratory. The *clinical procedure* has been described in Chapter 4. The study protocols are described below.

1. Blood flow rate (clinical observations)
This protocol was aimed at studying the effects of blood flow rate (Q_b) on calculated K_d values. The protocol was performed if the spontaneous blood flow through the filter was higher than 100 ml/min, because blood flow rate could only be decreased by clamping of the blood line. Pressures, spontaneous blood flow rate and ultrafiltration flow rate (Q_f) were measured two times, at the beginning and at the end of the experiment. At each experiment, by clamping the arterial or venous line, blood flow was lowered 4 times to varying degrees and in random order. Dialysate flow rate (Q_d) was set to 3 L/hr. Ultrafiltration flow rate was measured at each blood flow setting. Data were obtained with the AN-69, 0.6 m2 capillary dialyzer (Hospal, Multiflow-60).

II. Ultrafiltration flow rate (clinical observations)
This protocol was aimed at studying the effect of ultrafiltration flow rate on calculated K_d values. At each experiment, the ultrafiltration flow rate was changed 5 times, in 1 experiment 3 times, by increasing or decreasing the height of the ultrafiltration column. Dialysate flow rate was set to 2 L/hr. Pressures, blood flow rate and ultrafiltration flow rate were measured two times, at the beginning and at the end of the experiment. Data were obtained with the AN-69, 0.6 m2 capillary dialyzer (Hospal, Multiflow-60).

III. Dialysate flow rate (clinical observations)
This protocol was aimed at studying the effect of dialysate flow rate on calculated K_d values. After measuring pressures, blood flow rate and ultrafiltration rate, dialysate flow rate was set to 0.5, 1, 2 and 3 L/hr. At each dialysate flow rate samples were taken from blood and dialysate (see below). Data were obtained with the AN-69, 0.6 m2 capillary dialyzer (Hospal, Multiflow-60), with the AN-69, 0.23 m2 plate dialyzer (Hospal) and with a polysulfone 0.23 m2 capillary dialyzer (Sorin HFT02). Details on dialyzer geometry are given in Chapter 3 and 4.

IV. Laboratory protocol
In the laboratory, measurements of solute transport were performed at blood flow rates of 50, 100 and 200 ml/min and dialysate flow rates of 0.5, 1, 3 and 5 L/hr at a fixed ultrafiltration rate of 2 L/hr. Ultrafiltrate, collected during clinical hemofiltration, was used for blood substitute. Data were obtained with the AN-69, 0.6 m2 capillary dialyzer (Hospal, Multiflow-60) for creatinine and phosphate.

Sampling of blood and dialysate

Samples were taken from the arterial line and from spent dialysate. In the clinical studies, arterial samples were taken at the beginning and at the end of the experiments. Concentrations in between were derived by linear interpolation. In the laboratory, samples from the blood inlet and outlet were taken at each flow rate. Dialysate samples of the outlet were taken at each setting of dialysate, blood or ultrafiltrate flow rate. They were taken after equilibration for a time span that secured the passage of at least 500 ml of dialysate fluid, i.e. 10 times the content of the dialysate compartment. In each sample, concentrations of urea, creatinine and phosphate were determined and in blood samples total protein concentration and hematocrit were determined as well.

TECHNIQUES OF MEASUREMENT

Arterial and venous line *pressures* were measured electronically and dialysate pressure was calculated from the ultrafiltrate column height. *Blood flow rate* was measured in triplicate by air bubble displacement. In the clinical studies where blood flow rate was varied, it was measured both by air bubble displacement and by the echo transit time technique, using the Transonics^R Clamp-on flowmeter [5]. Both methods yielded similar values. In the laboratory studies blood flow rate was measured by means of an electromagnetic flow probe. *Dialysate flow rate* and *ultrafiltration* rate were measured by electronic weighing and by timed collection.

CALCULATIONS

Hydraulic permeability index (MI, [ml · hr^{-1} · mmHg^{-1}]) was calculated as:

$$MI = \frac{Q_f \cdot 60}{TMP} \qquad (1)$$

where TMP is transmembrane pressure difference, calculated as described in Chapter 4. The filter *resistance to blood flow* (R_f, [mmHg · min · ml^{-1}]) was calculated as:

$$R_f = \frac{P_i + P_o}{Q_b} \qquad (2)$$

where P_i and P_o are the hydrostatic pressures at the inlet and outlet of the filter respectively. If R_f was higher than 0.40, clotting of the filter may be the case. For this reason, 1 out of 6 experiments in protocol II and 5 out of 45 experiments in protocol III were discarded.

The *mass transfer coefficient of diffusion* (K_d, [µm/min]) was calculated by using the analytical expression given in Chapter 5:

$$n = \frac{K_d}{J_v} = \frac{\ln\left[\frac{Q_{do} \cdot C_{do} - Q_{wi} \cdot C_{wi}}{Q_{wi}(C_{do} - C_{wi})}\right]}{\ln\left[\frac{(Q_{wi} - Q_f)Q_{do}}{Q_{wi} \cdot Q_{di}}\right]} - 1 \qquad (3)$$

The relationships between blood, filtrate and dialysate flow rates and K_d were examined in two ways. First, we plotted K_d as a function of flow rate and performed linear regression analysis if applicable. Second, we used the approach suggested by Wilson [6] (see below). The reciprocal of K_d, i.e. the *total resistance to diffusion* (R, [min/μm]) is the sum of the resistances exerted by the blood compartment (R_b), by the dialysate compartment (R_d) and by the membrane (R_m) [8]:

$$\frac{1}{K_d} = R = R_b + R_d + R_m \qquad (4)$$

According to Wilson, the influence of dialysate flow rate on the resistance to diffusion of the dialysate compartment may be examined by plotting the total resistance to diffusion as a function of Q_d to the power -*y*, where the value of *y* is empirically determined so as to yield a straight line. The y-intercept is taken to represent R_b+R_m (see Figure 2). We likewise defined the total resistance to diffusion as follows:

$$R = a \cdot Q_b^{-x} + b \cdot Q_d^{-y} + c \qquad (5)$$

where $a \cdot Q_b^{-x}$ represents R_b, $b \cdot Q_d^{-y}$ represents R_d and c represents R_m. a, b, c, x and y are positive values, to be determined by linear regression analysis. Eq. 5 indicates that an increase of blood or dialysate flow rate results in a decrease of the resistance to diffusion, i.e. an increase of K_d (see also ref [3]).

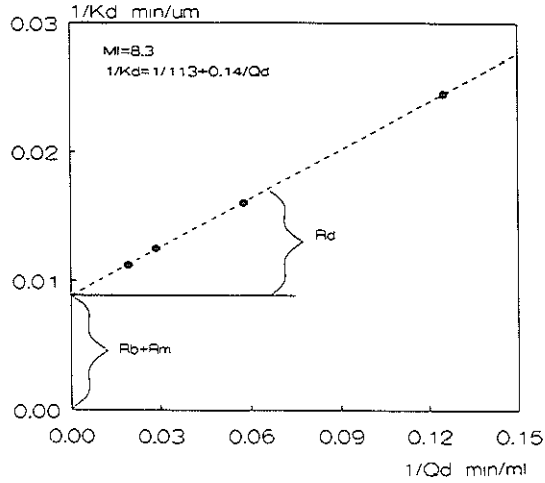

Figure 2. Example of a Wilson plot and the regression function obtained by linear regression analysis on data points shown.

RESULTS

Influence of blood flow rate

In protocol I, initial blood flow rate ranged from 105 to 195 ml/min. Filters had been used for 1 to 97 hours and MI ranged from 3 to 28 ml · hr^{-1} · $mmHg^{-1}$. During the experiment R_f did not change. With two filters that had been used for less than two hours, MI decreased by one fifth of the initial value.

Figure 3 shows K_d values at different blood flow rates. There was no apparent relationship. With linear regression analysis of K_d as a function of Q_b, 11 out of 13 slopes were not significantly different from zero (2 SE) and, of the remaining two, one slope was positive and the other slope was negative. The average slope was 0.00 (see Table 1).

Table 1. Effects of changes in blood and ultrafiltration flow rates on the mass transfer coefficient of diffusion of creatinine (K_d) and that of the reciprocal of dialysate flow rates on the resistance to diffusion of creatinine (R). Results of regression analyses. n=number of experiments. MF-60: AN-69, 0.6 m2 capillary dialyzer (Multiflow-60, Hospal, France). HFTO2: 0.23 m2 polysulfone capillary dialyzer (HFT-02, Sorin, Italy). CI: Confidence Interval.

Flow range ml/min	protocol	Dialyzer	n	Slope µm/ml	95% CI of the mean
	K_d vs Q_b:				
19-195	Clinic	MF-60	13	0.00	-0.06 - 0.06
50-200	Laboratory	MF-60	3	0.00	-0.01 - 0.00
	K_d vs Q_f:				
2-14	Clinic	MF-60	5	0.06	-1.04 - 1.16
	R vs Q_d^{-1}:				
8-50	Clinic	MF-60	15	0.16	0.14 - 0.18
8-85	Laboratory	MF-60	4	0.19	0.17 - 0.21
8-50	Clinic	Plate	11	0.11	0.10 - 0.12
8-50	Clinic	HFT02	14	0.11	0.07 - 0.15

Influence of ultrafiltration rate

In protocol II, initial ultrafiltration flow rate ranged from 6 to 11 ml/min. Filters had been used for 12 to 18 hours. Values of the hydraulic permeability index ranged from 11 to 14 ml $\cdot$ hr^{-1} $\cdot$ $mmHg^{-1}$.

Figure 4 shows K_d values at different ultrafiltration rates. Again, with linear regression analysis, slopes were not significantly different from zero (2 SE). The average slope was 0.06 µm/ml (see Table 1).

Influence of dialysate flow rate

In protocol III, MI ranged from 3 to 21. As shown in Figure 5, K_d increased to a maximum value with dialysate flow rates. Similar observations were made with the AN-69 0.6 m2 capillary dialyzer (n=15 experiments), the 0.43 m2 plate dialyzer (n=11) and the polysulfone 0.23 m2 capillary dialyzer (n=14).

For creatinine, the influence of dialysate flow rate was quantified according to Eq. 5 (see CALCULATIONS). Slopes obtained from the regression analysis of R as a function of Q_d^{-1} were all significantly different from zero (2 SE). The correlation coefficients (r) of the regression lines ranged from 0.91 to 1.00.

Both with the AN-69 capillary and plate dialyzers, the intercept of the regression line proved to be related to MI (Figure 6), whereas with the polysulfone capillary dialyzer this relationship could not be determined. For the AN-69 capillary dialyzer, we performed linear regression analysis on the intercept as a function of the reciprocal of MI (r=0.76). As the intercept equals the minimal resistance to diffusion obtained with infinite dialysate flow rates, the intercept was defined as the reciprocal of K_{dmax}. The relationship between K_{dmax} of creatinine and MI was given by:

$$K_{dmax} = \frac{MI}{12} \cdot 160 \quad (\text{for } MI < 12) \qquad K_{dmax} = 160 \quad (\text{for } MI \geq 12) \qquad (6)$$

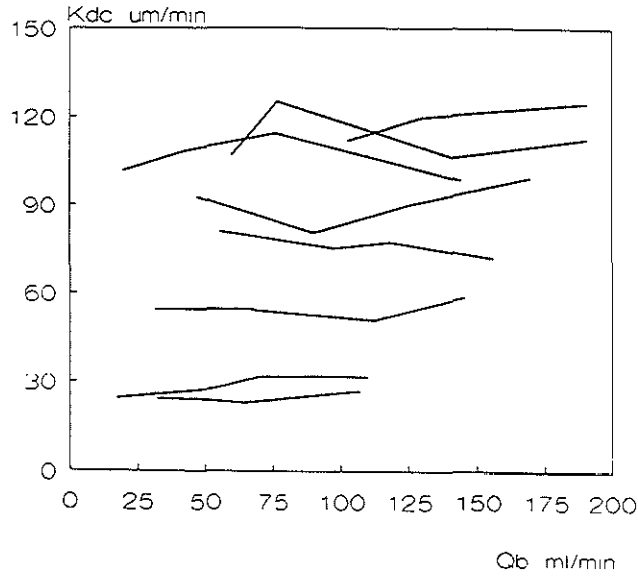

Figure 3. Diffusive mass transfer coefficient of creatinine (K_{dc}) for the AN-69 capillary dialyzer as a function of blood flow rate (Q_b). Each line represents one experiment.

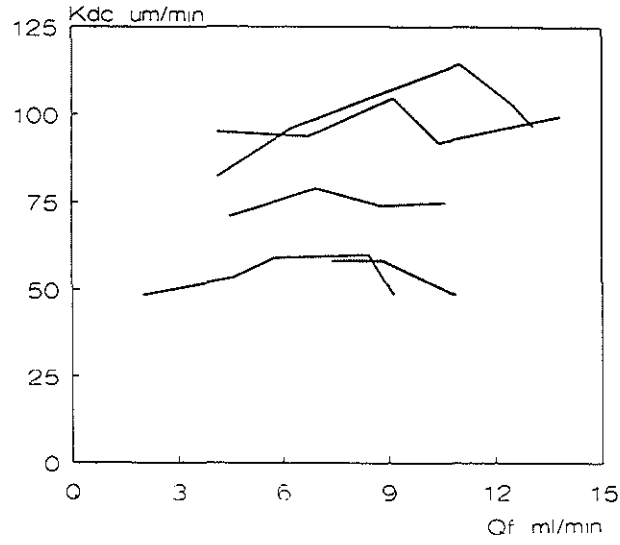

Figure 4. Diffusive mass transfer coefficient of creatinine (K_{dc}) for the AN-69 capillary dialyzer as a function of ultrafiltration flow rate. Each line represents one experiment.

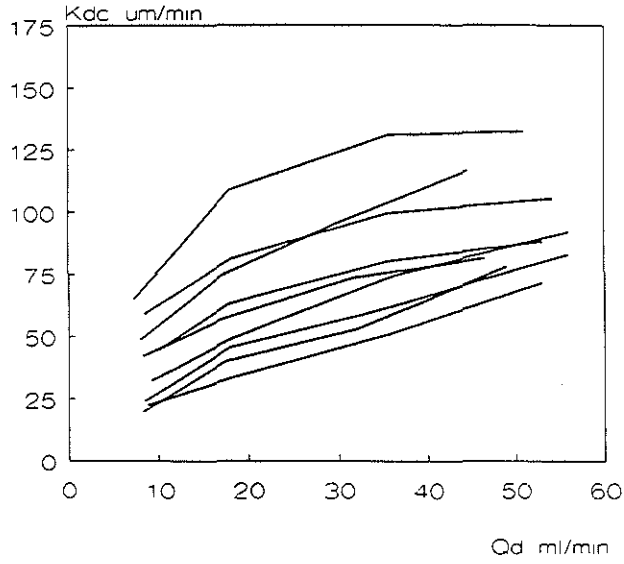

Figure 5. Diffusive mass transfer coefficient of creatinine (K_{dc}) for the AN-69 capillary dialyzer as a function of dialysate flow rate. Each line represents one experiment.

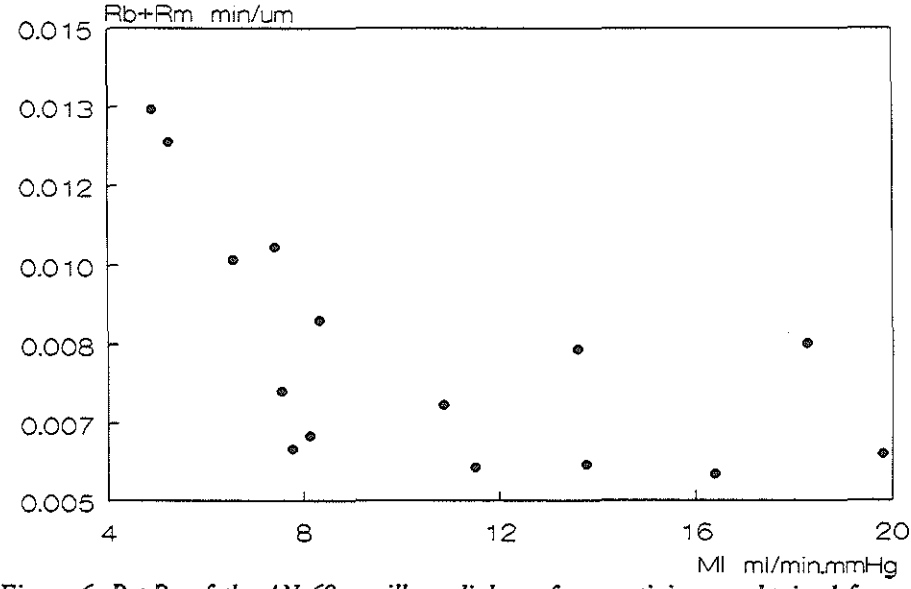

Figure 6. R_b+R_m of the AN 69 capillary dialyzer for creatinine as obtained from regression analysis on Wilson plots as a function of hydraulic permeability index of membrane (MI).

Validation of the model

Results from laboratory experiments

Results from the laboratory experiments were in accordance with clinical findings. The average slopes obtained from linear regression analysis of K_d as a function of Q_b and that obtained from the regression of R as a function of Q_d^{-1} are given in Table 1.

In all experiments, K_d values of urea and phosphate were closely related to the corresponding values of creatinine. The ratio of the K_d value of urea to that of creatinine averaged 1.32 (SEM=4, n=109) and the ratio of K_d of phosphate to that of creatinine averaged 0.75 (SEM=3, n=125).

DISCUSSION

With our model of combined convection and diffusion, we calculated the mass transfer coefficient of diffusion (K_d) based on the assumption of mixing cup concentrations. In the present study, we examined whether the same value of K_d may be used to extrapolate to solute clearance at different settings. We found that blood flow rate and ultrafiltration flow rate have no measurable influence on K_d. Accordingly, one may indeed use the model to predict solute clearance at blood flow and ultrafiltration rates, different from those during the experiment in which K_d was determined. On the other hand, dialysate flow rates (Q_d) does have an influence on K_d. Thus, when dialysate flow rate was increased from 0.5 to 3 L/hr, K_d values increased by approximately 100%. The effect of the dialysate flow rate on K_d was analyzed as described by Wilson [6]. The 'Wilson plots' allowed us both to estimate R_b+R_m and R_d separately. The increase of K_d with increasing Q_d may be explained by the existence of an unstirred layer in the dialysate compartment, or, at low dialysate flow rates, the distribution of dialysate over the compartment is inadequate, resulting in a partial use of the membrane surface area. Therefore, the increase of K_d with increasing Q_d, which may be ascribed to thinning of that unstirred layer in the dialysate compartment or an increase in the use of the membrane surface area, was quantified by a mathematical expression. Also, with the AN-69 dialyzers, K_d proved to be dependent on the hydraulic permeability index of the membrane (MI). Changes in K_d with different values of MI are contributed to a variability of R_b+R_m. As was shown in Chapter 4, MI decreases over time, probably due to protein absorption. Therefore, the variability of R_b+R_m may be caused by changes in R_m due to protein absorption on the membrane, whereas R_b is not variable. This explanation is

supported by the results of protocol I. Also, the influence of MI on K_d was quantified by a mathematical expression. By incorporating the mathematical relation of K_d with both Q_d and MI, one may allow for the influence of these parameters on K_d. This maneuver should allow to extrapolate to solute clearance at different dialysate flow rates and at different values of MI. Thus, for the AN-69 capillary dialyzer the predicting formula of K_d of creatinine becomes:

$$\frac{1}{K_d} = R = \frac{1}{K_{dmax}} + 0.15 \cdot Q_d^{-1} \qquad (7)$$

in which K_{dmax} is given by Eq. 6.
Since values of K_d of other solutes showed a fixed relationship with the value of K_d of creatinine obtained from the same experiment, this relationship can be used to estimate K_d of other solutes as well.

REFERENCES

1. Babb AL, Maurer CJ, Deloss LF, Popovich RP, McKee RE. The determination of membrane permeabilities and solute diffusivities with application to hemodialysis. Chem Eng Progr Symposium Series no 84, 1968; 64: 59-68.
2. Kooyman J.M. Comparative performance of artificial kidneys. Thesis, 1971. Technical University Delft, the Netherlands.
3. Sakai K. Technical determination of optimal dimensions of hollow fibre membranes for clinical dialysis. Nephrol Dial Transplant 1989; Suppl 4: 73-77.
4. Popovich RP, Cristopher TG, Babb AL. The effects of membrane diffusion and ultrafiltration properties on hemodialyzer design and performance. Chem Eng Progr Symposium Series no 114, 67: 105-115.
5. Burton RG, Gorewit RC. Ultrasonic flowmeter. Uses Wide-beam transit-time technique. Medical Electronics 1984; 15: 68-73.
6. Colton CK, Lowrie EG. Hemodialysis: Physical principles and technical considerations. In: The Kidney, Brenner, Rector. Saunders, New York 1981, 2nd ed., Vol. 2, page 2425-2489.
7. Jaffrin MY, Ding L, Laurent JM. Simultaneous convective and diffusive mass transfers in a hemodialyser. Journal of Biomechanical Engineering 1990; 112: 212-219.
8. Sigdell JE. Calculations of combined diffusive and convective mass transfer. Int J Artif Organs 1982; 5: 361-372.

CHAPTER 7

PREDICTION OF THE SOLUTE MASS TRANSFER COEFFICIENT OF DIFFUSION AND THE SOLUTE CLEARANCE RATE IN CONTINUOUS ARTERIOVENOUS HEMODIAFILTRATION

INTRODUCTION

The mass transfer coefficient of diffusion (K_d, [μm/min]), as calculated by our mathematical model of combined convection and diffusion, was found to be related to the hydraulic permeability index of the membrane (MI, [ml · hr^{-1} · $mmHg^{-1}$]) and dialysate flow rate (Q_d, [ml/min]). This relationship was mathematically expressed as:

$$\frac{1}{K_d} = \frac{1}{K_{dmax}} + \frac{0.15}{Q_d} \qquad (1)$$

where K_{dmax} of creatinine is given by:

$$K_{dmax} = \frac{MI}{12} \cdot 160, \quad \text{For } MI < 12: \qquad K_{dmax} = 160, \quad \text{For } MI \geq 12 \qquad (2)$$

In addition, a fixed relationship was found between K_d of creatinine (K_{dc}) and that of urea (K_{du}) and that of phosphate (K_{dp}):

$$K_{du} = K_{dc} \cdot 1.32 \qquad K_{dp} = K_{dc} \cdot 0.75 \qquad (3)$$

In the present chapter, we examined whether these formulas may be used to obtain a reliable prediction of K_d and solute clearance rate (Cl, [ml/min]). Furthermore, nomograms were constructed to facilitate these predictions in the clinical setting.

Input values for the prediction of K_d are dialysate flow rate and MI. For prediction of the clearance rate the value of plasma water flow rate at the filter inlet (Q_{wi}, [ml/min]) must be known. As both values of MI and Q_{wi} are not routinely measured in the clinic, formulas were constructed to estimate these values. In this way, prediction of clearance rates are more easily to perform in the clinical setting. Graphics were created to read the value of MI from the value of the ultrafiltration

flow rate and the value of Q_{wi} from the value of the mean arterial pressure of the patient. The influences of errors resulting from these estimations on the prediction of K_d and MI were calculated.

METHODS

Data were obtained from several clinical experiments, i.e from the experiments described in Chapter 6 and from the measurements of clearance rates of drugs (see Chapter 8), in which creatinine, urea and phosphate were measured simultaneously. All data were obtained with the AN-69 capillary dialyzer. Hydraulic permeability index of the membrane, resistance to blood flow of the dialyzer (R_f, [mmHg · min · ml^{-1}]) and ultrafiltration flow rate (Q_f, [ml/min]) were measured as described in Chapter 4. Dialysate flow rate was checked by an electronic weighing device. If the resistance to flow was higher than 0.40, data were discarded. The mass transfer coefficient of diffusion was calculated using the analytical expression as described in Chapter 5 (Eq. 33). K_d values of creatinine were predicted according to formulas 1 and 2 and that of urea and phosphate according to formulas 1, 2 and 3.

In accordance with our model, we defined solute clearance rate as:

$$Cl = \frac{Q_{do} \cdot C_{do}}{C_{wi}} \tag{4}$$

where Q_{do} and C_{do} are flow rate and solute concentration at the dialysate outlet side of the dialyzer respectively, and C_{wi} is the solute concentration in plasma water at the blood inlet side of the dialyzer. Clearance rate was predicted by substituting the predicted value of K_d in the following formula derived by van Geelen [1]:

$$Cl = Q_{do} \cdot \frac{(Q_{wi}/Q_{do})^{n+1} - (Q_{wo}/Q_{di})^{n+1}}{(Q_{wi}/Q_{do})^{n} - (Q_{wo}/Q_{di})^{n+1}} \tag{5}$$

where n is $K_d \cdot S/Q_f$, S is membrane surface area, Q_{wo} the plasma water flow at the dialyzer outlet and Q_{di} and Q_{do} are dialysate flow rates at the dialyzer inlet and outlet respectively. For both K_d and Cl, linear regression analysis was performed on the observed values as a function of the predicted values and 95% confidence intervals were determined.

A nomogram was constructed to obtain the value of plasma water flow from the observed mean arterial pressure of the patient (MAP, [mmHg]) according to the following formula:

$$Q_{wi} = \frac{MAP - P_{iv}}{0.44} \cdot (1 - Ht) \cdot (1 - 0.00107 \cdot C_{prot}) + f \cdot Ht \qquad (6)$$

where the intravenous pressure of the patient (P_{iv}, [mmHg]) was taken to be 10 mmHg, hematocrit (Ht) 0.30, total protein concentration in plasma (C_{prot}) 50 g/dl, the fractional volume distribution of solutes in blood cells (f) zero and the total resistance to flow of the catheters and the dialyzer was taken to be 0.44, which equals mean observed values (see Chapter 4). Note that, if predilution is used, the value of the predilution flow rate has to be added up to the plasma water flow rate. For errors in the estimation of Q_{wi} up to 50%, the resulting error in the value of the predicted clearance rate was calculated for Q_d=1 L/hr, MI=8 and Q_f=8 ml/min. The value of Q_{wi} and that of clearance rate at 0% error (starting value) were 100 ml/min and 22 ml/min respectively.

Furthermore, a nomogram was constructed to obtain a value of MI from the observed values of Q_f in ml/hr and MAP according to the following formula, assuming equal values of the resistance to flow of both the catheters:

$$MI = \frac{Q_f}{\frac{MAP + P_{iv}}{2} + P_d - COP} \qquad (7)$$

where the pressure in the dialysate compartment (P_d, [mmHg]) was taken to be -37, which is obtained with an ultrafiltration column height of 50 cm and the colloid osmotic pressure (COP, [mmHg]) was taken to be 20. Accordingly, for errors in the estimation of MI up to 50%, the resulting errors in the predicted value of K_d for Q_d=1 and 3 L/hr were calculated by using Eq. 1 and 2 (starting value of MI=8). Then, the impact was determined of an underestimation and overestimation of K_d up to 50% on the predicted clearance rate for Q_f=8 ml/min and Q_{wi}=100 ml/min. Herewith, starting values of K_d were predicted for Q_d=0.5, 1 and 3 L/hr and MI=8.

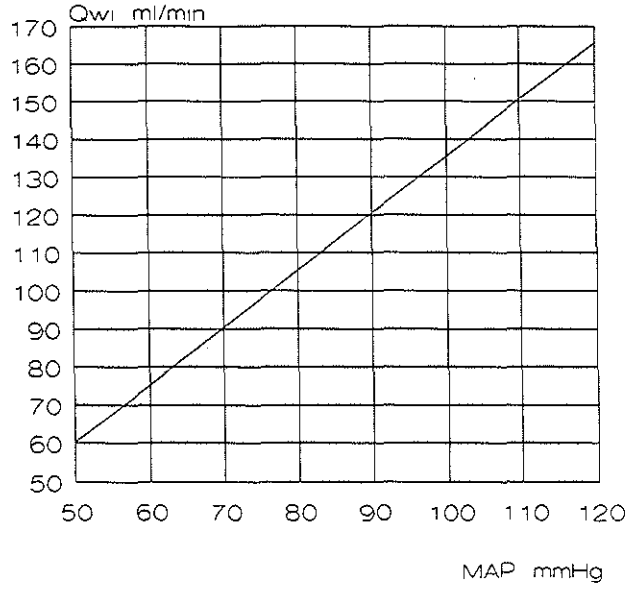

Figure 1. Expected plasma water flow rate as a function of mean arterial pressure (zero predilution flow rate and f=0).

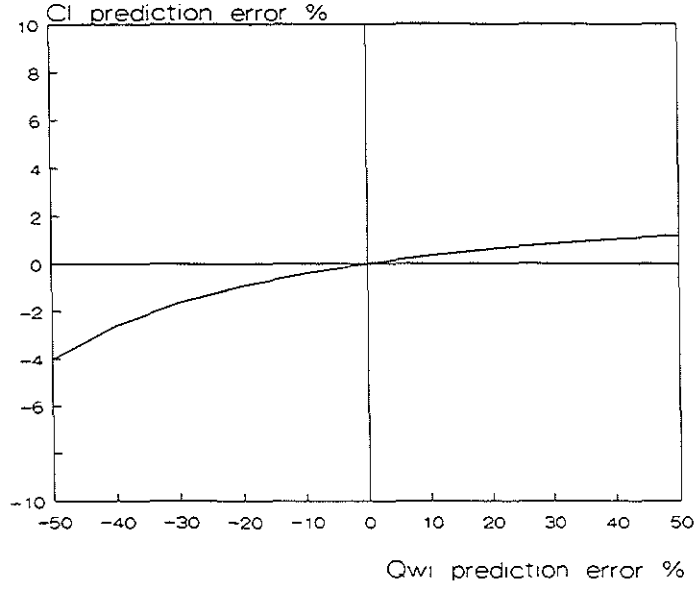

Figure 2. The error in terms of percentage in predicted clearance rates of creatinine as a function of an error in terms of percentage in the estimation of Q_{wi}.

RESULTS

From Figure 1, one can read the expected value of Q_{wi} by using the mean arterial pressure of the patient as input value. This Figure is based on values of the mean observed resistance of flow of the catheters and of the filter. Figure 2 shows the consequences of underestimation or overestimation of Q_{wi} on clearance rate. In Figure 3, the value of MI can be read from ultrafiltration flow rates for MAP values of 50, 70, 90 and 110 mmHg. Figure 4 shows the effect of an error in terms of percentage in MI on the prediction of K_d for Q_d=1 and 3 L/hr. The absolute error and the error in terms of percentage in clearance rates effected by an error in the predicted value of K_d are shown in Figures 5 and 6 respectively. Starting values for K_d were 35, 55 and 81 µm/min at Q_d=0.5, 1 and 3 L/hr respectively. Figures 7 and 8 show the observed values of K_d and Cl respectively of creatinine as a function of predicted values. The coefficient of determination (r^2) of K_d of creatinine was 0.73 (n=251) and that of clearance rate was 0.81 (n=255). For urea, these values were 0.70 (n=233) and 0.80 (n=249) and for phosphate 0.58 (n=230) and 0.71 (n=240) respectively.

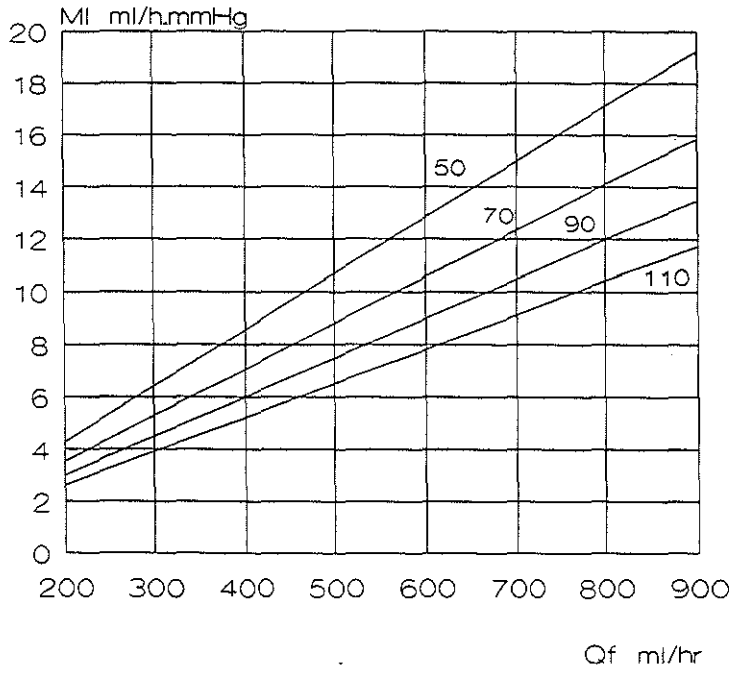

Figure 3. Expected values of MI as a function of ultrafiltration flow rate for mean arterial pressures of the patient of 50, 70, 90 and 110 mmHg.

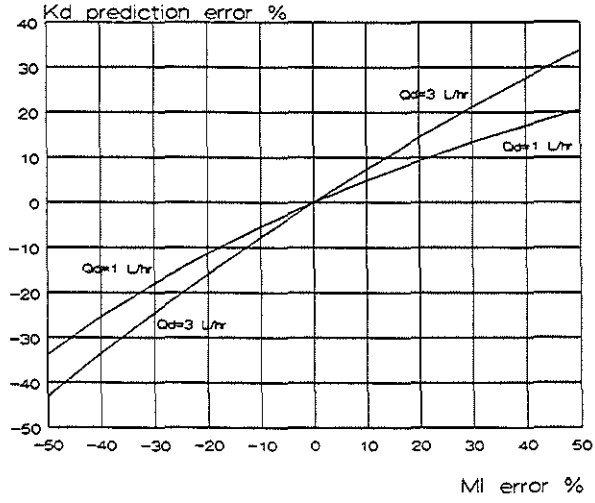

Figure 4. The error in terms of percentage in predicted K_d as a function of an error in terms of percentage in the estimation of MI (Q_d=1 L/hr and 3 L/hr).

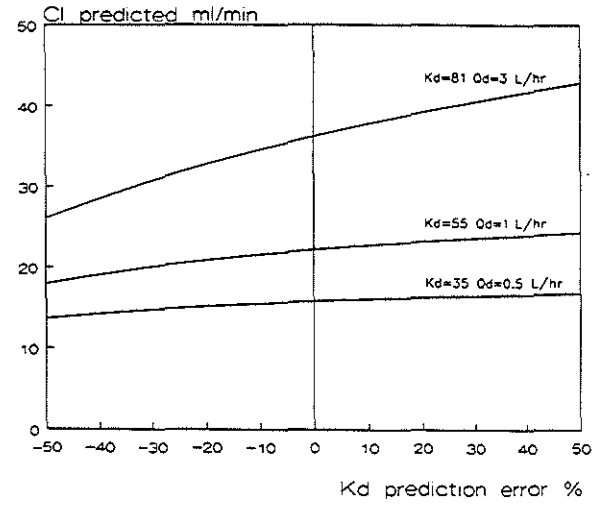

Figure 5. Predicted clearance rates of creatinine as a function of an error in terms of percentage in the predicted value of K_d.

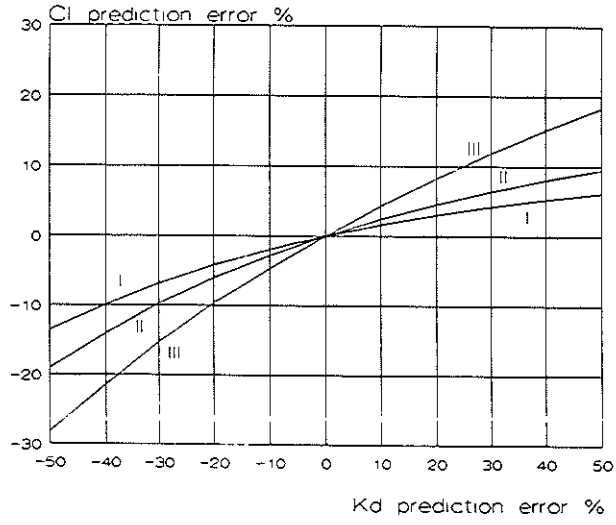

Figure 6. The error in terms of percentage in predicted clearance rates of creatinine as a function of an error in terms of percentage in the predicted value of K_d.
I = Q_d 0.5 L/hr, K_d = 35 µm/min
II = Q_d 1 L/hr, K_d = 55 µm/min
III= Q_d 3 L/hr, K_d = 81 µm/min

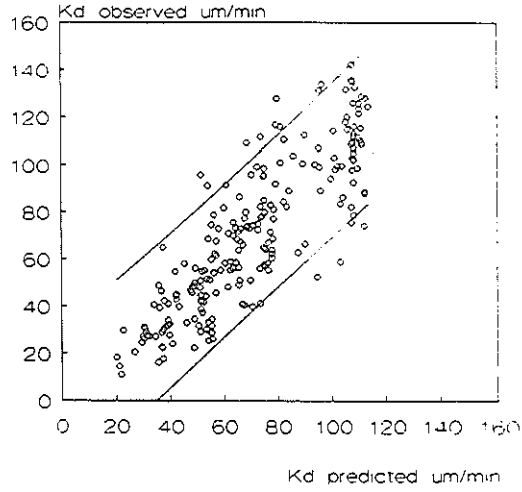

Figure 7. Observed values of K_d of creatinine as a function of predicted values and 95% confidence intervals. Data obtained with the AN-69 capillary dialyzer at different operational conditions.

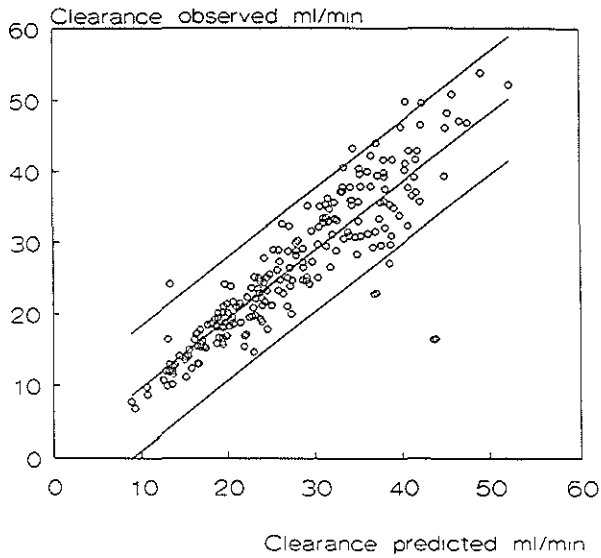

Figure 8. Observed values of creatinine clearance rate as a function of predicted values and 95% confidence intervals. Data obtained with the AN-69 capillary dialyzer at different operational conditions.

DISCUSSION

In this chapter the applicability of the prediction formulas of K_d of creatinine, as derived in Chapter 6, was examined. It was concluded that 73% of the variability of K_d of creatinine can be explained by variations in Q_d and MI. For prediction of K_d values of urea and phosphate, the predicted value of the K_d of creatinine was multiplied by the accompanying ratio. Comparing the predicted values of K_d of urea and phosphate with the observed values demonstrate that respectively 70% and 58% of the variability could be explained. Therefore, it can be concluded that the use of a fixed relationship between K_d of creatinine and that of other solutes is justified (Eq. 3). The main purpose of predicting K_d, is to obtain an indication of the expected clearance rate at different operational conditions. As clearance in CAVHD takes place by combined convection and diffusion, prediction of values of clearance rates will always be more accurate than prediction of K_d values. Therefore, explaining the variability in clearance rates was superior to that of K_d values.

The contribution of diffusive transport to the total transport of solutes increases with dialysate flow rate. Therefore, as was shown in Figure 6, the error of the predicted clearance rate generated by an error in the predicted K_d increases with dialysate flow rate. However, as the error in K_d was calculated in terms of percentage, the absolute change was higher at high dialysate flow rates with accordingly high K_d values.

Since values of Q_{wi} and MI are not readily available, nomograms are constructed. An underestimation or overestimation of Q_{wi} will induce a minimal error in the predicted clearance rate. Using an estimated value of MI, the error in the value of the predicted clearance rate is minimized by using the observed value of Q_f. In this way, an error in the estimation of MI depends only on the estimation of the transmembrane pressure difference. (see Eq. 1, Chapter 6). The transmembrane pressure difference can be calculated from the MAP, and mean values of the P_{iv}, the P_d, and the COP. If the ultrafiltration column height is 50 cm, the error in terms of percentage in MI due to a deviation of P_{iv} and COP from the values of 10 and 20 mmHg respectively, will not be higher than approximately 10%. Thus, when using the observed value of Q_f and MAP, errors in the estimation of MI would not be as high as is shown in Figure 4.

In conclusion, the prediction of clearance rates of different uremic solutes is feasible and can be simplified to be used in the clinical setting. In the next chapter, the feasibility of prediction of the clearance rate of drugs is examined.

REFERENCE

1. van Geelen JA. Hemodiafiltration, simultaneous application of hemodialysis and hemofiltration. Thesis, 1983. University of Limburg, Maastricht, the Netherlands.

CHAPTER 8

DRUG CLEARANCE BY CONTINUOUS ARTERIOVENOUS HEMODIAFILTRATION: ANALYSIS OF SIEVING COEFFICIENTS AND MASS TRANSFER COEFFICIENTS OF DIFFUSION

INTRODUCTION

With CAVHD, time-averaged clearance rates may be several fold higher than with either CAVH or conventional dialysis techniques. With the latter two techniques, it is known that some drugs are cleared to a significant extent [1-4]. Therefore, with CAVHD drug clearance rates may be high enough to warrant dosage adjustments. To determine dosage adjustments, insight into the determinants of transport is needed.

Clearance rate by CAVHD of uremic solutes can be reliable predicted by our mathematical model of combined convection and diffusion. This model can be further extended to transport of drugs. Important determinants of transport of drugs are the sieving coefficient and the mass transfer coefficient of diffusion (K_d, [μm/min]). They have to be experimentally determined. When the values of these two parameters are known, our model may be used to calculate drug clearance rates under a variety of operational conditions. In this study, clearance rates of urea, creatinine, uric acid, phosphate and of the antibiotics cefuroxime, cefotaxime, ceftazidime, imipenem, ciprofloxacin, tobramycin and vancomycin are measured in patients who were treated with CAVHD. In patients receiving imipenem, concentrations of cilastatin were measured too. By using the numerical mathematical model of hemodiafiltration (see Chapter 5), the data were analyzed in terms of sieving coefficients and mass transfer coefficients of diffusion. The relationship between K_d values of creatinine and K_d values of drugs were determined.

METHODS

The clinical protocol is described in Chapter 4. Drugs were given as clinically indicated. If an antibiotic was prescribed, the patient was eligible for this study.

Study protocol

First, the infusion pumps for dialysate and substitution fluid were turned off. The dialyzer condition was established by measuring the resistance to blood flow (R_f, [mmHg · min/ml]) and the membrane hydraulic permeability index (MI, [ml/h · mmHg]). Samples of blood and ultrafiltrate were taken to determine the drug's apparent sieving coefficient (see Calculations) and the free fraction. Then, the substitution fluid infusion pump was turned on and samples of blood and ultrafiltrate were taken again. After that, the dialysate flow rate was set to 1 L/hr. Dialysate samples were taken to determine clearance rates and diffusion coefficients of creatinine, urea, uric acid, phosphate and of the drug. The same procedure was repeated at a dialysate flow rate of 3 L/hr. Samples were taken after equilibration for a time span that secured the passage of at least 500 ml of ultrafiltrate or dialysate fluid, i.e. 10 times the content of the dialysate compartment. Finally, the dialysate pump was turned off and MI and R_f were determined again. The study protocol implied blood sampling to a total volume of 35 ml, which is 20 ml in excess of the routine.

Measurements

Pressures in the arterial and venous blood line (P_a and P_v, [mmHg]), pressure in the dialysate compartment (P_d, [mmHg]) and ultrafiltration rate (Q_f, [ml/min]) were measured as described in Chapter 4. Dialysate flow rate at the inlet of the dialyzer (Q_{di}, [ml/min]) was checked using an electronic weighing device. Blood flow (Q_b, [ml/min]) was determined either by measuring the time required for air bubble displacement over a certain length of tubing containing a volume of 13 ml or by measuring the transit time of an echo signal, using the Transonics^R HT101D flowmeter with a clamp-on probe around the blood line [5]. Both methods yielded similar values.

When the dialyzer condition was poor, i.e. when the resistance to blood flow was higher than 0.40 mmHg · min · ml^{-1} and/or ultrafiltration rate was less than 175 ml/min, the data were discarded.

Calculations

The dialyzer resistance to flow and the hydraulic permeability index of the membrane were calculated as described in Chapter 4. The sieving coefficient (s) was calculated as:

$$s = \frac{2 \cdot C_f}{C_{wi} + C_{wo}} \qquad (1)$$

with C_f the drug concentration in ultrafiltrate, and C_{wi} and C_{wo} the drug concentrations in plasma water at the blood inlet and outlet respectively (for calculation of C_{wi} and C_{wo} see Chapter 5). Note that this is the clinical definition of the sieving coefficient, which is equivalent with the physical definition of '*apparent*' sieving coefficient. The *true* sieving coefficient, i.e. the fraction of non protein bound solute that passes through the membrane during ultrafiltration, is taken to be one. With high flux membranes, this assumption is valid for solutes of up to several thousand Daltons. The *apparent* sieving coefficient of a solute, s, as calculated according to Eq. 1, i.e. the product of the *true* sieving coefficient and the *free fraction* should then be equal to the free fraction.

Clearance (Cl, [ml/min]), defined as the rate of mass transfer divided by the total concentration in plasma at the blood inlet, was calculated as:

$$Cl = \frac{Q_{do} \cdot C_{do}}{C_{pi}} \qquad (2)$$

Where Q_{do} and C_{do} are flow rate and solute concentration at the dialysate outlet of the dialyzer respectively, and C_{pi} is the solute concentration in plasma at the blood inlet side of the dialyzer.
From the observed flow rates and solute concentrations, K_d was calculated using the numerical model as described in Chapter 5.

Drug assays

Blood samples were centrifugated and the plasma was stored at -80°C. Total (bound plus free) drug concentrations were measured in plasma and in filtrate / dialysate. Concentrations of tobramycin and vancomycin were determined by a fluorescence polarization immunoassay [6]. The day to day variability of the assay of tobramycin was 4% and that of vancomycin 7%. Concentrations of cefuroxime, cefotaxime, ceftazidime, imipenem, ciprofloxacin and cilastatin were determined by H.P.L.C. [7-

11] with slight modifications. The day to day variability of the H.P.L.C. assay was 6% for cefuroxime, 7% for cefotaxime, 7% for ceftazidime, 7% for imipenem and 5% for ciprofloxacin.

To determine drug protein binding, plasma samples were centrifuged through a porous membrane of regenerated cellulose (Centri-free system, Amicon, U.S.A.) with a molecular cut-off of 30, 000 Daltons. The free fraction was calculated as the ratio of the concentration in the filtrate to that in plasma water. Protein binding of imipenem was not determined, since plasma samples containing imipenem were immediately stabilized by buffering to pH 6.5, by which protein binding is reduced. Protein binding of ciprofloxacin was not determined.

Table 1. Range of drug clearance rates during CAVH and CAVHD.
[1]: Total of measurements at dialysate flow of 1 L/hr and 3 L/hr.

DRUG	n[1]	Q_f	Cl_{cavh}	Cl_{cavhd} 1 L/hr	Cl_{cavhd} 3 L/hr
		ml/hr	ml/min	ml/min	ml/min
Cefuroxime	22	270-990	4-14	7-26	10-42
Cefotaxime	13	380-990	5-13	9-20	17-25
Ceftazidime	24	240-890	4-14	13-30	17-38
Imipenem	23	180-720	4-12	8-34	17-49
Ciprofloxacin	4	410-490	7-8	18-23	24-39
Tobramycin	30	240-880	3-12	13-24	17-32
Vancomycin	6	330-740	4-8	8-20	11-20
Cilastatin	24	200-720	2-9	6-20	7-24

RESULTS

The study protocol was performed 53 times in 32 patients with 19 dialyzers. With 9 protocols, the patient received two different antibiotics. Therefore, the total amount of measurements of clearance of antibiotics was performed 62 times, each measurement at two dialysate flow rates. Due to time the protocol needed to be performed, sieving coefficients were not determined at every protocol. Both for cefotaxime and ciprofloxacin, sieving coefficients were determined two times separately and at one of these occasions, clearance rate of cefotaxime was measured only at a dialysate flow rate of 1 L/hr. For imipenem, at one protocol, the

concentration of spent dialysate at a dialysate flow rate of 3 L/hr was too low to determine reliably and for tobramycin this occurred at 1 protocol for both dialysate flow rates. Blood flow rate was 125 (SD 32) ml/min and net ultrafiltration rate was 540 (SD 225) ml/hr. At a dialysate flow rate of 1 L/hr, urea clearance rate was 24 (SD 4) ml/min and creatinine clearance was 21 (SD 5) ml/min. At a dialysate flow rate of 3 L/hr these values were 42 (SD 9) and 32 (SD 7) ml/min respectively. At the time of measurements, dialyzers had been used for an average time of 50 hrs (range 0.75-291 hrs). The hydraulic permeability index of the membrane and the resistance to flow have not changed during the experiment.

Ranges of drug clearance rates are presented in Table 1. Sieving coefficients, measured free fractions and free fraction of normals are presented in Table 2.
The value of the sieving coefficient itself was not related to either the hydraulic permeability index of the membrane (MI) or to the rate of ultrafiltration (see Figure 1). The sieving coefficient was not different from the corresponding free fraction, as determined in the laboratory. The free fraction in our patients was, however, different from that in normal subjects (see Table 2).

The value of K_d of creatinine was 71 ± 30 (range 20 to 155) µm/min. This variability was largely explained by differences in membrane permeability, as reflected by the hydraulic permeability index, and by differences in dialysate flow rate (see Chapter 7). K_d values of a number of solutes, expressed as a percentage of the corresponding K_d of creatinine, are given in Table 3. Seventeen K_d values of drugs resulted in negative values or an error. K_d values were related to the solute molecular weight (see Figure 2). Regression analysis of the logarithm of K_d as a function of the logarithm of molecular weight (MW, [Daltons]) yielded the equation:

$$\frac{K_d}{K_{dc}} = \left(\frac{MW}{113}\right)^{-0.42} \qquad (3)$$

For some of the drugs, however, K_d values were appreciably higher than expected according to the regression equation. Using only the mass transfer coefficient of antibiotics (n=7), regression analysis yielded an exponent of -0.44 (r=0.67).

Table 2. Comparison of free fraction and sieving coefficient. The sieving coefficient during CAVH is not different from the free fraction as determined in the laboratory. Values of the measured free fraction and the apparent sieving coefficient in ICU patients were averaged to obtain the value of F, which will be used to predict clearance rates (see Chapter 9).

DRUG	Free fraction %				sieving coeff. %		F
	normals	[ref]	patients	n	patients	n	
Cefuroxime	67	[18]	78 ± 8	12	81 ± 10	21	0.80
Cefotaxime	60	[19]	77 ± 7	9	76 ± 12	14	0.76
Ceftazidime	83	[20]	86 ± 5	5	95 ± 5	12	0.92
Imipenem	80	[21]			100 ± 14	22	1.00
Ciprofloxacin	75	[22]			102 ± 7	6	1.02
Tobramycin	100	[23]	79 ± 5	9	83 ± 7	19	0.82
Vancomycin	45	[24]	56	1	68 ± 7	5	0.67
Cilastatin	20	[25]			68 ± 2	20	0.68

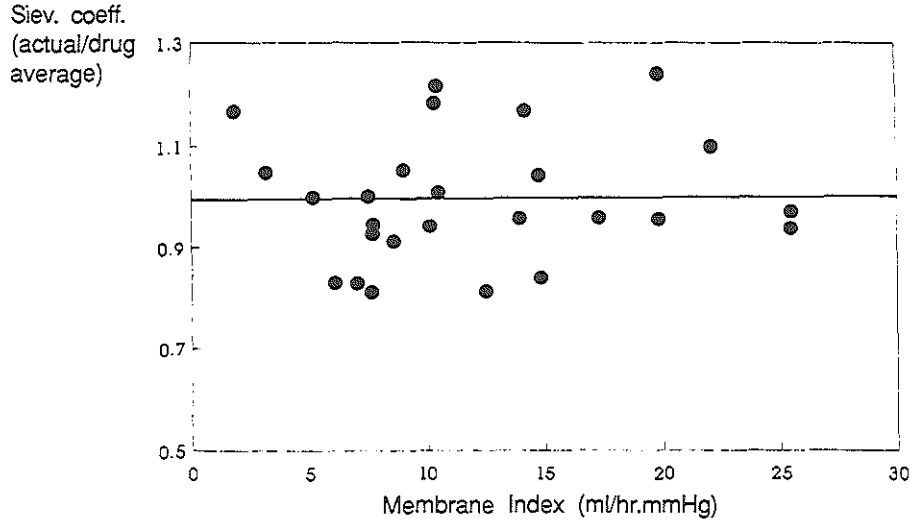

Figure 1. Relationship of the sieving coefficient of drugs (s) with the hydraulic permeability index of the membrane (MI).

Table 3. Solute molecular weight (MW) and mass transfer coefficient of diffusion (K_d) expressed as a percentage of the corresponding K_d of creatinine (K_{dc}).

[1] Estimated molecular weight in blood: At pH 7.40 with pKa 7.21, 39% is taken to be present as insoluble $Ca(H_2PO_4)_2$ and 62% as $Ca(HPO_4)$.
[2] In-vitro data supplied by D. Pouchoulin, Hospal C.O.T., Lyon, France.

SOLUTE	MW	K_d/K_{dc} %	SEM	n
Urea	60	132	4	109
Lactate	90	93	2	2
Creatinine	113	100		
Uric acid	168	93	4	123
Phosphate	174[1]	75	3	125
Vitamin B_{12}	1355	24[2]	1	5
Imipenem	317	68	8	20
Ciprofloxacin	331	85	12	2
Cilastatin	384	56	5	21
Cefuroxime	424	72	7	21
Cefotaxime	455	37	7	11
Tobramycin	468	72	6	26
Ceftazidime	547	66	6	22
Vancomycin	1449	37	4	5

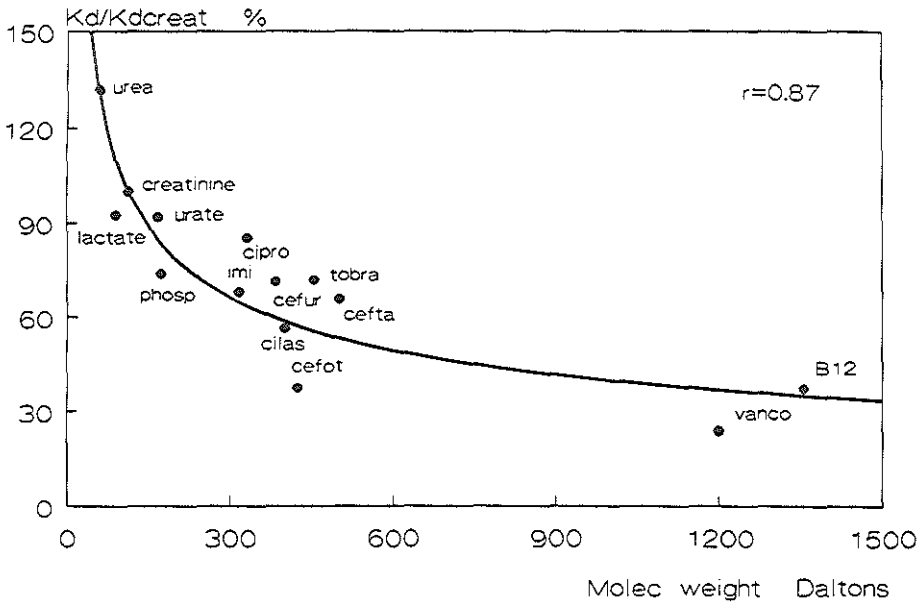

Figure 2. Relationship between K_d and solute molecular weight (MW). K_d values were expressed as a fraction of the corresponding K_d of creatinine (K_{dc}). Numerical values are given in Table 3.
Linear regression analysis of $Ln(K_d / K_{dc})$ as a function of Ln(MW) yielded a correlation coefficient (r) of 0.87.

DISCUSSION

In the previous chapter, the feasibility of the prediction of the value of K_d of creatinine based on dialysate flow rate and the hydraulic permeability index of the membrane was demonstrated. To use this model for prediction of drugclearance, the ratio of K_d of creatinine to that of the drug and the sieving coefficient of the drug was determined. The present study yielded two important results.

First, it was demonstrated that a drug's apparent sieving coefficient may be equated to its non-protein bound fraction. The latter may be determined in the laboratory. Since, in patients, the non protein bound fraction may differ remarkably from values in normals, it would be worthwhile to have the free fraction routinely determined in a blood sample. The binding of acidic drugs may be decreased due to uremia, low levels of albumin, high levels of bilirubin and free fatty acids or due to competition by other drugs [12-14]. The binding of basic drugs may be increased due

to increased levels of α_1-acid glycoproteins, one of the acute phase proteins [15]. In general our data on sieving coefficients were roughly in accordance with data of several studies given by Bickley et al [16] and Kroh et al [17].

Second, we found a relationship between K_d/K_{dc} and solute molecular weight. With the AN-69 capillary dialyzer, drug clearance rates can now be predicted by the model as follows. First, dialysate flow rate and the membrane hydraulic permeability are determined for the estimation of K_d of creatinine. Then K_d of the drug is estimated, either from published values of K_d/K_{dc} (see Table 3) or from an estimation of K_d/K_{dc} based on the drug molecular weight. Then the free fraction, F, is either taken from published values or determined in the laboratory. The values are used for input in the model, by which drug transport may then be calculated for an average plasma water flow rate or estimated from the mean arterial pressure of the patient. (the influence of differences in blood flow rate is small). The whole procedure will be demonstrated in Chapter 9, in which predicted values of clearance rate of drugs will be compared to observed values.

It should be noted that the findings in this study are restricted to the dialyzer we used, the AN-69 capillary dialyzer. In case of other membranes with a smaller pore size or electric charge might cause the drug sieving coefficient to be different than its free fraction. Furthermore, it may be expected that the relationship between K_d and molecular weight depends on the membrane resistance to diffusion and its contribution to the overall resistance to diffusion of the dialyzer. This methodology for the analysis of drug clearance by CAVHD, however, should be readily applicable to other dialyzers.

In conclusion, this study shows the feasibility of determining free fractions and K_d values of drugs. With these parameters the clearance during CAVHD may be predicted for different operational conditions. In the next chapter the reliability of such predictions will be examined and consequences for dosage adaptations will be considered.

REFERENCES

1. Golper TA, Bennett WM. Drug removal by continuous arteriovenous haemofiltration. A review of the evidence in poisoned patients. Medical toxicology 1988; 3: 341-349.
2. Kroh UF, Dehne M, El Abed K, Feußner KD, Hofmann W, lennartz H. Drug dosage during continuous hemofiltration: Pharmacokinetics and practical implications. Contrib Neprol 1991; 93: 127-130.
3. Slugg PH, Haug MT, Bosworth C, Paganini EP. Comparative vancomycin kinetics in intensive care unit patients with acute renal failure: Intermittent hemodialysis versus continuous hemofiltration hemodialysis. Contrib Neprol 1991; 93: 140-142.
4. Bennett WM, Arronoff GR, Morrison G, Golper TA, Pulliam J, Wolfson M, Singer I. Drug describing in renal failure: Dosing guidelines for adults. Am J of Kidney Disease 1983; 3: 155-193.
5. Burton RG, Gorewit RC. Ultrasonic flowmeter. Uses Wide-beam transit-time technique. Medical Electronics 1984; 15: 68-73.
6. Jolley ME, Stroupe SD, Wang CJ. Fluorescence polarization immunoassay I. Monitoring aminoglycoside antibiotics in serum and plasma. Clin Chem 1981; 27: 1190-1191.
7. Signs SA, File TM, Tan JS. High-pressure liquid chromatographic method for analysis of cephalosporins. Antimicrob Agents Chemother 1984; 26: 652-655.
8. Ayrton J. Assay of ceftazidime in biological fluids using high-pressure liquid chromatography. J Antimicrob Chemother 1981; 8 (Suppl B): 227-231.
9. Gravallese DA, Musson DG, Pauliukonis LT, Bayne WF. Determinations of imipenem in human plasma and urine by high-performance liquid chromatography. Comparison with microbiological methodology and stability. J Chrom 1984; 310: 71-84.
10. Myers CM, Blumer JL. Determination of imipenem and cilastatin in serum by high pressure liquid chromatography. Antimicrobial Agents and Chemotherapy 1984; 26: 78-81.
11. Brogard JM, Jehl F, Monteil H, Adloff M, Blickle JF, Levy P. Comparison of high liquid chromatography and microbiological assay for the determination of biliary elimination of ciprofloxacin in humans. Antimicrob Agents Chemother 1985; 28: 311-314.
12. Craig WA, Su B: Protein binding and the antimicrobial effects: Antibiotics in laboratory medicine. Lorian V. editor, second edition. Williams and Wilkins 1985, Chapter 13.

13. Perucca E, Grimaldi R, Crema A: Interpretation of drug levels in acute and chronic disease states. Clinical Pharmacokinetics 10; 498-513 1985.
14. Bodemham A, Shelly MP, Park GR: The altered pharmacokinetics and pharmacodynamics of drugs commonly used in critically ill patients. Clinical Pharmacokinetics 14; 347-373 1988.
15. Piafsky KM: Disease-induced changes in the plasma binding of basic drugs. Clinical Pharmacokinetics 1980; 5: 246-262.
16. Bickley SK: Drug dosing during continuous arteriovenous hemofiltration. Clinical Pharmacy 1988; 7: 198-206.
17. Kroh U, Hofmann W, Dehne M, El Abed K, Lennartz H: Dosisanpassung von pharmaka während kontinuierlicher hämofiltration. Anaesthesist 1989; 38: 225-232.
18. Bundtzen RW, Toothaker RD, Nielson OS, Mansen PO, Welling PG, Craig WA: Pharmacokinetics of cefuroxime in normal and impaired renal function: Comparison of high-pressure liquid chromatography and microbiological assays. Antimicrobial Agents and Chemotherapy 1981; 19: 443-449.
19. Fillastre JP, Leroy A, Humbert G, Godin M: Pharmacokinetics of cefotaxime in subjects with normal and impaired renal function. Journal of Antimicrobial Chemotherapy 1980; 6 suppl A: 103-111.
20. O'Callaghan CH, Acred P, Harped PB, Ryan DM, Kirby SM, Harding SM: GR 20263, a new broadspectrum cephalosporin with anti-pseudomonal activity. Antimicrobial Agents and Chemotherapy 1980; 17: 876-883.
21. Gibson TP, Demetriades JL, . Bland JA: Imipenem/cilastatin: Pharmacokinetic profile in renal insufficiency. The American Journal of Medicine 1985; 78 suppl 6a: 54-61.
22. Robberts DE, Williams JD: Ciprofloxacin in renal failure. Journal of Antimicrobial Chemotherapy 1989; 23: 820-823.
23. Gordon RC, Regamey C, Kirby WMM: Serum protein binding of the aminoglycoside antibiotics. Antimicrobial Agents and Chemotherapy 1972; 2: 214-216.
24. Moellering RC: Pharmacokinetics of vancomycin. Journal of Antimicrobial Chemotherapy 1984; 14 suppl D: 43-52.
25. Calandra GB, Brown KR, Grad LC, Akonkhai VI, Wang C, Aziz M. Review of experiences and tolerability in the first 2516 patients treated with imipenem/cilastatin. The American Journal of Medicine 1985; 78 suppl 6a: 65-70.

CHAPTER 9

DRUG CLEARANCE BY CONTINUOUS ARTERIOVENOUS HEMODIAFILTRATION: PREDICTION OF DRUG CLEARANCE RATE AND RECOMMENDED DOSE ADAPTATIONS FOR SEVEN ANTIBIOTICS

INTRODUCTION

In the previous chapter, clearance rates (Cl, [ml/min]) by CAVHD of different drugs were examined. Data were analyzed in terms of sieving coefficients and mass transfer coefficients of diffusion (K_d, [µm/min]). The ratio of the mass transfer coefficient of diffusion of drugs to that of creatinine was determined. As was shown in Chapter 6, clearance rates by CAVHD of uremic solutes other than creatinine could be predicted when the predicting formula of K_d of creatinine was extended by the ratio of K_d of the uremic solute to that of creatinine. In this chapter, the feasibility of predicting clearance rates of drugs, which have an apparent sieving coefficient lower than one, will be examined.

As patients treated by CAVHD are nearly always anuric, the removal of drugs which are normally excreted by the human kidney can occur predominantly by CAVHD. This is especially true if the protein binding of the drug is low, if the volume of distribution is small and if the non-renal clearance rate is low in comparison to the clearance rate by CAVHD. If a drug meets the demands as stated above, treatment by CAVHD will warrant dosage adaptations. Most previous studies on clearance of drugs by continuous renal replacements techniques focused on CAVH [1-5]. Recently, some studies have been published on drug clearance by CAVHD [6-8]. However, little is known about the required dosage regimens of drugs during treatment by CAVHD.

In the present chapter, drug clearance rates by CAVHD at different operational conditions are predicted and compared to observed values. Dosage adaptations are calculated for anuric patients treated by CAVHD at dialysate flow rates of 1 L/hr and 3 L/hr.

METHODS

Prediction of K_d and clearance rates of drugs

Clearance rates of cefuroxime, cefotaxime, ceftazidime, imipenem, tobramycin, vancomycin, ciprofloxacin and cilastatin were measured during CAVH and during CAVHD at a dialysate flow rate of 1 and 3 L/hr. The study protocol as well as the analysis of data has been described in Chapter 8.

The mass transfer coefficient of diffusion of drugs was predicted using the predicting formula of K_d of creatinine as described in Chapter 6, multiplied by the ratio of K_d of the drug to that of creatinine as given in Chapter 8. The mass transfer coefficient of diffusion was calculated by the numerical method as described in Chapter 5.

Predicted values of drug clearance were calculated by incorporating the predicted values of K_d in the following formula:

$$Cl = Q_{do} \cdot \frac{(Q_{wi}/Q_{do})^{n+1} - (Q_{wo}/Q_{di})^{n+1}}{(Q_{wi}/Q_{do})^{n} - (Q_{wo}/Q_{di})^{n+1}} \cdot F \cdot 1.05 \qquad (1)$$

where $n = K_d \cdot S/Q_f$, S [m^2] is membrane surface area, Q_{wo} [ml/min] the plasma water flow at the dialyzer outlet, Q_{di} and Q_{do} [ml/min] are dialysate flow rates at the dialyzer inlet and outlet respectively and F is the average of the apparent sieving coefficient and the free fraction of the drug concerned as given in Chapter 8, Table 2. To calculate plasma clearance rate from plasma water clearance rate, the latter is multiplied by 1.05, to account for the volume fraction of proteins. The whole procedure of calculating predicted values in the clinical setting is given in Figure 1. Observed plasma clearance rates were calculated as:

$$Cl = \frac{Q_{do} \cdot C_{do}}{C_{pi}} \qquad (2)$$

Linear regression analysis was performed for both predicted K_d values and clearance rates by CAVHD as a function of the observed values and 95% confidence intervals were calculated.

Example: Tobramycin (K_d/K_{dc}=0.72 F=0.82)

1	P_a = 68 mmHg π = 20 mmHg	P_v = 32 mmHg P_d = -30 cmH_2O ---> TMP = 51 mmHg	(Eq. 2, Chp 4)
2	TMP = 51 mmHg Q_f = 500 ml/hr	---> MI = 10 ml/hr·mmHg	(Eq. 6, Chp 4)*
3	MI = 10 ml/hr · mmHg Q_{di} = 2 L/hr	---> K_{dc} = 83 µm/min	(Eqs. 6, 7, Chp 6)
4	K_{dc} = 83 µm/min K_d/K_{dc} = 0.72	---> K_d = 60 µm/min	
5	Q_{bi} = 117 ml/min* Q_{di} = 33 ml/min Q_f = 8 ml/min Q_{pred} = 5 ml/min f = 0 S = 0.6 m^2 F = 0.82 Ht = 0.30 C_{prot} = 50 mg/L K_d = 60 µm/min C_{pi} = 10 mmol/L ---> C_{do} = 6 mmol/L (for procedure, see Figure 1, Chp 5)		(Eq. 11, Chp 5)
6	Q_{do} = 41 ml/min C_{do} = 6 mmol/L C_{pi} = 10 mmol/L ---> Clearance = 22 ml/min (Eq. 2, Chp 9)		

Figure 1. Algorithm for the prediction of drug clearance rate in CAVHD. For abbreviations see previous chapters or abbreviationlist.
** The value of MI and Q_{wi} can also be read from the nomograms (Chp 7).*

Dosage adaptations

The drug half life ($T_{½}ß$) during CAVHD treatment was calculated by using the formula:

$$T_{½}\ ß = \frac{0.693 \cdot V_z}{Cl} \qquad (3)$$

where V_z is the distribution volume of the drug [9]. Values of drug protein binding, of distribution volume, and of total and non-renal clearance rates were taken from the literature (see Table 1). If possible, all values, except the values of clearance rates in normals, were taken from studies, which obtained data from critically ill patients. Recommendations regarding dose adjustments were based on changes in the drug

clearance rates. For every drug, the average clearance rates by CAVHD at dialysate flow rates of 1 L/hr and 3 L/hr were used to calculate dose adaptations. A one compartment model of pharmacokinetics was used to calculate doses and dose intervals that led to the desired levels. Time related changes in drug concentrations were calculated according to:

$$C_{pt} = C_{p0} \cdot e^{-\frac{Cl \cdot t}{V_z}} \qquad (4)$$

where C_{p0} is the initial plasma concentration, C_{pt} is the plasma concentration after a time span t. Desired levels were determined by taking into account the drugs' mode of action and their toxicity [10-12]. Thus, for beta-lactams and imipenem, we aimed for plasma concentrations continuously above the minimal inhibitory concentration (MIC) of most common pathogens. For tobramycin the area under the curve (AUC) is probably the main determinant of efficacy [13]. Therefore, for this antibiotic, we aimed for high peak levels with trough levels low enough to reduce the risk of serious toxicity. For vancomycin the same strategy was followed. For ciprofloxacin, we aimed for high peak levels and trough levels not falling to low.

RESULTS

Figure 2 shows the correlation between the observed and predicted values of the K_d of all drug together (n=120). The coefficient of determination (r^2) was 0.42. Eight values were considered as outlayers.

Figure 3 shows predicted values of plasma clearance rate versus observed values of each drugs separately. In Figure 4, the correlation between the predicted clearance rates and the observed values are given for all drugs together. The coefficient of determination was 0.64, n=146. Values of ranges of drug clearance rates by CAVH and by CAVHD at a dialysate flow rate of 1 and 3 L/hr are given in Chapter 8. Average values ± SD of clearance rates at a dialysate flow rate of 1 L/hr and of 3 L/hr were for cefuroxime 15 ± 5 and 25 ± 9, for cefotaxime 14 ± 3 and 21 ± 3, for ceftazidime 18 ± 5 and 27 ± 6, for imipenem 18 ± 7 and 31 ± 9, for ciprofloxacin 21 ± 2 and 26 ± 6, for tobramycin 19 ± 3 and 26 ± 4, for vancomycin 15 ± 4 and 17 ± 4 and for cilastatin 12 ± 4 and 17 ± 5 ml/min respectively.

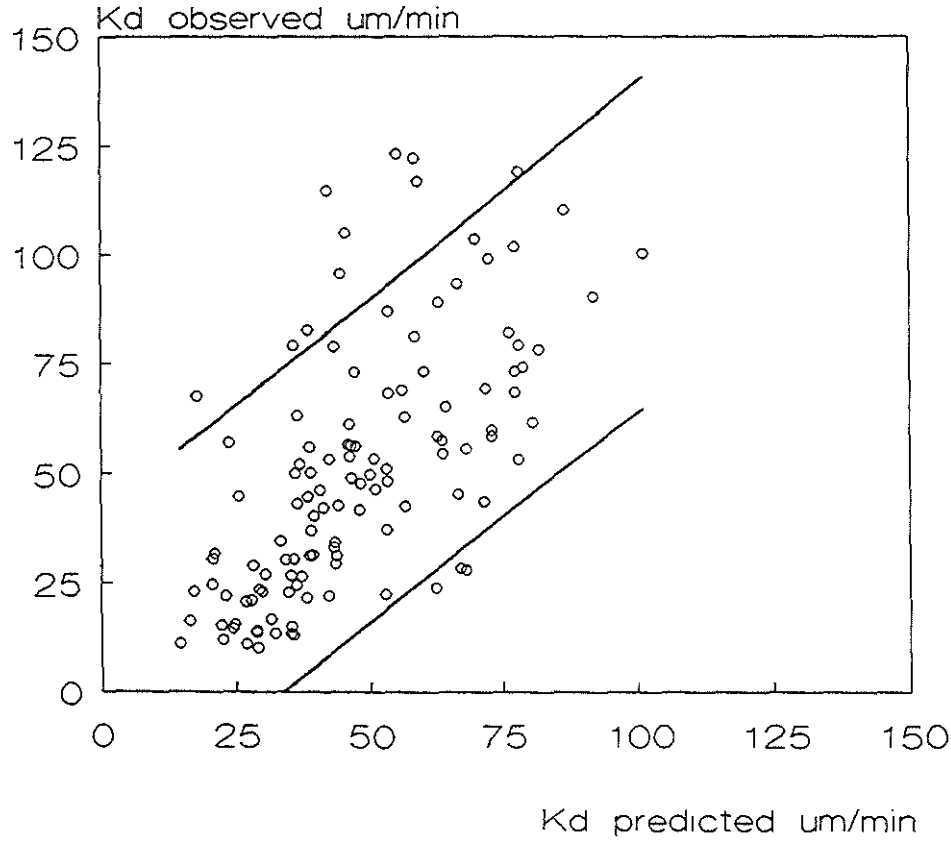

Figure 2. Comparison of observed values of K_d of eight different drugs calculated from membrane surface area, flow rates and drug concentrations, with values predicted from dialysate flow rate, membrane hydraulic permeability and the ratio K_d/K_{dc}. The lines show the 95% confidence intervals.

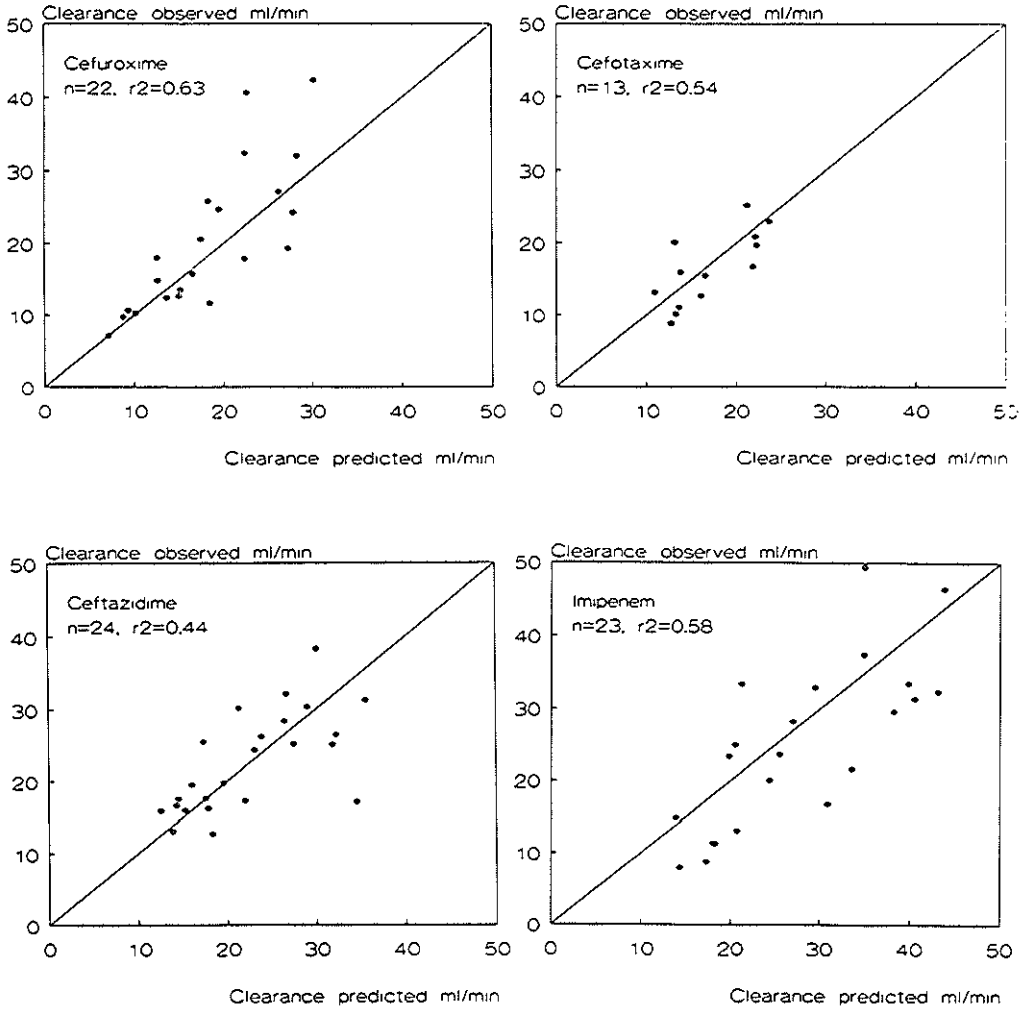

Figure 3. Clearance observed versus clearance predicted of each drug separately. Line of identity is given.

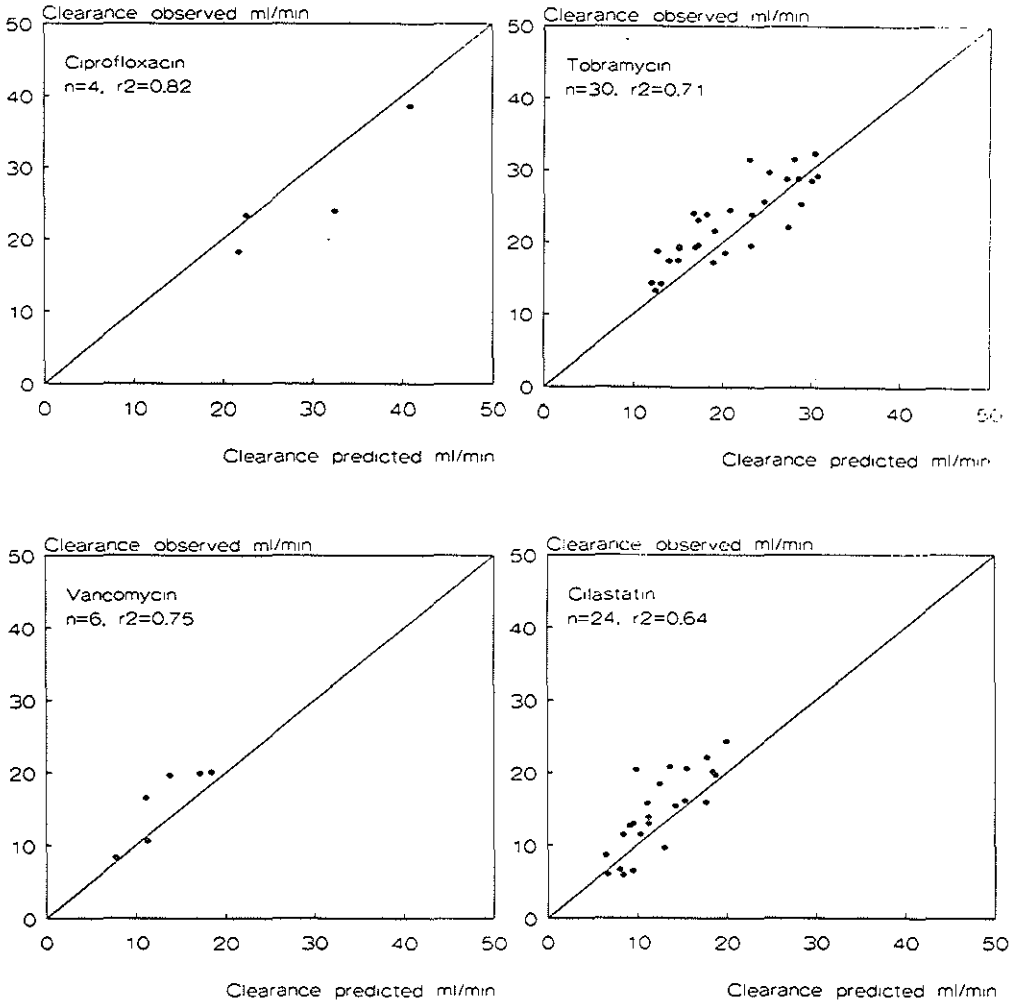
Clearance observed ml/min
Ciprofloxacin
n=4, r2=0.82
Clearance predicted ml/min
Clearance observed ml/min
Tobramycin
n=30, r2=0.71
Clearance predicted ml/min
Clearance observed ml/min
Vancomycin
n=6, r2=0.75
Clearance predicted ml/min
Clearance observed ml/min
Cilastatin
n=24, r2=0.64
Clearance predicted ml/min

Figure 3.

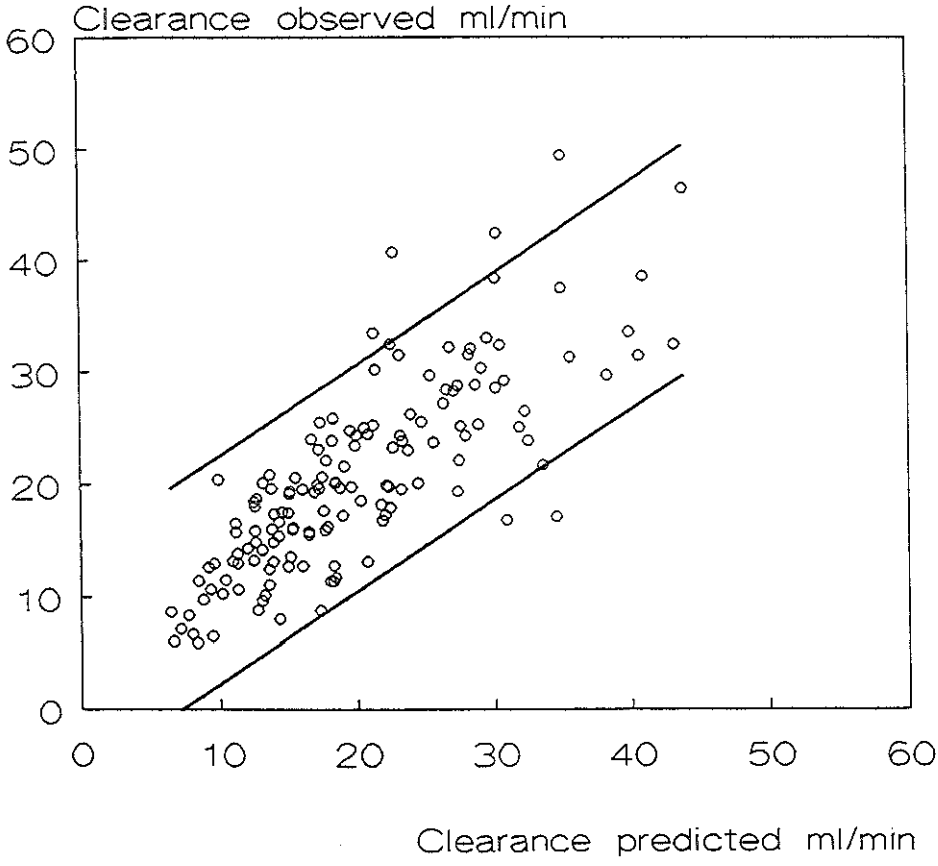

Figure 4. Clearance observed versus clearance predicted of eight different drugs together. The lines show the 95% confidence intervals.

Table 1. Volume of distribution, clearance rates and half lives in normals and in anuric patients with and without treatment by CAVHD.
[1] Data taken from literature.
[2] Sum of non-renal clearance rate and average clearance by CAVHD.
[3] Calculated by using Eq. 3 (body weight 70 kg).

Drug	V_z[1] [L/kg]	Clearance [ml/min]:				Half life [hr])				References
		normal[1]	anuric[1]	anuric CAVHD 1 L/hr[2]	anuric CAVHD 3 L/hr[2]	normal[3]	anuric[3]	anuric CAVHD 1 L/hr[3]	anuric CAVHD 3 L/hr[3]	
cefuroxime	0.23	115	5	20	30	1.7	38.7	9.3	6.2	[30]
cefotaxime	0.37	353	143	157	164	1.1	2.4	1.9	1.8	[31-35]
ceftazidime	0.18	115	8	26	35	1.7	25.3	5.6	4.2	[33, 34, 36-38]
imipenem	0.31	245	116	134	147	1.0	2.2	1.9	1.7	[4, 39-41]
ciprofloxacin	2.61	521	254	275	280	4.3	8.2	6.4	6.2	[42]
tobramycin	0.28	84	7	26	33	1.8	40.8	8.7	6.9	[43-45]
vancomycin	0.35	121	<5	20	22	3.7	90.2	14.2	12.9	[46-49]

Mean drug clearance rates and corresponding plasma half lives are given in Table 1. Differences between the values of clearance rate and half lives in the untreated anuric state and during treatment by CAVHD, were most pronounced for cefuroxime, ceftazidime, tobramycin and vancomycin. In the anuric state, adjustment of drug dosage was necessary for all antibiotics. During CAVHD treatment, further adjustment was required for cefuroxime, ceftazidime, tobramycin and vancomycin. Results of cilastatin will be discussed in Chapter 10. Guidelines for drug dosage in patients with untreated anuria and in patients treated by CAVHD are given in Table 2. Since the volume of distribution may effect drug half-life, the volume of distribution was varied in the model. An increasing or decreasing of V_z by 1.5 times did not affect the results in such a way that calculated dose or dose intervals needed to be adjusted.

Table 2: Guidelines for dosage adjustment in CAVHD and the aimed peak and trough levels.
1) Second and later administration: give half the standard dose.
2) Give half the standard dose.
3) Lean body mass
4) Adjust dosage according to peak and trough levels, measured respectively one hour after start of the infusion and shortly before a new dose.

Drug	Standard dose	Dose interval [hrs]:					
		normal	anuric	anuric CAVHD 1 L/hr	anuric CAVHD 3 L/hr	peak level mg/L	trough level mg/L
cefuroxime	750 mg	6	48	12	12	-	-
cefotaxime	1000 mg	6	8	8	8	-	-
ceftazidime	1000 mg	8	48[1]	12[1]	12[1]	-	-
imipenem	500 mg	6	12	12	12	-	-
ciprofloxacin	200 mg	12	12[2]	12[2]	12[2]	-	-
tobramycin	3 mg/kg[3]	12[4]	48-72[4]	24-48[4]	24[4]	8-10	< 2
vancomycin	500 mg	6[4]	48-72[4]	24-48[4]	24-48[4]	> 25	< 10

DISCUSSION

Prediction of clearance rates

In case of CAVH, the clearance rate is the product of the sieving coefficient and the rate of ultrafiltration. The latter is determined by the trans membrane pressure difference, which depends on operational conditions, and on the hydraulic permeability of the dialyzer, which decreases over time. Therefore, even for a given dialyzer, the clearance rate by CAVH is quite variable. It can, however, easily be estimated from the sieving coefficient and the rate of ultrafiltration.

Clearance by CAVHD, on the other hand, is determined by convective and diffusive transport. Diffusive transport is determined by the concentration gradient between blood and dialysate and the mass transfer coefficient of diffusion. Moreover, at high dialysate flow rates the mass transfer coefficient of diffusion is increased. A high ultrafiltration rate implies a high hydraulic permeability, which is associated with a high diffusive permeability, thus a high K_d value. Furthermore, the value of K_d corrected for operational conditions depends on the solute molecular weight. Therefore, it can be concluded that a mathematical model is required to estimate drug clearance by CAVHD. The use of the prediction formulas of K_d of creatinine, together with the ratio of K_d of drugs to that of creatinine as introduced in Chapter 8, resulted in a fairly accurate estimation of the clearance rate of drugs.

Furthermore, one can use this prediction model to estimate the clearance rate of other drugs or of solutes used in case of self-poisoning. The molecular weight and protein binding are input parameters and, when an indication is needed for the contribution of CAVHD to the total clearance rate, the endogenous clearance rate and the volume of distribution has to be known.

Dose adjustments

Dose adjustments of antibiotics are usually necessary for anuric patients, especially when clearance in these patients is low compared to that in normal subjects. If these patients are treated by CAVHD, the dosage regimen may be adjusted again. One might determine drug clearance by CAVHD in individual cases and determine drug dosage accordingly. For clinical practice, however, it is more convenient to use standard dosage regimens for patients treated by CAVHD, based on average clearance rates by CAVHD. Moreover, if one use such dosage regimens, a possible delay in time of establishing the desired plasma levels of the drug will be avoided.

In this study, we calculated dosage regimens to be used for anuric patients treated by CAVHD. The averaged observed values of drug clearance rates, used to calculate these dosage regimens, were approximately equal to the values of drug clearance rates, predicted by taking an average value of ultrafiltration flow rate and membrane index. Therefore, it is concluded that the calculated dose adaptations are based on average operational conditions. For each drug, the effect of the calculated dose adaptation on the plasma drug concentrations was considered when using input values of the drug clearance rate by CAVHD higher and lower as the averaged value. It was concluded that a considerable deviation in drug clearance rate by CAVHD from the value of the averaged clearance rate could take place before the recommended dose regimens were no longer appropriate. We used literature data on values of the volume of distribution measured in normal subjects. There have been several reports in the literature on changes in distribution volume in intensive care patients [14-18]. Data are still to scarce, however, to determine whether and to what extent appreciable changes really occur.

When constructing treatment regimens, the dose-efficacy relationship of antibiotics [10-12] and toxicity of certain antibiotics has to be regarded.

Killing of bacteria by beta-lactams is time dependent [12]. Furthermore, there is no concentration dependent killing above the MIC. These killing characteristics of beta-lactams would demand sustained concentrations above the MIC of the infectious organism. In animal models, continuous serum concentrations above the MIC of the infecting organism have been shown to be more efficacious, compared to transient peaks [11, 19]. Also, clinical outcome has been shown to be correlated to the time above the MIC of the infecting organism [20]. Therefore, for these antibiotics, we aimed for plasma levels continuously above the MIC of most common pathogens.

In contrast to beta-lactams, aminoglycosides do show concentration dependent killing activity on Gram-negative aerobes [10] and killing is relatively fast. This has been shown in vitro [21] as well as in vivo studies [22]. High peak concentrations have been found to be a major determinant of clinical response [23]. Furthermore, aminoglycosides show a postantibiotic effect against staphylococci as well as against various Gram-negatives [24, 25]. Vogelman et al [13] found a reduction of efficacy when the dosing interval was longer than the time period during which the serum levels exceeded the MIC plus the duration of the postantibiotic effect. Several studies conclude that the AUC is the main determinant of efficacy [13, 26]. Apart from efficacy, toxicity is an important issue. Nephrotoxicity, as well as oto- and vestibulotoxicity are major side-effects of aminoglycosides. Aminoglycosides are actively transported into the proximal tubular cells, and this transport is saturable [27, 28]. These findings have led to a decreased dosing frequency in the last few years

[29]. When reconstructing a dosage regimen of aminoglycosides during treatment by CAVHD, we considered these factors. Thus, we paid particular attention to trough levels low enough to minimize toxicity, and the dosing interval was increased rather than the dose was lowered.

The quinolones (ciprofloxacin) have a concentration dependent killing. Therefore, priority was given to high peak levels and a long dosing interval [12].

The most important finding of this study is that for cefuroxime, ceftazidime, tobramycin and vancomycin, the dosage regimen, used for anuric untreated patients, must be changed when the patient are treated by CAVHD. Failure to recognize this may easily lead to suboptimal drug levels and therapeutic failure. For the same reason, when there are alternative drugs of choice, clinicians may prefer drugs for which the influence of CAVHD on plasma levels can be neglected. Cefotaxime, imipenem and ciprofloxacin needed no dose adaptation during CAVHD. This was due to the relatively high non-renal clearance rates of these drugs, compared to that of CAVHD. It should be pointed out that the dosage regimens are theoretically derived from data obtained by a number of different studies. Although these dosage regimens are currently used in the clinic, the validity of these regimens needs confirmation. In the future, studies have to be performed to determine plasma drug levels over time with the present dosage recommendations.

REFERENCES

1. Bickley SK. Drug dosing during continuous arteriovenous hemofiltration. Clinical Pharmacy 1988; 7: 198-206.
2. Golper TA, Wedel SK, Kaplan AA, Saad AM, Donta ST, Paganini EP. Drug removal during continuous arteriovenous hemofiltration: theory and clinical observations. The International Journal of Artificial Organs 1985; 8: 307-312.
3. Keller E, Fecht H, Bohler J, Schollmeyer P. Single-dose kinetics of imipenem/cilastatin during continuous arteriovenous hemofiltration in intensive care patients. Nephrol Dial Transplant 1989; 4: 640-645.
4. Kroh U, Hofmann W, Dehne M, El Abed K, Lennartz H. Dosisanpassung von pharmaka während kontinuierlicher hämofiltration. Anaesthesist 1989; 38: 225-232.
5. Kroh UF, Dehne M, El Abed K, Feußner KD, Hofmann W, Lennartz H. Drug dosage during continuous arteriovenous hemofiltration. Contrib Nephrol 1991; 93: 127-130.
6. Davies SP, Kox WJ, Brown EA. Clearance studies in patients with acute renal failure treated by continuous arteriovenous haemodialysis. Contrib Nephrol 1991; 93: 117-119.
7. Reetze-Bonorden P, Bohler J, Kohler C, Schollmeyer P, Keller E. Elimination of vancomycin in patients on continuous arteriovenous hemodialysis. Contrib Nephrol 1991; 93: 135-139.
8. Slugg PH, Haug MT, Bosworth C, Paganini EP. Comparitive vancomycin kinetics in intensive care unit patients with acute renal failure: Intermittent hemodialysis versus continuous hemofiltration hemodialysis. Contrib Nephrol 1991; 93: 140-142.
9. Allen L, Kimura K, MacKichan J, Ritschell WA. Manual of symbols, equations and definitions in pharmacokinetics. J Clin Pharmacol 1982; 22S: 1-23.
10. Vogelman B, Craig WA. Kinetics of antimicrobial activity. Journal of Pediatrics 1986; 108: 835-840.
11. Roosendaal R, Bakker-Woudenberg IAJ, van den Berghe-van Raffe M, Vink-van den Berg JC, Michel MF. Impact of the dosage schedule on the efficacy of ceftazidime, gentamicin and ciprofloxacin in Klebsiella pneumoniae pneumonia and septicemia in leucopenic rats. Eur J Clin Microbiol Infect Dis 1989; 8: 878-887.
12. Cars O. Craig WA. General discussion on antibiotic dosing. Scand J Infect Dis 1991; 74S: 282-282.

13. Vogelman B, Gudmundsson S, Legett J, Turnidge J, Ebert S, Craig WA. Correlation of antimicrobial pharmacokinetic parameters with therapeutic efficacy in an animal model. The Journal of Infectious Disease 1988; 158: 831-845.
14. Perucca E, Grimaldi R, Crema A. Interpretation of drug levels in acute and chronic disease states. Clinical Pharmacokinetics 1985; 10: 498-513.
15. Bodemham A, Shelly MP, Park GR. The altered pharmacokinetics and pharmacodynamics of drugs commonly used in critically ill patients. Clinical Pharmacokinetics 1988; 14: 347-373.
16. Klotz U. Pathophysiological and disease-induced changes in drug distribution volume: Pharmacokinetic implications. Clinical Pharmacokinetics 1976; 1: 204-218.
17. Gibaldi M. Drug distribution in renal failure. The American Journal of Medicine 1977; 62: 471-474.
18. van Dalen R, Vree TB. Pharmacokinetics of antibiotics in critically ill patients. Intensive Care Medicine 1990; 16 S3: S235-S238.
19. Mordenti JJ, Quintiliam R, Nightingale CH. Combination antibiotic therapy, comparison of constant infusion and intermittent bolus dosing in an experimental animal model. J Antimicrob Chemother 1985; 15S: 41-45.
20. Schentag JJ. Correlations of pharmacokinetic parameters to efficacy of antibiotics: Relationship between serumconcentrations, MIC values, bacterial eradication in patients with gram-negative pneumonia. Scand J Infect Dis 1991; 74S: 218-234.
21. Auwera P van der, Klastersky J. Serum bactericidal activity and postantibiotic effect in serum of patients with urinary tract infection receiving high dose amikacin. Antimicrob Agents Chemother. 1987; 31: 1061-8.
22. Flueckiger U, C Feller AU Gerber. Dose-response curves in a man-adapted model: A novel view of comparative in vivo assessment of antibiotics. Program and abstracts of the twenty-sixth interscience conference on antimicrobial agents and chemotherapy, New Orleans, LA. 1986. American Society for Microbiology, Washington, DC. Abstract 577, page 202.
23. Moore RD, Lietman PS, Smith CR. Clinical response to aminoglycoside therapy:importance of the ratio of peak concentration to minimal inhibitory concentration. J Infectious Dis. 1987; 155: 93-9.
24. Vogelman BS, Craig WA. Postantibiotic effects. J Antimicrob Chemother. 1985; 15 SA: 37-46.

25. Craig WA, Gudmundsson S. The postantibiotic effect. In: Lorian V. (ed) Antibiotics in medicine, 2nd ed. Baltimore: Willaiams and Williams page 515-536.
26. Gerber AU, Wiprachter P, Stettlewr-Spichger U, Lebeh G. Constant infusion vs intermittent doses of gentamycin against Pseudomoas aeruginosa in vitro. J Infectious Dis. 1982; 155: 93-9.
27. De Broe ME, Verbist L, Verpooten GA. Influence of dosage schedule on renal cortical accumulation of amikacin and tobramycin in man. J Antimicrob Chemother. 1991; 27 SC: 41-47.
28. Verpooten GA, Giuliano RA, Verbist L, Eestermans G, De Broe ME. Once daily dosing decreases renal accumulation of gentamicin and netilmicin. Clin Pharmacology Therapeutics. 1989; 45: 22-7.
29. Tulkens PM. Efficacy and safety of aminoglycosides once-a-day: experimental and clinical data. Scand J Infect Dis 1991; 74S: 249-257.
30. Bundtzen RW, Toothaker RD, Nielson OS, Mansen PO, Welling PG, Craig WA. Pharmacokinetics of cefuroxime in normal and impaired renal function: Comparison of high-pressure liquid chromatography and microbiological assays. Antimicrobial Agents and Chemotherapy 1981; 19: 443-449.
31. Fu KP, Aswapokee P, Ho I, Matthijssen C, Neu H. Pharmacokinetics of cefotaxime. Antimicrobial Agents and Chemotherapy 1979; 16: 592-597.
32. Luthy R, Blaser J, Bonetti A, Simmen H, Wise R, Siegenthaler W. Comparative multiple-dose pharmacokinetics of cefotaxime, moxalactam and ceftazidime. Antimicrobial Agents and Chemotherapy 1981; 20: 567-575.
33. Balant L, Dayer P, Auckenthaler R. Clinical pharmacokinetics of the third generation cephalosporins. Clinical Pharmacokinetics 1985; 10: 101-143.
34. de Klerk Sommers, Walters L, van Wyk M, Harding SM, Paton AM, Ayrton J. Pharmacokinetics of ceftazidime in male and female volunteers. Antimicrobial Agents and Chemotherapy 1983; 23: 892-896.
35. Luthy R, Münch R, Blaser J, Bhend H, Giegenthaler W. Human pharmacology of cefotaxime (HR 756), a new cephalosporin. Antimicrobial Agents and Chemotherapy 1979; 16: 127-133.
36. Armstrong GC, Wise R, Brown RM, Hancox J. Comparison of ceftazidime and cefamandole. Pharmacokinetics and blister fluid concentrations. Antimicrobial Agents and Chemotherapy 1981; 20: 356-358.
37. Mouton JW, Horrevorts AM, Mulder PGH, Prens EP, Michel MF. Pharmacokinetics of ceftazidime in serum and suction blister fluid during continuous and intermittent infusions in healthy volunteers. Antimicrobial Agents and Chemotherapy 1990; 34: 2307-2311.

38. Leroy A, Leguy F, Borsa F, Spencer GR, Fillastre JP, Humbert G. Pharmacokinetics of ceftazidime in normal and uremic subjects. Antimicrobial Agents and Chemotherapy 1984; 25: 638-642.
39. Gibson TP, Demetriades JL, Bland JA. Imipenem/cilastatin: Pharmacokinetic profile in renal insufficiency. The American Journal of Medicine 1985: 78 suppl 6a: 54-61.
40. Wise R, Donovan MR, Lockley J, Drumm J, Andrews JM. The pharmacokinetics and tissue penetration of imipenem. Journal of Antimicrobial Chemotherapy 1986; 18 suppl E: 93-101.
41. Verpooten GA, Verbist L, Buntinx AP, Entwistle LA, Jones KH, de Broe ME. The pharmacokinetics of imipenem (thienamycin-formamidine) and the renal dehydropeptidase inhibitor cilastatin sodium in normal subjects and patients with renal failure. British Journal of Pharmacology 1984; 18: 183-193.
42. Drusano GL, Weir M, Forrest A, Plaisance K, Emm T, Standiford HC. Pharmacokinetics of intravenously administered ciprofloxacin in patients with various degrees of renal function. Antimicrobial Agents and Chemotherapy 1987; 31: 860-864.
43. Adelman M, Evans E, Schentag JJ. Two-compartment comparison of gentamycin and tobramycin in normal volunteers. Antimicrobial Agents and Chemotherapy 1982; 22: 800-804.
44. Levy J, Smith AL, Koup JR, Williams-Warren J, Ramsey B. Disposition of tobramycin in patients with cystic fibrosis: A prospective controlled study. The Journal of Pediatrics 1984; 101: 117-124.
45. Zarowitch BJ, Anadan JV, Dumler F, Jayanshankar J, Levin N. Continuous arteriovenous hemofiltration of aminoglycoside antibiotics in critically ill patients. J Clin Pharmacol 1986; 26: 686-689.
46. Blouin RA, Bauer CA, Miller DD, Record KE, Griffen WO. Vancomycin pharmacokinetics in normal and morbidly obese subjects. Antimicrobial Agents and Chemotherapy 1982; 21: 575-580.
47. Brown N, Ho DHW, Fong KLL, Bogerd L, Maksymiuk A, Bolivar R, Fainstein V, Bodey GP. Effects of hepatic function on vancomycin clinical pharmacology. Antimicrobial Agents and Chemotherapy 1983; 23: 603-609.
48. Blevins RD, Halstenson CE, Salem NG, Matzke GR. Pharmacokinetics of vancomycin in patients undergoing continuous ambulatory peritoneal dialysis. Antimicrobial Agents and Chemotherapy 1984; 25: 603-606.
49. Nielsen HE, Hansen HE, Korsager B, Skov PE. Renal excretion of vancomycin in kidney disease. Acta Med. Scand. 1975; 197: 261-264.

CHAPTER 10

CLEARANCE OF IMIPENEM/CILASTATIN IN ACUTE RENAL FAILURE PATIENTS TREATED BY CONTINUOUS ARTERIOVENOUS HEMODIAFILTRATION*

INTRODUCTION

The antibiotic Tiënam[R] (MSD/USA) is the combination of imipenem, a broad spectrum thienamycin antibiotic belonging to the antibiotic class of carbapenem, and of cilastatin, an inhibitor of renal dehydropeptidase-I, the enzyme responsible for the metabolism of imipenem in renal tubular cells. The addition of cilastatin serves both to prevent nephrotoxicity by imipenem and causes the intact drug to be excreted into the urine [1, 2]. Although imipenem and cilastatin differ with respect to protein binding, their volumes of distribution and routes of metabolism, their plasma half lives are quite similar in normal subjects. Imipenem/cilastatin is often used in patients with acute renal failure due to sepsis. In case of renal failure, however, the plasma half life of imipenem is little altered whereas that of cilastatin is very much prolonged. It would seem questionable, therefore, whether the use of the fixed dose combination is justified in these patients. In Chapter 9, results of the rate of removal of imipenem and cilastatin with continuous arteriovenous hemodiafiltration were given. In this chapter, the consequences of using imipenem/cilastatin in a fixed dose combination are analyzed in patients with renal failure when untreated and when treated by continuous arteriovenous hemodiafiltration.

METHODS

The clinical and study protocols are described in Chapter 8. Analysis and calculations of these data were described in Chapters 8 and 9. Data of clearance rates of imipenem and cilastatin were compared and consequences of using these drugs in a fixed dose combination were considered. Concentrations in time of imipenem and cilastatin were calculated for acute renal failure patients untreated and treated by CAVHD at a dialysate flow rate of 1 L/hr and 3 L/hr. Average values of drug distribution volume, clearance rates in normals and in anuric patients and plasma half

* Reprinted in revised form from Intensive Care Med. 1992, 18: 282-285

Table 1: Pharmacokinetics of imipenem and cilastatin.
[1] Data taken from literature.
[2] Sum of non-renal clearance rate and average clearance by CAVH and CAVHD.
[3] Calculated by using Eq. 3, Chapter 9 (body weight 70 kg).

Drug	V_z[1] [L/kg]	Clearance [ml/min]:					Calculated half life [hrs][3]					References
		normal[1]	anuric[1]	anuric CAVH[2]	anuric CAVHD 1 L/hr[2]	anuric CAVHD 3 L/hr[2]	normal	anuric	anuric CAVH	anuric CAVHD 1 L/hr	anuric CAVHD 3 L/hr	
imipenem	0.31	245	116	125	134	149	1.0	2.2	1.9	1.9	1.7	[3-6]
cilastatin	0.24	230	3	9	13	21	0.9	89	21.6	14.9	9.2	[3, 6-9]

lives were taken from the literature (see Chapter 9). Time related changes in drug concentrations were calculated according to:

$$C_{p_t} = C_{p_0} \cdot e^{-\frac{Cl \cdot t}{V_z}} \qquad (1)$$

where C_{p0} is the initial plasma concentration, C_{pt} is the plasma concentration after a time span t after a dose application, and Cl is clearance rate. Literature data on volume of distribution, normal and anuric clearance rates were combined with the average clearance rates by CAVHD to construct plots of plasma drug concentrations in time for imipenem and cilastatin.
Results are given as average ± SD.

RESULTS

The average clearance by CAVH (i.e. at zero dialysate flow rate) was 7 ± 3 ml/min (range 4-12) for imipenem and 6 ± 2 ml/min (range 2-9) for cilastatin. Results of clearance rate by CAVHD were already presented in Chapter 9. The implications of the observed clearance rate by CAVHD for total drug clearance rates and half lives of both imipenem and cilastatin are presented in Table 1. From this Table one can see that treatment of the anuric patient with CAVHD at Q_d 1 or 3 L/hr increases the clearance rate of imipenem by 15% or 25% and that of cilastatin by 335% or 600% respectively.

The usual dosage of Tiënam^R in our hospital is one intravenous dose (500 mg of imipenem + 500 mg of cilastatin) 4 times daily. Since, in patients with renal failure, the half-life of imipenem increases from 1.0 to 2.2 hrs, it was suggested in Chapter 9 that the dose interval in these patients should be doubled, i.e. one dose twice daily. The decrease of the half-life of imipenem by CAVHD is relatively small. Therefore, during CAVHD, no further dose adjustment is deemed necessary. Half live of cilastatin however, increases in patients with renal failure from 0.9 to 89 hrs. With the above dosage regimens, it was calculated by using Eq. 1, that plasma concentrations of imipenem and cilastatin run parallel in normal subjects (Figure 1). In patients with renal failure, before treatment with CAVHD, cilastatin accumulates. Over 5 days, a seven fold increase in plasma concentrations may be expected to occur (Figure 2). After institution of CAVHD, there is a four fold increase of the clearance rate of cilastatin and plasma concentrations decrease to approximately two times the concentration in normal subjects (Figure 3). Indeed, plasma concentrations of cilastatin ranged from 37-75 mg/L on the first day of CAVHD treatment and from

13-49 mg/L thereafter. These concentrations depend on the duration of the treatment with imipenem/cilastatin, the duration of the treatment by CAVHD and the time-span between administering the drug and taking the blood sample.

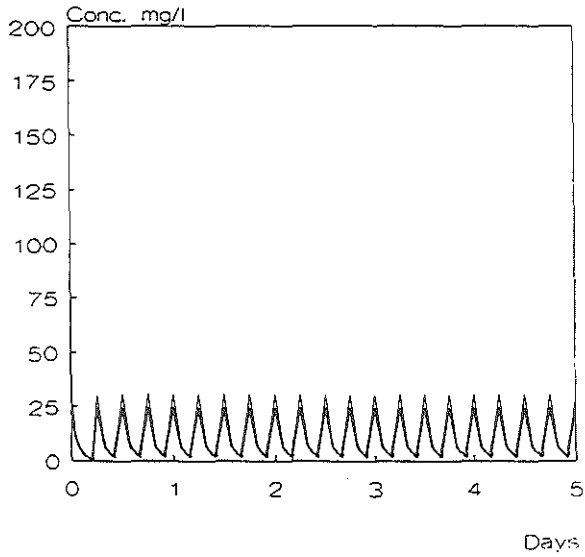

Figure 1. Plasma concentration of imipenem and cilastatin in time in normal subjects.

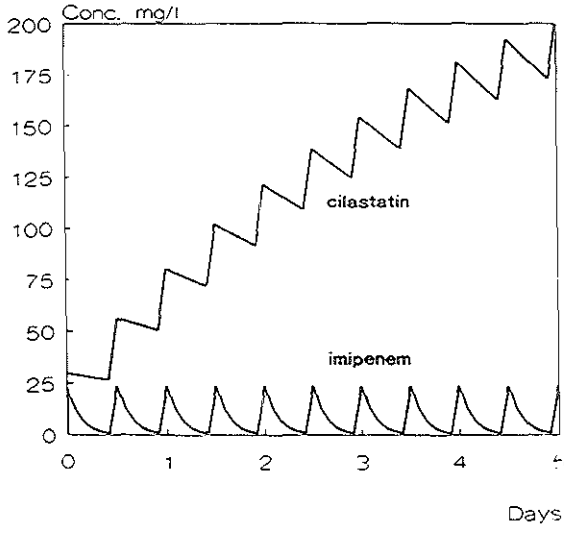

Figure 2. Plasma concentration of imipenem and cilastatin in time in anuric patients without renal replacement therapy.

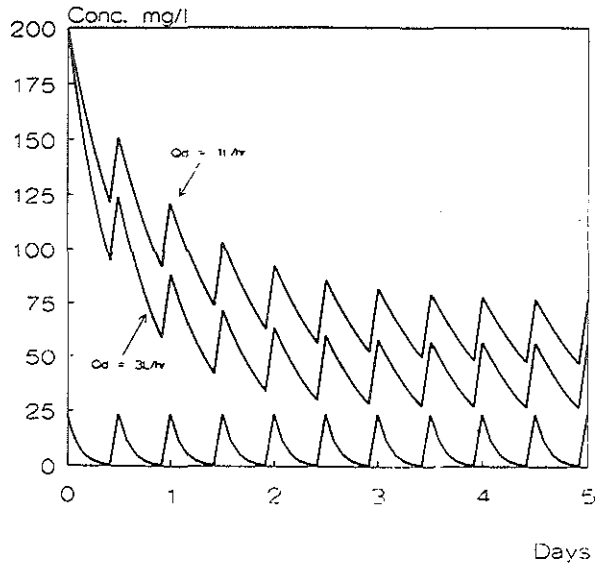

Figure 3. Plasma concentration of imipenem and cilastatin in time in anuric patients in whom CAVHD treatment is started 5 days after initiating drug treatment.
(With imipenem, plasma levels calculated for dialysate flow rates of 1 L/hr and of 3 L/hr are indistinguishable.)

DISCUSSION

For CAVH and CAVHD high flux membranes, such as AN-69, polysulfone and polyamide, are used. With these membranes solutes of up to several thousands Daltons, can freely pass through the membrane pores but proteins can not. In Chapter 8, it was shown that, at least with AN-69, the apparent sieving coefficient of a drug equals its non-protein bound fraction. Accordingly, our data indicate that protein binding of imipenem (MW 317) was 0% and that of cilastatin (MW 384) was 30%. These values, determined in intensive care patients, are considerably lower than those reported for normal subjects, i.e. 20% for imipenem and 44% for cilastatin [3].

Dosage regimens of imipenem/cilastatin are based only on desired levels of the antibiotic imipenem. In the anuric state, even after dose adjustment, the use of the fixed dose combination will lead to an overdosage of cilastatin. Although no evident toxicity of cilastatin has been reported so far [1, 3], the inevitable accumulation of this drug is to be regarded as undesirable. After hemofiltration or dialysis treatment

is instituted, however, accumulation of cilastatin may be reversed, depending on the type of treatment. This is caused by the contribution of such treatment to the total drug clearance, which is proportionally greater for cilastatin than for imipenem. With CAVHD, at a dialysate flow rate of only 1 L/hr, the clearance rate will be twice as high as with CAVH due to the addition of diffusive transport. Serious accumulation of cilastatin is thereby avoided. In case of continuous veno-venous hemofiltration (CVVH), an ultrafiltration flow rate of 1200 ml/hr would be needed to achieve clearance rates similar to those obtained by CAVHD. In view of the above considerations, for patients with renal failure, who are treated with CAVHD, the use of the fixed dose combination of imipenem/cilastatin may be justified.

REFERENCES

1. Birnbaum J, Kahan FM, Kropp H, Mcdonald JS: Carbapenems, a new class of beta lactam antibiotics. The American Journal of Medicine 1985; 78 suppl 6a: 3-21.
2. Berman SJ, Sugihari JG, Nakamura JM, Wong EGC, Musgrave JE, Wong LMF, Siemsen AM. Multiple dose study of imipenem/cilastatin in patients with end-stage renal disease undergoing long term hemodialysis. The American Journal of Medicine 1985; 78 suppl 6a: 113-116.
3. Calandra GB, Brown KR, Grad LC, Akonkhai VI, Wang C, Aziz M. Review of experiences and tolerability in the first 2516 patients treated with imipenem/cilastatin. The American Journal of Medicine 1985; 78 suppl 6a: 65-70.
4. Kroh U, Hofmann W, Dehne M, El Abed K, Lennartz H: Dosisanpassung von pharmaka während kontinuierlicher hämofiltration. Anaesthesist 1989; 38: 225-232.
5. Wise R, Donovan MR, Lockley J, Drumm J, Andrews JM: The pharmacokinetics and tissue penetration of imipenem. Journal of Antimicrobial Chemotherapy 1986; 18 suppl E: 93-101.
6. Verpooten GA, Verbist L, Buntinx AP, Entwistle LA, Jones KH, de Broe ME: The pharmacokinetics of imipenem (thienamycin-formamidine) and the renal dehydropeptidase inhibitor cilastatin sodium in normal subjects and patients with renal failure. British Journal of Pharmacology 1984; 18: 183-193.
7. Drusano GL, Weir M, Forrest A, Plaisance K, Emm T, Standiford HC: Pharmacokinetics of intravenously administered ciprofloxacin in patients with various degrees of renal function. Antimicrobial Agents and Chemotherapy 1987; 31: 860-864.
8. Keller E, Fecht H, Bohler J, Schollmeyer P: Single-dose kinetics of imipenem/cilastatin during continuous arteriovenous hemofiltration in intensive care patients. Nephrol Dial Transplant 1989; 4: 640-645.
9. Rogers JD, Meisinger MAP, Ferber F, Calandra GB, Demetriades JL, Bland JA: Pharmacokinetics of imipenem and cilastatin in volunteers. Reviews of infectious Diseases 1985; 7 suppl 3: 435-446.

CHAPTER 11

ACUTE RENAL FAILURE IN INTENSIVE CARE PATIENTS: A FOLLOW UP OF 236 PATIENTS TREATED BY CONTINUOUS ARTERIOVENOUS HEMODIAFILTRATION OR INTERMITTENT HEMODIALYSIS

INTRODUCTION

In the Second World War, mortality of acute renal failure amongst wounded servicemen was reported to be 91% [1]. Immediately upon the introduction of hemodialysis in 1942 by Kolff, mortality of post surgical tubular necrosis decreased to 50-60% [1]. Mortality rates of critically ill patients, however, have remained very high. Explanations for these high mortality rates may be that nowadays patients are older, more complicated surgery is performed and severely ill patients, who, in prior years, would not have survived, may develop renal failure [2,3]. Indeed, according to various studies, mortality rates of critically ill patients with acute renal failure range from 58% to 89% [4-9]. Differences between these figures are related to the need of renal replacement therapy and 'co-morbidity'.

After the introduction of continuous methods of dialysis, a number of studies were performed to examine whether this technique may improve survival. Bartlett et al found a survival rate of 12% in patients treated by intermittent hemodialysis and a survival rate in 28% in patients treated by continuous dialysis but this was not a statistically significant difference. A positive caloric balance did significantly improve the outcome. Therefore, he concluded that, as with continuous methods a positive caloric balance was easier to obtain, this method was to be preferred [9, 10]. Weiss et al recorded a 45% survival rate of patients treated with CAVH [11]. McDonald et al, described in their retrospective study a trend of decreasing mortality from 85% to 72% in patients, who needed dialysis treatment, after introduction of CAVHD [12]. Kierdorf described in his randomized retrospective study a significantly lower survival rate of 78% of patients treated by continuous venovenous hemofiltration (CVVH) compared to a survival rate of 93% of patients treated by intermittent hemodialysis [13]. However, comparisons of outcome are always frustrated by the heterogeneousness of the patient groups and the quality of medical care in general.

Several studies describe the influence of clinical parameters on outcome. Corwin et al found that the presence of sepsis and non-recovery of renal function were important predictors of death [8]. The factors of old age, sepsis and gastrointestinal

disease were associated with a poor prognosis in the study of Routh et al [14]. Lohr et al found fatal outcome to be related to a systolic blood pressure lower than 110 mmHg at the start of dialysis [15]. Furthermore, Lien et al demonstrated that among 15 patients with hypotension for more than one week, who were treated by IHD, none survived [16]. In their study, hypotension was defined as to exist when inotropic agents were necessary to maintain adequate blood pressure support.

In the University Hospital Dijkzigt, before 1984, acute renal failure used to be treated by intermittent methods. In case of severe hemodynamic shock, no dialysis treatment could be given at all. Continuous arteriovenous hemofiltration (CAVH) and hemodiafiltration (CAVHD) were first introduced in 1984 and 1986 respectively. With these techniques virtually all patients with acute renal failure could be treated. In this chapter, the clinical outcome is presented of 236 intensive care patients with acute renal insufficiency who received dialysis treatment. A critical condition of the patient never precluded dialysis treatment, but did influence the choice of a specific dialysis technique, i.e. intermittent hemodialysis or CAVHD. As the choice of the dialysis technique depended on the condition of the patient, the effect of treatment modality on mortality cannot be determined. We did compare duration of renal insufficiency and clinical outcome for patients with renal failure of different etiologies.

METHODS

Between 1985 and 1991, 236 patients with acute renal insufficiency received renal replacement therapy. Acute renal insufficiency was diagnosed if the patient had remained anuric for more than 24 hours and/or if serum creatinine concentration had risen at least two-fold to more than 700 µmol/L. If, at this stage, no spontaneous improvement was expected, renal replacement therapy was started. Eighty-nine patients were treated by intermittent hemodialysis (IHD) and 147 patients were treated by CAVHD. No patient with pre-existing chronic renal failure was included.

Patients were treated with CAVHD in case of hemodynamic instability and/or neurological instability. A threatening respiratory failure, not due to fluid overload, was also an indication for treatment by CAVHD. Most patients treated by CAVHD required artificial ventilation as well as vasopressor support.

CAVHD was performed as described in Chapter 4. Intermittent hemodialysis was performed with a AN-69 plate dialyzer (Hospal) with a dialysate flow rate of 500 ml/min, a blood flow rate of 100-150 ml/min and a sodium concentration in dialysate fluid of 140-145 mmol/L.

Outcome

Patients were prospectively divided into four groups according to the clinical setting in which acute renal failure occurred:

- A_0: patients with untractable shock (systolic pressure <100 mmHg at start of treatment).
- A_1: patients who had undergone aortic surgery or cardiac valve surgery.
- A_2: patients who had been in shock, but whose blood pressure had now improved (including those who still had vasopressor support).
- A_3: patient with renal failure due to some tubulotoxic injury.

Data on duration of renal failure and clinical outcome were collected. Renal function was taken to have recovered on the day of the last dialysis session. Patients, whose renal function had recovered, were followed for the time they were hospitalized, to determine mortality (from any cause) in this period, defined as 'late hospital death'. In patients treated by CAVHD, also the occurrence of sepsis and/or multi organ failure was recorded. Sepsis/MOF was diagnosed if the patient had a hemodynamic shock with low systemic vascular resistance, together with an infection and fever and/or a thrombocytopenia or multi organ failure of undetermined origin. Three patients switched over to peritoneal dialysis, and from three patients, no data on follow up were available due to transfer to another hospital. Data of these patients were excluded from analysis. Statistical analysis was performed by using the Chi-square test. Results are given as means ± standard deviation or, when appropriate, medians and range.

RESULTS

From 1985 to 1991, an increasing percentage of patients was treated with CAVHD. In 1991, 90% of all patients were treated by this method (Figure 1). The age distribution of all patients is shown in Figure 2. Mean age was 58 ± 7. Mean age of patients treated by CAVHD was not different from that of patients treated by IHD. Mortality was not related to age (Figure 2). Data on recovery from renal function and survival for each patient group are given in Table 1. From the patients treated by CAVHD, 26% belonged to group A_0, whereas this percentage was only 6% for the group of patients treated by IHD

The duration of renal insufficiency is shown in Figure 3. The duration of treatment for all patients was 8 days (range 1-71). For patients treated by IHD this value was 7 days (range 1-62) and for patients treated by CAVHD this value was 10 days (range 1-71). Recovery of renal function occurred in 60% of all patients. Of patients treated by IHD 69% recovered and of the patients treated by CAVHD 53%.

Table 2 shows p-values for recovery and survival for IHD, CAVHD and the 4 different patient groups. Patient groups A_3 and A_2, showed significantly higher values of recovery and survival compared to those of patient group A_0. Figure 4 and 5 show recovery and survival rate of each diagnostic group.

Overall patient survival rate was 44%. The survival rate of the group treated by IHD was 57% (n=86) and that of the group treated by CAVHD was 37% (n=144). In patients who died, the period from starting dialysis treatment to death was 11 days (range 1-125). For patients treated by IHD this value was 10 days (range 1-96) and for patients treated by CAVHD this value was 13 days (range 1-125). Late hospital death occurred more frequently in the group of patients treated by CAVHD compared to that treated by IHD (p =0.09). Patient group A_0 showed the highest rate (37.5%) and patient group A_2 showed the lowest rate (20%) of late hospital death.

Table 1. Outcome of patients treated by CAVHD or IHD. For definition of A_0-A_3 see METHODS.

CONTINUOUS ARTERIOVENOUS HEMODIAFILTRATION				
	n	Died during dialysis treatment	Recovered from renal function	Late hospital death
A_0	37	23	14	6
A_1	27	13	14	7
A_2	70	27	43	10
A_3	10	4	6	1
Total	144	67	77	24

INTERMITTENT HEMODIALYSIS				
	n	Died during dialysis treatment	Recovered from renal function	Late hospital death
A_0	5	3	2	0
A_1	34	15	19	3
A_2	29	7	22	3
A_3	18	2	16	4
Total	86	27	59	10

Outcome

Table 2: p-values calculated with the Chi-square test of different group of patients. For abbreviations and definition of A_0-A_3 see METHODS.

GROUP	RECOVERY p-value	SURVIVAL p-value
IHD vs CAVHD total group	0.03	0.005
IHD vs CAVHD without sepsis/MOF	0.50	0.02
IHD vs CAVHD with sepsis/MOF	0.007	0.006
CAVHD; with sepsis/MOF vs without sepsis/MOF	0.11	0.95
A_0 vs A_1	0.16	0.20
A_0 vs A_2	0.004	0.003
A_0 vs A_3	0.002	0.004
A_1 vs A_2	0.20	0.10
A_1 vs A_3	0.08	0.07
A_2 vs A_3	0.07	0.58

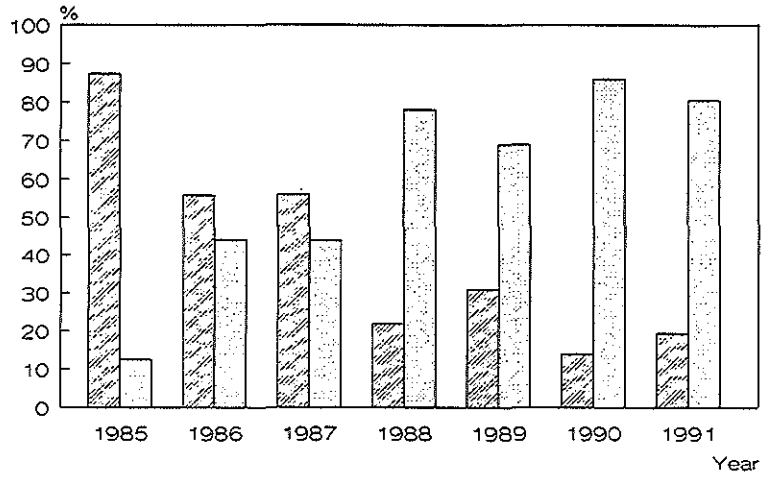

Figure 1. Percentage of use of IHD and CAVHD from 1985 to 1991.
Dashed column: IHD
Dotted column: CAVHD

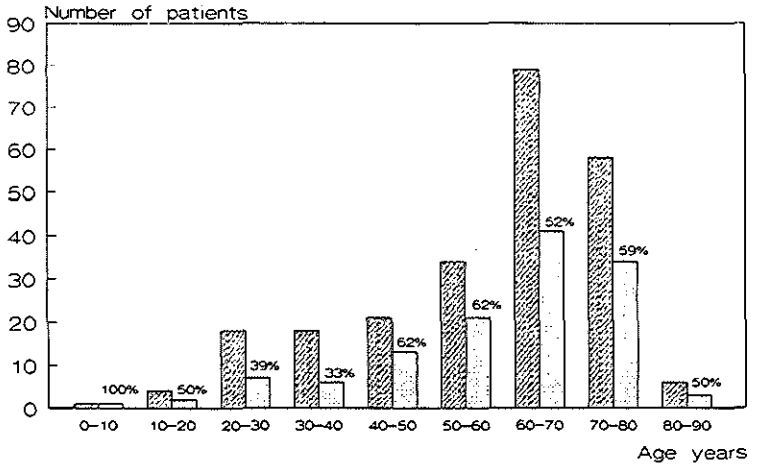

Figure 2. Age distribution of patients with acute renal failure treated by IHD or CAVHD.
Dashed column: total numbers,
Dotted column: number of patients who died during renal replacement treatment or thereafter. Percentages of mortality of each age-group are given above each dotted column.

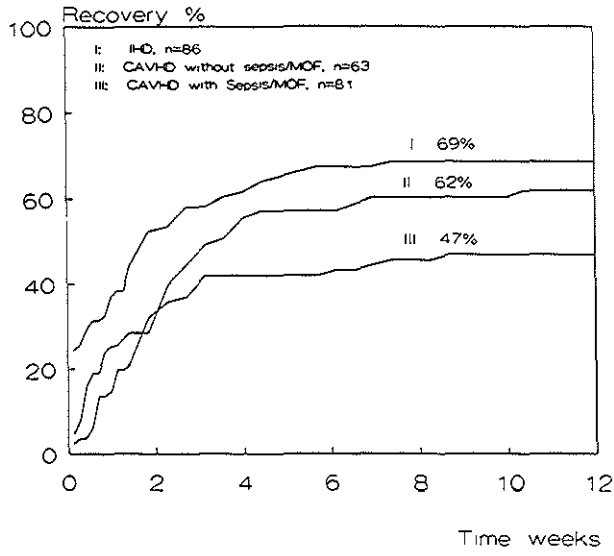

Figure 3. Recovery of renal function of patients treated by IHD (I), patients treated by CAVHD without sepsis and/or MOF (II) and patients treated by CAVHD with sepsis and/or MOF (III).

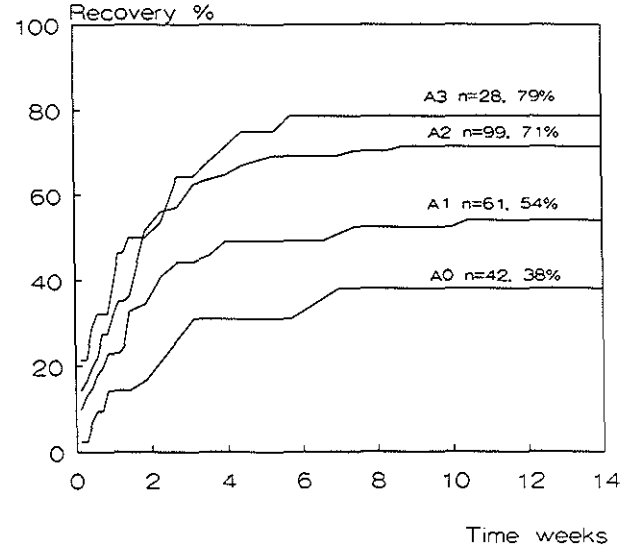

Figure 4. Recovery of renal function of each diagnosis group. For definition of A_0-A_3, see METHODS.

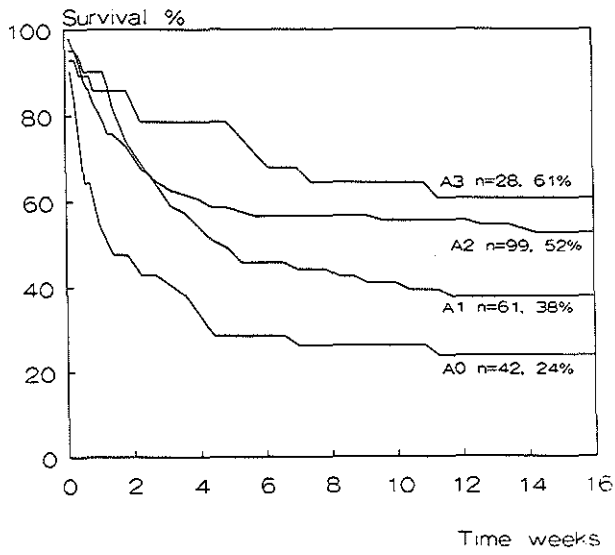

Figure 5. Long-term survival of each diagnosis group. For definition of A_0-A_3, see METHODS. Survival is defined as 'dismissed from hospital'.

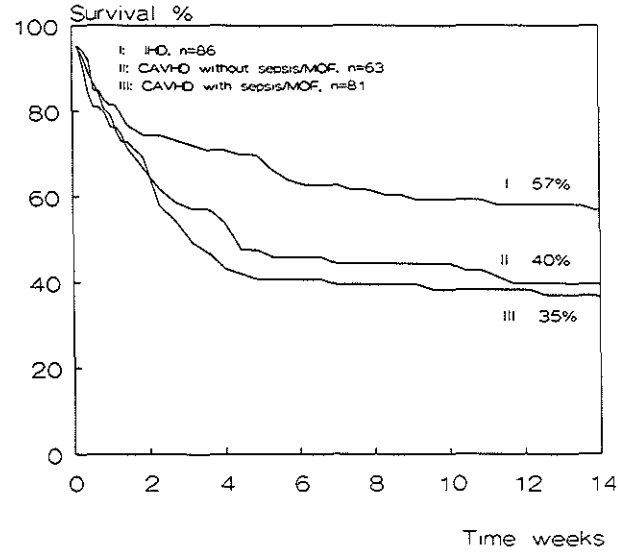

Figure 6. Long-term survival of patients treated by IHD (I), patients treated by CAVHD without sepsis and/or MOF (II) and patients treated by CAVHD with sepsis and/or MOF (III). Survival is defined as 'dismissed from hospital'.

DISCUSSION

It is generally agreed that in patients with acute renal failure mortality is caused by the underlying disease. This is borne out by a study by Mentzer et al, showing that a mortality rate of only 6% in 236 patients with post-operative acute tubular necrosis of a transplanted kidney [17]. Although mortality is a function of the underlying disease, the choice of renal replacement therapy may perhaps influence the outcome. In several studies continuous dialysis techniques are recommended for the treatment of critically ill patients. However, no randomized or severity matched prospective study has been realized yet, to evaluate the superiority of either the intermittent or the continuous mode of dialysis.

Also this study cannot answer this question. Therefore, the first three p-values in Table 2 can only be used to value the bias in the choice of a specific dialysis technique. Indeed, from Table 2 and Figure 3 and 5, it is clear that patients treated by IHD have a significantly higher recovery and survival rate than patients treated by CAVHD. This difference is likely to be due to the large group of patients with sepsis/MOF, treated by CAVHD. However, a statistically difference between recovery or survival rates of patients treated by CAVHD with or without sepsis/MOF could not be determined. Others found that presence of sepsis was related to survival [8, 14, 18], but Lien et al demonstrated that the presence of sepsis was not significantly different between survivors and non-survivors [16]. That we found no difference in outcome of our patients with or without sepsis/MOF may be explained by the critical illness of all patients treated by CAVHD, which accounts for high mortality rates, even in absence of sepsis or MOF. This is confirmed by the statistically higher survival rate of patients treated by IHD compared to patients without sepsis/MOF, who are treated by CAVHD. Also, as 'late hospital death' occurred more frequently in patients treated by CAVHD, it can be concluded that these patients were more severely ill than patients treated by IHD. Furthermore, patients from group A_0 were predominantly (88%) treated by CAVHD, indicating that CAVHD was used primarily for patients with poor condition. This is in accordance with the approach of our department to treat these patients preferably by CAVHD.

In some studies it is reported that mortality increases with age [7, 14, 19], but others have not [20, 21]. Our results did not show any relation of mortality rate with age.

This retrospective study does not answer the question whether the introduction of CAVHD has improved the prognosis of severely patients with acute renal failure. Evidence suggesting that prognosis in severely ill patients can be improved by

CAVHD, can be deduced from the observation that our patients with hemodynamic shock (A_0), who were predominantly treated by CAVHD, showed a survival rate of 24%. Lien et al [16] described no survivors in patients with hypotension for more than one week, who were treated by IHD. In conclusion, from 230 intensive care patients with acute renal failure, a recovery rate of renal function of 60% and a patient survival rate of 44% was obtained. Comparing these values with literature data, it can be concluded that these results are quite satisfactory.

REFERENCES

1. Cameron JS. Acute renal failure in the intensive care today. Intensive Care Medicine 1986; 12: 64-70.
2. Stott RB, Cameron JS, Ogg CS, Bewick M. Why the persistently high mortality in acute renal failure? Lancet 1972; 8: 75-78.
3. Butkus DE. Persistent high mortality in acute renal failure. Are we asking the right questions? Archives of Internal Medicine 1983: 143: 209-212.
4. Kumon K, Tanaka K, Hirata T, Naito Y, Fujita T. Organ failures due to low cardiac output syndrome following open heart surgery. Japanese Circulation Journal 1986; 50: 329-335.
5. Gillespie DJ, Marsh HMM, Divertie MB, Meadows JA. Clinical outcome of respiratory failure in patients requiring prolonged (>24 hours) mechanical ventilation. Chest 1990; 3: 364-369.
6. Kraman S, Khan F, Patel S, Seriff N. Renal failure in the respiratory intensive care unit. Critical Care Medicine 1979; 7: 263-266.
7. Spiegel DM, Ullian ME, Zerbe GO, Berl T. Determinants of survival and recovery in acute renal failure patients dialyzed in intensive-care units. Am J Nephrol 1991; 11: 44-47.
8. Corwin HL, Teplick RS, Schreiber MJ, Fang LST, Bonventre JV, Coggins CH. Prediction of outcome in acute renal failure Am J Nephrol 1987; 7: 8-12.
9. Bartlett RH, Mault JR, Dechert RE, Palmer J, Swartz RD, Port FK. Continuous arteriovenous hemofiltration: Improved survival in surgical acute renal failure? Surgery 1986; 100: 400-408.
10. Bartlett RH, Bosch J, Geronemus R, Paganini E, Ronco C, Swartz R. Continuous arteriovenous hemofiltration for acute renal failure. Trans Am Soc Artif Intern Organs 1988; 34: 67-77.
11. Weiss L, Danielson BG, Wikström B, Hedstrand U, Wahlberg J. Continuous arteriovenous hemofiltration in the treatment of 100 critically ill patients with acute renal failure: Report on clinical outcome and nutritional aspects. Clinical Nephrology 1989; 4: 184-189.
12. McDonald BR, Mehta RL. Decreased mortality in patients with acute renal failure undergoing continuous arteriovenous hemodialysis Contr Nephrol 1991; 93: 51-56.
13. Kierdorf H. Continuous versus intermittent treatment: Clinical results in acute renal failure. Contr Nephrol 1991; 93: 1-12.

14. Routh GS, Briggs JD, Mone JG, Ledingham McA. Survival from acute renal failure with and without multiple organ failure. Postgraduate Medical Journal 1980; 56: 244-247.
15. Lohr JW, McFarlane MJ, Grantham JJ. A clinical index to predict survival in acute renal failure patients requiring dialysis. Am J Kidney Diseases 1988; 11: 254-259.
16. Lien J, Chan V. Risk factors influencing survival in acute renal failure treated by hemodialysis. Arch Intern Med 1985; 145: 2067-2069.
17. Mentzer SJ, Fryd DS, Kjellstrand CM. Why do patients with postsurgical acute tubular necrosis die? Arch. Sur. 1985; 120: 907-910.
18. Gornick CC, Kjellstrand CM. Acute renal failure complicating aortic aneurysm surgery. Nephron 1983; 35: 145-157.
19. Knauss WA, Draper EA, Douglas MS, Wagner P, Zimmerman JE. Prognosis in acute organ-system failure. Ann Surg 1985;202: 685-693.
20. Rasmussen HH, Pitt EA, Ibels LS, McNeil DR. Prediction of outcome in acute renal failure by discriminant analysis of clinical variables. Arch Intern Med 1985; 145: 2015-2018.
21. Abreo K, Moorthy V, Osborne M. Changing patterns and outcome of acute renal failure requiring hemodialysis. Arch Intern Med 1986; 146: 1338-1341.

CHAPTER 12

SUMMARY

Continuous arteriovenous hemodiafiltration (CAVHD) is a dialysis modality used to treat intensive care patients. In this thesis, the clinical use, the impact of filter design and membrane and the mechanism of solute transport of continuous arteriovenous hemodiafiltration (CAVHD) are described.
A mathematical model of solute transport by combined convection and diffusion was developed and applied to clinical and laboratory data. From these data, a prediction model of clearance rates of uremic solutes and drugs was derived. Furthermore, the impact of clearance of drugs by CAVHD on dose adjustments was determined. Finally, the outcome of patients with acute renal insufficiency, treated by intermittent hemodialysis or CAVHD was described.

Chapter 1:

Chapter 1 gives a short history of hemodialysis. Different mechanism of solute transport and terminology are discussed.

Continuous arteriovenous hemofiltration (CAVH) and continuous arteriovenous hemodiafiltration (CAVHD) were introduced in the Dijkzigt University hospital in 1984 and 1985 respectively. Continuous hemodialysis is performed 24 hours a day, like the human kidney, intermittent hemodialysis is performed just a few hours a day. CAVHD is characterized by the use of a small surface membrane with a high hydraulic permeability, a spontaneous blood flow obtained by the pressure difference between an artery and a vein, a spontaneous ultrafiltrate flow and a low dialysate flow rate of 1-3 L/hr.

Chapter 2:

In this chapter, a short overview is given of clinical problems encountered with intermittent machine-hemodialysis, with emphasis on the possible consequences for critically ill patients.

The most frequent complication is dialysis-induced hypotension. Also, with neurologically unstable patients, intermittent hemodialysis may impair the neurological condition as a result of sudden changes in pH and osmolality.

Chapter 3:

In this chapter, the indications for CAVHD are described.
The most important indication for treatment by CAVHD is the combination of renal failure and circulatory instability. Neurological instability or the need for high clearance rates in severe catabolic patients is another indication for treatment by CAVHD. Also, after kidney transplantation in a patient with primary hyperoxaluria, plasma oxalate levels can be kept low by using CAVHD. CAVHD is contraindicated if the extracorporeal circuit interferes with the mobilisation of the patient.
In this chapter, the necessities are described and guidelines for application for the technique are given.

Chapter 4:

For capillary hemofilters, the resistance to flow may be predicted from the filter geometry by using Poiseuille's law, assuming laminar flow. Blood viscosity can be calculated from hematocrit, protein concentration and temperature. However, observed filter resistance to flow was two to three times higher than the predicted value. Comparison of actual blood viscosity with the calculated value showed that blood viscosity was grossly underestimated. Herewith, part of the discrepancy between measured and predicted values could be explained. Further discrepancies between these values could be explained if the fiber diameter would be a mere 8 % lower than the value given by the manufacturer.

Chapter 5:

Existing models of hemodialysis are not likely to be useful for the analysis of solute transport in CAVHD, as solute transport in CAVHD differs from that in intermittent hemodialysis, The most important differences are:

1. With CAVHD, solute transport occurs by simultaneous convection and diffusion.
2. With CAVHD, dialysate flow rates (10-30 ml/min) are very low compared to blood flow rate (100-250 ml/min).
   Also, dialysate flow rates might be too low for optimal distribution of dialysate over the dialysate compartment.

3. CAVHD is a continuous technique. With prolonged use of the filter, deterioration of the membrane is likely not only to decrease the rate of ultrafiltration but also to impair diffusive transport.

Therefore, a new mathematical model of combined convection and diffusion in CAVHD was developed. Three important assumptions were made:
1. A homogeneously distribution of blood and dialysate over their respective compartments.
2. A constant membrane permeability for ultrafiltration and for diffusion over the entire membrane length.
3. No variations of solute concentration in the radial direction were considered, i.e. calculations are based on local "mixing cup" concentrations.

Using this model, a numerical as well as an analytical solution of the mass transfer coefficient of diffusion (K_d) could be given.

Chapter 6:

In this chapter, the assumption of mixing cup concentrations in the model was validated. This assumption is valid when compartments are well stirred, a condition which can be approached if flows are turbulent. A radial concentration gradient can be influenced by axial flow rates. Blood flow rate had no measurable influence on the calculated value of K_d. Dialysate flow rates (Q_d), however, did have an influence on K_d. The calculated value of K_d increased with increasing dialysate flow rates. This may be explained by the existence of an unstirred layer in the dialysate compartment, or, at low dialysate flow rates, the distribution of dialysate over the compartment is inadequate, resulting in a partial use of the membrane surface area. Also, K_d proved to be dependent on the hydraulic permeability index of the membrane (MI). The relationship of K_d with Q_d and MI was quantified by a mathematical expression.

Chapter 7:

In this chapter the applicability of the prediction formulas of the mass transfer coefficient of diffusion (Kd) of creatinine, as derived in chapter 6, was examined. It was concluded that 73% of the variability of Kd and 81% of the variability of the clearance rate of creatinine can be explained by variations in Qd and MI. The value

of plasma water flow rate at the filter inlet (Q_{wi}) is needed to predict clearance rate. This value is, like the value of MI, not readily available in the clinical setting. Therefore, nomograms were constructed to read estimated values of Q_{wi} from the mean arterial pressure (MAP) and estimated values of MI from the MAP and the ultrafiltration flow rate.

Chapter 8:

In this chapter, we applied the model to the transport of drugs. Sieving coefficients of the drugs and the relation of K_d and molecular weight of the drugs were examined for cefuroxime, cefotaxime, ceftazidime, imipenem, cilastatin, ciprofloxacin, tobramycin and vancomycin.
Two important results were obtained. First, it was demonstrated that the sieving coefficient of the drug may be equated to its non-protein bound fraction, which may be determined in the laboratory. Second, we found a fixed relationship between the ratio of K_d of drugs to that of creatinine and the molecular weight of the drug.

Chapter 9:

In this chapter, the feasibility of predicting clearance rates of drugs and consequences for dose adaptations were considered. The use of the prediction formula of Kd of creatinine, together with the ratio of Kd of drugs to that of creatinine resulted in a fairly accurate estimation of the clearance rate of drugs. This estimation is accurate enough to be used in the clinic.

For each drug, dose adaptations were calculated based on average operational conditions. For anuric patients treated by CAVHD, dose adaptations were needed for cefuroxime, ceftazidime, tobramycin and vancomycin. Failure to recognize this may easily lead to suboptimal drug levels and therapeutic failure. For cefotaxime, imipenem and ciprofloxacin this was not needed. Therefore, the dosage regimens of cefotaxim, imipenem and ciprofloxacin used for anuric patients, can also be used for anuric patients treated by CAVHD.

Chapter 10:

Tiënam^{R} is the combination of imipenem and cilastatin. When using this combination in patients with renal failure, one should take into account the more prolonged half life of cilastatin in comparison with that of imipenem. In the anuric state, even after dose adjustment, which is based on desired plasma levels of imipenem, the use of the fixed dose combination will lead to an overdosage of cilastatin. However, after institution of CAVHD, clearance rate of cilastatin increases four fold and serious accumulation of cilastatin is thereby avoided.

Chapter 11:

We studied the clinical outcome of 236 critically ill patients with acute renal insufficiency, who received dialysis treatment either by intermittent hemodialysis or CAVHD. In general, mortality rates of these patients are very high. In our patients, recovery rate of the kidney was 60% and survival rate of the patient was 44%. Survival rate depended on the clinical setting in which acute renal failure was acquired, or the clinical condition of the patient at start of the dialysis treatment. Death after recovery of renal function occurred more frequently in the group of patients treated by CAVHD. This suggests, that patients treated by CAVHD were more severely ill than patients, who could be treated by intermittent techniques. Patients with untractable shock at start of dialysis treatment were predominantly treated by CAVHD and showed a survival rate of 24%. Before the introduction of CAVHD, dialysis could hardly be performed in such patients. Therefore, from this observation it may be deduced that prognosis of these severely patients was improved by the introduction of CAVHD.

CHAPTER 13

SAMENVATTING

Continue arterioveneuze hemodiafiltratie (CAVHD) is een dialyse techniek die gebruikt wordt voor de behandeling van patiënten met nierinsufficiëntie die verpleegd worden op een intensive care afdeling. In dit proefschrift is het klinisch gebruik, de invloed van de kunstnier op het slagen van de behandeling en het mechanisme van massatransport bij CAVHD beschreven.

Een wiskundig model van massatransport bij het bestaan van een gelijktijdig convectief en diffusief transport werd ontwikkeld en meetresultaten verkregen in de kliniek en het laboratorium werden hiermee geanalyseerd. Gebaseerd op deze analyse kon een model ontwikkeld worden ten behoeve van de voorspelling van de klaring van uremische stoffen en geneesmiddelen. Tevens werd de noodzaak tot aanpassen van de dosis van diverse geneesmiddelen als gevolg van de klaring door CAVHD bestudeerd. Ten slotte zijn het herstel van nierfunctie en mortaliteit beschreven van een groep patiënten met acute nierinsufficientie, die behandeld werden met intermitterende hemodialyse of CAVHD.

Hoofdstuk 1:

In dit hoofdstuk wordt in het kort de historie van de hemodialyse beschreven. Ook worden de verschillende mechanismen van massatransport en de bijbehorende terminologie behandeld.

Continue arterioveneuze hemofiltratie (CAVH) en continue arterioveneuze hemodiafiltratie (CAVHD) werden respectievelijk in 1984 en 1985 geïntroduceerd in het Academisch ziekenhuis Dijkzigt te Rotterdam. Continue dialyse wordt, overeenkomstig de menselijke nier, 24 uur per dag uitgevoerd; intermitterende dialyse daarentegen wordt enkele uren per dag uitgevoerd. CAVHD wordt gekarakteriseerd door het gebruik van een membraan met een klein oppervlak en een hoge hydraulische permeabiliteit, een spontaan op gang gebrachte bloed stroom middels het drukverschil tussen een arterie en een vene, een spontane ultrafiltratie stroom en een lage dialysaat stroomsnelheid van 1-3 L/uur.

Hoofdstuk 2:

In dit hoofdstuk wordt een kort overzicht gegeven van klinische problemen zoals die kunnen ontstaan tijdens behandeling met intermitterende hemodialyse. Hierbij is de nadruk gelegd op de mogelijke consequenties voor patiënten die verpleegd worden op een intensive care afdeling.

De meest voorkomende complicatie tijdens dialyse is hypotensie. Ook kan, door te plotselinge veranderingen in de pH en de osmolariteit van het bloed, de neurologische toestand van een neurologisch reeds instabiele patiënt verslechteren.

Hoofdstuk 3:

In dit hoofdstuk komen de indicaties voor de behandeling met CAVHD aan bod. De belangrijkste indicatie voor behandeling met CAVHD, is de combinatie van nierfalen en circulatoire instabiliteit. Overige indicaties zijn een neurologische instabiliteit of de behoefte aan hoge klaringssnelheden bij ernstig katabole patiënten. Ook kan met behulp van behandeling met CAVHD de plasma spiegel van oxalaat van een patiënt met primaire hyperoxalurie voldoende laag gehouden worden na een niertransplantatie. CAVHD is gecontraïndiceerd als het extracorporele circuit interfereert met de mobilisatie van de patiënt.
Verder worden in dit hoofdstuk de benodigdheden en een leidraad voor het gebruik voor CAVHD beschreven.

Hoofdstuk 4:

Als men aanneemt dat er sprake is van een laminaire bloedstroom, kan de stromingsweerstand van capillaire hemofilters voorspeld worden met behulp van de wet van Poiseuille. De viscositeit van bloed kan berekend worden uit de waarde van de hematocriet, de eiwit concentratie en de temperatuur. Echter, de waarde van de geobserveerde stromingsweerstand van het filter was twee tot drie keer zo hoog dan de door ons voorspelde waarde. Vergelijking van de waarde van de gemeten viscositeit van bloed met de berekende waarde liet echter zien dat de gebruikte berekening van de viscositeit in een te lage waarde resulteerde. Een deel van de discrepantie tussen de geobserveerde en berekende stromingsweerstand kon hiermee verklaard worden. De overblijvende discrepantie tussen de berekende en gemeten waarde van de stromingsweerstand kon worden verklaard door de interne diameter

van de capillairen van het filter 8% lager aan te nemen dan door de fabrikant wordt opgegeven.

Hoofdstuk 5:

Reeds bestaande modellen van het massatransport tijdens hemodialyse kunnen niet gebruikt worden voor de analyse van het massatransport tijdens CAVHD. Redenen hiervoor zijn dat het transport tijdens CAVHD verschilt met het transport tijdens hemodialyse. De belangrijkste verschillen zijn:

1. Massatransport bij CAVHD vindt plaats middels gelijktijdige convectie en diffusie.
2. Stroomsnelheden van dialysaat (10-30 ml/min) bij CAVHD zijn erg laag vergeleken met stroomsnelheden van bloed (100-250 ml/min).
   Ook zou de stroomsnelheid van het dialysaat te laag kunnen zijn om een optimale distributie van het dialysaat in het dialysaat-compartiment te bewerkstelligen.
3. CAVHD is een continue techniek. Door het langdurig gebruik van eenzelfde membraan, ligt het niet alleen voor de hand dat de ultrafiltratie stroomsnelheid afneemt in de tijd, maar ook dat het diffusieve transport zou kunnen afnemen in de tijd.

Vanwege deze verschillen werd een nieuw wiskundig model, toepasbaar op de situatie bij CAVHD, van gecombineerde convectie en diffusie ontwikkeld. Hierbij zijn drie belangrijke aannamen gedaan:

1. De distributie van bloed en dialysaat in de respectieve compartimenten is homogeen.
2. De permeabiliteit voor ultrafiltratie en diffusie is over de gehele lengte van de membraan constant.
3. Variaties in concentraties in de radiale richting werden niet in beschouwing genomen, hierdoor werden de berekeningen dus gebaseerd op lokale "mixing cup" concentraties.

Met dit model kon een numerieke en een analytische afleiding van de massatransport coëfficiënt voor diffusie (K_d) gegeven worden.

Hoofdstuk 6:

In dit hoofdstuk werd de aanname 'de aanwezigheid van "mixing cup" concentraties' gevalideerd. Deze aanname is valide, als de inhoud van de compartimenten homogeen zijn, een conditie die benaderd kan worden als de stromen turbulent zijn. Een radiale concentratie gradiënt kan beïnvloed worden door axiale stroomsnelheden. De stroomsnelheid van bloed had geen meetbare invloed op de waarde van de K_d. De stroomsnelheid van dialysaat (Q_d) had echter wel een invloed op de waarde van de K_d. Dit kan verklaard worden door het bestaan van een grenslaag in het dialysaatcompartiment, of, bij lage dialysaat stroomsnelheden, door een inadequate distributie van het dialysaat over het gehele compartiment wat resulteert in het gebruik van slechts een gedeelte van het membraanoppervlak. Ook bleek de K_d afhankelijk te zijn van de hydraulische permeabiliteit index van de membraan (MI). De vastgestelde relatie tussen de K_d met de Q_d en MI werd uitgedrukt in een aantal formules.

Hoofdstuk 7:

In dit hoofdstuk werd de bruikbaarheid van de formules, zoals afgeleid in Hoofdstuk 6, getoetst voor het voorspellen van de massatransport coëfficiënt voor diffusie van creatinine. Het bleek dat voor creatinine 73% van de variabiliteit in de K_d en 81% van de variabiliteit in de klaring verklaard kon worden door variaties in de Q_d en MI. Om de klaringssnelheid te voorspellen moet de waarde van de stroomsnelheid van plasma water (Q_{wi}) bekend zijn. Deze waarde is, evenals de waarde van de MI, in de klinische situatie niet direct voorhanden. Daarom werden nomogrammen geconstrueerd, waarin waarden van Q_{wi} afgelezen kunnen worden met gebruik van de waarde van de gemiddelde arteriële druk en waarden van MI afgelezen kunnen worden met gebruik van de waarde van de gemiddelde arteriële druk en de stroomsnelheid van ultrafiltratie.

Hoofdstuk 8:

In dit hoofdstuk werd het transportmodel toegepast op transport van geneesmiddelen, i.c. antibiotica. De "sieving" coëfficiënten van de geneesmiddelen en de relatie tussen de K_d en het molekuul gewicht werden onderzocht voor cefuroxim, cefotaxim, ceftazidim, imipenem, cilastatine, ciprofloxacine, tobramycine en vancomycine.

Hiermee werden twee belangrijke resultaten verkregen. Ten eerste, de "sieving" coëfficiënt mocht gelijk gesteld worden aan de vrije fractie van het antibioticum, welke laatste gemeten kan worden in het laboratorium. Ten tweede, er bleek een vaste relatie te bestaan tussen de ratio van de K_d van de antibiotica t.o.v de K_d van creatinine met het molekuul gewicht van het antibiotica.

Hoofdstuk 9:

In dit hoofdstuk werd de mogelijkheid onderzocht of de klaringssnelheid van antibiotica door CAVHD voldoende betrouwbaar te voorspellen was. Het gebruik van de voorspellingsformule van de K_d van creatinine tezamen met de ratio van de K_d van het antibioticum t.o.v. de Kd van creatinine, leverde een zodanige voorspelling van de klaringssnelheid van deze antibiotica op, dat deze klinisch goed bruikbaar is.

Tevens werd onderzocht of deze klaring consequenties heeft, zodanig dat het doseringsschema van een patiënt die met CAVHD behandeld wordt, veranderd moet worden. Doseringsaanpassingen, gebaseerd op gemiddelde condities van de kunstnier, werden berekend voor elk gemeten antibiotica. Het bleek, dat voor patiënten met anurie die behandeld werden met CAVHD, een doseringsaanpassing nodig was bij het gebruik van cefuroxim, ceftazidim, tobramycine en vancomycine. Als aanpassing van de dosering tijdens behandeling met CAVHD wordt nagelaten, kunnen te lage antibioticaspiegels met daarbij falen van de antibiotische therapie zeer wel mogelijk zijn. Bij het gebruik van cefotaxim, imipenem of ciprofloxine werd deze aanpassing niet noodzakelijk geacht. Bij gebruik van deze laatst genoemde geneesmiddelen kan voor een anurische patiënt die behandeld wordt met CAVHD, hetzelfde doseringsschema gebruikt worden als dat voor anurische patiënten, die niet gedialyseerd worden.

Hoofdstuk 10:

Het geneesmiddel Tiënam^R is een combinatie van 500 mg imipenem en 500 mg cilastatine. Als men dit geneesmiddel gebruikt bij patiënten met anurie, moet men rekening houden met het feit dat de halfwaardetijd van cilastatine in vergelijking met imipenem sterker verlengd is. Als de patiënt anurisch is, wordt een aangepaste dosering gebruikt, berekend op gewenste spiegels van imipenem. Dit leidt tot een overdosis van cilastatine. Echter, als deze patiënt behandeld wordt met CAVHD, zal

de klaringssnelheid van cilastatine viervoudig toenemen en daardoor wordt ernstige accumulatie van cilastatine vermeden.

Hoofdstuk 11:

In dit hoofdstuk is het herstel van de nierfunctie en de mortaliteit bestudeerd van 236 patiënten met acuut nierfalen die behandeld werden op een intensive care afdeling. Deze patiënten werden of behandeld met intermitterende dialyse of met CAVHD. In het algemeen is de mortaliteit van deze patiënten erg hoog. Bij de beschreven groep patiënten herstelde de nierfunctie in 60%. Het overlevingspercentage was 44%. Het percentage van overleving was gecorreleerd met de onderliggende ziekte of met de klinische toestand van de patiënt bij aanvang van de dialyse behandeling. De groep patiënten die met CAVHD werden behandeld hadden een hogere mortaliteit na herstel van de nierfunctie. Dit impliceert dat patiënten die een behandeling middels CAVHD kregen, zieker waren dan patiënten die een behandeling middels intermitterende hemodialyse konden ondergaan. Van de patiënten, die bij de aanvang van de dialysebehandeling in een onbehandelbare hemodynamische shock verkeerden, overleefden 24%. Deze patiënten werden voornamelijk gedialyseerd middels CAVHD. In het verleden, voor de introductie van CAVHD, konden deze patiënten niet of nauwelijks een dialyse behandeling verdragen. Hieruit zou men voorzichtig de conclusie kunnen trekken dat het gebruik van CAVHD, voor deze ernstig zieke patiënten een verbetering van hun overlevingskansen heeft gegeven.

LIST OF PUBLICATIONS

1. Vincent HH, van Ittersum FJ, Akçahuseyin E, van Duyl WA, Vos MC, Schalekamp MADH.
Solute transport in continuous arteriovenous hemodiafiltration. A new mathematical model applied to clinical data.
Blood Purification 1990; 8: 149-159.

2. Vincent HH, Akçahuseyin E, Vos MC, van Ittersum FJ, van Duyl WA, Schalekamp MADH.
Determinants of blood flow and ultrafiltration in continuous arteriovenous haemodiafiltration: Theoretical predictions and laboratory and clinical observations.
Nephrology Dialysis Transplantation 1990; 5: 1031-1037.

3. Vincent HH, Vos MC.
The use of continuous arteriovenous hemodiafiltration in multiple organ failure patients.
Applied Cardiopulmonary Pathophysiology 1991; 4: 109-116.

4. Akçahuseyin E, Vincent HH, Vos MC, van Duyl WA.
Continue arterioveneuze hemodiafiltratie (CAVHD).
Klinische Fysica 1991; 2: 87-92.

5. Vincent HH, Akçahuseyin E, Vos MC, van Duyl WA, Schalekamp MADH.
Continuous arteriovenous hemodiafiltration: Filter design and blood flow rate.
Contributions to Nephrology 1991; 93: 196-198.

6. Vincent HH, Vos MC, van Duyl WA.
Solute transport in hemodiafiltration: A new mathematical model to analyse dialyser performance.
Contributions to Nephrology 1991; 93: 199-201.

7. Vos MC, Vincent HH.
Continuous arteriovenous hemodiafiltration: Predicting the clearance of drugs.
Contributions to Nephrology 1991; 93: 143-145.

8. Vos MC, Vincent HH.
Continue arterioveneuze haemodiafiltratie. Een nieuwe nierfunctie vervangende techniek.
Nederlands Tijdschrift voor Geneeskunde 1992; 136: 561-565.

9. Vincent HH, Vos MC, Akçahuseyin E, van Duyl WA, Schalekamp MADH.
Blood flow, ultrafiltration and solute transport rate in continuous arteriovenous haemodiafiltration: The AN-69 plate haemofilter.
Nephrology Dialysis Transplantation 1992; 7: 29-34.

10. Vos MC, Vincent HH, IJzerman EPF.
Clearance of Imipenem/Cilastatin in acute renal failure patients treated by continuous hemodiafiltration (CAVHD).
Intensive Care Medicine 1992; 18: 282-285.

11. Golper TA, Gleason JR, Vincent HH, Vos MC.
Drug removal during high efficiency and high flux hemodialysis.
In: Hemodialysis: High efficiency treatment. Ed. Juan P Bosch. Churchill Livingstone. New York 1993, page 175-208.

12. Vincent HH, Vos MC, Akçahuseyin E, Goessens WHF, van Duyl WA, Schalekamp MADH.
Drug clearance by continuous arteriovenous hemodiafiltration (CAVHD). Analysis of sieving coefficient and mass transfer coefficient of diffusion.
Blood Purification 1993: in press.

13. Vincent HH, Roggekamp MC, Vos MC.
Clearance of desferrioxamine and aluminoxamine by dialysis using the 1.1 m^2 cellulose-triacetate dialyser.
(Submitted).

14. Vos MC, Vincent HH, IJzerman EPF, Stamkott A, Vogel M, Mouton JW.
Drug clearance by continuous hemodiafiltration (CAVHD). Results with the AN-69 capillary hemofilter and recommended dose adjustments.
(Submitted).

15. Vos MC, Vincent HH.
Acute renal failure in intensive care patients: A follow up of 236 patients treated by continuous arteriovenous hemodiafiltration or intermittent hemodialysis.
(Submitted).

16. Akçahuseyin E, Vos MC, Vincent HH, van Duyl WA.
Sensitivity analysis of a mathematical model on continuous arteriovenous hemodiafiltration (CAVHD).
(In preparation).

17. Akçahuseyin E, Vos MC, Vincent HH, van Duyl WA.
A mathematical model on solute transport in continuous arteriovenous hemodiafiltration (CAVHD): The influence of taking into account the decrease in volume flux over the length of the dialyzer.
(In preparation).

All published material as mentioned above, has been used in this thesis with permission of the original source.

NAWOORD

Dit proefschrift is het resultaat van een samenwerkingsproject tussen de afdelingen Interne Geneeskunde I en Biomedische Natuurkunde en Technologie van de Erasmus Universiteit Rotterdam. Velen hebben hieraan hun medewerking verleend. Zonder iemand tekort te willen doen, wil ik een aantal personen op deze plaats apart vermelden. Prof. Dr. M.A.D.H. Schalekamp, bedankt voor uw directe bereidwilligheid om mijn promotor te zijn. Uw kritische commentaar op het manuscript is voor mij van grote waarde geweest. Prof. Dr. W.A. Weimar en Dr. R.T. Krediet wil ik bedanken voor het kritisch lezen van het manuscript en hun waardevolle commentaar.
Een hardwerkende en vooral gezellige onderzoeksgroep was de basis waarop dit proefschrift kon ontstaan.

Dr. H.H. Vincent, mijn directe begeleider, vertegenwoordigde hierin de klinische discipline, al was fysica hem niet vreemd en was de initiator van dit onderzoek. Beste Jeroen, je bent een "co-promotor" van onschatbare waarde geweest. Je altijd goede humeur hoezeer ik ook 'een slabak van woorden' wist te creëren en je talent om alles altijd weer netjes op een rijtje te zetten heeft mij enorm aangemoedigd. Jouw vermogen om een onderzoek op te zetten en de resultaten helder te interpreteren en formuleren, zal voor mij een voorbeeld blijven. De tomeloze energie die je op (en over) wist te brengen, heeft er mede toe geleid dat aan het eind van onze 2½-jarige samenwerking dit proefschrift voor een groot deel voltooid kon zijn. Na deze periode wist ik je per post, flop, fax of telefoon lastig te vallen, waardoor nog vele grote en kleine vragen mijnerzijds beantwoord werden, waarvoor mijn dank.

Ir. W.A. van Duyl vertegenwoordigde de begeleiding van het fysische onderdeel van dit onderzoek. Beste Wim, met weemoed denk ik terug aan de vrijdagen van 11 tot 1 en de altijd openstaande deur om fysische vraagstukken door te nemen. Je kritische stem in de voortgang en analyse van het onderzoek, je aandacht en medeleven ook voor niet-wetenschappelijke problemen zijn onmisbaar geweest. Ik wist je in je drukste tijd te overspoelen met telkens weer nieuwe hoofdstukken, maar toch vond je iedere keer weer de energie om er veel aandacht aan te besteden, waarvoor mijn dank.

Ir. E. Akçahuseyin was ons rekenwonder. Beste Emin, heerlijk waren die discussies met jou, of het nu fysica, politiek, trouwen, Turkije of Nederland betrof. Jouw vermogen om wiskundige afleidingen te creeëren is van groot belang geweest. Zonder jouw "K_d" was dit proefschrift er dan ook niet geweest. Met veel geduld heb je me de essenties van het transport duidelijk gemaakt, waarvoor mijn dank.

Hans de Bakker, bedankt voor je onmisbare technische steun tijdens de metingen en hulp bij het oplossen van vele problemen. De stagiaires André de Mol, Marco Poot en William Altheer dank ik voor hun aktieve en enthousiaste uitvoeringen van de stromingsweerstand en flow metingen.

Alle medewerkers van de afdeling Dialyse dank ik voor hun enthousiasme en medeleven en koffie. Hun bewaarzucht voor alles wat anders in de prullenbak was verdwenen, heeft veel in-vitro proeven mogelijk gemaakt. Fons, jij bent een speciale. De puinhoop en het waterballet die ik op jouw kamer mocht veroorzaken, zullen me nog lang heugen!

De Intensive Care afdelingen van het Dijkzigt ziekenhuis ben ik zeer erkentelijk voor het geduld en de medewerking tijdens mijn regelmatig urenlange aanwezigheid.

De afdeling Medische Microbiologie, in het bijzonder Johan Mouton, Ed IJzermans en Marius Vogel, wil ik bedanken voor de prettige samenwerking. Johan, ondanks mijn haast, mijn gebrek aan tijd en dat ik het liever gisteren dan vandaag af wilde hebben, heb je gelukkig de moed nooit opgegeven.

Een ieder verder, die ik benaderd heb voor meedenken, luisteren en beantwoorden of uitvoeren van alle mogelijke en onmogelijke vragen, wil ik op deze plaats hiervoor bedanken.

De paranimfen Jolien Tuyl en Gerda Verpoorte ben ik nog veel verschuldigd voor de hulp bij het regelen van alles wat er bij een promotie komt kijken. Bedankt!

Mijn huidige werkgever, de Maatschap Artsen-microbioloog Brabant, wil ik op deze plaats bedanken voor de gelegenheid die zij mij hebben geboden om dit werk te voltooien.

Hans, allebei in het "promotie-schuitje" en toch hebben we het gezellig weten te houden!

Aan mijn ouders, die mij gestimuleerd hebben om te studeren en vooral verder te gaan dan dat alleen, wil ik dit proefschrift opdragen.

CURRICULUM VITAE

The author was born on the 17th of February 1961 in Bergen op Zoom, the Netherlands. She obtained the diploma 'Atheneum β' at the 'Christelijk Lyceum' in Gouda. In 1981 she started the medical study at the Erasmus University Medical School in Rotterdam, where she graduated 'cum laude' in September 1988.
From September 1988 till September 1989, she worked as a medical officer in the field of social security at the 'Gemeenschappelijk Administratie Kantoor (GAK)'.
From September 1989 till March 1992, she was a research fellow, supervised by Dr. H.H. Vincent, nephrologist, Internal Medicine I, University Hospital Dijkzigt (head of the department: Prof.Dr. M.A.D.H. Schalekamp). This thesis was prepared at the department of Internal Medicine I and at the department of Biomedical Fysics and Technology of the Erasmus University Rotterdam (Dr. W.A. van Duyl).
In March 1992, she commenced a specialist training in Medical Microbiology at the St. Elizabeth Hospital in Tilburg (Dr. M.F. Peeters).