HAEMODIALYSIS TREATMENT MONITORED ON-LINE BY ULTRA VIOLET ABSORBANCE

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To Pia,
Rebecca & David

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Haemodialysis Treatment Monitored On-line by Ultra Violet Absorbance

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Science is to confirm how something is, not how it should be, and beyond its domain different kinds of appraisements and ethical judgements are always needed (my translation).

Einstein A (1879-1955)

Preface

THIS THESIS IS BASED upon work performed at the Department of Nephrology, University Hospital of Linköping, County Council of Östergötland and the Departments of Medicine and Care (IMV), Division of Nursing Science and Biomedical Engineering (IMT), Linköping University.

As a registered nurse with several years working experience of haemodialysis patients, it has been a great challenge to participate in the development of a new technique, which in the future may be used by staff in haemodialysis units, perhaps in haemodialysis at intensive care and perhaps even by patients themselves during home haemodialysis. Furthermore, this work has attempted to bridge the gap between patient and technology as well as different professions such as biomedical engineering, medicine and nursing, thus bringing an interdisciplinary focus on dialysis monitoring into the sphere of biomedical optics.

The Swedish Competence Centre for Non-invasive Medical Measurements, NIMED supported the studies in this thesis. Financial support from the University Hospital, Linköping was given for parts of the work in Papers II and III.

A basic part of the thesis is the ultra violet (UV) light used for the measurements, a light that is invisible to the human eye. The star that is necessary for life on earth, our sun (front page) is an enormous UV-source. In this work a lamp has been used as a light source, when an old technique, spectroscopy, has been developed for a new application. The present thesis will show that the UV-technique is capable of estimating parameters in the same manner as for other already available systems. It is also shown that the UV- technique offers a unique opportunity to visualise the ongoing

clearance process during a dialysis treatment that is not possible by other available on-line monitoring techniques.

The future work that already has begun, when this thesis was written, will focus on new ways to look at dialysis clearance and investigate other markers for dialysis efficiency than those today.

I and my colleauges hope that this is only the beginning of something new that will eventually be of use to the dialysis patients in the future.

Fredrik Uhlin

Abstract

THIS THESIS DESCRIBES AND EVALUATES an optical method utilizing ultra violet (UV) absorbance for on-line monitoring of haemodialysis treatment. Increased efficiency of haemodialysis treatment is considered to correlate to decreased morbidity and mortality when urea clearance (Kt/V) is elevated. However, further improvements have not been achieved at a higher Kt/V. The mortality rate in the haemodialysis population is still high (27% in Sweden)

Urea as the clinical marker is under discussion, partly due to urea being non-toxic, but also that the uraemic syndrom is the result of a cumulative retention of innumerable involved compounds.

On-line monitoring systems based on urea determination for improved dialysis efficiency have been suggested and developed in different settings over the last two decades, but have not achieved worldwide utilisation as routine clinical equipment.

This thesis demonstrates that the UV-technique utilising 280, 285 and 297 nm is capable of estimating dialysis efficiency in therms of Kt/V, nutritional status in terms of protein catabolic rate (PCR), with the same characteristics as existing methods. One novel finding using UV-absorbance with high sampling rates is the on-line visualisation of the clearance process for following variations in clearance caused by clinical events and disturbances as well as during and after adjustments. The fact that the UV-absorbance technique does not measure urea directly but has high correlation to several other both UV-absorbing and not-absorbing solutes makes it suitable to reflect a more overall solute retention process. Finally, a new efficiency parameter based on the calculation of the area under UV- curve (clearance curve), is suggested to reflect the total removal of some solutes.

In summary the UV-technique has the potential to be an additional tool to evaluate improvements of dialysis efficiency, which may result in decreased morbidity, longer life span and enhanced quality of life for the haemodialysis patients.

List of Papers

THE MATERIAL FOR THIS THESIS CONSISTS of five Papers, four are published in international scientific journals, and one is in manuscript. The Papers will be referred to in the text by their Roman numerals:

I. UHLIN F, FRIDOLIN I, LINDBERG L-G AND MAGNUSSON M: Estimation of delivered dialysis dose by on-line monitoring of the UV-absorbance in the spent dialysate. American Journal of Kidney Diseases, Vol 41, No 5 (May), 2003.

II. UHLIN F, FRIDOLIN I, LINDBERG L-G AND MAGNUSSON M: Estimation of total removed urea and protein catabolic rate by on-line monitoring of the UV-absorbance in the spent dialysate. Nephrology Dialysis & Transplantation, Vol 20, No 11 (Nov), 2005.

III. UHLIN F, FRIDOLIN I, MAGNUSSON M AND LINDBERG L-G: Dialysis dose (Kt/V) and the sensitivity of clearance variation using; on-line measurement of the UV-absorbance, ionic dialysance, dialysate-urea and blood-urea. Nephrology Dialysis & Transplantation, Vol 21, No 8 (Aug), 2006.

IV. UHLIN F, FRIDOLIN I, MAGNUSSON AND M LINDBERG L-G: Ultra violet absorbance on-line measurement utilized to monitor clinical events during haemodialysis. EDTNA-ERCA J, Journal XXXII, No 3 (Jul-Sep), 2006.

V. UHLIN F, PETTERSSON J, FERNSTRÖM A AND LINDBERG L-G: Complementary parameter for dialysis efficiency based on UV-absorbance monitoring. In Manuscript.

ADDITION:

¤ *Paper III* has been selected for the Journal Club, with 500 members, to be discussed wordwide, and authors to answer questions, Aug-Sep 2006.

¤ *Paper IV* was written after invitation from the Journal Editor. The paper is based on the presentation (oral and poster) at the EDTNA-ERCA conference in Vienna, 2005

BESIDE THE PUBLICATIONS IN THIS THESIS, part of the material and additional findings has been published at the following conferences and in one non-reviewed paper.

– UHLIN F, FRIDOLIN I, LINDBERG L-G AND MAGNUSSON M. Non-invasive monitoring of haemodialysis - UV-absorbance, Regional meeting in nephrology /renal care. Apr. 2004 Linköping, Sweden

– UHLIN F, FRIDOLIN I, LINDBERG L-G AND MAGNUSSON M. Protein Catabolic Rate Estimated by On-line Monitoring of the UV-absorbance of the Spent Dialysate. American Society of Nephrology, ASN, renal week, Nov. 2004, St.Louis, Missouri, USA.

– UHLIN F, FRIDOLIN I, LINDBERG L-G AND MAGNUSSON M. Clearance variations monitored by on-line UV-absorbance during haemodialysis. Nordic Baltic Conference on Biomedical Engineering and Medical Physics (NBC) Jun 2005, Umeå, Sweden

– UHLIN F, FRIDOLIN I, LINDBERG L-G AND MAGNUSSON M. On-line monitoring of the spent dialysate during haemodialysis using UV-absorbance. European Dialysis Transplant Nurse Association – European Renal Care Association, EDTNA-ERCA, Sep 2005, Vienna, Austria. *Became the winner of poster scholarship.*

– FRIDOLIN I, UHLIN F AND LINDBERG L-G. Total removed uric acid during dialysis estimated by on-line ultra violet absorbance in the spent dialysate. European Medical and Biological Engineering Conference (EMBEC) 2005, Prague, Czech Republic

– UHLIN F. UV-light to monitor haemodialysis. Dialäsen No 1, 2006. Magazine in Swedish for staff in nephrology,

– UHLIN F. UV-spectroscopy-can it be used to quantify dialysis? European Society of Artificial Organs, ESAO, conference, Jun 2006, Umeå, Sweden

– FRIDOLIN I, UHLIN F, LINDBERG L-G AND MAGNUSSON M. Accurate estimation of delivered dialysis dose by on-line ultra violet absorbance in the spent dialysate. European Renal Association- European Dialysis and Transplantation Association, ERA-EDTA, Jul, 2006, Glasgow, United Kingdom

Contents

Abbreviations

$AUCa^{297}$- area under the UV-absorbance curve at the wavelength of 297 nm
CRF - chronic renal failure
D - dalton
DCTool - Dose Calculation Tool, software from Fresenius medical care
ESRD - end-stage renal disease
GFR - glomerular filtration rate
HD - haemodialysis
HPLC - high performance liquid chromatogram
ID – ionic dialysance
K - clearance
Kt/V - dialysis dose
MW - molecular weight
OCM - On-line Clearance Monitor from Fresenius medical care.
PCR - Protein Catabolic Rate
nPCRw - Protein Catabolic Rate normalized to the bodyweight
PD - peritoneal dialysis
RF - renal failur
TDC - Total Dialysate Collection
TRU - Total Removed Urea
URR - urea reduction ratio
UM - Urea Monitor 1000, from Baxter Healthcare Corp.
UV - ultraviolet
λ - wavelength

Introduction

THIS THESIS FOCUS ON A PATIENT GROUP that have multifactorial concerns as a consequence to their End Stage Renal Disease (ESRD): physically due to loss of kidney function, socially due to the time of dialysis treatment and psychologically due to the fact that suffering from a serious disease, with an uncertain future awakens existential concerns, with a high risk of complications and early death related both to disease and treatment.

The number of patients treated with ESRD in Sweden was 7377 in 2005 including patients in dialysis and patients living with a transplanted kidney[1]. Of those, 3414 are treated with dialysis, 2697 in haemodialysis (HD), and 717 in peritoneal dialysis (PD). In the world the number of patients in haemodialysis is approximately 1.3 millon[2]. This thesis will focus on the HD population.

There is a strong correlation between increased dialysis efficiency, (dialysis dose) evaluated as urea reduction in the blood during dialysis treatment, and decreased morbidity and longer life span[3-5]. Dialysis treatment can only to some extent replace the functions of the native kidney and other functions have to be corrected medically and by diet recommendations. Despite dialysis treatment there are still functions of the native kidney that cannot be replaced, which results in symptoms of uraemia more or less still remaining. The efficiency of dialysis treatment has, however, been improved over the last decades. The term “adecuacy of dialysis” include other factors than dialysis dose[6] and its definition are in constant change. However, despite great improvements of the dialysis technique and anaemia correction during the 1990s the mortality rate in the dialysis population is still high, 27% /year in Sweden[1], but is varying between different contries. This can partly be explained by the fact that the population is ageing and there is no real age limit for being treated by

dialysis today. The uraemic syndrome with a trying treatment, especially to cardiovascular system [8,9] and often in combination with underlying co-morbidity, may also explain the high mortality.

During the history of dialysis the physician evaluated the patient's treatment first by only reducing the symptoms but in later years an objective parameter has been used[10]. Blood-urea became an accepted parameter worldwide and several mathematical formulas were developed for dose calculations based on urea determination.[11] Finally a consensus was reached using the Daugirdas second-generation formula from 1993.[12]

Urea has several advantages e.g. easy to dialyse, easy to measure, reflects nutrition status; and its removal is considered to correlate with morbidity and mortality and has long clinical experience. But the role of urea as a marker is controversial [13] and the blood sampling procedure of post dialysis blood-urea has a risk of error due to how it is performed by the nursing staff.

During the last two decades urea on-line monitoring systems for dialysis efficiency have been developed with different settings, but without gaining a worldwide acceptance as a routine evaluation tool at dialysis units.[14]

With the patient in focus, the over all aim of this thesis was to develop and assess the UV-absorbance technique for on-line monitoring of dialysis patients.

Background

BEING A PATIENT IN END STAGE RENAL DISEASE (ESRD) gives multidimensional consequences and involves many aspects in daily life[15] as well as the life situation of next of kin to an ESRD patient often being affected dramatically[16] . Dialysis is a life-saving treatment for kidney failure and the patient often has to accept the new life situation and a considerable emotional adaptation to the technology, which maintain their lives.[17] The uraemic symptoms are not complete resolved, despite dialysis treatment, and the patients have to learn to live with their symptoms[18]. The situation as a ESRD patient bound to the dialysis machine is surrounded by several stressors; physiological e.g. the toxic effect on almost all organic systems in the body that uraemia result in, [19] psychological e.g. related to changes of body function and disfiguring changes that occur to the body[20] e.g. scars from fistula constructions and needles[21], disruption of basic needs such as thirst, sexuality[19] and several other limitations compared to earlier life situation[22]. The health-related quality of life is profoundly affected in these patients[23].

The Kidney

The main functions of the kidney can be named as excretory, regulatory and metabolic. The excretory function is the excretion of water-soluble metabolic waste products e.g. urea, creatinine and uric acid. The kidney is responsible for the regulation of body water volume and osmolality, acid-base- and electrolyte balance. The metabolic area is the production and secretion of hormones, such as rennin and EPO (erythropoietin) and activation of vitamin D.

About 25% of the cardiac output at rest passes the kidneys, which allows a great glomerular filtration rate (GFR). The primary filtrated

volume can reach 180 L per day before reaborption of water and selection of dissolved substances from the tubular fluid back to the blood stream. The end product of this process are the secondary urine, 1-2 L / day, which leaves the body as urine.[24, 25]

Renal failure

Renal failure (RF) is characterized by the progressive decline in the capacity of the kidneys to eliminate toxic solutes.[26] RF is divided into acute- (ARF) and chronic renal failure (CRF). ARF is an acute damage of the kidney tissues often reversible or partly reversible, caused by hypoxic, toxins etc. e.g. after serious trauma, surgery, intoxications.[27] CRF usually shows a progressive decrease of GFR and is usually irreversible and related to increased blood levels of azotemic substances. CRF develops in stages during different time periods, up to decades. Only in the last stage, ESRD, is renal replacement therapy e.g. haemodialysis needed. Most people with a decrease in renal function will never reach ESRD. It is worth mentioning that the renal function is decreased successively as a result of normal ageing. The most common causes of CRF are the primary renal diseases; chronic glomerulonephritis (of infectious or immune origin), polycystic disease, pyelonephritis (ascending infection of the urinary tract) and the secondary renal diseases; diabetes mellitus, renal arteriosclerosis e.g. due to hypertension (leading to nephrosclerosis), systemic vasculitis, amyloidosis, myeloma.[28]

As described above CRF has a wide range of causes, but they all result in “uraemia” in the case of ESRD.

Uraemia and its symptoms

Uraemia is an intoxication wrote Jonas Bergström 1985.[29] Uraemia is derived from two Greek words, which mean urine in the blood. The uraemic syndrome involves almost all organs and organ systems and gives a number of symptoms, functional disturbance of enzymes, organells and cells leads to an overall change for the worse which untreated ends in coma and death. During the 1700-century, observations from Holland by

Boerhaave H. (1733) and in France by Rouelle H. (1752) described an unknown "soapy" substance in the urine.[30] Between 1797 and 1808 Fourcroy A. and Vauquelin N. isolated and crystallized this molecule and called it urea.[30] During the 1800-century several researchers investigated the mechanisms of clinical RF and methods detecting urea concentration in blood were developed and urea became accepted as a valuable practical marker of RF. But urea was not accepted as a toxic substance that causes the uraemic syndrome[30] and there we are still today. Despite several decades of pathophysiological studies, the uraemic syndrome remains not completely defined[26]. The uraemic syndrome is a complex "intoxication" of retention of nitrogenous waste products resulting in multifactorial problems where the disturbances in several metabolic functions are reflected in clinical problems. Several organs and organ systems are affected; cardio-vascular system (hypertension, pericarditis and heart failure), peripheral nervous system (polyneuropati) central nervous system (poor memory, loss of concentration and slower mental ability), haematology (anaemia, bleeding tendencies), coagulation, immune status (immunosupression), endocrinology, loss of sexual function, gastrointestinal (anorexia, nausea, vomiting, changed taste), dermatological (pruritus, bleeding and bruising of the skin, yellow pigmentation of the skin), bones (skeletal damage and bone pain), hypercalemia, metabolic acidosis and biochemical alterations (enzymatic processes, drug binding etc.)[27,31-33] Abnormalities such as cardiac hypertrophy and cardiomyopathy are frequent findings in renal failure[31]. Atherosclerosis is a major risk factor in patients with CRF[34] and increased mortality has been described[35]. Atherosclerotic plaque grows faster in uraemic patients[36].

Urea

As previously mentioned, urea has been used as a marker of uraemic retention for over 100 years and its role as a marker for dialysis adequacy has been discussed and argued. Urea is an organic compound of carbon, nitrogen, oxygen and hydrogen, $(NH_2)_2CO$, and the molar mass is 60.07

g/mol. The so called urea cycle is carbon dioxide, water, asparate and ammonia in a metabolic pathway which is necessary because ammonia is a common metabolic waste product mostly from the breakdown of amino acids and must be neutralized due to its toxicity.

Urea is the most accepted uraemic marker, but there is a controversy as to its role in the uraemic intoxication[37]. Urea seems to be a surrogate marker and representative for the removal of other solutes with impact on morbidity and survival[13].

Uraemic toxins

Urea shows a kinetic behaviour that is not representative for all uraemic retained solutes, yet including other water-soluble solutes[38]. Many of the solutes affecting metabolism have retention and elimination characteristics that are different from the traditional markers for uraemia, urea and creatinine[38]. At least 90 organic compounds have been retained in uraemia[13]. The retained organic compounds may be divided into three groups, small, water soluble solutes with a molecule weight (MW) <500 Dalton (D) (e.g. urea and creatinine), protein-bound solutes (e.g. hippuric acid, indoxyl sulphate and P-cresol) and middle molecules MW >500 D (e.g. β-2 microglobulin, Cystatin C, IL 6 and Leptin) [13]. Solutes removed by an artificial kidney, dialyser, during hemodialysis differ in part from those eliminated by the normal kidney[39]. Uraemic toxins have been defined as compounds causing uraemic symptoms and/or functional disturbances in patients with renal failure[40]. The uraemic syndrome is a result of the retention of compounds and also due to disturbed hormonal and enzymatic homeostasis[26].

A lot of research has tried to identify the uraemic toxin/toxins that may be responsible for the uraemic syndrome. The search for uremic toxins has been overestimated without taking into account that cumulative retention of innumerable compounds is involved[41]. Even inorganic compounds such as water, potassium and sodium may be called toxic as well, if they are insufficiently removed[42]. In vivo studies using rats, and also in humans, indicate that overload of uraemic toxins also accelerates the loss of renal

function and disruption of glomerular architecture[43, 44]. The protein binding is suspected to restrain removal during dialysis of several known toxins such as hippuric acid and indoxyl sulfate, which are cleared through the peritubular secretory pathway by the native kidney[45]. This indicates that it is important saving renal residual function even in dialysis patients. Several protein-bound uraemic toxins have a negative impact on many functions such as residual renal function, glucose intolerance, inflammation, drug binding[46] and vascular damage.[47, 48]

As earlier mentioned, urea as a marker for dialysis adequacy has been discussed and other molecules have been identified and purposed as more important concerning dialysis adequacy. The problem is that many of these compounds are difficult to remove by conventional HD due to either their protein binding and/or that their molecule size is greater than the pores in the membrane of the dialyser.

The research performed by the European Uraemic Toxin (EUTox) Work group has been followed with great interest forefronting the question: Could some of these identified molecules be measured with new techniques?

Since thirty years, the high performance liquid chromatogram (HPLC) technique, which utilizes UV after steps of molecule separations, has been used by several reaserchers to detect uraemic substances in plasma, serum and dialysate[49-56].

Living with End Stage Renal Disease (ESRD)

A PERSON THAT HAS REACHED THE ESRD LEVEL has two alternatives to survive;

1) *Kidney transplantation* from a living or a dead donor gives a life similar to the life before renal failure. There are many medical factors that have to be fulfilled if transplantation can be done, which results in that a large group of patients treated with renal replacement therapy (dialysis) never will be suitable for transplantation during their life time. The lack of donors has resulted in a queue situation often of three years or more (Sweden), if the criterion for transplantation is fulfilled. During this time the patients usually have to be dialysed.

2) *Dialysis treatment* is available in two main modalities, haemodialysis (HD) and peritoneal dialysis (PD). Continuous Ambulatory Peritoneal Dialysis (CAPD) is one variant of PD and an alternative when there still is a renal residual function left. PD is based on the osmotic pressure that is created in the peritoneum cave after infuse of a hypertone sterile solution containing electrolytes and dextrose into the peritoneal cavity through a permanently installed transcutaneous catheter. A substantial diffusion of waste products in combination with the osmosic power drains by convection the capillaries in peritoneum of plasma water, which after a few hours is drained into the orginal container. This process is repeated with fresh solution 4-6 times a day.

Haemodialysis

The first successful haemodialysis treatment in human was reported in 1944[10]. Haemodialysis as a routine treatment for RF was initiated in the 1960s and has become a main treatment for ESRD.

Haemodialysis has two main functions 1) ultrafiltration (UF) of excess fluid 2) diffusion of waste solutes and electrolytes, across a semipermiable membrane.

In a haemodialysis unit it is necessary to have a water plant, which produces clean water for the dialysis machines. Drinking water is normally used for the production of dialysis water, called RO-water (RO = reverse osmosis). The drinking water is passing through several steps of filters before it enters into the dialysis machine, Fig 1. The dialysis machine produces the dialysis fluid, called dialysate, by mixing RO-water, with electrolytes and bicarbonate.

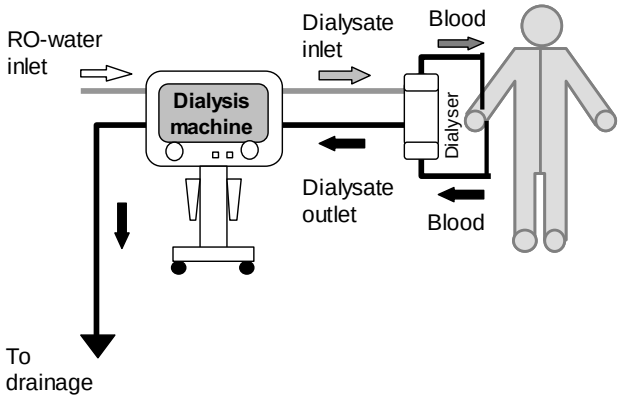


Figure 1. Schematically set up of a dialysis treatment

Dialysis machines are available at several performance levels from different manufactures but all have the same main two functional parts. A blood part consisting of a blood pump, pumping the blood from the "artery

needle" through the dialyser (artificial kidney) back to the patient via the "venous needle", Fig 2. For safety at the blood-side; blood flow, line pressures (arterious and venous), trans membrane pressure (TMP) and air trap are monitored constantly.

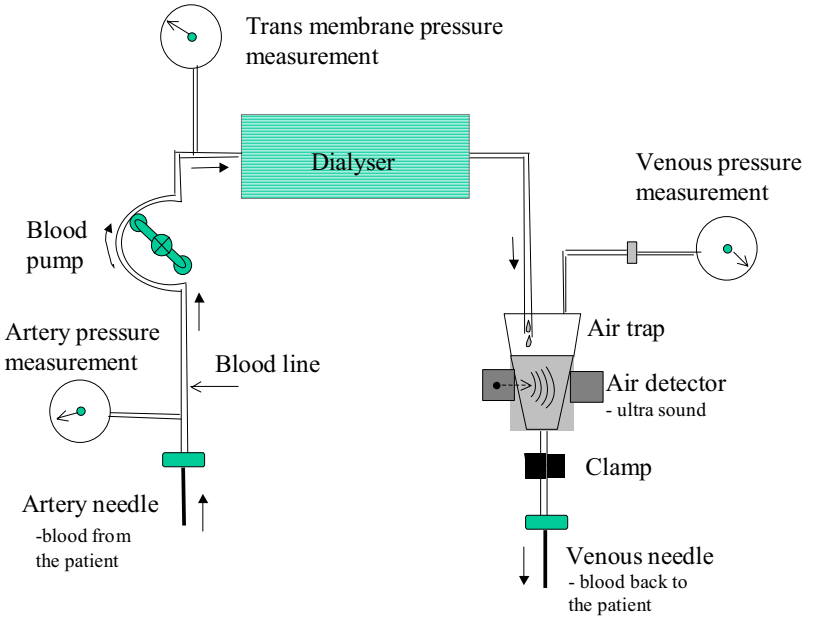


Fig. 2. The blood-part of the dialysis machine schematically

The second part, the dialysate-side, which removes waste solutes from blood and corrects the electrolyte, pH balance in the blood, and ultrafiltration of the blood from excess water by building up a negative pressure on the dialysate outlet, Fig 3. Safety in this part is maintained by constant monitoring of temperature, conductivity, UF control, volume control and a blood leak detector.

The dialyser is the functional unit, Fig 3, of the extracorporeal circuit and is available for different performances such as hollow fibre or parallel plate dialyzer and different material regarding membrane types e.g. cellulose, modified cellulose and synthetic membranes fibre type. The

capillary dialyser (used in our studies) contains thousands of small semipermeable fibres that are permeable for small solutes which allow diffusion from blood side to dialysate side, but non-permeable for larger substances such as proteins and blood cells that have to be remain in the body.

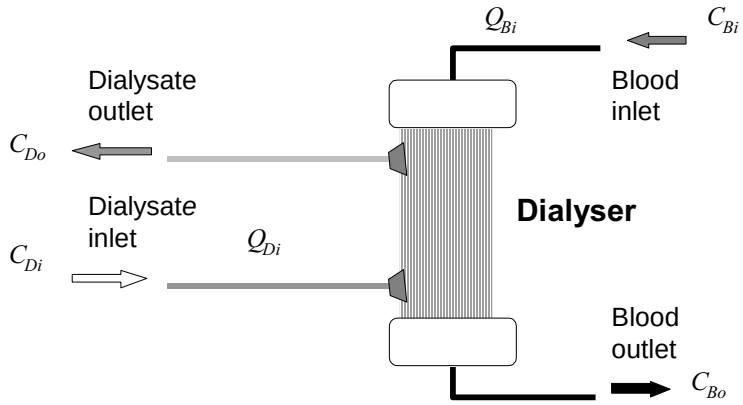


Figure 3. Capillary dialyser, note that the blood- and dialysate-flow is in the opposite direction, which maintain the concentration gradient across the membrane, for a maximal solute removal performance

The urea removal during dialysis can be explained by a dialysate-side mass balance, Eq. 1, which indicates that the dialysate outlet substance concentration C_{Do} is linearly related to the blood inlet substance concentration C_{Bi} [57]. For urea, which is a small solute and is transported over the dialyser membrane mainly by diffusion this relationship can be expressed as:

$$C_{Do} = \frac{K}{Q_{Di}} C_{Bi} \qquad (1)$$

where Q_{Di} is the rate of dialysate flow into the dialyzer in mL/min and K is the dialyser blood urea clearance in mL/min[57,58].

Blood access

To perform haemodialysis an access to the blood circuit is necessary. Arterio-Venous fistulas (AV-fistula), grafts and central dialysis catheters are the most common types of equipment. A well functioning blood access is a determining factor for an effective haemodialysis treatment. An AV-fistula is often the first choice (in Sweden) when a blood access for haemodialysis is planned. A surgical connection between artery and vein is performed to increase the blood flow in the vein, where the dialysis needles then is inserted, Fig 4.

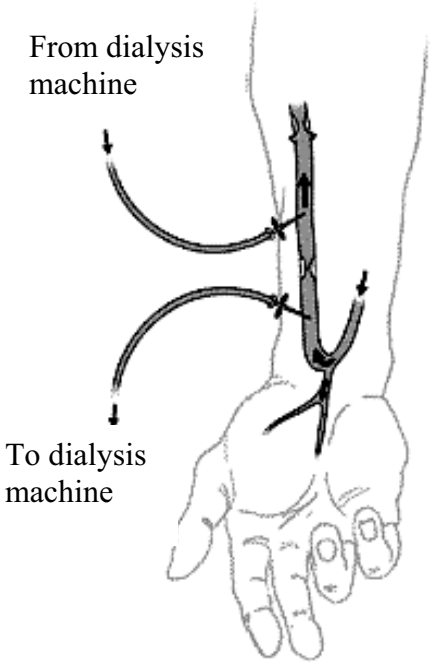


Figure 4. AV-fistula and two applyed needles, one delivers blood to the dialysis machine and one needle deliver the cleaned blood back to the patient

Transport of substances during haemodialysis

The primary goal of dialysis is to prevent the accumulation of toxic solutes in the patients' tissues by removing them from the blood[59]. The removal of solutes from the blood compartment decreases the concentration of solutes, and sets up tissue to blood gradients all through the body that refill the blood compartment with solutes. The degree of each gradient is dependent on properties of both the membrane and the solute behaviour, for example transport rates over the membrane of the solute or solute mobilization from tissue in the body[59]. The dialyser removes the solute that is the normal marker, urea, rapidly. The main transport mechanism of waste solutes during HD is diffusion over a semipermiable membrane in the dialyser, Fig 3, and it is in the nature of the diffusion process, that a higher gradient gives higher diffusion rates, which means that the diffusion is highest at the beginning of the dialysis treatment.

The other natural force filtering solutes across the semipermeable membrane in the dialyser is, convection where solutes movement occurs due to bulk movement of a solvent, as a result of a difference in hydrostatic pressure over the membrane created by the dialysis machine. The total clearance, *K,* will then be the sum of the diffusive and convective clearances in mL/min.

The low permeable dialyzers (low flux) cannot remove molecules with a weight greater than 10 000 D and the high permeable (high flux) membrane not greater than 30 000 D. This can be compared with the human basal membrane in glomerulus that is permeable for molecules up to the size of albumin of 69 000 D Fig 5.

The sieving coefficient of a substance, i.e. rate of movement of solute relative to solvent, gives information of the diffusion possibilities of the substance. Sieving coefficient 1 means that the substance is 100 % and 0 is 0 % permeability, respectively. Urea as a small sized molecule has sieving 1 in low flux, high flux membranes as well as the human glomerulus, but in case of larger molecules e.g. β_2-microglobulin, Table 1, the sieving for glomerulus is 1, approximately 0.8 for high flux and near 0 for low flux membranes, Fig 5.

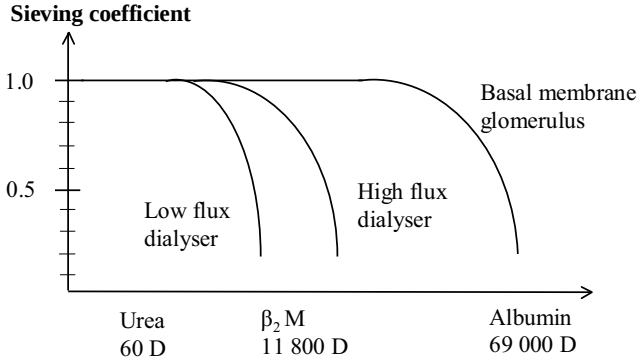


Figure 5. Illustration of sieving coefficients for urea, β2-microglobulin and albumin through a low flux-, high flux membrane and glomerulus respectively

This means that molecules above a certain size will be accumulated in the body, which may give long-term complications in dialysis patients. Table 1 shows examples of molecules ordained according to their molecular weight in Dalton those are of interest in the treatment of ESRD patients in the clinical workday.

Table 1. A few molecules and their molecular weight

Substance	Molecular weight in Dalton (D)
Albumin	69 000
β_2-microglobulin	11 800
Uric acid	168
Creatinine	113
Phosphate	96
Urea	60
Calcium	40
Potassium	39
Sodium	23
Bicarbonate	61
Water	18

To improve the clearance of waste products that normally would be removed easily by the healthy kidney, e.g β_2-microglobulin, dialysis techniques have become more sophisticated. The diffusive transport is overrepresented in HD, but dialysis modalities to enhance the convective transport of substances, similar to the human glomeruli are available, haemodialfiltration (HDF) and haemofiltration (HF), respectively.

The Dialysate

The fluid that is mixed by the dialysis machine is called dialysate. The dialysate is pumped normally with a flow rate of 500 ml/min (can be adjusted) through the dialyser at the opposite side, to the patients' blood, of the semipermiable membrane (Fig 3). The compositions of the dialysate create a concentration gradient to promote diffusion over the membrane. The pure dialysate not containing waste products from the patient has a composition with the purpose to normalising the plasma water, electrolytes, pH, and waste solute removal, in the patient. Table 2 shows the range of common solute concentration in dialysate and in serum (healty and uraemic), respectively[27, 28].

Table 2. The concentration of solutes in dialysate compared to serum

Solute	Concentration in the dialysate (mmol/L)	Concentration in serum (mmol/L) healthy	(uraemic)
Sodium	135-145	136-146	
Potassium	0-4	3.5-5.0	(4.5-6.5)
Calcium	1.0-2.0	2.2-2.6	
Magnesium	0.25-1.0	0.7-1.1	
Clorides	98-112	98-106	
Bicarbonate	27-38	22-28	
Glucose	0-11	3.3-5.6	
Acetate	2.5-10	<0.1	
Urea	0	3,5- 8,2	(20-40)
Creatinine	0	70-115	(400-800)

Haemodialysis complications

The most common complications during haemodialysis are *hypotension* especially when the ultrafiltration rate is high and a large amount of fluid relative to the plasma volume is removed. The fluid rate removal in the dialyser exceeds the plasma-refilling rate in the patient and the blood pressure falls as a consequense of decreased cardiac filling. *Muscle cramps* is also rather common in association with hypotension as well as *nausea*, *vomiting and headache*, which besides hypotension can be an early manifestation of a systemic and neurological syndrome called *disequilibrium,* which in serious cases can lead to coma. One explanation of *disequilibrium syndrome* is that it is caused by rapid shifts of solutes probably in combination with changes in pH between the plasma in the intravascular compartment and the intracellular fluid in the brain cells. The plasma become hypotonic compared to the brain cells and water shifts from the plasma to brain tissue, which results in brain oedema. Complications related to the vascular access also occur[27, 32,60,61].

Dialysis adequacy

When kidneys fail, dialysis is necessary to remove waste products from the blood. One waste product is urea, but urea itself is not very toxic, but its level is suggested to represents the level of many other waste products that built up in the blood when kidneys fail. Two urea-based parameters are generally used to assess dialysis adequacy clinically today, also recommended by national and international guidelines[62-64], namely urea reduction ratio (URR) and Kt/V. Twenty years ago dialysis adequacy was equal to Kt/V[65] but today, parameters based on urea clearance are only one component of dialysis adequacy[6]. "Adequate dialysis" should also involve other parameters considered in the care of dialysis patients such as volume status, blood pressure control, nutrition, and anaemia correction[6].

The mathematically expression of URR[66], i.e. the reduction in urea as a result of dialysis in one dialysis treatment, is commonly expressed as a percentage:

$$URR = \frac{C_0 - C_t}{C_0} * 100\% \quad (1)$$

where C_0 and C_t are the blood urea concentrations before and at the end of the dialysis respectively, measured in mmol/L[62]. An average should exceed 65% [62]. The urea kinetic parameter, Kt/V is expressed as:

$$Kt/V = -\ln\frac{C_t}{C_0} \quad (2)$$

where K is the dialyzer clearance expressed in mL/min, and t is the time in minutes. V is the distribution volume of urea in the body in mL, which means the volume of fluid that a patient's body contains. Assuming that urea is distributed in a single pool (sp) volume in the body is commonly used, urea generation rate and ultrafiltration are negligible during the session and that the ratio K/V remains constant over the dialysis. These assumtions lead to the equation.[12, 67-69]

$$spKt/V = -\ln\left(\frac{C_t}{C_0} - 0.008\frac{T}{60}\right) + \left(4 - 3.5\frac{C_t}{C_0}\right)\frac{UF}{W} \quad (3)$$

where T is the dialysis session length in min and UF is the total ultrafiltration in kg and W is the patient's dry body weight in kg.

Equation 3, the Daugirdas second-generation formula[12] has been recommended by guidelines for evaluation of HD.[62-64] The fact that the body is a multicompartment environment and that urea generation is still going during dialysis treatment has made these calculations controversial and debatable. Studies have shown that compartment effects from immediate post-dialysis concentrations[70-72] could lead to significantly overestimations of urea removal. To take into account those effects Kt/V can be calculated in terms of equilibrated Kt/V (eKt/V). [73]

The eKt/V are usually about 15-20 % lower than spKt/V and is predicted from the rate of dialysis (*K/V*) and the sp*Kt/V* according to the double-pool model (Schneditz -Daugirdas formula) [74], as:

$$eKt/V = spKt/V - \frac{0.6}{(T/60)} spKt/V + 0.03\,. \tag{4}$$

for peripheral arterio-venous blood access. The use of eKt/V gives more accurate quantification of intradialytic urea removal.

Several studies have demonstrated a relationship between dialysis doses, measured as *Kt/V* or *URR* and morbidity and mortality in haemodialysis patients[3,4,75-78], but several questions concerning how to define and determine the quality and adequacy of dialysis are under debate[79-81]. Recent studies e.g. the HEMO-study show no difference in survival between patients being dialysed at Kt/V normal (1.3) compared to high Kt/V (1.7) [82]. This must indicate that the clearance of small molecules, represented by urea, has an impact on patient outcome up to a certain level of Kt/V.

In the context of dialysis it should be considered that even if the HD characteristics remain constant it is difficult to attain a prescribed *Kt/V* due to a great variability among different haemodialysis sessions (e.g. variability in the whole body urea clearance) [80] also, in larger HD-patients, difficulties can arise in achieving the goal *Kt/V* [83]. Variations in dialysis efficiency between different sessions may also be due to e.g. changes in blood flow, access recirculation, treatment time and decreased clearance of dialysers. This in turn may lead to inadequate dialysis treatment for the patients. The national and international guidelines recommend at least one monthly control of dialysis dose in terms of either URR or spKt/V.[62-64]

Total body water and compartment effects

In the body the total body water (TBW) is multicompartmentally distributed. The relative size of the amount of fluid in each compartment is shown in Fig 6. The greatest amount of fluid in the

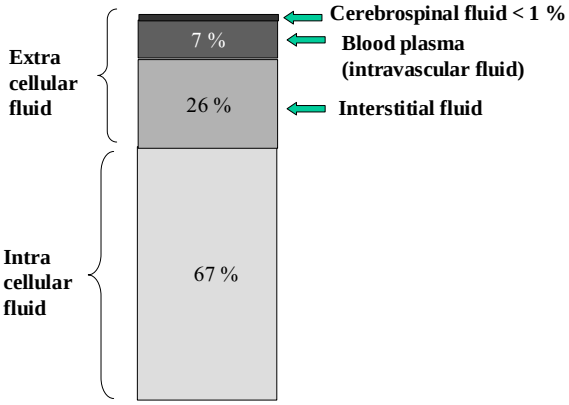


Figure 6. Distribution of the total body water

body is distributed inside the cells (intracellular) and the next is placed between the cells (interstitial). The blood plasma that is accessible with dialysis equipment is approximately 7 % of TBW[24]. The clearance process of solutes in TBW is therefore dependent on the intercompartmental transport rate of solutes; which varies between different solutes and osmotically active solutes can cause movement of water across a membrane. Healthy kidneys' "working" 24 hours/day and a kind of steady state are built up where the difference between compartments is small. After a dialysis treatment, on the other hand, disequilibrium gradually disperse but complete equilibrium for some solutes e.g. phosphate may not be restored for several hours[84]. This means that there is a delay in actual concentration of solutes, in our case urea, at different compartments during and after haemodialysis treatment, where only the blood compartment is available for dialysis[85]. This may in turn result in an overestimation of haemodialysis dose[86-88]. Factors that affect post-dialysis rebound in urea

concentration are access recirculation, cardiopulmonary recirculation and movement of urea from poorly accessible tissue compartments[89]. This rebound effect, has to be taken into account during post dialysis blood sampling procedure when evaluating the efficinecy of dialysis[62-64]. Other factors that influence the solute movement in general are: electrostatic charge, hydrophilicity/phobicity, protein binding, multicompartment behaviour and resistance of cell membranes towards gradient dependent transfer.[90]

The distribution volume of urea (V) is often an uncertain variable and may affect the calculation of dialysis dose, Kt/V. It has been stated that post 30 minutes dialysis, urea concentration is the most accurate method to calculate equilibrated Kt/V (eKt/V) [91] but it is often clinically impractical, therefore studies have been performed investigating if intra dialytic urea measurements could replace the 30 min post dialysis sample.[91,92]

On-line monitoring of dialysis efficiency in the spent dialysate has been suggested to have several advantages; one of them is elimiation of the uncertain post dialysis urea concentration value.

On-line monitoring equipment

ARE ON-LINE MONITORING EQIPMENT TOOLS OR TOYS? [96] This is an important question that must be asked during the development of new technical equipment. Which parameters can be monitored in the care of dialysis patients? Are we drowning in too much information? Is there any risk in using the equipment?

Several on-line monitoring systems for haemodialysis using different technologies have been developed over the years, able to monitor blood pressure, ultrafiltration (UF) control, temperature, conductivity and blood flow, during hemodialysis[97]. The existence of automatic control of several parameters is obvious and is clearly related to the safety and performance of the treatment, and several technical modalities are incorporated in the dialysis machines today. Other automatic control systems such as monitors for blood volume changes, hematocrit and O_2 (Crit-line) and dialysis dose monitors are not equipped as standard by all manufactures of dialysis machines.

"Urea monitoring during dialysis: the wave of future" wrote Lindsay R et al. 15 years ago[98] and since then several authors have suggested that on-line, real-time dialysis monitoring during every dialysis treatment is a valuable tool to ensure the desired quality for all dialysis treatments[98-104]. However on-line therapy, adequacy-monitoring systems have not found a wide utilization as clinical routines. Possible reasons could be high initial and running costs, need of disposals and extra work for the staff. The only available system for dialysis adequacy estimation is the ionic dialysance method.[105] This method can easily be integrated into the dialysis machine and no disposals are needed. The method is described below.

Urea monitors

Enzymatic sensors

Monitors that more or less continously measure urea concentration in a flow of fluid have disappeared from the market today. The monitors applied on the spent dialysate are Biotrack (Bio-Care Corp., Hsinchu, Taiwan) [106], DQM (Gambro Lundia AB, Lund, Sweden) [107,108] and BioStat 1000 (Baxter Healthcare Corporation, McGaw Park, Illinois) used in Papers I and II [109].

There are some differences in the analysis method for determining urea concentration in these devices. The BioStat 1000 (UM) used in Studies I and II, will be shortly described here. The technique is designed to measure urea concentration on-line in the effluent dialysate stream. The UM utilizes an ammonium ion sensor that measures the amount of ammonium ion (NH_4^+) determined directly by an ion-specific electrode [103,109]:

$$CO[NH_2]_2 + H_2O \xrightarrow{\text{urease}} 2NH_3 + CO_2 \qquad (5)$$

$$NH_3 + H^+ \longrightarrow NH_4^+$$

Hydrolysis of urea, $CO\ [NH_2]_2$, produces NH_4^+, thus creating an electrical potential difference between two electrodes that is then amplified and recorded [103, 110]. A membrane with the enzyme urease is the catalyst to the chemical reaction when it comes in contact with urea in the spent dialysate. Fig. 7 shows an on-line measurement using the UM in Paper I. The concentration of urea in mmol/L is measured every 5 minutes and the exponential decay is demonstrated.

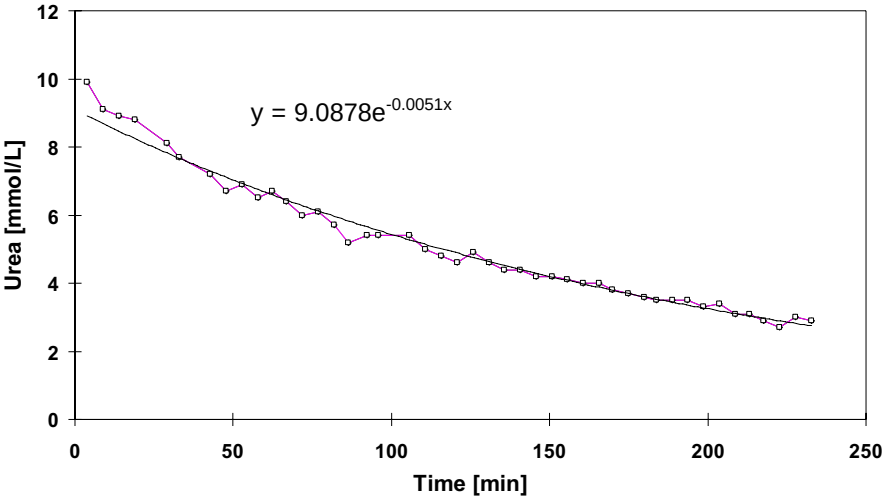


Fig. 7 shows a session were UM is used in paper I.

Dialysis adequacy has been validated in several clinical studies using the monitors listed above.[110-121]

Conductivity sensor; ionic dialysance

Since the early 1990s the concepts of conductivity measurements have been reported.[105, 122] The conductivity methodology named as the effective ionic dialysance method (ionic dialysance = *ID*) is equipped in two dialysis mashines, the Diascan (COT, Hospal, Meyzeu, France) [123-129] and OCM (Fresenius Medical Care, Germany) [130,131] used in Paper III. The method can be defined as the dialysance of mobile electrolytes through the dialysis membrane corrected for recirculation and ultrafiltration. It is based on the fact that the diffusion coefficients of sodium and urea are similar at 37º C, through a dialysis membrane. Sodium dialysance can therefore be used as a marker for urea. The calculation of *ID* is based on measurements of dialysate conductivity, C (only here, otherwise c = conentration) at the

dialyser inlet ($C_{d\ in}$) and outlet ($C_{d\ out}$) [105,122] and the value of $C_{d\ out}$ for a given $C_{d\ in}$ is dependent on both the patient's plasma water conductivity and the ionic dialysance. In order to extract *ID*, measurements are performed at 2 levels of $C_{d\ in}$.

Assuming that *ID* is equivalent to the urea clearance *K*, the parameter *Kt/V* can be assessed. [133-136] The use of anthropometrical calculations often results in an oversestimated V, which gives an underestimated Kt/V[93, 94]. Fresenius has developed a software Dose Calculation Tool (DCTool; Fresenius Medical Care, Germany) used in Paper III, where a more accurate V is calculated using blood samples and clearance from OCM.

Studies have focused on determining an accurate V either assessed by conductivity monitoring[95] and it has also been suggested that the product of Kt, in mL/min is a better expression of dialysis clearance, due to V not being involved.

Electromagnetic radiation

SEVERAL GREAT AND FAMOUS SCIENTISTS have studied and described the nature of light e.g. Isaac Newton, James Clerk Maxwell and Albert Einstein. It has been discussed if the light is a particle or a wave but in modern quantum mechanics it has been stated that the light has a nature of both, "the doubel nature of the light" [137]. Visible electromagnetic radiation, and other electromagnetic radiation, acts like waves and at the same time they act like a beam of particles that is the carrier of light and named photons. The shorter the wavelength of the photon the more energy it carries. Shorter wavelengths have therefore different effects, e.g. infra red (IR) is felt as heat, visual (Vis) radiation excites the chemistry of the eye and ultra violet (UV) radiation may lead to burns, but long radio waves are generally benign [137]. Fig 8 shows an illustration of the electromagnetic spectrum range.

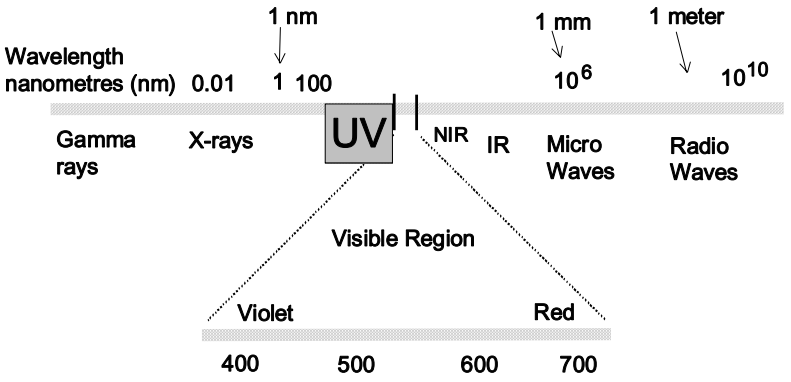


Figure 8. Electromagnetic spectrum from the shortest wavelength, gamma radiation to longest, radio waves.
Free from http://en.wikipedia.org/wiki/Electromagnetic_radiation

Visual (Vis) light is per definition electromagnetic radiation between 390-770 nm and IR 760 nm-0.5 mm. Even if the UV wavelength range 190-380 nm was considered in an early stage, the wavelength 280, 285 297 nm was exclusively utilized in this thesis (Paper I-V).

In order to utilize electromagnetic radiation in the UV-range and solute absorbance the sample is often applied in a cuvette, Fig 9 placed in an instrument, called a spectrophotometer, where different wavelengths can be selected as single ones or scanned over an optical wavelength range. The spectrophotometer determines the amount of the ingoing light that is absorbed by the sample. The intensity of the light illuminating the sample is symbolized by I_0 and I, Fig. 9, symbolizes the intensity of the light after passing the sample.

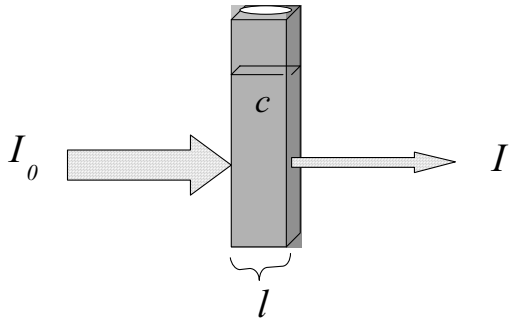


Figure 9. A cuvette containing solution. The absorbance is dependent on the path length l, the concentration of solutes c, and the millimolar absorptivity by the solute, ε

The Beer- Lambert law states that the absorbance of light intensity is proportional to the concentration of the substance. It means that the amount of UV-light absorbed when passing through a cuvette (manufactured by UV-transparent material such as quartz) with spent dialysate is linearly dependent on the concentration c [mol/L] of the absorbing solute, the optical pathlength in (l) [m] (the thickness of the

cuvette) and the extinction coefficient ε [m^{-1} $(mol/L)^{-1}$] (even called the molar absorptivity), Fig. 9, at a certain wavelength (λ). [138]

If I_0 is the intensity of the incident light and I is the intensity transmitted light through the medium, is the absorbance (A), dimensionless.

$$A = \log_{10} \frac{I_0}{I} = \varepsilon \; cl \tag{6}$$

If ε is known for a substance the absorbance (A) can be calculated by multiplying the pathlength (depth of the cuvette) and the concentration of the substance. If ε is known for a substance and A is obtained from a measurement, it is possible to derive the concentration as:

$$c = \frac{A}{\varepsilon \; l} \tag{7}$$

In our case, when the spent dialysate contains several different absorbing compounds, the overall extinction coefficient is the linear sum of the contributions of each compound. However all the components are not identified and probably there is interference between different substances which make it difficult to separate and determine the concentrations of each solute.

A of a mixed solution, obtained by a double beam spectrophotometer, is given by the Lambert -Beer law as [139,140]:

$$A = \log \frac{I_0}{I_{r+s}} - \log \frac{I_0}{I_r} = \log \frac{I_r}{I_{r+s}} \tag{8}$$

where I_0 is the intensity of incident light from the light source I_r is the intensity of transmitted light through the reference solution (e.g. pure dialysate) and I_{r+s} is the summated intensity of transmitted light through

the reference solution mixed with the solution under study (e.g. pure dialysate + waste products from the blood).

Aims of the thesis

THE OVERALL AIM WAS TO assess the UV-absorbance technique for on-line monitoring of dialysis patients.

The specific AIMS of the studies were to:

- compare the delivered dialysis dose in terms of Kt/V calculated from the UV absorbance in the spent dialysate on-line, with different available methods
- compare the delivered dialysis dose and the sensitiveness for clearance variation using the UV absorbance at the wavelength of 297 nm and different available methods
- compare the total removed urea and protein catabolic rate estimated with UV absorbance in the spent dialysate on-line with different available methods
- show that the UV-absorbance curve instantaneously can reflect clearance variations and disturbances of different origin
- suggest a new efficiency parameter, the area under UV-curve, that may give a better measure of the dialysis efficiency compared to other methods

Subjects

THE PATIENTS IN STUDY I-IV WERE ALL selected from the Department of Nephrology, University Hospital in Linköping. The inclusion criteria were clinically stability and a well functioning vascular access. The meaning of stable was specified as; dialysis treatment of the patient normally pass without problems and interruptions, patient related as well as vascular access related. The selection of stable patients was important to reduce the risk of disturbances and influences of different kinds; which could raise difficulties when evaluating the UV-method in the early development phase. The low number of interruptions and alarm situations in Paper IV confirm the population of a non-problematic patient group. In Paper V, 6 patients were randomised from one patient group of 20 individuals. In this study problematic treatments were preferable. The last (7 th) patient, included in Study V, was selected due to repeated vascular problems. More detailed information about the studied patients is presented in each paper, respectively.

Number of patiens and number of studied dialysis sessions in the studies:
Paper I, 13 patients, in 84 dialysis sessions
Paper II, 10 patients, in 40 dialysis sessions
Paper III, 6 patients, in 18 dialysis sessions
Paper IV, 16 patients, in 108 dialysis sessions
Paper V, 7 patients, in 7 dialysis sessions

Several patients occur in several studies and a total number of 23 different patients have been studied during 116 dialysis sessions within a time period of 8 years (1998-2006).

Ethics and normalization

All clinical tests have been performed after approval by the Ethical Committee in Linköping, Sweden. The patients have been informed orally and in written. The patients were also informed that they could drop out the study whenever they liked, whithout explaination or any changes in their normal dialysis treatment and care. The author has also been present during the experiments and has answered any questions that arose.

Only in a few dialysis sessions was the treatment changed compared to the normal treatment of the patients. In Paper III in one session of three the blood flow for all patients was reduced. To exclude any risks of hyperkalemia the plasma potassium was checked before start of treatment. In Paper II i.e. the subgroup in paper I all patients used the same type of dialyser to standardise the material. In Paper V all patients used the same low or high flux membrane dialyser to minimize the number of different dialysers with different characteristics.

Safety aspects of the instrumentation connected to the drain tube of the dialysis machine was discussed thoroughly by the researchers and also by the local Medical Technical Department at Linköping University Hospital. The potential risk at inspection was leakage current if the cuvette should be broken and fluids reach the electrical parts of the spectrophotometer. This in turn could establish a current through the patient via the fistula with a potential risk of heart failure. Several safety actions were taken e.g. the measuring chamber water thight and strengthening the drain tubes' attachment to the cuvette and earth connection of the spectrophotometer. Finnaly staff from the Medical Technical Department gave an approval.

The method of on-line monitoring of dialysis using absorption of ultra violet radiation

IT WAS A CHALLENGE TO INVESTIGATE to adapt the technique of UV spectroscopy to an on-line monitoring performance, measuring on-line up to 5 hours. UV-radiation of 254 nm in transmission mode through an external loop of spent dialysate was reported 25 years ago by Gal and Grof, [142,143] but further development has not been presented. Another technique, used in laboratory environment that utilizes UV-absorbance, is high performance liquid chromatogram (HPLC) for separation and identification of contents of complex biological fluids. [53-55]

Instrumentation during the studies

Two instruments have been used for the determination of UV-absorbance during the work. An UV/Vis spectrophotometer UVIKON 943, Kontron, Italy was used in study I-IV and an UV/Vis/NIR spectrophotometer JASCO V-570, JASCO Corp., Tokyo, Japan, in study V, with an accuracy of ± 1% and ± 0.3%, respectively.

During on-line measurement a specially designed circular flow cuvette was used in Paper I-IV and a quadratic cuvette manufactures by JASCO was used in Paper V. In both cases the cuvette depth = optical pathlength was approximately 10 mm. This ensured an unobstructed dialysate flow through the cuvette (usually 500 mL/min) and a sufficient absorbance signal level, Fig 10.

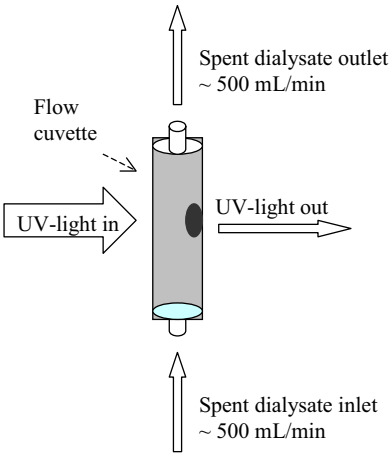


Figure 10. Flow cuvette, where UV-light enters and leaves the flowing spent dialysate

Choice of reference

During on-line measurement the pure dialysate was used as the reference (see Beer-Lambert law I_r = pure dialysate) and a fixed wavelength had to be chosen for the whole treatment. The absorbance baseline level was, after the pure flowing dialysate had been stabilized in temperature and conductivity, set to zero when the pure dialysate was flowing through the cuvette, Fig 10.

Choice of wavelength

Earlier studies of correlation between UV and urea indicated that the wavelength range 280 to 320 was to be preferred for on-line mearurement [144]. In Papers I and II the wavelength of 280 nm and 285 nm were used. In Papers III and V, 297 nm was used, in order to clearly lie inside the suitable wavelength range.

Methodological tests and considerations

Urease producing bacteria have been mentioned as a source of error when collecting spent dialysate e.g. in a tank during, total dialysate collection (TDC). [145] To minimize the risk of bacterial contamination of the TDC samples (Papers II, V) a careful cleaning of the tank with antibacterial solution was performed after each treatment. A bacteriological growth test was performed sending spent dialysate taken from the tank at 15 min and at 270 min, to the bacterial laboratory for analysis. No growth of bacteria was oberved.

The laboratory samples were analyzed of urea concentration within 1-4 hours in Papers I-III and within 1-2 hours in Paper V, after end of treatment. Therefore the first samples taken being analysed up to 9 h after sampling. The influence of time variation was therefore also tested. A sample with spent dialysate was divided into 7 test tubes and sent to the laboratory one per day for seven days. There were no significant differences in urea concentration in those analyses.

A poorly mixed dialysate in the tank in Papers II and V may also hypothetically be a source of error. To evaluate this, samples were taken from the tank at two different places, after stirring and sent to the laboratory for analysis (n = 30). No significant differences were found.

The measurement accuracy of the instrumentation at the laboratory was tested by sending identical samples in 10 different test tubes. The difference between tested concentrations was in accordance with the error of ± 5% reported by the laboratory at that time.

A baseline test was performed, on the flowing pure dialysate, to investigate if the UV-absorbance was sensitive to changes in temperature, conductivity, dialysate flow, vibrations, and movements of the cuvette. The test shows that movements of the cuvette and hard thrusts against the spectrophotometer could result in disturbance in the UV-measurement and even baseline displacement. The UV-absorbance was not affected by maximum variations in conductivity and dialysate flow rate of pure dialysate. When the temperature of the dialysate fluid was maximal changed (from 35-40º C), the variation was only of 0.001 Absorbances

(A), which then could be disregulated compared to the measure range 0.5-4 A.

As a test of instrumental stability, UV-absorbance at 297 nm was measured on-line on the flowing pure dialysate during 5 hours, and the variation seen was a drift of the instrument of 0.001 A, again considered to not influence the measurements.

In vitro tests

In the first clinical study (Paper I) a mean difference of 8% was found between eKt/V calculated from UV-absorbance compared to blood. This difference was suggested to depend on the fact of that with UV (at the studied wavelengths), reflected clearance of other molecules with slightly larger molecule weight and lower elimination rate. This assumption was tested under experimentally controlled situations. An in vitro test was performed with total control of the urea distribution volume (V), where a cistern (10 L) of spent haemofiltrate was used as "patient" and dialysed for 2 h, the set-up is shown in Fig. 11.

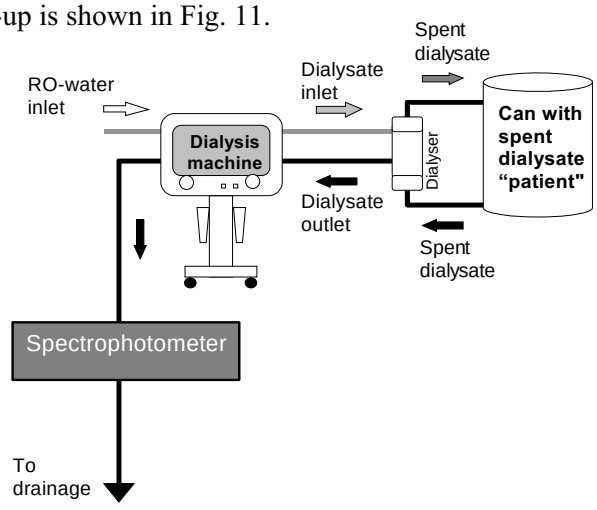


Figure 11. Set up during on-line in vitro tests. The can was filled with spent ultrafiltrate or spent dialysate

To raise the urea concentration to plasma levels, 5 g /10L urea (urea from Sigma Chemical co, St.Louis, MO, USA) was added. The result of 10 in vitro sessions showed that clearance of UV-absorbing solutes was approximately 10% lower than clearance for urea concentration in the spent dialysate. Fig. 12 shows a 120 min dialysis session where 10L spent haemofiltrate was dialysed.

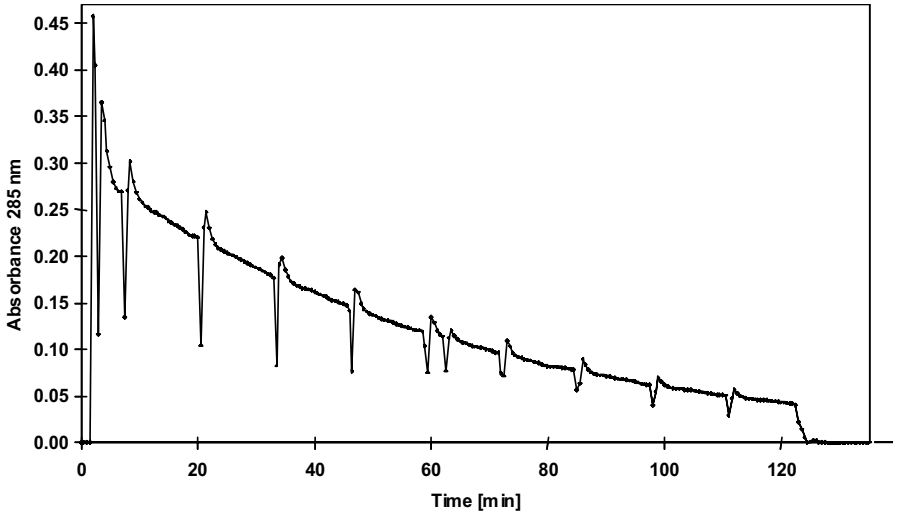


Figure 12. In vitro measurement on-line, where UV-absorbance at 285 nm, is plotted against time, during simulated dialysis.

Lower elimination rate of UV absorbing solutes may not be the whole explanation to the difference. In Study III it was found that the number of measuring points affected the slope and therefore Kt/V more than first expected. The slope of UV-absorbance was lowered if more samples were added to the curve; the same phenomenon was seen in blood- and dialysate- urea concentration if more values were included in the slope (Paper III [146]).

Correlation to urea

If the dialysis dose in terms of Kt/V should be estimated by UV-absorbance there must exist a good correlation between urea concentration and UV-absorbance [141,147]. Urea is not an UV-absorbing solute at the wavelength (280, 285, 297 nm) used for on-line monitoring.

The correlation between dialysate urea concentration and UV-absorbance is very high r = 0.99-1.00 for every single session Fig 13. However, when plotting all patients (n = 40) in Paper II, Fig. 14, the regression coefficient decreases to 0.68 despite that all patients used the same typ of dialyser.

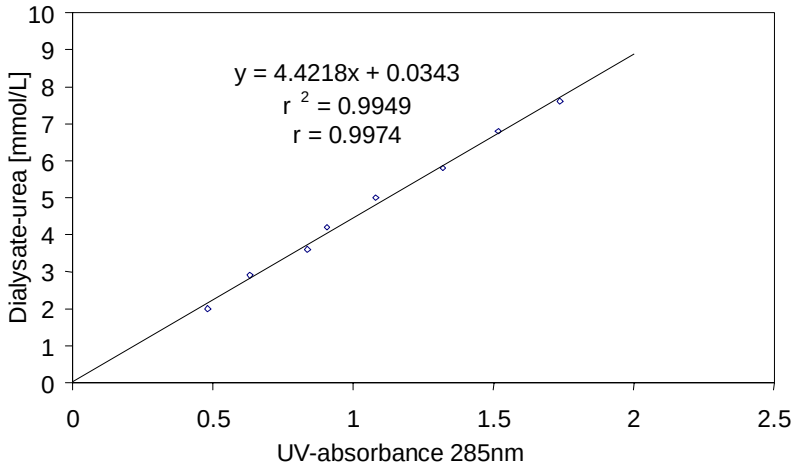


Figure 13. The correlation between dialysate-urea and UV-absorbance in a single treatment where 10 samples of urea concentration were taken from the drain tube (Paper II)

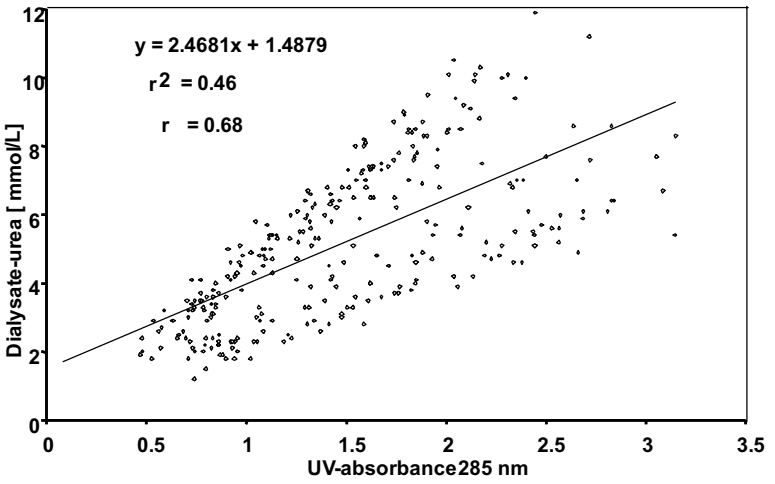


Figure 14. The correlation between dialysate urea concentration and UV-absorbance (Paper II).

Fig 14 shows a correlation coefficient of 0.68 between UV-absorbance and dialysate urea concentration in 40 treatments (10 patients). The low correlation on a group level is probably due to several patient related factors. The discrepancy is larger at higer urea concentration in the beginning of the treatment. This maybe due to the fact that UV-absorbance reflects the amount of other solutes with varying removal rates. The used dialyser type was the same in all treatments (n = 40), sub group in Paper I, which means that the observed discrepancy in a group level not is related to different dialyser conditions.

In addition to the study in Paper III, the correlation for each patient was tested in 3 treatments (6 patients) and r varied between 0.98 and 0.99.
In summery it seems as the correlation between urea concentration and UV-absorbance is patient specific and, at least, stable for three weeks (Paper II[146]).

Estimation of delivered dialysis dose (Papers I, III & V)

WHEN INTRODUCING A NEW METHODOLGY first a comparative study with existing methods for dialysis quality evaluations concerning absolute values and standard deviation (SD) should be made. Both the well-established Kt/V calculations from blood-urea but also commercially existing on-line monitoring alternatives should be included. In the first study (Paper I) comparisons were made with eKt/V calculated from blood-, dialysate-urea and the earlier commercially available UM from Baxter. Paper III includes a similar comparison but the UM was replaced by OCM from Fresenius. In this study a lowering of clearance was also performed in one of three subsequent treatments of each patient.

Sampling and laboratory analysis (all Papers)

Blood samples were drawn before the start of dialysis treatment (C_0) and immediately at the end of the treatment (C_t) in Papers I-V. The slow flow sampling technique was used in paper III and V [62]. Dialysate samples were taken before dialysis (pure dialysate), used as the reference solution during scannings, when the dialysis machine was prepared for starting and the conductivity was stable, and after 5, 15, 30, 60, 90, 120, 180, 240 minutes (270, 300 if the treatment was longer than 240 minutes) in Papers I-V. If a periodical self-test or alarm occurred during a timetabled sampling, the sample was instead taken after 1 to 3 minutes depending on whether the UV-absorbance monitoring curve had been stabilized. In Paper V a logging computer guided the samplings to not interfer with the self-tests.

The concentrations of urea were determined at the Clinical Chemistry Laboratory at Linköping University Hospital using standardised methods.

The accuracy of the method for determination of urea in dialysate and blood was ± 5% paper I-IV, ± 4 % in Paper V and in dialysate for creatinine ± 5 %, urate ± 3 % and finally phosphate ± 5 % in Paper V.

Calculation of Kt/V

From the differential equation, describing urea mass balance during a dialysis session, it can be determined that the average value of the Kt/V during a session may be approximated as the slope from the natural logarithm (ln) plot of the urea blood concentration in the blood, S_B versus time. Hence:

$$Kt/V \approx -S_B T \approx -S_D T \tag{9}$$

where T is the dialysis session length in min and V is the distribution volume of urea in the body in mL. This equation would hold strictly if urea obeys fixed volume and single pool kinetics and no urea is generated during the session [148]. S_B may be replaced by the slope from the natural logarithmic plot of the urea concentration in the spent dialysate (S_D) versus time. In order to calculate Kt/V from the on-line UV-absorbance, the slope of blood and dialysate urea concentration was replaced by the slope of the UV absorbance (Sa) versus time ($Kt/V \approx - Sa * T$), Paper I [149].

Assuming that urea is distributed in a single pool volume in the body, that urea generation rate and ultrafiltration are negligible during the session and that the ratio K/V remains constant over the dialysis the following equation holds: [65-68]

$$Kt/V = -\ln \frac{C_t}{C_0} \tag{10}$$

According to Equations 9 and 10 we obtain:

$$\frac{C_t}{C_0} \approx \exp(-Kt/V) \approx \exp(S_B T) \approx \exp(S_D T) \approx \exp(S_a T) \qquad (11)$$

if the slopes are used instead of the blood urea concentrations, which is the equivalent when using two measuring points, and the previously mentioned assumptions are fulfilled.

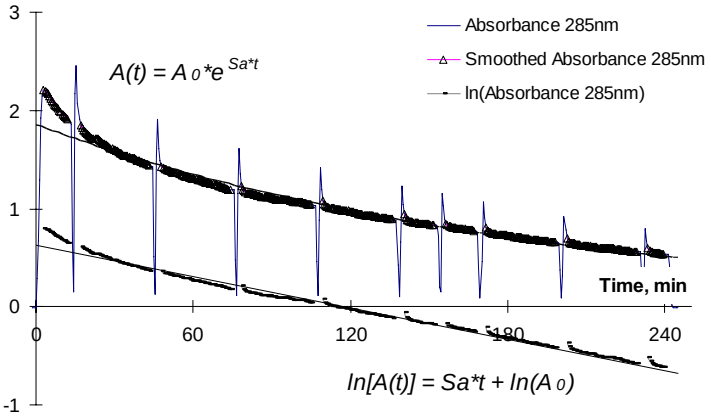


Figure 15. A typical UV-absorbance curve (wavelength 285 nm) where the absorbace is plotted against time. The natural logarithmic slope (ln) is also shown (Paper I).

Using the UV-absorbance slope, Fig 15, according to Equation 3 the Daugirdas-based monocompartmental equation can be written as:

$$spKt/Va = -\ln\left(\exp(S_a T) - 0.008\frac{T}{60}\right) + \left(4 - 3.5\exp(S_a T)\right)\frac{UF}{W} \qquad (12)$$

The equilibrated Kt/V from UV-absorbance, eKt/Va, according to the rate adjustment method [69], is predicted from the rate of dialysis (K/V) and the spKt/V as:

$$eKt/Va = spKt/Va - \frac{0.6}{(T/60)} spKt/V\ a + 0.03 \qquad (13)$$

The rate adjustment method predicts that the urea rebound is related to the rate of dialysis or dialysis efficiency [73]. The clinical set up in Paper I is shown in Fig 16.

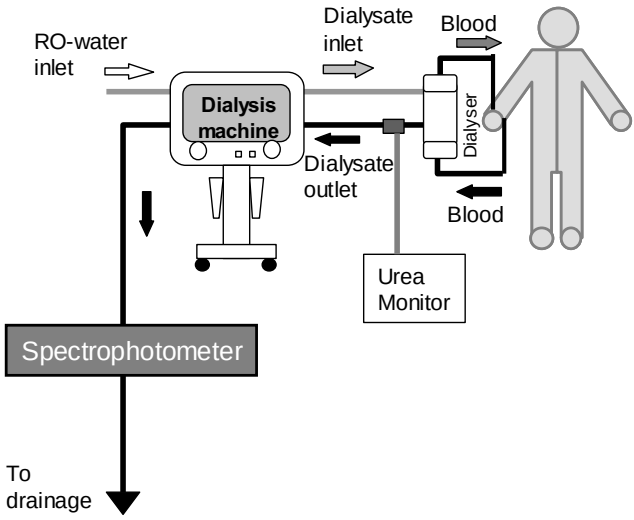


Figure 16. The clinical set up in Paper I. The spectrophotometer and the Urea Monitor 1000 is connected to the drain tube of the dialysis machine

Table 3 shows a summary of eKt/V from Papers I, III, V. Standard deviation (SD) were in the same magnitude for all compared methods and eKt/V from UV-absorbance showed a slightly lower eKt/V compared to blood in all studies.

Tabe 3. eKt/V in mean and ± SD

Paper number	UV	Blood	Dialysate	UM	OCM	Number treatments	Number patients
I	1.19 ± 0.23	1.30 ± 0.20	1.26 ± 0.21	----------	----------	84	13
I, subset	1.16 ± 0.18	1.23 ± 0.17	1.18 ± 0.15	1.24 ± 0.18	----------	40	10
III	1.21 ± 0.20	1.30 ± 0.20	1.32 ± 0.21	----------	1.31 ± 0.21	18	6
V	1.12 ± 0.18	1.16 ± 0.20	1.21 ± 0.22	----------	----------	7	7

Estimating urea-Kt/V using UV-absorbance seems to be possible with satisfying accuracy; the mean eKt/V-value was slightly lower, 8% in Paper I [149] , 7% in Paper III [146] and 4 % in Paper V, compared to blood-urea eKt/V.

Sensitiveness of variations in dialysis clearance

Next step was to investigate the sensitivity of clearance variations during dialysis (Paper III).

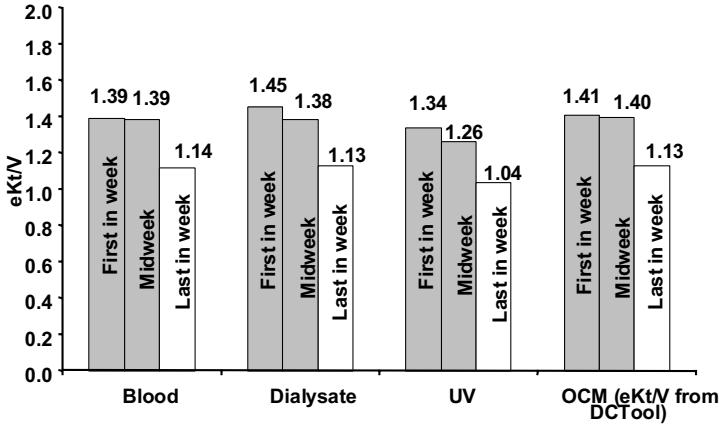


Fig. 17. The response of clearance reduction in eKt/V during the last session in the week, in comparison with first-and mid-week session (Paper III).

Fig. 17 demonstrates that the relative response of the manipulated clearance reduction is similar for the four methods. The reduction in eKt/V compared to the midweek session were; 18 % for blood, 18 % for dialysate, 17 % for UV-absorbance and 19 % for OCM, respectively. [146]

Estimating Protein Catabolic Rate from Total Removed Urea (Paper II)

ANOTHER PARAMETER DERIVED FROM UREA calculations is the nutrition parameter Protein Catabolic Rate (PCR); which also, like dialysis dose, in different studies has shown to correlate to morbidity and mortality [150,151].

PCR is widely accepted as a marker of protein nutritional status and is equivalent to dietary protein intake in stable dialysis patients [152]. The urea generation rate is not constant over the interdialytic period [153]and day-to-day variations in daily protein intake may result in PCR fluctuating significantly; therefore an average of a seven-day period has been proposed [154]. PCR calculated from Total Removed Urea (TRU) has been studied by Garred et al [154] and fractional factors of PCR calculations for different treatment days in the week have been developed, enabling the estimation of a seven-day cycle with one dialysis treatment [154].

In order to transform UV-absorbance (dimensionless) to dialysate-urea (D_{urea}) [mmol/L] a good correlation must exist between the two variables [141]. The transformation is based on the regression line between UV-absorbance and D_{urea} (Fig 13).

The regression line from the first dialysis for each patient was used for the subsequent three treatments (not in serial) when calculating TRU and nPCRw.

Total dialysate collection

Total Dialysate Collection (TDC) is often mentioned as the ”gold standard” when measuring the total removal of urea [155]. TDC is cumbersome as in clinical routine and sources of error during TDC, such as bacteria producing urease [145] and dilution from fresh dialysate during bypass mode, have been mentioned [156], see methodological considerations, page 53.

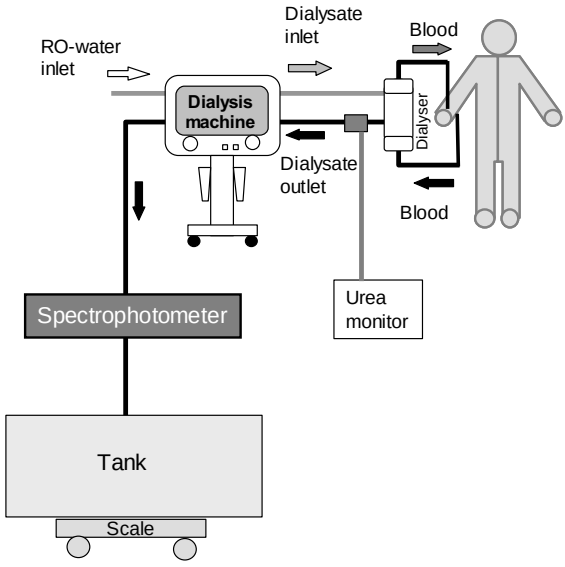


Fig. 18. The clinical set up in Paper II.

Fig. 18 shows the same set up as in Paper I except for the addition of the tank, equipped with a scale, where all spent dialysate was collected and weighted (Paper II).

Estimation of TRU

One way to estimate TRU, assuming that the dialysate flow, Qd(t), is constant and the total ultra filtration (UF) is known, is to use the following equation [157]:

$$TRU(mmol) = Urea[mean] * (Qd * T + UF) \tag{14}$$

where Urea[mean] in mmol/L is the mean urea concentration in the spent dialysate of the particular haemodialysis session. For the TRU calculations Urea [mean] = D_{total} was utilised, where D_{total} is the urea concentration in the tank at the end of dialysis.

In a similar way TRU may be calculated from the on-line UV-absorbance (TRUa) curve as:

$$TRUa(mmol) = (Slope * MeanA + Intercept) * (Qd * T + UF) \tag{15}$$

where the MeanA is the mean of all UV-absorbance (A) values from the start to the end of the dialysis, Qd is the rate of the dialysate flow in L/min, T is the dialysis session length in minutes and UF is the total ultra-filtrated volume in L during the session. The regression line between the UV-absorbance and D_{urea} from one on-line measurement gives the Slope and the Intercept inserted in Equation 15 when determining TRUa of the following sessions. TRU from TDC (reference method) was calculated as D_{total} (mmol/L)* collected weight (kg), assuming that 1kg =1L of the dialysate. TRU was also obtained from UM readings. TRU from the three methods was finally compared regarding mean values.

When comparing TRU the calculated values in Paper II were 559 ± 108.50 estimated from UV-absorbance, 632.70 ± 127.79 measured by UM and finally 548.13 ± 126.41 from TDC.

PCR calculated from TRU

The PCR calculation, from TDC and UV-absorbance, was based on a theory by Garred et al [158], where a calculation of urea removal is expressed as a fraction of the week's urea generation. The fraction varies with the day of the week and was found to be essentially constant among patients on a given day [158]. The amount of urea could therefore be approximated from measuring urea concentration from only one of the three treatments and PCR could be calculated as:

$$nPCRw = Factor1,2or3\left(\frac{TRU1,2or3}{BW}\right) + 0.17 \qquad (16)$$

where TRU 1,2 or 3 (expressed in grams of urea nitrogen) is the TRU from the first (1), midweek (2) or last dialysis in week (3) and Factor 1,2 or 3 is the fractional factor for the first (1), midweek (2) and last treatment (3) of the week respectively; factor 1 = 2.45; 2 = 2.89; 3 = 3.10 [158]. Obligatory loss of dietary protein in stools and via skin shedding represents the constant term 0.17 (g protein/kg body weight/day). The dry body weight (BW) was used for normalisation of PCR (nPCRw).

In Paper II a very good agreement between PCR from UV-absorbance and TDC was shown, Table 4.

Table 4 Mean values of nPCRw in g/kg/day ± SD, Paper II

	TDC	**UV-absorbance**	**UM**
nPCRw ± SD	0.808 ±0.175	0.818 ± 0.170	0.869 ± 0.184

Monitoring clinical events by UV-absorbance (Papers III & IV)

PAPER IV (AND EXAMPLES IN PAPER III) IS DESCRIPTIVE and shows that due to the high sampling rate of the UV-absorbance the method is sensitive to different kinds of disturbances, e.g. alarm of conductivity (dialysate in by-pass) artery-, venous pressure (blood-pump stop) and restricted flow in artery needle due to low blood pressure or troubling needle placement. These events are rather common in dialysis treatment and occasionally affect dialysis clearance. In Fig. 19, the UV-response to a blood pressure fall and the following interventions are shown. The UV-absorbance was lowered, even when blood-flow (Qb) was unchanged (195-225 min), most certainly due to difficulties to achieve the pre-set Qb by the dialysis machine.

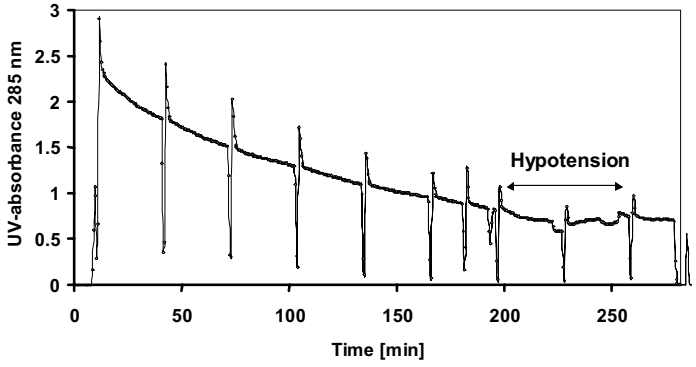


Figure 19. A period of hypotension, visualised as a decrease in UV-absorbance.

Fig. 20 shows a conductivity alarm resulting in by-pass of dialysis fluid in 10 min. After the interruption a new basline level is seen, most certain due to rebound of solutes during the period of by-pass of dialysate.

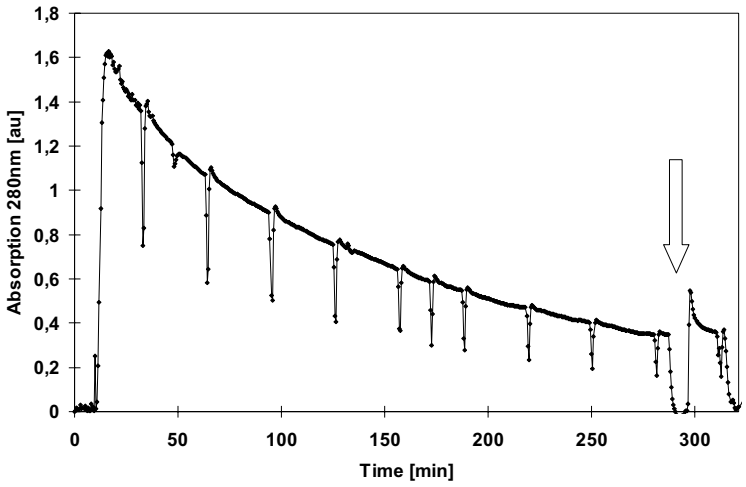


Fig. 20. A conductivity alarm of 10 min (arrow), were the dialysate fluid is set automatically in by-pass by the dialysis machine (Paper IV).

The use of UV-absorbance shows the possibilities to not only notify alarm effects as in Fig. 20, but also to give direct feedback after interventions resulting in clearance changes as in Fig. 21. (Paper III)

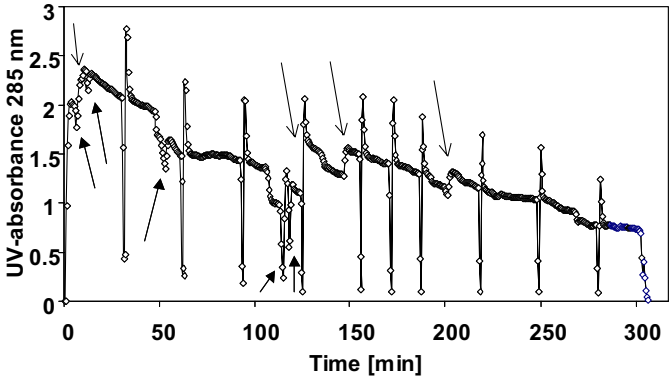
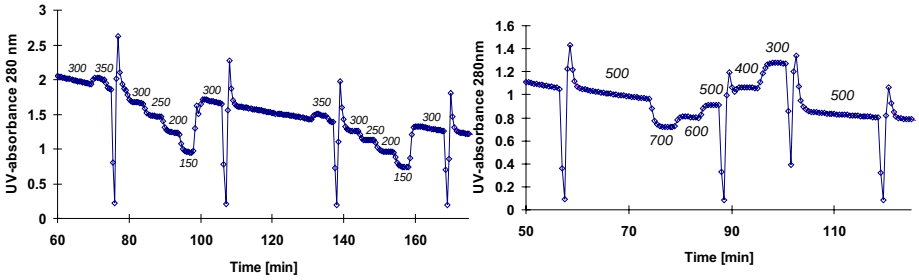


Figure 21. A troublesome treatment caused by restricted flow in artery needle. Arrows under curve=alarm of low artery pressure and arrows above curve=interventions by needle corrections (Paper III)

New baseline levels in UV-absorbance were observed after the 10-min interruption in Fig. 20 and after the needle corrections in Fig. 21.
Manipulation of Qb and dialysate-floe (Qd) has shown to have a very pronounced effect on the UV-absorbance, Fig 22 (Paper III).



Figs. 22. Manipulations of the blood flow (left) and dialysate flow (right) respectively (Paper III) in two different patients. The flow rates are presented in the figure in mL/min.

The new baselines that occur after the flow changes, Fig 22, must be interpreted with care, when calculating Kt/V from the slope. The visualisation of the clearance process is a novel finding by the UV-method and one advantage of using a method with high sampling rate. The earlier

clinically available Urea monitor 1000 (UM) from Baxter Health Corp. IL, USA, suggests a rejection of sessions with 5 or more urea measurements deviating from the expected decay [159]. The clinical benefit of the UV-absorbance system would be to monitor troublesome treatments where dialysis clearance can be adjusted on-line. Probably it is just those troublesome sessions that would have the greatest advantage to be identified and adjusted.

Area under curve as a parameter for dialysis efficiency (Paper V)

BASED ON THE RESULTS OF SLOPE EFFECTS in troublesome treatments with disruptions etc. (Papers III and IV), the need of a more complete parameter of the clearance process is suggested in this chapter. A new parameter i.e. that takes into consideration deviations and interruptions during treatment without mathematical trickiness. In stationary conditions the slope seems to be adequate to use for the Kt/V calculations (paper I). When using the slope, on the dialysate-side, incorrect interpretations can be made if the blood- or dialysate flow is changed during the treatment. In Fig. 23, the effect of a decrease in blood flow is illustrated. The change seen in urea concentration is the opposite on the blood-side compared to the dialysate-side.

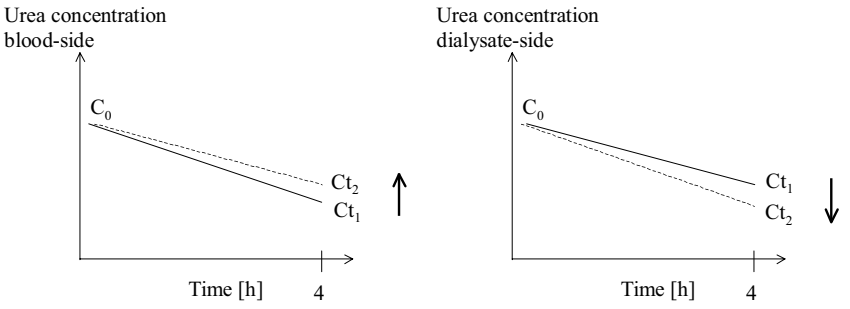


Figure 23. The effect of a change in blood flow during dialysis.
C_0 = pre dialysis urea concentration, Ct_1 = post dialysis urea concentration without change and Ct_2 = post dialysis urea concentration with change.

The course of events on the dialysate-side is also applicable for the UV-absorbance measurements.

Therefore a hypothesis came up; that Area Under the UV-absorbance Curve at 297 nm $AUCa^{297}$ could be a reliable parameter that reflects the total clearance of UV-absorbing solutes during a dialysis session.
To investigate this, TDC was performed and samples were taken from the tank at 5, 15, 30, 60, 120, 180 min and at the end. Concentrations of urea, creatinine, urate, phosphate were analysed at the laboratory, which gave the accumulated removal of these solutes at this time. The $AUCa^{297}$ were calculated in parts at the same time as the samples were taken. Fig 24 shows how the areas were divided when also a dialysate sample was taken from the tank.

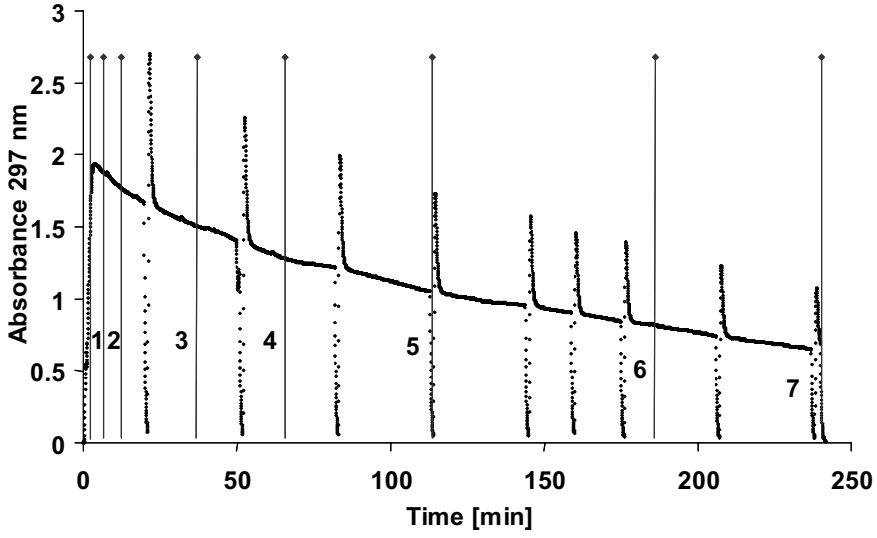


Figure 24. $AUCa^{297}$ divided in sub areas according to the samples taken from the tank, 1 to 7 in the figure. Those sub areas where then correlated to the total removal of the studied solutes.

Correlations were studied between the accumulated parts of $AUCa^{297}$ and the accumulated total removed solute. The correlation was very high

for each patient (1 or near 1 for the four solutes) and was lower when the correlation was performed in group.

Fig. 25 shows the correlation between four well-known solutes in dialysis treatment and $AUCa^{297}$ in 7 patients (in one dialysis session each).

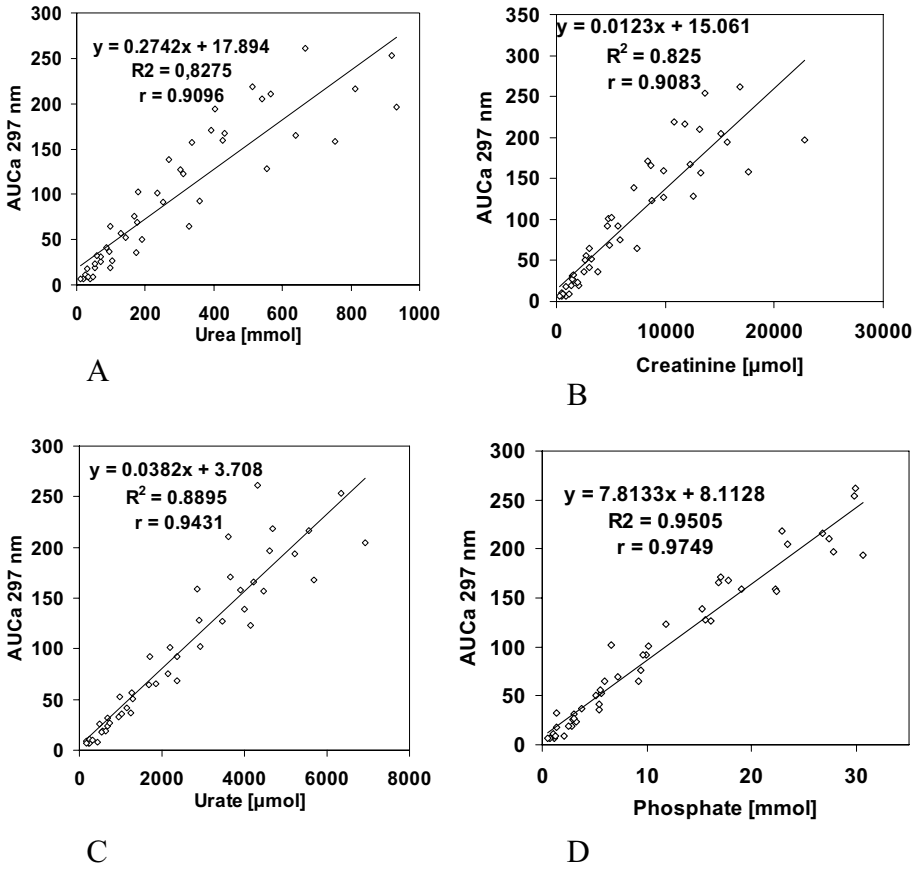


Fig. 25. The correlation between accumulated areas of $AUCa^{297}$ correlated to accumulated total removal of urea (A), creatinine (B), urate (C) and phosphate (D)

Despite the fact that only one of the solutes, urat is UV-active in the range of 297 nm the total removal of these studied solutes showed an

indication that the correlation between the $AUCa^{297}$ and urea, creatinine, urate and phosphate is rather high, even at a group level.

The $AUCa^{297}$ may be a complementary new parameter to evaluate dialysis clearance where events and clearance variations during treatment is included, and may therefore give a more reliable estimation of the total solute clearance compared to existing methods.

General discussion

THE DIALYSIS MACHINES ANNO 2006 ARE advanced devices of high technology and sophisticated regulatory features. The machines are equipped with monitoring tools for safety [97]; some manufacturers also have a dialysis efficiency monitoring system such as the ionic dialysance (*ID*) technique even though the equipment is not commonly used in clinical routine.

This thesis demonstrates that UV-absorbance technique utilising the wavelengths 280, 285 and 297 nm, is capable of monitoring dialysis efficiency in terms of Kt/V in the same manner as used worldwide and recommended blood-urea Kt/V, by direct urea quantification monitoring system Biostat 1000 and the *ID*-method (Papers I, III).

The nutrition parameter, PCR (Protein Catabolic Rate), can be estimated by UV-absorbance and agrees well with the "gold standard", the technique for total dialysate collection, namely TDC, (Paper II).

A slightly lower mean eKt/V using UV-absorbance (Papers I, III) has been observed but with similar SD of the difference compared to other methods.

The relative response of the UV-technique to a manipulated clearance reduction is similar in terms of eKt/V compared to other methods (Papers III).

One novel finding using UV-absorbance is the on-line visualisation of the clearance process, for identifying variations in clearance caused by clinical events and disturbances (Fig. 26) as well as during and after adjustments (Papers III-V). Complications related to the interpretation of Kt/V determined by UV-absorbance and other methods were discussed in Papers III, V. Therefore this thesis also suggests a plausible solution to this issue by introducing a new parameter, the area under curve derived from the UV-absorbance on-line measurements (AUCa), which takes into account deviations, interruptions and adjustments during the whole session

(Paper V). This was manifested by a good correlation between AUCa and total removal of urea, creatinine, urate and phosphate (Paper V). It will in upcoming research be of utmost importance to investigate the correlation between AUCa and several other solutes with clinical significance in dialysis.

By means of the UV-technique Fridolin et al. (2002) showed a good correlation between UV-absorbance and certain removed solutes, such as urea, creatinine and uric acid, in the spent dialysate and lower correlation for other solutes such as potassium, phosphate and β_2-microglobulin for every single dialysis session.[141] The mean absorbance contribution from every compound is dependent on the used wavelengths. The major contribution to the total absorbance, among the solutes mentioned above, arises from uric acid at the observed wavelengths 280, 285 and 297 nm [144] used in this thesis.

As mentioned above, the eKt/V calculated from UV-absorbance showed a slightly lower mean value compared with eKt/V determined from blood. Possible reasons for the higher values from blood are that several UV-absorbing solutes removed by HD are of a higher molecular weight than urea, known from HPLC studies [49-56] and probably have lower clearance. Data (not published) from in vitro dialysis using spent haemofiltrate and with a fixed volume, *V,* of 10 L and *t* of 120 min (n = 10) demonstrated that *K* determined from UV-absorbance is approximately 10 % lower than for urea, meaning lower Kt/V. In practice, if the purpose is to approach blood urea Kt/V, the mean difference value between blood and UV-absorbance Kt/V values can be eliminated by an algorithm [160], including dependent parameters such as eKt/V, t, dialyser urea clearance in vitro, dry body weight. Another explanation to the difference is that the number of measuring points that the slope was based which affects the slope calculation (Paper III). If the number was reduced to only max and min Kt/V using UV-absorbance approached that of blood (Paper III).

It is known that the dialyser's permeability affects the solute clearance. The high flux membranes have higher sieving coefficients for molecules of a larger size compared to low flux membranes (Fig. 5). This is an issue that is insufficiently investigated in this study, but the correlation seen

between dialysate-urea and UV-absorbance is high independent of the dialyser used (high- or low flux). In a sub-study of 6 patients treated with low flux (n = 6) and within a few weeks with high flux membrane (n = 6), the correlations were near 1 between UV-absorbance and urea in all cases (data not shown). To study removal of higher molecule weight solutes with the UV-technique, one can monitor during haemofiltration, where all solutes and water are removed by convection, which facilitates the transport of larger molecules. Fig. 26 shows one dialysis session when isolated ultrafiltration was performed at the end stage of the dialysis session in order to remove extra fluid from the patient. The low level of UV-absorbance corresponds to a slow clearance rate of solutes that are transported by convection.

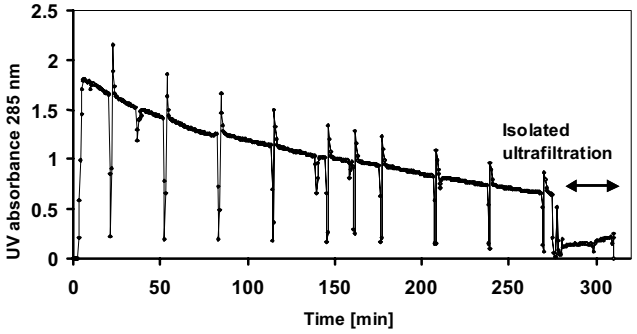


Figure 26. Isolated ultra filtration after dialysis treatment (i.e. no dialysis fluid trough the dialyser). A few alams is also seen at 40, 140 and 160 min corresponding to blood pump stops.

Urea is not responsible for the uraemic syndrome itself. [26,30] Furthermore, the mortality in the haemodialyis population is still high[1] and the effects of inadequate dialysis are not immediately apparent. It may take up to several years until the effects of sub-optimal therapy appear as long-term effects. This has lead to discussion concerning if other markers are more suitable for evaluation of dialysis efficiency, but some of those markers are unfortunately difficult to dialyse, due to their size or protein binding. Urea as a marker for dialysis efficiency is controversial [161] and as Vanhoder et al

(1995) stated at the NDT Second symposium on uraemic toxins "There is an urgent need to identify new markers replacing urea" [40]. The search for uraemic toxins has been overestimated without taking into account that a cumulative retention of innumerable compounds is involved [41]. However, one cannot ignore the fact that a relationship between *Kt/V* urea (and *URR*) and mortality and morbidity has been demonstrated in uraemic patients [3,4,75-77,162,163] despite the fact that urea is considered to be non-toxic [37,164].
The UV-method, by which can estimate the elimination of other toxic or non-toxic substances that are retained in uraemic patients with potential clinical significance, may overcome the problems with urea. At the same time the monitoring of a large number of UV-absorbing solutes, may give additional information about the dialysis clearance process not assessable with other methods.

If the UV-technique is taken to a clinical implementation, the staff at a dialysis unit must be able to handle the medical considerations; i.e. there must be a balance between medical science, nursing care and monitoring technical facilities, areas that cannot be separated. Only then can the UV-technique be used as a new tool to reach treatment goals evaluated by nephrologists and the dialysis team. This approach may also be suitable for patients treated with home haemodialysis as a monitoring tool both for the patient at home as well as for the staff.

Our studies have shown that the UV-absorbance curve is like a "fingerprint" of each patient's dialysis clearance, which can be used when individual different dialysis settings are to be evaluated. The UV-technique is the first method that has given a profile to the clearance process, not only a path from point A to point B giving a measure (Kt/V), but also information about what is happening to the patients on the way during a dialysis session.

One potential clinical drawback of the UV-method may be interference from other compounds and/or drugs, which can influence the UV-absorbance.

There are technical concerns to take into account when going into a commercial phase. In fact this is already considered during the

development of a prototype UV-monitor manufactured by LDI, Tallinn, Estonia.

Future and development

A question for future work is; can UV-monitoring be used in an intensive care unit, in unstable patients, evaluating dialysis efficiency in acute renal failure, especially intoxications; Perhaps UV-absorbance by itself is more suitable in this patient group compared to urea evaluation.

Other wavelength ranges in the electromagnetic field e.g. visible (VIS) and Near Infra Red (NIR) [165-168] may be of interest for monitoring urea and other compounds.

The ideal monitoring scene in a dialysis clinic or in home dialysis may be a combination of several monitoring modalities. Fig 27 presents a vision of this monitoring system that hopefully can increase the understanding of patient-related processes during dialysis. Information may come via haemodynamic parameters gained from sensing the patient (ECG, blood pressure, bio impedance, optical sensors etc.), dialysis machine parameters and dialysis parameters from the UV-monitor. This information from all sub-parts may separately or by multifactor sampling and analysis approach an optimal dialysis treatment.

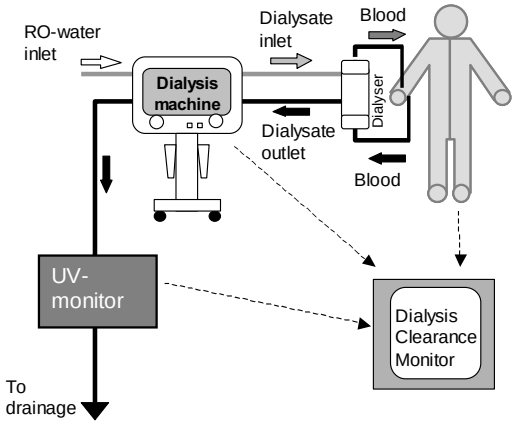


Figure 27. A vision of a dialysis monitoring system that considers information from the patient, dialysis machine parameters and solute clearance.

Summary and conclusions

A NEW OPTICAL METHOD for monitoring the solutes in the spent dialysate utilising UV-absorption is presented.

The major findings and advantages are:

- Estimation of dialysis efficiency in terms of Kt/V, nutritional status in terms of protein catabolic rate (PCR).
- Immediate identification of any deviations in dialysis treatment and feedback after adjustments that have an impact on the clearance process.
- The calculation of the area under UV- curve (clearance curve) is suggested to reflect the total removal of solutes.
- A real time continuous, on-line measurement of spent dialysate, which does not require blood samples.

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