Safety and biological aspects of present techniques of haemodialysis

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Umeå 2006

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ABSTRACT

Introduction: Haemodialysis (HD) is a treatment in which blood from the patient is lead through a tubing system into a dialysis device in a extracorporeal circuit. This circuit contains semipermeable membranes (dialyzer). Blood with uraemic toxins flows on one side, and a salt solution flows on the other side. The salt solution flushes away waste products that have passed the membrane by diffusion or convection through small pores. From there the blood returns to the patient through a tubing system that contains an air-trap and a sensor to avoid air contamination in the blood. Besides air contamination, this treatment is burdened with safety problems such as biocompatibility, electrical safety and mechanical safety. The aim of this thesis was to investigate the safety issues in haemodialysis devices regarding leakage current and air contamination during standard procedures and simulated fault conditions. Does the dialysis device constitute a risk for the patient?

Methods: To determine the extent of leakage current in HD machines, measurements at the filter-coupling site were performed in vitro according to the safety standard, IEC 601-1, in 5 types of dialysis machines. To determine, in vitro, to what extent blood and priming fluid allowed leakage current to pass to the patient, leakage current were also measured in the blood lines. The blood line was filled with blood from donors or priming fluid in eight different runs. To determine if leakage current could influence biocompatibility, a Fresenius 2008C dialysis machine and 8 hemophan dialyzers were used. Blood lines contained about 400 ml heparinized blood from each of 8 different donors (in vitro). C3d was measured, in vitro, before start of a simulated dialysis and at 15, 30, 45 and 60 min. during standard dialysis procedure. Then 1.5 mA current was switched on and additional samples were drawn at 75 and 90 min. Some patients need a central dialysis catheter (CDC) for access, placed close to or within the heart. To analyze if leakage current during standard HD would influence the ECG, patients with CDC or with AV-fistula as access were investigated. To analyse if air contamination could occur without activating security alarms in the dialysis device, various modes of in vitro dialysis settings were studied, some using a dextran solution to mimic blood viscosity. Besides visual inspection an ultrasound detector for microemboli and microbubbles was also used.

Results: The data showed leakage current at the filter coupling site that was significantly higher for some devices than for others. The leakage current could pass through blood and priming fluid. It exceeded the *cardiac floating* (CF)-safety limit (<50μA) at the top of the CDC using the test *mains on applied part* for saline (median 1008μA), for blood (median 610μA) and for a *single fault condition* using saline (median 68 μA) or blood (47 μA). The leakage current experiments showed that complement activation worsened as the leakage current increased. During standard dialysis arrhythmia could occur. Microbubbles were visible at the bottom of the air-trap and bubbles could pass the air-trap towards the venous line without triggering the alarm. During recirculation, several ml of air could be collected in an intermediate bag after the venous line. Ultrasound showed the presence of bubbles of sizes 2.5-50 μm as well as more than 50 μm silently passing to the venous line in all runs performed.

In conclusion, the data showed that a leakage current in HD devices can be high enough to be a safety risk for the patient. This risk is greater if a *single fault* arises in the dialysis machine or another device connected to the same patient, or during *mains contact to the patient*. Then the current flow may be high enough to cause arrhythmia for the patient, especially when using a CDC. There is also reason for concern that micro bubble transmission may occur without inducing an alarm. These factors need to be looked over to improve safety regulations and optimize HD treatment and service schedules.

Key words: Haemodialysis, Safety, Leakage current, Central dialysis catheter, Microbubbles, Microemboli, Air contamination.

LIST OF PAPERS

I **Jonsson P, Stegmayr BG**. Current leakage in hemodialysis machines may be a safety risk for patients. *Artif Organs* 2000;24(12):977-81.

II **Jonsson P, Eliasson G, Stegmayr BG**. Blood lines conduct leakage current during haemodialysis: a potential safety risk during first failure, especially for patients with central dialysis catheter as access. *Med Biol Eng Comput* 2005;43(6):731-8.

III **Jonsson P, Forsberg U, Niklasson J, Stegmayr BG**. Electrical current leakage during hemodialysis may increase blood-membrane interaction. *Int J Artif Organs* 2001;24(3):136-9

IV **Jonsson P, Karlsson M, Wiklund U, Jensen S M, Stegmayr B** Measurement of cardiac rhythm in connection to haemodialysis with focus on a possible interference due to leakage current. A pilot study of patients in chronic haemodialysis. In manuscript, to be submitted.

V. **Jonsson P, Karlsson L, Forsberg U, Gref M, Stegmayr C, Stegmayr B.** Air microbubbles pass the security system of the dialysis device without alarming. *Artif Organs, in press,* 2007.

LIST OF ABBREVIATIONS

AV-fistula	arterio-venous fistula
AV-graft	arterio-venous (artificial) graft
CDC	Central dialysis catheter
LC	leakage current
UF	ultrafiltration
HD	haemodialysis
HF	haemofiltration
HDF	Haemodialfiltration, a combination of HD and HF
LSD	least significant digit
MD	measuring devise defined in IEC 60 601-1
SD1	Standard deviation along new y-axis, Poancaré plot, see Arrhythmia analysis
SD2	Standard deviation along new x-axis, Poancaré plot, see Arrhythmia analysis
AC current	Alternating voltage/current
DC	Direct current or continuous current
QA-90	Metron QA-90 electrical safety analyser
IEC	International Electric Committee. Organisation for international standardisations
(IEC #75)	International standard. General requirements for basic safety and essential performance.
General standard	(IEC #75)
IEC 601	(IEC #75)
IEC 601-2-16	IEC standard, Particular requirements for the safety of haemodialysis, hemodiafiltration, hemofiltration equipment

Terminology defined in IEC 601. This is simplified descriptions:

Applied part	A electrode or part intended to be in contact with a patient

Safety levels for leakage current are divided in:

B	*Body* recommended for patient applications
BF	*Body Floating* recommended for patient applications
CF	*Cardiac floating,* recommended for cardiac application

Leakage current in *applied parts* is measured in following conditions:

Normal condition	No failure in the equipment
Single fault condition	One single failure is simulated in the equipment.
Mains on applied part	Mains voltage x1.1 over a 47kohm resistance are connected to the applied part.

INTRODUCTION

Uraemia

Uraemia is a toxic condition resulting from renal failure. When kidney function is severely compromised urea and other toxic metabolites are retained in the body (Vanholder, 2001 #99). The reduced kidney function also results in a reduction in the ability to excrete water. Water is added to the body every time the patient eats or drinks, and the water accumulates. This causes the body to be overloaded with water. Excess water in the lungs causes pulmonary oedema. Some of the other symptoms of renal failure include:

fatigue and respiratory distress due to anaemia caused by a reduction of the hormone, erythropoietin, produced by the kidneys,
fatigue, neuromuscular dysfunction, arrhythmia, convulsions, somnolence and death due to salt imbalance, especially due to excess potassium, phosphate, carbonate and hydrogen in the blood,
gastrointestinal discomfort and diarrhoea due to various retained metabolites,
skin abnormality “uraemic frost”,
impaired resistance to infections due to impaired leukocyte function,
increased bleeding time and bleeding risk due to platelet (thrombocyte) dysfunction,
neurological dysfunction/manifestation,
blurred vision, and
cardiac dysfunction and vessel impairment with increased prevalence of calcified vessels.

(Vanholder, 2001 #99)

In the past there was no help for patients with chronic renal disease. If they did not recover by themselves they died in uraemia.

In the 1820s Richard Bright described the connection between pathological changes in the kidneys that could be seen at autopsy and uraemic symptoms. He described oedema in the face, arms and legs, fluid in the stomach, protein in the urine, seizures and unconsciousness prior to death. The described sickness was called 'Brights illness'. During the later part of the 19th century it became known that the uraemic poison in the blood was a rest product of the metabolic breakdown of proteins, and these rest products were removed by the kidneys in healthy people. The logical conclusion was that these patients should be treated with “uraemia diet”. That diet contained mainly fat and carbohydrates and very little protein. That diet together with rest, were the prescribed treatment. Beside this, the doctor could offer anaesthesia to reduce the pain and agitation.

In the beginning of a slowly progressive chronic kidney disease the symptoms are milder and appear less evident; the patient may just feel somewhat tired, feel sick and vomit. The described protein-restricted food is not tasty and not easy to eat. The uraemia itself may reduce appetite which results in

malnutrition. During starvation the body breaks down muscle and other body proteins to create energy, and that worsens the condition. In the end stage of kidney failure, if dialysis is not performed, the patient may suffer from pain and agony. The overload of water can shorten the suffering by filling the lungs and the patient drowns by pulmonary oedema, internally (Ahlvall, 1984 #89).

Dialysis

The word “dialysis” comes from the Greek words, “dia,” that means through, and “lysis,” which means to dissolve. Dialysis is a physical process whereby particles in a solution are transported through a membrane. The process is facilitated by different concentrations on both sides of the membrane, aiming to achieve an equilibrium by diffusion (Ahlvall, 1984 #89).

Need for renal replacement

Before there was an effective treatment for uraemia, healthcare could only offer the protein-reduced diet and recommended rest to give the kidneys a chance to recover. The patients that could not recover died. A better treatment was needed. The first reported use of dialysis was in 1910. The group consisted of three Americans, Abel, Turner and Rownthree (McBride, 1979 #88), who experimented on the use of a dialysis technique in a chemical analysis setting. They tried to measure the concentrations of solutes in the blood during such a procedure. The chemical analyses were disturbed by the proteins in the blood. The problems were solved by first dialysing the blood using a semipermeable membrane and thereafter analysing the substances in the dialysis fluid. The blood from an animal was sent through a tube of collodium (cellulose nitrate) that was able to allow diffusion of small particles to the surrounding fluid while proteins and other larger molecules could not pass the membrane. A lot of tubes were connected in parallel and put into a chamber of glass, and the chamber was filled with a dialysis fluid. The fluid contained a salt composition like that of the blood, so as not to disturb the salt balance in the blood. The device was called an artificial kidney. To prevent coagulation in the blood they used an extract from the heads of medicinal leeches. The membrane tubes were handmade. A bar of glass was dipped into a high-viscosity solution of cellulose nitrate so that a thin membrane was formed on the surface of the bar. The procedure was repeated, as in dipping candles, until the membrane had a thickness that made it possible to take it out off the glass bar without causing a rupture.

The start of experimental dialysis treatment

In 1920, the German doctor, George Haas, tried to treat patients with uraemia using the same type of artificial kidney with several dialysis columns in parallel. Every treatment needed a new artificial kidney and the production was time-consuming. Furthermore, no patient survived, and the experiments were stopped after six runs without success.

During World War II, doctor Willem Kolff tried to treat patients suffering from uraemia in Kampen, Holland (McBride, 1979 #88). Together with the engineer, Hendrik Berk, he built a dialysis device that had a closed, extra-corporal system including a dialyzer that treated the patient and continuously gave blood back to the patient. It had a capacity to dialyse higher quantities of blood than the previous experiments, and after many trials they succeeded to save the life of the first patient (Drukker, 1986 #40). The construction they used was a semipermeable blood line which was wound up in a cylindrical net. The cylinder rotated in a bath of dialysis fluid. The part of the semipermeable line that was placed down in the bath enabled waste products to be dialysed over a 2.4 m^2 membrane surface. The rotation of the winding created a flow, as a blood pump, in the system. Kolff had to treat 17 patients before one patient survived. From then on it was possible to successfully treat acute uraemia with dialysis. The dialysis treatment demanded access to the blood circulation. For every treatment they needed the use of an artery and a vein. After each treatment the used vessels could not be used again for another treatment, and the physicians had to find new vessels. If the patient ran out of vessels that could be used as dialysis access and the kidney function still had not recovered, then there was nothing more to offer, and the patient died. Kollf and other pioneers such as Ahlwall showed poor outcomes in the beginning and were strongly criticised by opponents who preferred conservative treatment. During this time Kolff and the other pioneers noticed more and more safety issues to overcome. Prevention of clotting was a problem which had been already noticed by Haas in 1920 (McBride, 1979 #88) Using Kolffs system, physicians noted problems such as haemolysis due to the moving parts and couplings in the system. Blood loss was also a problem; blood was lost due to disconnection of the blood lines, loss across and during rupture of the membrane (noted by manual inspection) and within the system (Drukker, 1986 #40). The blood compartment had such a large volume that if it would be filled with blood from the patient the patient would bleed to death (Ahlvall, 1984 #89). Therefore, blood from donors had to be used to pre-fill the system. They also prevented air embolism by inserting a bubble chamber in the blood line. To prevent microbiological contamination, the system was sterilised prior to dialysis. The Kolff system was used in army hospitals during the Korean War. In Korea it was improved to function despite loss of power supply.

Evolution during experimental treatments

The coil dialyzer, first described by Bodo von Garrelts, enabled an even lower priming volume but needed a blood pump for blood flow. The membrane was formed as a coil and put into a bath of dialysis fluid (Ahlvall, 1984 #89; Drukker, 1986 #40). A plate dialyzer was invented by Fredrik Kil (Ahlvall, 1984 #89). It enabled low blood flow resistance and blood flow could be achieved from the arterial pressure itself. The first commercially available artificial kidney dialyzer was a twin coil dialyzer produced by Travenol Laboratories, and was

based on an invention by Kollf, who is now in Cleveland, and Bruno Watschinger(McBride, 1979 #88). The first disposable parallel flow dialyzer was invented by Ahlvall and further improved and produced by Gambro Inc (Drukker, 1986 #40). Industrial methods are now used to produce large numbers of single-use dialyzers of coil, plate or hollow-fibre design.

Dialysis as an ordinary clinical treatment in 1960.

In 1960 the first long-lasting blood access was developed by Scribner et al. This plastic tube coupling is called the Scribner shunt. It made repeated dialyses from the same access possible and therefore made it possible to maintain life in patients with chronic renal failure. From then on it was possible to survive for longer periods of time in haemodialysis with chronic renal failure. This became a big challenge and an expensive struggle for healthcare systems around the world. Long-term dialysis approaches demanded a reliable, easy to maintain, less expensive dialysis apparatus and routines that required fewer personnel (and thus were less expensive). A technical evolution had started and many different systems were tried. Dialysis started to become an ordinary treatment for patients with acute renal failure and chronic renal failure. The dialyzer sizes were successively reduced, and the blood volumes necessary in the systems were reduced.

Interest from the industry

When the experimental dialysis period was over and dialysis had become more or less routine, doctors began even to treat patients with chronic uraemia. The numbers of dialyzers, other equipment and resources needed increased tremendously. The industry showed an increasing interest for the growing market. The industrial interest in the dialysis machines became a factor in the evolution of the dialysis technique. When dialysis had become a standard procedure, the quality of the equipment became standardized, the equipment became more effective and easier to use, and the equipment was designed to be used in a safer manner. The need for space at the clinic and the struggle for a normalized life for the patient brought up thoughts of home dialysis with portable machines (Ahlvall, 1984 #89). One approach for home dialysis was to put the coil dialyzer into an ordinary top-loaded washing machine and fill it with the dialysis fluid (Nosé, 2000 #91). However, the washing machine company did not want to be associated with the experiment. That concept really worked but it did not become widely accepted. Other home dialysis programs started when reliable techniques were available.

Priorities for treatment: a matter of life and death

The patients chosen for haemodialysis were those considered to have the best health, and best chances for survival, and those who were the most valuable to the society. The judgement was traumatic but necessary due to the limited

resources during several years. During the following decade better resources for dialysis, less expensive dialysis systems, and improved treatment techniques allowed more and more patients with renal failure to receive dialysis in the developed countries.

Dialysis today

Active renal replacement today can be divided into three principles:

1) Transplantation involves the surgical placement of a healthy kidney from a donor into the uraemic patient.

2) Intracorporeal dialysis or peritoneal dialysis uses the peritoneal membrane as the dialysis membrane. The dialysis fluid is poured into the peritoneal cavity through specific dialysis catheters, and the uraemic solutes diffuse into the dialysis fluid. The fluid is then removed through the same catheters.

3) Haemodialysis, also called extracorporeal dialysis or blood dialysis, involves leading the blood from the body, purifying it from uraemic toxins during contact with a semipermeable membrane and then returning the blood to the body. I will only focus my thesis on this type of dialysis.

Access techniques in extracorporeal dialysis or haemodialysis

In haemodialysis some of the patient's blood transports the uraemic toxins through synthetic tubes to the dialysis membrane where dialysis takes place. The dialysis access is important because a relatively large flow of blood is required. Basically two different techniques are currently in use to achieve access. An arterio-venous fistula (AV-fistula) connects an artery to a vein, thus allowing a high blood flow in the vein. That vein is then used as an access for dialysis needles. The vein can be replaced by an artificial vessel, called a graft, if necessary. The majority of the haemodialysis patients in Sweden today have an AV-fistula or AV-graft to enable dialysis access through needles. Alternatively, a double lumen catheter can be inserted into the vena cava or vena femoralis of the patient. Most commonly, the central venous catheter for dialysis purposes is inserted through the right internal jugular vein. The catheter tip is located in the vena cava close to the entry into the heart or down into the upper part of the right atrium of the heart (Canaud, 2004 #119).

Dialysis machine

The dialysis machine is used to achieve two main goals and can be divided into two main systems.

The blood system

The blood system is that portion of the dialysis machine which transports and monitors the blood from the patient, through the dialyzer and back again to the patient's blood stream. The tubing set for the blood is normally made of PVC specific for the machine model and contains measuring points for monitoring

pressure and air. To provide blood flow in the lines the dialysis machine normally has a peristaltic pump. To measure occlusion in the needle that is sucking blood from the patient, a line is usually connected prior to the blood pump and it is attached to a pressure transducer. After the blood pump there can be a line to administer anticoagulant through a connector to the inlet before the blood enters the dialysis filter. A second blood tubing (venous line) is connected to the blood outlet, after the dialyzer, and leads the blood back to the patient. In the venous line there is a chamber inserted that is used as an air-trap (venous chamber) before blood enters the patient. At the top of this air-trap there is a connection to make it possible to evacuate. In the ordinary dialysis systems the line to the venous pressure transducer is also connected at the top of the air-trap.

Fluid system

The fluid system in the dialysis machine has the main goal to prepare and administer the dialysis fluid at the fluid side of the dialysis membrane and to control the extent of ultrafiltration of water that is removed from the patient's blood. Normally, the dialysis fluid is prepared by the fluid system online just before entering the filter. The dialysis fluid is blended using a mixture of purified water and concentrates of electrolytes. The system also controls the temperature of the fluid to prevent adverse effects from either heating or cooling the patient during treatment. Between treatments the fluid system has software programs that enable disinfection of the system using heating or chemical disinfectants. A combination of heating and chemicals is used to improve disinfectant efficiency.

Blood distribution

The distribution of blood through the extracorporeal system exposes the blood to a significant number of risks related to contamination, reactions to foreign material, mechanical damage and blood loss. For safety and quality goals the blood compartment has to be constructed to minimize these risks while still maintaining sufficient blood flow through the dialysing system and back to the patient to remove uraemic toxins.

The tubes that enable blood to perfuse the dialysis filter are divided into an arterial part and a venous part. The arterial part represents the blood inlet line from the access from the patient until the entry into the dialysis filter (dialyzer). This part contains an extra access line for continuous addition of anticoagulant such as heparin. The blood pump segment is thicker and located within the housing of the electric roller, the blood pump. There is also a connection to an arterial pressure monitor which monitors the pressure in the blood from the patient (arterial access). If the arterial access is occluded the arterial pressure alarm is activated (light signal and sound). If the arterial access is restricted the negative pressure in the blood line, together with the blood flow reading on the blood pump, can be used to calculate the effective blood flow (Stragier, 1996 #96). Some modern dialysis monitors do this calculation automatically.

Monitoring of the negative pressure on the arterial side is also important to avoid haemolysis due to excessive negative pressure (Fracos GC, 1983 #92). On the other side of the blood pump, the positive pressure side, another tube can be added to allow measurement of filter inlet pressure to trigger an alarm if the flow through the filter is restricted by, e.g., coagulation. If there were no alarm, an excessively high pressure in the blood might cause the dialysis membrane to rupture and cause loss of blood into the dialysis fluid circuit. This pressure monitoring upstream of the dialyzer is not yet common practice, probably because it is not required by the particular standards for dialysis machines. However, it improves the safety and quality of the dialysis treatment if it is used. High positive pressure can also cause haemolysis (Descamps C, 1994 #93; Polaschegg, 2004 #54). Downstream from the dialysis membrane (dialyzer) another tubing is connected which is called the venous part. This represents the return line of the cleansed blood back to the patient. This holds tubing to measure venous pressure changes. In addition, an air-trap or chamber, called venous chamber, is present shortly after the dialyzer and allows air ejected from the blood line to avoid air contamination into the patient. An air detector is present prior to the return access to the patient. It can be located at the venous chamber or at the venous line. By measuring differences in transmission of ultrasound or light through the bloodstream it detects the presence of air contamination that could be a risk for the patient. If such contamination is detected by this sensor the blood pump is stopped and an impulse is sent to a clamp that stops the blood flow back to the patient.

Dialysis filter or dialyzer

The capillary dialyzer is made by a synthetic housing containing an entry for blood from the arterial tube into the more than 10,000 synthetic capillary fibres in the dialyzer. At the other end of these fibres the blood enters into the venous tubing. Dialysis fluid, which has been mixed within the dialysis device, is perfused along the outside of the fibres. The dialysis fluid enters at the end where the blood leaves and exits at the end where the blood enters. This makes a counter current system; the dialysis fluid and blood flow in opposite directions outside/inside the capillaries. The semi-permeable membranes of the capillary fibres contain pores of a size that permit electrolytes and uraemic toxins to pass through the membrane. This is either by diffusion, if there is a gradient in concentration of any substance present (haemodialysis), or by convection, when fluid containing uraemic solutes is pressed through the fibres (haemofiltration). The blood from the patient that is to be purified from uraemic toxins flows on the blood side of the membrane. To provide diffusion over the membrane the dialysis fluid flows on the other side of the membrane, normally in the opposite direction to that of the blood. The dialysis fluid is a mixture of electrolytes that are also present in the blood (Na^+, K^+, Cl^-, Ca^{++}, Mg^{++}, carbonate$^-$). The mixture can be varied depending on the metabolic condition of the patient. The uraemic toxins in

the blood are not present in the freshly mixed dialysis fluid, and therefore a gradient is present between the concentration in the blood and the dialysis fluid (dialysate). The membrane areas used are between 1.5m^2 and 2.5m^2. Most dialyzers contain capillary fibres as membranes formed to hollow fibres. Other dialyzers contain flat sheets of dialysis membranes. The bloodstream is usually inside of the capillaries or within every other layer of the flat sheets.

Transport over the membrane

During dialysis the transportation of solutes and water over the membrane mainly occur by three physical principles: diffusion, ultrafiltration and convection.

Diffusion principle

Diffusion through a membrane is driven by the gradient of concentrations across that membrane. If there is a higher concentration of a solute on one side of the membrane than on the other, the concentration gradient forces that particular solute to move over the membrane until equality is achieved. Diffusion movement is faster for smaller molecules than for larger. The process is also affected by the steric configuration of the molecule and its electrostatic properties. The size of the pores in the membrane and the electrostatic properties of the membranes can also help or hinder the diffusion of the molecules. The dialysis fluid does not contain uremic toxins and therefore the concentration gradient forces the uremic toxins from the blood, through the membrane and to the dialysis fluid.

Ultrafiltration principle

When pressure is applied over a membrane which is permeable for a fluid, it forces a flow of fluid from the high-pressure side to the low-pressure side. This is called ultrafiltration (UF). This principle is mainly used for the removal of water from the patient. The dialysis machines have various different technical approaches to calculate such removal. The accuracy of fluid removal is a critical parameter in dialysis practice and directly affects the fluid balance of the patient. The medical staff must estimate the patient's dry weight and weigh the patient before and after dialysis. This allows a comparison of the actual fluid removal and that calculated by the dialysis machine after the treatment. During the treatment one has to rely on the UF-system and the safety system for UF in the dialysis machine.

Convection principle

During ultrafiltration across a semi-permeable membrane the flow contains both water and various uraemic and physiological solutes. This transportation of solutes is called convection. It forces all solutes which are small enough to pass through the pores of the membrane to the other side. As long they are small

enough to pass through the pores there is roughly no difference in transportation rate. The rate of transport depends less on their size as compared with diffusion. The convective transport is proportional to the flow over the membrane.

Haemodialysis (HD)

During haemodialysis the removal of uraemic toxins is mainly driven by diffusion. To improve the diffusion rate one normally uses contra-directional (counter-current) flow for the blood and the dialysate. Some ultrafiltration is also normally achieved during HD to limit the overload of water in the patient. The ultrafiltration causes some convection over the membrane.

Haemofiltration (HF)

During haemofiltration the transportation of solutes is done only with convection. A high amount of water is ultrafiltered from the blood through the membrane, and that water transports solutes from the blood. Before returning the blood to the patient, now at a high haematocrit, it has to be filled up again with a haemofiltration solution to prevent the patient from suffering hypovolaemia and hypotension, otherwise caused by drained blood vessels. This technique is effective for the removal of uraemic toxins that are just in the size to pass the membrane pores, but not as effective as HD in removing small molecules of uraemic toxins.

Haemodiafiltration (HDF)

A combination of HD and HF is called haemodiafiltration (HDF). This results in the effect that a combination of diffusion and convection is achieved using both dialysate fluid to perfuse on the outside of the capillaries and also a high ultrafiltration rate. In addition, substitution fluid has to be administrated to the patient to keep fluid level acceptable.

Safety in biomedical engineering, IEC 601

During the beginning of 1970 and 1980 international standards were established concerning general medical electrical equipment. In Europe this was done by an International Electric Committee (IEC). In the USA, a parallel standardisation was going on by another organisation, the Association for the Advancement of Medical Instrumentation. The IEC standard system is built around a general standard for medical electrical equipment and so called collaterals. They provide general recommendations for maximum risk exposure such as maximum leakage of electrical current in the surroundings of a patient. The safety philosophy is based on *first fault* safe equipment. The equipment shall be safe for the patient and the staff during both normal conditions and during a *first fault* condition. This means that even during any failure, no matter what, the equipment should not harm the patient or the medical staff. In addition, it should

be possible for the operator to discover the fault in a reasonable time before a second failure can occur.

Fail life and fail safe

Safety in a critical system can be achieved by the use of redundancy or diversity. Redundant systems are those which use two or more systems to achieve the needed task. If one system fails, another or several other systems should take over the function in a safe manner. Redundant systems have the drawback that they are complex and expensive. Building an aeroplane is a good example of when redundancy is needed. It is used when the system must be able to operate even after a failure has occurred. The redundant system is therefore also called a fail life system. If one system fails, another system functions and preserves life.

Diversity is another method to achieve safety in critical systems. It can only be used if the operating system can be shut down without causing immediate injury to the patient. Then there is only need of one operating system, but it has to be tested to be sure that it is in order. In addition, there has to be a safety system that monitors the operation and puts the operating system in a safe state during a failure. This principle is called a *fail safe* system. If a failure occurs, the machine shuts down so as to preserve the safety of the patient. This principle of diversity or *fail safe* is the safety principle normally used for the handling of most of the risks in dialysis machines. Both diversity and redundancy dramatically reduce the probability that a failure will cause an injury to the patient. There must be two or more functions that fail to cause an injury to the patient. The probability for a breakdown in each system that can cause injury to the patient can be estimated, and then the total risk can be calculated by multiplying all of the probabilities together. For example, if a system that dilutes the concentrate used for the dialysate has a probability for a breakdown at 1/100 hours and the system that monitors the dilution system has a probability for a breakdown at 1/1000 hours, then the probability for both systems to fail at the same time is (1/100) x (1/1000) =1/100,000 hours.

The frequency of electrical distribution

When the first electrical supply systems were under construction the inventor, Edison, tried to convince the costumers of the danger of alternating current during promotion of his own dead-current system. During his campaign he executed cats and dogs, and once even an elephant, and he even provided the electric chair for legal executions of prisoners. The electric chair is still in use, but the power distribution net around the world is mainly 50 and 60 Hz alternating current net (Wikipedia #97; Berbari, 2001 #101). This frequency is known to be the worst for adverse effects on the heart (P Åke Öberg, 1984 #94) (IEC #95) but is supposed to be beneficial due to less losses in the net and economic relations for construction of the distribution net.

Physiological effects of electric current

When using medical electrical equipment, there is always a risk to come in contact with unwanted electrical current. Depending on the amount of current, how concentrated the current is in the tissue, where the current is concentrated, and the frequency of the current can cause several effects. At the least it can cause excitation of nerve cells, muscle cells and heart cells or a heating effect (IEC #95) (P Åke Öberg, 1984 #94). These effects are used in different medical applications such as diathermia, pacing and defibrillation. In uncontrolled conditions these effects can also cause adverse effects such as damage due to burning during diathermia or ventricular fibrillation (Watson, 1973 #81; Starmer, 1973 #79). The physiological effects of electric current depend on the amplitude, frequency and duration. The adverse effects to a human or an animal also depend upon other factors such as on location of the flow of current, body weight and the threshold for excitation. When a human is exposed to 50 or 60Hz current there are mainly two fatal conditions that must be avoided: macroshock and microshock.

Ventricular fibrillation

Macroshock occurs when the current is applied between two extremities or through the skin with such intensity that the current density in the heart exceeds the threshold for ventricular fibrillation. At high current levels this situation is also a risk for cramp in the respiratory musculature.

Microshock is a condition in which an electrode in contact with the heart concentrates enough current in the heart to induce ventricular fibrillation. Microshock occurs during exposure to smaller amounts of current than macroshock, and microshock can be fatal in the range of current that is under the threshold for the sensitivity of the skin to perceive the current (P Åke Öberg, 1984 #94). The original work from Starmer and Watson published in 1973 provided data from electrical current applied by different types of electrodes to the heart of humans and dogs. They showed that besides the amount of current, also the concentration of current (current density), in the tissue of the heart is of importance. The threshold for ventricular fibrillation was lower when using a larger electrode area (Watson, 1973 #81; Starmer, 1973 #79). The data from small electrodes, 1.25-2mm^2, and the level of electrical current that could cause ventricular fibrillation when applied to the human heart, have been used by the IEC to estimate the probability for ventricular fibrillation. The safety levels for both *normal condition* and *single fault condition* for leakage current in cardiac applications in the general standard have been based on this estimation (IEC #75).

Cardiovascular collapse

There is very little published data about electrical current safety thresholds in cardiac applications, but a paper published in 1999 showed that an electrical current applied to the heart can cause cardiovascular collapse at levels under the

ventricular fibrillation threshold. Those authors suggested that the safety standard should use the threshold for cardiovascular collapse rather than the ventricular fibrillation threshold as the basis for safety recommendations in the *single fault* condition (Swerdlow, 1999 #80). Their suggestion was that leakage currents in *cardiac* applications lasting for 5 seconds or more should be limited to a maximum 20μA. Their recommendation has not been adopted by the IEC so far.

Electrical safety in biomedical engineering

Any medical electrical equipment in contact with a patient may permit an accidental flow of electrical current through the patient and to ground (leakage current). If two or more different electrical machines are used in the surroundings of the patient, a summation of the current from those machines can occur due to the concentration of the current at one point around an applied part that provides a low-resistance pathway to ground. The IEC general standard (IEC #75) specifies limits for different types of leakage current (Table 1) from different parts of the equipment such as in safety ground connector, parts in the housing of the equipment and parts intended to be applied to the patient's body. The applied parts are classified into three groups to provide different safety levels for leakage current groups depending on the degree of contact with the heart: *Body* (B), *Body Floating* (*BF*), and *Cardiac Floating* (*CF*). *Body* and *body floating* and recommended for parts applied to the body externally or internally except *cardiac* applications. The classifications, *body floating* and *cardiac floating*, provide a higher grade of safety according to safety against *mains on applied part*. This means that beside limits for currents generated by the equipment, insulation or isolation of circuits is also needed to avoid receiving eventual current generated by other equipment. The classification limits the *body floating* part to act as a grounding point. Parts classified as *body* have no limit for *mains on applied part* and might allow concentration of unlimited current from other sources to its electrical connection point. *Cardiac floating* is the only classification that is recommended for *cardiac* applications and is the classification that allows the least leakage current.

Table 1. Limits for leakage current in IEC 601

Limits for leakage current in IEC 601 (μA)			
	μA		
	Normal condition	*Single fault condition*	*Mains on applied part*
Body	100	500	No limit
Body floating	100	500	5000
Cardiac floating	10	50	50
Total leakage current (third edition)	100	100	100

The limit for leakage current in *cardiac* applications in the IEC general standard (IEC #75) is mainly based on the original works by Starmer et al (Starmer, 1973 #79) and Watson et al. (Watson, 1973 #81); those studies involved current applied to the hearts of dogs and humans. Those works concerned the effect of microshock when the current was applied directly to the heart, and the authors pointing out the probability of fatal outcome at different current levels. In the general IEC standard there is also an estimation of the probability for ventricular fibrillation in relation to the amount of exposure to electric current based on the data from Stamer and Watson (IEC #75).

Overall safety issues for dialysis machines

The system has to be safe and must not expose the patient to hazardous situations during the extracorporeal treatment such as hazardous energies or unwanted changes in blood solutes, blood loss or air infusion.

Over the years the IEC started to develop particular standards for specific types of medical electrical equipment. These particular standards are more specific in terms of construction of specific types of equipment. In 1983 the first particular standard for dialysis machines was published IEC 601-2-16. For instance, this standard stated that there should be a safety device to prevent air infusion and there should be a maximum number of times for by-passing an alarm. Further, conductivity and temperature limits were stated.

Recommendations about acceptable levels of leakage currents and general standard vs. collateral standard for haemodialysis machines

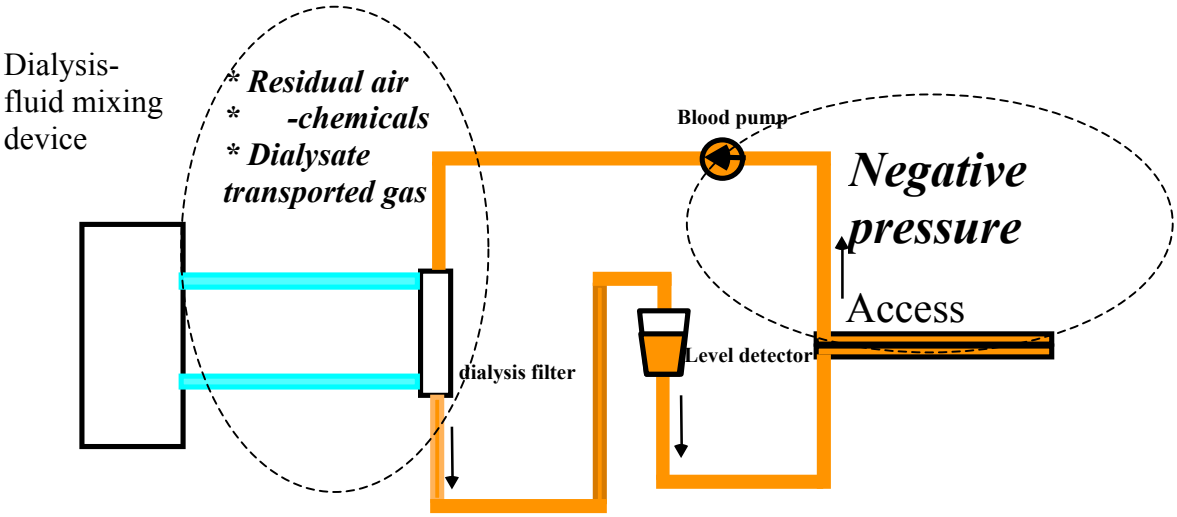
In the general standard for biomedical equipment there is a specific class for connections that are suitable for *cardiac* applications, i.e., *cardiac floating* (*CF*). However, recommendations for dialysis devices, in the first particular standard for dialysis machines, stated a lower degree of safety (*Body* or *B*). The dialysis

access is mainly an AV-fistula located in an arm and cannot be considered as a *cardiac* application. However, the blood itself is rather conductive and might lead a proportion of eventual leakage current to the heart. Despite this, M. C. Deller stated in 1974 that the dialyzer and lines represent a protective impedance of some 400k_ between the patient and the dialysis machine and "As far as primary electrical hazards are concerned, dialysis should be considered as being a relatively safe procedure" (Deller, 1979 #74). In addition, a substantial minority of the dialysis patients today, 20-25%, use central venous catheters as dialysis access, with the tip close to or within the right atrium of the heart. In that situation, the electrical safety classification, *B*, should be disputed. In the second edition of the dialysis machine standard published (1998) there is no statement about the electrical classification, so the recommendations in the general standard can reasonably be adopted. However, the manufacturers usually stick to the old classification due to economic and practical arguments. There is no *Cardiac floating*, *CF*, dialysis machine yet built, except one for intensive care. That is why this work was started, and after the publication of Paper I, the manufacturers tend to recommend potential equalisation for the dialysis machine.

Infusion of air

Extracorporeal treatment of blood, such as haemodialysis, involves the risk of air or gas infusion (Polaschegg, 2004 #54). To avoid air contamination of the blood the extracorporeal system has to be tight. All pieces in the extracorporeal system are connected using standardized couplings to a closed system. The priming procedure is carefully clarified by the manufacturers. To reduce the risk of air contamination to the patient, it is common to have a de-airing chamber in the blood line on the venous side (venous chamber) prior to the infusion site of processed blood. In that chamber larger air bubbles are supposed to rise out of the blood and thereby the chamber enables evacuation of air. Air detectors are also used on the return line to prevent air infusion to the patient. Exposure of blood to air or gas can have different causes (Fig. 1).

Figure 1. Risks of air infusion



Negative pressure

In general, any leak in the blood system that contains a negative pressure relative to the air pressure will result in blood contaminated by air. Therefore, a higher flow causes more extensive pressure differences in the extracorporeal system and a more negative pressure at the suction-side. During haemodialysis the blood flow and treatment time differ a lot between dialysis departments and different countries. Therefore, the risk for exposure of blood to air might differ when using different dialysis procedures. For example, a standard haemodialysis in Sweden lasts approximately 4.5h with a 300 ml/min blood flow.

Residual air

From the manufacturer, it is common to distribute the blood-line needles and filters empty. That means that they are filled with air or gas. The user is supposed to prime the tubing system and dialyzer with one to two litres of saline prior to the treatment. Residual air in the system, after priming, is therefore another possible source of air contamination. There are so called “wet filters”, distributed filled with a priming fluid, on the market, but they seem to be rarely used in Europe. Gas dissolved in the dialysis fluid can also diffuse through the pores in the membrane. However, modern dialysis machines that produce dialysis fluid have degassing functions included in the system. Residual disinfectants or process chemicals in the dialysis system can also result in the development of gas in the blood. An example of that was the “Croatian” or “Baxter” filter accident (Shaldon, 2002 #84) in 2000, described below. Overall, the most common reason for gas in the blood is supposed to be residual air or a leak in the system at the negative side in the “blood circuit” of the tubing (Polaschegg, 2004 #56).

Accidents and incidents, air/gas infusion

In 2000 there were reports about many sudden deaths during dialysis, and Baxter filters made in Ronneby, Sweden, were suspected, but cleared by TÜF Product service GmbH. After even more fatal cases the Baxter filter was finally blamed for the accidents. Residuals of a perfluorecarbon (PF5070) used to find leakages, were left in several filters in the same batch. When the filters were used at clinics in Croatia they reported 21 deaths during dialysis in Croatia and A total of 53 all over the world (Ward, 2002 #83). In some cases foam in blood was reported. Filters that did not pass the integrity test were regularly fixed. The hollow fibres were filled with PF5070 and pressurised on the dialysate side. Leaking hollow fibres generated bubbles at the end. The leaking fibres were then sealed at both ends by hand. Some of the normal fibres around the leaky fibres were also sealed. However, some of the normal fibres were only sealed at one end. After the sealing procedure, the filters were rinsed, but hollow fibres with one end sealed did not get cleaned through the rinsing procedure. During dialysis the chemical was dissolved in contact with blood and developed gas in the blood at low pressure. Overall 53 patients died around the world during this accident (Shaldon, 2002 #84).

In 1993 a fatal accident occurred at Danderyd Hospital in Sweden (Socialstyrelsen #43). A dialysis patient died by air infusion after an air-infusion alarm was overridden twice. After that accident the organisation for Dialysis Engineers and Dialysis Nurses in Sweden asked for improvement of safety measures against air infusion and air embolism due to overridden alarms. Besides that report, other incidents have been reported in Sweden in which air bubbles where sighted in the tubing system downstream of the air detector(#85). Note that the microembolic findings were detected in the subclavian vein of dialysis patients (Droste, 2003 #8; Droste, 2002 #10; Rolle, 2000 #7). Findings of microemboli have also been noted in the dialysis device during conventional dialysis {Badylak, 1984 #73;

Infusion of air 601-2-16

In the IEC standard for dialysis machines, 601-2-16 2nd ed., it is stated that air in the blood line is regarded as a *normal condition.* However, it is also stated that there has to be a system to prevent air infusion. The standard does not state an alarm limit for air infusion nor how to evaluate or measure that the protective system aimed against gas or air infusion provides enough safety. This can look a bit cryptic and be hard to understand. The term *normal condition* is a term in the standard that indicates that the system must be safe during one additional failure, *single fault condition*. This can be interpreted to mean that there have to be safety systems that protect the patient from air infusion with a reliability of a double safety system. Air detectors can be doubled or there can be a double system that monitors the air contamination. The receiver crystal in the detector can trigger an alarm if air is detected. If the alarm is started by an air detector, then the safety

system has to close a clamp at the return line of blood to the patient and stop the blood pump. Both these efforts will prevent the patient from immediate air infusion.

Is there a safe level of air infusion?

The dialysis standard does not state which volume or flow/leakage of air that should trigger an alarm. Neither the general standard nor the dialysis machines' standard provides a method to evaluate or test the efficiency of the safety system against air infusion. Perhaps this is because there is no "common sense" about a safe level of air infusion.(Polaschegg, 2004 #54).Therefore, the IEC standard is leaving the decision and the responsibility to the manufacturer to state the limit for maximum air infusion before the alarm is activated. It is also an open question as to how to measure the air infusion threshold. In the standard for infusion pumps (IEC 60601-2-24, 1998 #59) it is stated that an air infusion of 1ml/15min , not counting bubbles smaller than 50µm, is not considered as a safety hazard. The fatal dose for air embolism is considered much higher on the venous side than air embolism on the arterial side. (Barak, 2005 #66) (Kurusz, 1995 #41) (Polaschegg, 2004 #55).

Microinfusion of air or gas

If gas bubbles are infused in blood Kurutsz wrote "Carbon dioxide or oxygen emboli are less harmful, while air, being composed primarily of nitrogen, persist in the circulation "(Kurusz, 1995 #41).

The clinical relevance of one event of microinfusion of gas during dialysis (venous side) seams to be disputable. In three reviews, by Kurusz et al 1995(Kurusz, 1995 #41), Polaschegg and Levin (Polaschegg, 2004 #55), Barak and Katz (Barak, 2005 #66), on air infusion, their conclusions differ, each quoting a number of references. This is a short summary including a few of those references:

Hills reported that blood bubbles with diameters less than 250µm during ascent disintegrate into bubbles of 40 µm after collision, but bubbles over 350µm coalesce at collision (Hills, 1974 #63). Furthermore, the small bubbles will disappear rapidly in non over-saturated solutions. In clinical situations, this would lead to production of lots of small bubbles able to block small vessels (Polaschegg, 2004 #55).

Bubbles less than 40µm in diameter

Very small bubbles are relatively short lived in the circulation. They will shrink and collapse largely due to surface tension (Kurusz, 1995 #41; Hlastala MP, 1973 #103; Polaschegg, 2004 #55). However, Barak suggested that the lifetime of microbubbles in blood has been underestimated. The Epstein-plesset equation underestimates the lifetime for a gas bubble in the blood and even more

for a gas bubble trapped in a vessel with diameter less than the bubble (Branger, 1999 #105) (Barak, 2005 #66).

Bubble/blood interaction

Kurusz suggested that air emboli activate the coagulation process: "Air emboli represent a foreign surface to blood. Activation of both cellular and non-cellular components occurs and may have consequences for the patient after disappearance of the bubbles" (Kurusz, 1995 #41).

Endothelial effects

Kurusz also suggested adverse endothelial effects: "Air embolism disrupts endothelial integrity resulting in increased vascular permeability" (Kurusz, 1995 #41). Persson and Hansson. (Persson LI, 1978 #104) suggested that endothelial dysfunction following air embolism might be due to shearing stress exerted on endothelial cells due to bubble contact at the liquid-air interface.

Effects in capillaries

The immediate effect is obstruction of blood flow. This causes tissue ischaemia in the capillary, and the surrounding tissue suffers from hypoxia. Inflammatory responses and complement activation take place because the bubble is a foreign material (Barak, 2005 #66). Further mechanical tissue damage to the capillary endothelial wall, inflammatory responses and complement activation further activate the coagulation cascade and induce a platelet cascade (Barak, 2005 #66).

Effects in the lungs

Microbubbles of 28 μm trapped in arterioles of dogs shrink to 5μm within 5 min and then pass through the capillary to the venous circulation (Presson, 1989 #113; Polaschegg, 2004 #55). Small air emboli are cleared from the lung rapidly by forced ventilation using sulphur hexafluoride and oxygen mixtures which should support the hypothesis that air-trapped in the lung is cleared by diffusion to the alveoli (Sergysels R, 1978 #114) (Polaschegg, 2004 #55). In contrast, Barak stated that microbubbles that originate from dialysis tubes or filter flow in the venous vasculature are trapped in the circulation of the lung. The dialysis patient suffers from both acute and chronic lung injury due to micro bubble showers originating from the dialysis machine. This might explain the high pulmonary morbidity among haemodialysis patients (Barak, 2005 #66).

Information and responsibility

There have been discussions about "alternative" producers of disposable dialysis tubing sets for dialysis machines. Does the safety system for air infusion give the same level of safety if "alternative" blood lines, instead of the "original" or intended manufacturer's blood lines, are used? The producers of dialysis

machines have avoided answering this question clearly; they have also failed to state the relevant mechanisms and criteria for the safe systems and the tubing.

AIMS

The general aim of this dissertation was to study the technical safety situation during a standard haemodialysis.

Aim 1: to test if leakage current can pass through the dialysate couplings.

Is the electrical safety situation in the dialysate couplings acceptable for the patient according to the limits and recommendations in the general standard for medical electrical equipment (IEC #75)? Paper I aimed to investigate the extent of different types of leakage current in four different types of dialysis machines in *normal* and in *single fault conditions* that might occur.

Aim 2: to test if leakage current can pass through the dialysis tubing system to the patient.

Paper I showed that leakage current may occur in dialysate couplings. Could such current be lead through the dialysis tubing system to such an extent that it could constitute a risk to harm or be fatal to the patient? The in vitro experiments tested both a priming fluid (saline) and whole blood, simulating normal haemodialysis conditions with various simulated hazards.

Aim 3: to test if leakage current across the dialysis membrane affects the blood.

Papers I and II showed increased risk for leakage of electric current through the dialysate compartment and blood compartment in a haemodialysis system. The aim of this study was to evaluate whether such electrical current presented over a dialysis membrane could worsen the biocompatibility, here measured by complement activation.

Aim 4: to detect any possible changes in heart rhythm during a standard dialysis due to leakage current.

The aim of this study was to evaluate if dialysis patients during a standard haemodialysis show altered heart rhythm that could be due to leakage current which is acceptable according to the current IEC 601 standards.

Aim 5: to detect any possible air infusion which can evade the present safety system for air bubble detection.

Blood is contaminated with air in the blood lines during standard dialysis. A safety system is mandatory to prevent the patient from air infusion. This study was performed to analyze if, and to what extent, air-contaminated blood could pass this safety system during standard haemodialysis without inducing an alarm.

MATERIALS AND METHODS

Paper I, Dialysis machines

Seventeen dialysis machines were investigated: Gambro AK10 (n=5), Gambro AK100 (n=3), Fresenius 2008C (n=3), 2008E (n=2) and 4008E (n=4). All machines were equipped according to the manufacturer's specifications. All had electric safety classification: class *I-body*, according to the general international standards for medical electrical equipment (International Electric Committee, IEC 60 601-1 [2, 3]; (IEC 60601-1 #75) and were tested for electrical safety according to those same international standards.

With only one exception, the first measurement on each machine was performed just after a regular maintenance had been performed by a technician representing the manufacturer. With only one exception, the second measurement on each machine was performed 1-2 years later. On each of those two occasions, all of the measurements were repeated twice, and the highest value from each test was recorded for each year, and the mean value of the recordings on each individual dialysis machine was used to represent that device. The differences between years for the recordings on each device were within the range of (in)accuracy when reading the upper end of the visual scales on the Rigel analogue instrument. Due to lack of various dialysis devices at our hospital one of the Fresenius 2008C machines was located and measured at the Dialysis Unit at the Department of Nephrology at Karolinska Hospital in Stockholm, and that machine was only measured once, and that measurement was not immediately after a regular maintenance.

Electrical safety analyser, Rigel

The measurements of leakage current were performed according to the general IEC (International Electric Committee) standard using a safety tester called Rigel (model 233, Research Limited, Sutton, UK). The manual we used was a modified Swedish version. Unfortunately, the description of the measurement circuitry in that manual was unclear, and led to the fact that Figures 1 and 2 in Paper I are misleading. A clarification is given below:

Patient leakage current was measured by a "measuring devise" (MD) including a patient equivalent impedance as described in IEC 601 (IEC #75) with an impedance of 1 k_ in the power line frequency range. A low-pass filter with -3dB at 1 kHz removed the high-frequency components. The voltage over a 1-k_ resistor was measured to record the leakage current. During *normal condition* the power distribution was normal and the safety ground connector was intact, but the mains connectors could be measured straight or reversed. During *patient leakage single fault* condition (test step 12), the safety ground was also disconnected.

In the measuring circuitry for *mains on applied part* the power net frequency was generated by a 1:1.1 transformer. In Sweden, with a 230V AC-net, the

transformer generated about 250V AC. The current was applied over a 47-k_ resistance through the MD to the selected applied part.

Earth leakage current in *normal condition* was measured by MD in series with the safety earth cable in the mains socket.

This means that measurements of leakage current were done according to the general standard for medical electrical devices. The three Rigel instruments at the Clinical Engineering Department of Umeå University Hospital are regularly sent for calibration once a year. These instruments are used for the electrical safety analyses for many different hospital instruments.

Measurement of leakage currents

All measurements of leakage current were performed with the dialysis machine in *normal operation*, dialysis fluid flow in the dialysis lines, all of the alarms were in operating condition but no alarms became activated, and no failures were simulated. This condition is referred to as *normal* operation and alarm free.

Four types of leakage current were recorded according to the general IEC standard 601:

Under *normal condition*, the dialysis machine was in *normal operation* and alarm free, and no electrical failures were simulated.

1) Earth leakage current (ELn). The amount of electrical current leakage was measured under *normal condition* in the ground wire.

2)Patient leakage current, *normal condition.* The current from the *applied part,* through a patient-equivalent impedance to the ground was measured according to the general safety standard (IEC #75) Patient Current, *normal condition*, PCn)

In single fault condition, the machine was still running in *normal operation* and alarm free. Two electrical failures were simulated separately:

3)Patient leakage current, *single fault condition*. The patient leakage current was measured when the ground wire to the dialysis machine was broken (disconnected). (Patient Current, broken ground, PC_{bGR}).

4)Mains on applied part. The current that goes to the *applied part*, if connected to mains voltage over an impedance specified in the general standard (IEC #75), was measured. This tested the protection in the *applied part* for current possibly generated by another defective electrical device in the surroundings that the patient might touch or be connected to. (External current, Exc).

Due to the risk of permanent damage to the electrical system, the test *mains on applied part* was not allowed to be performed by the Swedish supplier of the Fresenius 4008E dialysis machine. This question was not raised for the other dialysis machines.

During measurements of patient leakage current we had to define an applied part. The measuring point, chosen according to the particular IEC standard for

haemodialysis equipment, was in the dialysis fluid line, at the site of the connectors to the dialysis filter (dialyzer). A copper tube was inserted between the dialyzer couplings to have a defined galvanic connection to an *applied part*. (See Fig. 2 below in method paper II, "x-paper I") All measurements were done with the system in *operating condition*, and we found normal conductivity, temperature and flow in the dialysis fluid lines. To also analyse the protection in the dialysis machines against leakage current, possibly generated by ambient electrical equipment going through to the patient and to the dialysis access, we used *BF* or *CF* mode on the Rigel instrument. The switch to select safety class, and the x10-scale button to select the best scale for reading the analogue instrument, were used.

Statistical significance was determined using Student's independent, 2-tailed t-test, and $p < 0.05$ was considered as significant. The numbers were small. However, the technical device in *normal condition* was assumed to have a very small variance for the variables measured, and therefore the above statistical test was used.

Accuracy of the Rigel safety analyser

The analogue scales on the Riegel safety analyser are read visually. I estimate that the accuracy of each reading at the upper end of each scale is as shown in Table 2.

Table 2. Estimated accuracy of a reading on the Rigel safety analyser

Estimated accuracy of a reading on each scale	
Scale on the Riegel safety analyser	Estimated accuracy when reading the upper end of the scale
0-10 µA	± 0.2 µA
10-50 µA	± 1 µA
50-100 µA	± 2 µA
100-500 µA	± 10 µA
500-1000 µA	± 20 µA
1000-5000 µA	± 100 µA

Paper II, Blood used

This *in vitro* investigation was done using blood from 8 persons after informed consent (4 blood donors and 4 patients with polyglobulia or polycythaemia vera). Blood concentrates from the donors were prepared as leukocyte-depleted concentrates of erythrocytes and were diluted by plasma that had been stored frozen and then thawed to reconstitute the composition of regular

blood. From the 4 others the blood was received as whole blood using heparin as anticoagulant (5000 units/500 ml) in the collecting bag. The ethical committee approved the protocol.

Priming solution and dialysis fluid

Isotonic sodium chloride, 0.9% NaCl (saline), from Pharmalink, was used as priming solution in the blood lines. A Fresenius 2008C haemodialysis machine prepared the dialysis fluid from the two-components, concentrate SKF 203 and Duolys B, to a standard conductivity, according to standard procedure, and that resulted in a solution of 14.25mS/cm and a temperature of 37.3 ^{o}C. This was checked with a reference instrument, MESA MEDICAL/90 DX.

Electrical safety analyser

Leakage current was analysed using a Metron QA-90 electrical safety analyser (QA-90), programmed for class I, *CF* measurements. We tested the QA-90 in generating maximum current during *mains on applied part* by connecting the "patient leads" on the safety analyser to the safety ground. The maximum reading on *mains on applied part* was 5200µA. According to the QA90 manual the accuracy of current measurements is ± 2% of full scale ± 1 Least Significant Digit (LSD), and the resolution is 1µA in the 0-100µA range and in the 100-1000 µA range. In the range 1.0 – 10.0 mA the accuracy is ± 1% ± 1LSD and the resolution is 1 µA. If the digital instrument, QA 90, shows 5200 ± 1 LSD, that means that the deviation according to the display is from 5199 to 5201. The analyser is normally calibrated once a year, but at the time for the measurements one calibration procedure was missing. Instead, there had been a service done on the safety analyser at the time for calibration. In the service protocol there was noted that the calibration was "OK" but there was no calibration protocol. The month after the measurements the machine was recalibrated, and the protocol then showed that the instrument was inside the specification and no adjustments had been necessary.

The patient leakage current was tested by applying a 100-µA source, and the reading was 100µA. *Mains on applied part* was tested over different calibrated resistances. For the QA-90 instrument, the calibration readings for *mains on applied part* are shown in Table 3. The calibration of the resistances used in the calibrating procedure for QA-90 are shown in Table 4.

Table 3. Mains on applied part (MOAP), QA-90 serial number: 11173, year 2000-2006

Mains on applied part (MOAP), QA-90 serial number: 11173, year 2000-2006					
		Calibration readings, µA			
	N	Minimum	Maximum	Mean	Std. Deviation
MOAP,2M_	6	122	123	122.7	0.51
MOAP,5M_	6	23	25	23.8	0.89
MOAP, 50M_	6	2.0	4.9	3.3	1.18

Table 4. Summary of the calibrations done on the resistances used in Table 3

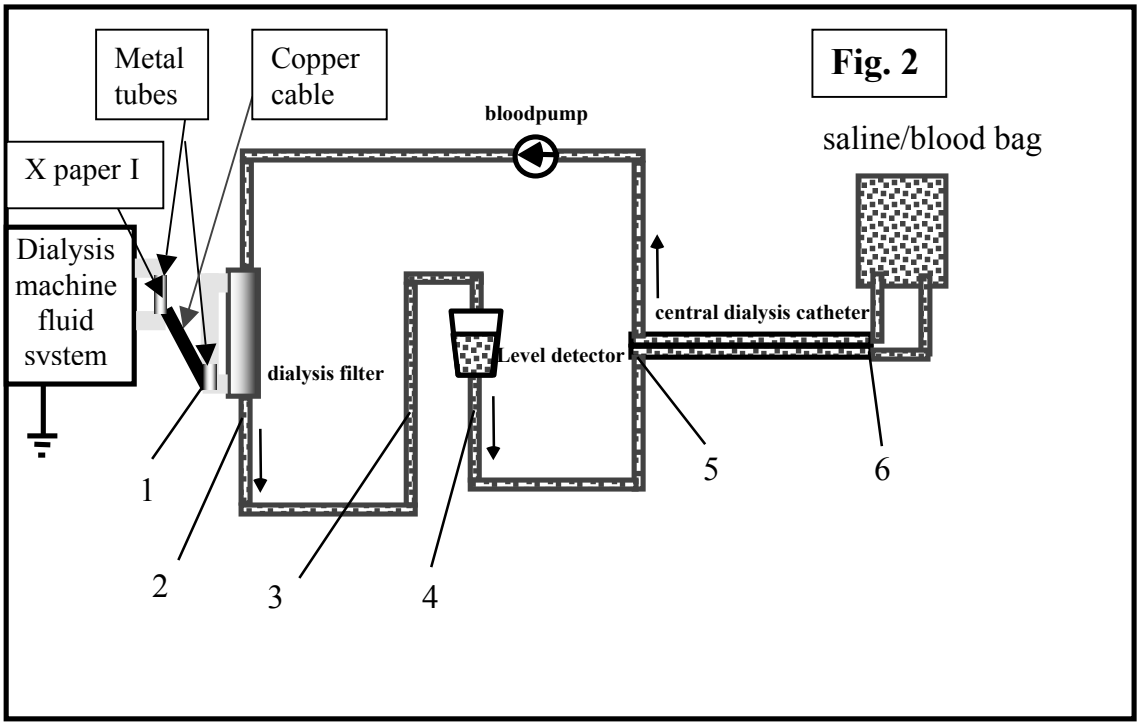
Summary of the calibrations done on the resistances used in Table 3					
		Resistance, _			
	N	Minimum	Maximum	Mean	Std. Deviation
TR, 2M_	6	1.99	2.01	2.005	0.009
TR, 5M_	6	9.97	10.08	10.045	0.054
TR, 50M_	6	49.83	50.37	50.201	0.262

Dialysis system

The dialysis machine was equipped with an "extracorporeal circuit" and was assembled from dialysis filter GFS +12 (Gambro, Lund Sweden) and tubing set from Baxter (Seraflo b*lood line* ref: 236-467G) and a central dialysis catheter (CDC) was a Permcath (40cm, dual lumen, batch 17749-001, Quinton Instrument, Bothell, WA). The blood line had an inner diameter of approximately 5mm, a length of 3550mm and a venous bubble trap with a diameter of 30mm. The inner diameters of the CDC lumens were 1.9mm. Dialysis needles were connected at the end of the blood lines, but they were inserted in the central dialysis catheter as galvanic measuring points *(applied part)*. Dialysis needles were also used as measuring electrodes in the blood line system at various sites.

During this *in vitro* setting saline (0.9% NaCl) was used as priming solution on both the blood and on the dialysis-fluid sides of the dialysis filter. During the measurements of leakage current saline and then blood were used as the fluid in the blood lines. The fluid was recirculated through the dialysis tubing set with a double lumen (CDC) at the end. Needles were fixed into the lumen of the tubing set at the venous side of the CDC to measure electrical current within the fluid stream (Fig. 2).

Figure 2. In vitro measurement of leakage current



Saline, instead of dialysis fluid, was put in the dialysis filter. To avoid changes in the ion concentration during the dialysis of this small fluid volume, approx. 450 ml, only a galvanic connection was made between the dialysis fluid tubes of the dialysis machine and the dialysis fluid compartment of the dialysis filter. A metal tube (stainless steel) was connected between both filter connectors on the dialysis fluid lines of the dialysis machine (Fig. 2). A silicone tube line was connected between both dialysis connectors on the dialyzer. The silicone tube line was cut and a small metal tube (stainless steel) was inserted in between the silicone tube halves between the dialysate connectors of the dialyzer (Fig. 2, measurement point MP1). The metal connector at the tube fixed at the dialysis fluid part of the circuit was connected galvanically with a copper cable to the metal tube between the dialysis fluid connectors. Thereby the electrical connection between the dialyzer and the dialysis tubes was present as it is used during standard dialysis treatment, without changing the ion concentration in the test solution/blood during the experimental dialysis procedure. Measuring points (Fig. 2) were: MP1, dialysis fluid; MP2, blood tube just downstream from the dialyzer; MP3, the blood sampling site prior to the venous bubble trap; MP4, the blood line downstream from the venous bubble trap; MP5, the blood line just upstream from the site of the Luer connector (needle or catheter); MP6, inserted in the lumen at the tip of central venous catheter edge (“close to the heart” location if used during regular dialysis). All electrodes in the blood line were inserted in the venous line except MP6 where one needle was inserted in each lumen. They were used together as one measuring point (electrically in parallel).

The measurements were made using either manual mode (measurement of mains on applied part) or automatic mode. The QA-90 changed the power line configuration to the analysed equipment during the test at all test steps according to IEC 601-1. This resulted in several sequences of power loss. During automatic mode, the QA90 was set to start measurements 5 seconds after the power to the dialysis machine had been turned on, and we restarted the flow in the machine as fast as possible by pressing the dialysis start button. Measurements were recorded for *normal condition*, *single fault condition* (broken protective earth connection, Fig. 2 in Paper II, Br1 open) and *mains on applied part* (leakage current from an external device connected to the blood line).

Statistics

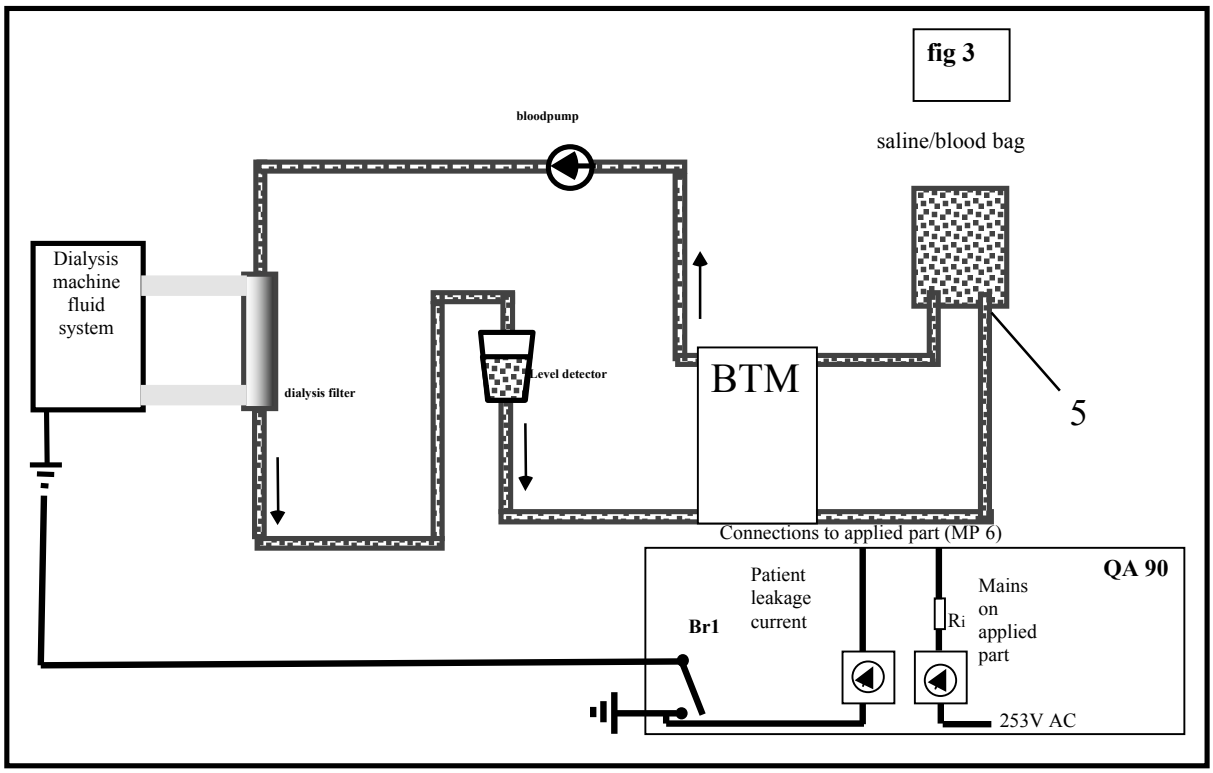
Paired non-parametric statistics (Wilcoxon test) were performed for all analyses. A significance level of $p<0.05$ was chosen. SPSS software was used. The highest values obtained are given in the text if not otherwise stated.

Addendum to Paper II. In vitro measurement of leakage current through diluted or concentrated blood during *mains on the applied part*

One blood bag of 0.4l blood from a haemochromatosis patient (male) was collected. 15,000IU Heparin was injected into the blood bag, and the bag was stored in a refrigerator.

A dialysis system was prepared (Fig. 3), and a single dialysis run was performed in vitro. Leakage current during *mains on applied part* was measured as the blood was diluted by the addition of successive boluses of saline or concentrated by ultrafiltration.

Figure 3. In vitro measurements of leakage current during *mains on the applied part* through diluted or concentrated blood



A dialysis machine, Fresenius 4008H, equipped with a blood temperature monitor (BTM), was preparing dialysate from a Biosol 301 A- concentrate and Bicbag (Fresenius). The composition of the concentrate was Na: 138, Cl: 109, K: 3, Ca: 1, Mg: 0.5 Acetate: 3, Glucose: 5 (mmol/l). The conductivity was 14.1 mS/sm2 and the temperature was set to: 37.5 ^{o}C. A Fresenius blood line (AV set FMC) was connected to a dialysis filter (F8HPS) and attached to the machine. The blood compartment was primed with priming saline from Meda and the dialysis side of the membrane by the dialysate. Needles (Bionic 16g) were connected to the blood line and the arterial needle was inserted in the blood bag and the system was filled up with blood. The venous needle was also inserted into the blood bag and the blood was recirculated at a blood flow of 200 ml/min. The QA90 instrument *applied part* connector was connected to the venous needle.

Measuring procedure: When the arterial temperature recording on the BTM was stable the leakage current during *mains on applied part* was recorded and blood samples were taken. Levels of albumin, Haemoglobin (Hb), erythrocyte volume fraction (EVF), erythrocyte particle concentration (EPK) were analysed.

Dilution procedure: Saline was injected into the blood line in steps of 60ml and the measuring procedure was repeated. The dilution procedure was repeated 8 times. (Two blood samples were missed).

Ultrafiltration procedure: The dialysis machine was programmed to ultrafilterd a volume from the recirculating system and when it was finished the

blood was recirculated for a period of time corresponding to the temperature stabilisations in the measuring procedure (approx. 10 min). The *mains on applied part* reading was monitored, and when stable, a new measuring procedure was begun. Three ultrafiltration procedures were done stepwise.

Calculation of "bag difference": The concentration differences during dilution and ultrafiltration were calculated, and blood sample volumes were included in those calculations.

Test for correlation: The bag difference and the levels of the analysed substitutes from blood samples were tested for linear correlation with leakage current using Pearsons test for correlation.

Paper III, dialysis system

The dialysis system used was Fresenius A 2008 C. Buffer solutions used for dialysis fluid were D210 (acid concentrate, Gambro, Lund, Sweden) together with buffer solution Duolys B (Fresenius), blended to a final concentration of Na 140, Cl 110, Mg 0.5, Ca 1.75, K 3.0, HCO_3^- 34 and acetate 3.0 mmol/l by the machine. The same type of dialyzer and tubing set were used each time. To decrease the dilution factor and priming volume, the tubing set was shortened. The dialysis machine was disinfected by heat prior to each use. The dialyzer was rinsed with 1.5 litre saline before dialysis. This fluid was mostly removed before the experiment. In all tests dialysis fluid flow was 500 ml/min, blood flow was 100 ml/min, and dialysis fluid temperature was 37.0 ^{o}C. Dialysis needles were inserted in sampling ports prior to and past the dialyzer and used as parallel connected electrodes in the blood compartment. Approximately 350 g blood was collected from each of eight blood donors after informed consent was obtained. Seven of them were healthy male blood donors and one was a haemochromatosis patient. Each blood bag contained 1000 Units heparin (in one bag only 800 Units). The priming fluid (saline) in the tubing and dialyzer caused a partial dilution. Hollow-fibre dialyzers were used. The dialysis membranes were hemophan membranes and had been steam-sterilised (GFS +12, Gambro).

Paper III, methods

Blood from the donors was recirculated in the extra corporeal system of the dialysis machine, and the dialysis fluid flow was set at 500ml/min. During this *in vitro* dialysis, blood samples were taken for analysis every 15 minutes. After 1 hour of *in vitro* dialysis DC voltage was applied between the needles and the ground connector in the dialysis fluid. The voltage was increased to achieve an electric current in the system of maximum 1.5 mA. This current was considered as a provocation test to indicate if leakage could have any effect on the blood-membrane interaction. A second limit was used to the applied DC voltage that forced the current. It was limited to 50V, so in some runs the current was under 1.5mA.

The voltage limit was selected due to the maximum DC voltage differences in the electronics in the machines used (+25V and -25V). The anode was on the blood side, except in one run where, by mistake, the cathode was the blood electrode. The blood sampling every 15 min persisted during exposure to the electric current in the system until a total of 1.5 hour *in vitro* dialysis had been performed.

Blood sampling and analysis

The blood samples were analysed for concentrations of complement component C3d, albumin, haematocrit and electrolytes. Blood samples for C3d were immediately cooled on ice and kept so until centrifugation. After centrifugation the plasma samples were frozen at -20º until analysis. C3d was analyzed with rocket immune electrophoresis technique (Stegmayr, 1989 #125). The values were adjusted to the serum albumin and haematocrit to correct the C3d samples for the dilution by priming fluid or eventual dialysis fluid imbalance (effect of an eventual ultrafiltration) during dialysis.

Statistics

Software (Statworks) was used for analysis of data by non-parametric paired Wilcoxon signed rank test. Later analyses were done with SPSS. A two tailed $P<0.05$ was considered as significant.

Paper IV,

This paper can not be e-published according to the copyright rules. Until peer review is finished it is only described briefly:

Forty-five patients were investigated with ECG and by Poincaré analyses arrhythmia where evaluated before connection of the dialysis tubes to the patient, shortly after the start, before the end of the dialysis and after disconnection of the tubes.

Paper V,

The paper "Air microbubbles pass the security system of the dialysis device without alarming" can not be e-publish yet according to the copyright rules. Different methods were used to in vitro evaluate imaginable bubbles silently passing the air detector.

An abstract from the ESAO Congress in Umeå 21-24 June 2006 of a part of this work was published in:
Air microbubbles pass the security system of the dialysis device without alarming. **Jonsson P, Karlsson L, Forsberg U, Gref M, Stegmayr C, Stegmayr B.** International Journal of Artificial Organs, 2006, 29 (5):523.

The full text article will soon be available:
Jonsson P, Karlsson L, Forsberg U, Gref M, Stegmayr C, Stegmayr B. Air microbubbles pass the security system of the dialysis device without alarming. *Artif Organs, in press,* 2007.

RESULTS

Paper I

According to these data all of these devices apply to their given safety level (*B*) when filter couplings for the dialysis fluid are considered as applied part. They even comply with one step higher degree of safety (*BF*) but they do not comply with the recommended safety level for *cardiac* applications (*CF*).
Figures 7-10 show the distribution of the single data for each device under various conditions. The limit for *cardiac floating* is given by a hatched line.

Figure 7. ELn Earth leakage, normal condition

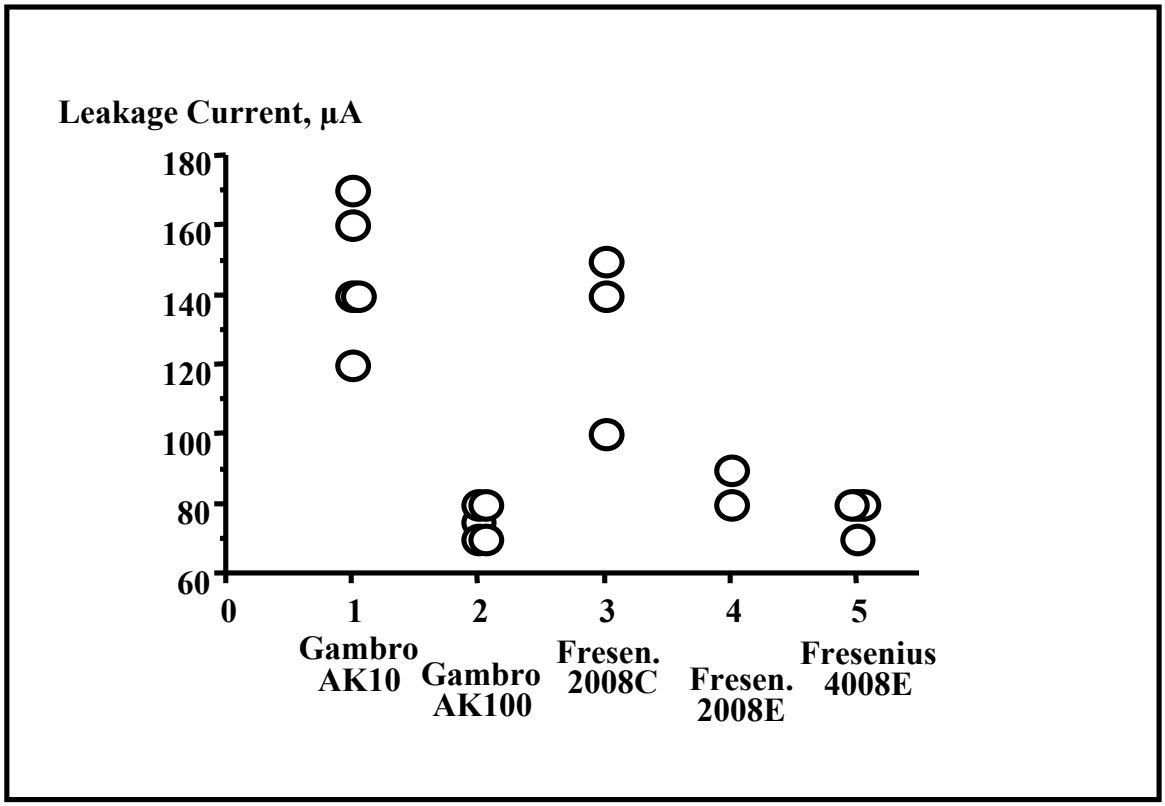


Figure 8. PCn patient current, normal condition or patient leakage current normal condition in IEC 601-1

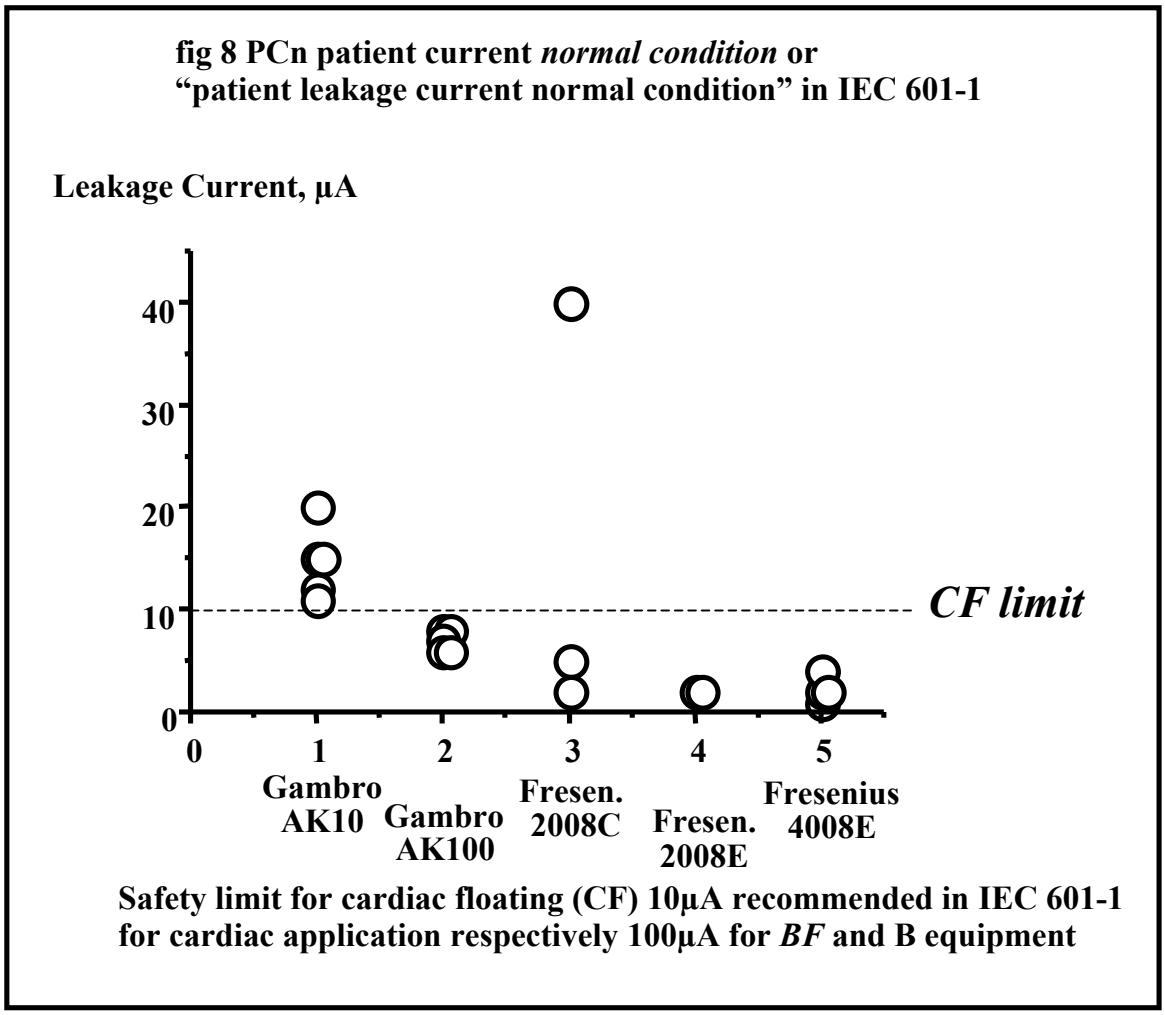


Figure 8: Plots for each measurement of leakage current for different devices-normal condition. (The dot at 40 **µA** at 2008C is a high value due to a failure in a capacitator in a conductive level detector in the fluid system. After service the leakage current in normal condition was 3 **µA** the following two years. The value after repair, 3 **µA,** was used in the paper I statistic.)

Figure 9. Patient current, broken ground, PC_{bGR} or patient leakage current single fault condition in IEC 601-1

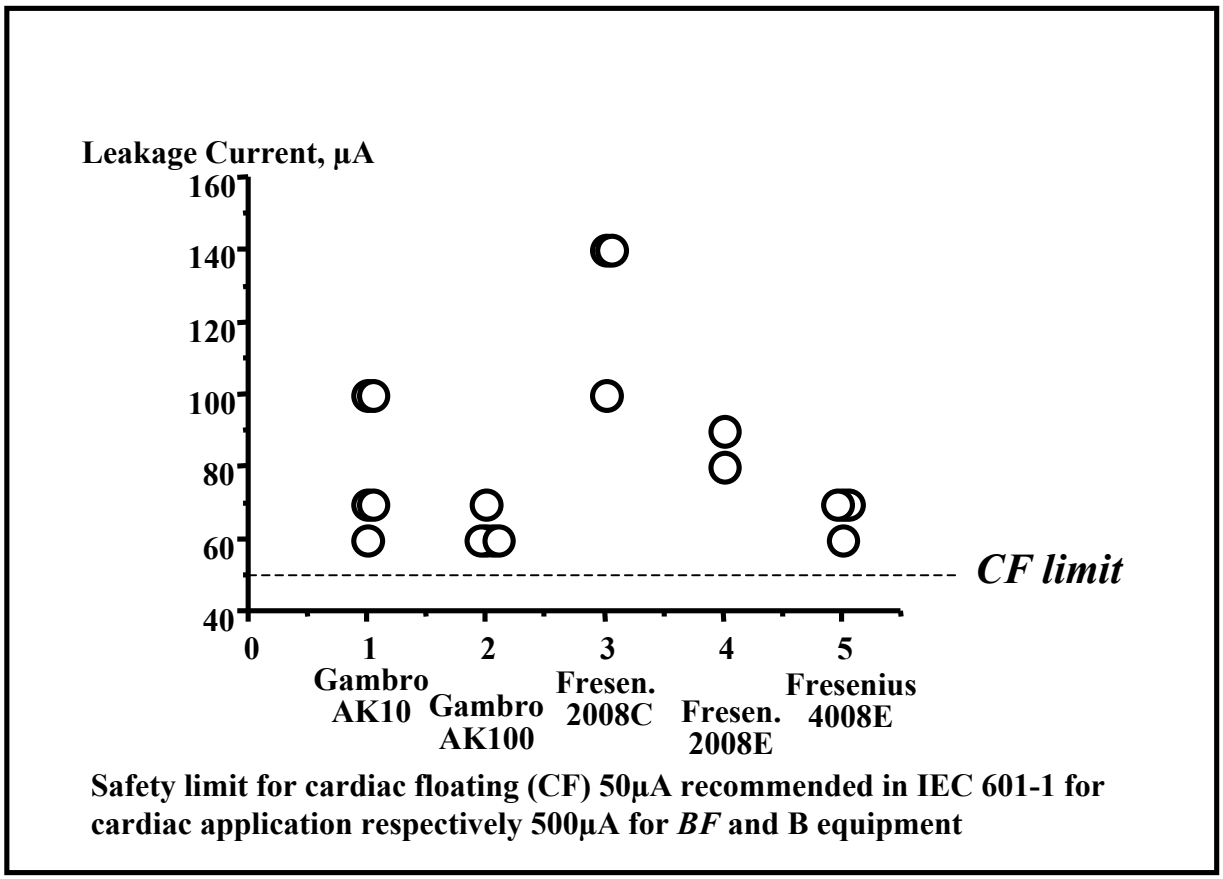
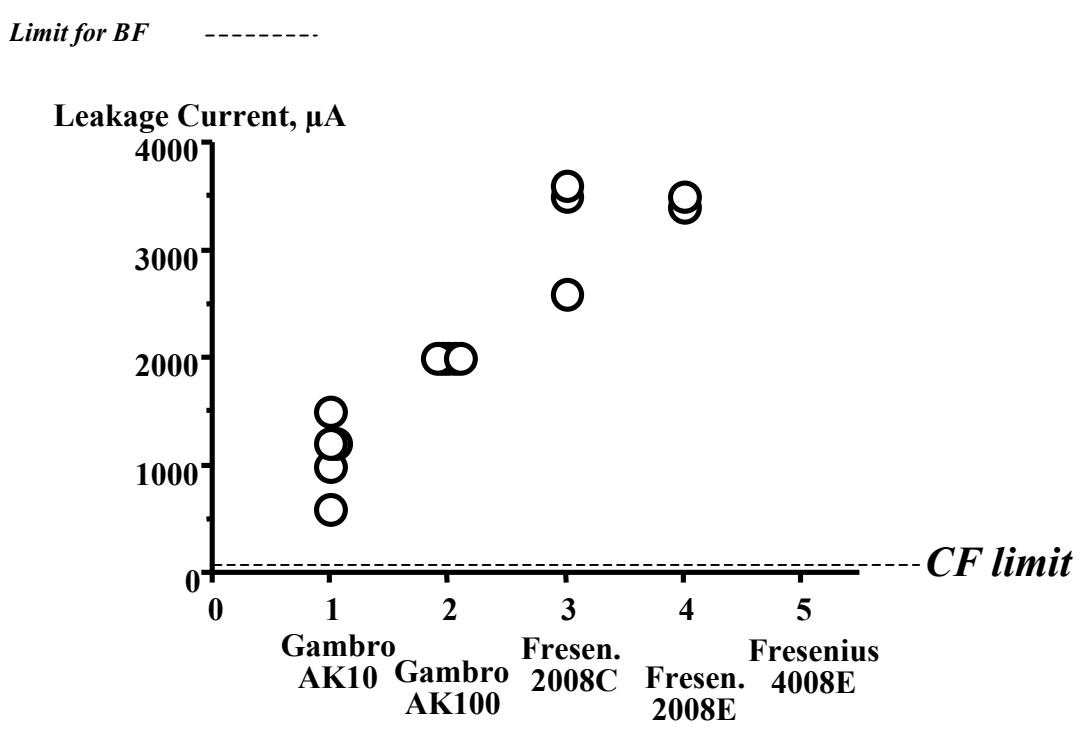


Figure 9: Plots for each measurement of leakage current for different devices- patient leakage current - single fault condition.

Figure 10. Exc, external current or *mains on applied part* in IEC 601-1



Safety limit for cardiac floating (CF) 50µA recommended in IEC 601-1 for cardiac application, respectively 5mA for *BF* and no limit for B equipment

In Table 7 the statistical analyses for comparison between devices are given. Since the material is small the statistics are given using the Student's test with correction for skewed distribution (using Levenes test) but also non parametric statistics (Mann Whitney).

For the reader it is more important to notice the data in relation to the safety limits set in IEC 601-1. For comparison the limits for *Cardiac* applications *CF* and other applied parts *B* and *BF* in *normal condition* (PCn), *single fault condition* (PC_{bGR}) and *mains on applied part* (Exc) are inserted in the figures.

Table 7. Earth leakage compared between dialysis machine models.
P-values are given according to Students test/Mann Whitney (non parametric test)

Earth leakage P- values are given according to Students test/Mann Whitney (non parametric test)				
Machine model:	AK10	AK100	Fr 2008C	Fr 2008E
AK100	0.001/0.008			
Fr 2008C	ns/ns	ns/0.024		
Fr 2008E	0.009/0.051	ns/ns	ns/ns	
Fr4008E	0.001/0.012	ns/ns	ns/0.028	ns/ns

Table 8. Patient current, normal condition (PCn) compared between dialysis machine models PCn

PCn patient current, *normal condition* P- values are given according to Students test/Mann Whitney (non parametric test)				
Machine model:	AK10	AK100	Fr 2008C	Fr 2008E
AK100	0.002/0.008			
Fr 2008C	ns/ns	ns/ns		
Fr 2008E	0.005/0.049	0.001/0.047	ns/ns	
Fr4008E	0.001/0.014	0.001/0.013	ns/ns	ns/ns

Table 9. Patient Current,*single fault condition* compared between dialysis machine models.

(Broken ground, PC_{bGR})

Patient Current,*single fault condition* (Broken ground, PC_{bGR}) P- values are given according to Students test/Mann Whitney (non parametric test)				
	AK10	AK100	Fr 2008C	Fr 2008E
AK100	0.097/ns			
Fr 2008C	0.020/0.044	0.037/0.016		
Fr 2008E	ns/ns	0.003/0.033	ns/ns	
Fr4008E	ns/ns	ns/ns	0.043/0.026	0.022/0.049

Table 10. Exc, external current or *mains on applied part* compared between dialysis machine models.

Exc, external current *or mains on applied part*			
	AK10	AK100	Fr 2008C
AK100	0.004/0.008		
Fr 2008C	0.001/0.024	ns/0.010	
Fr 2008E	0.001/0.051	0.001/0.016	ns/ns
Fr4008E*	-*	-	-

Paper II

Tables 11 and 12 and Figures 11and 12 show data from automatic safety measurements according to IEC 60-601-1 using the safety analysis device QA90. Note that differences appeared unexpectedly during the automatic mode of safety measurement with the QA90 device. This depended upon the intermittent power to the dialysis device as determined by the QA90. The QA90 turned the current *on* and *off* automatically to perform the different safety measurements. When the current was turned *off* an air gap appeared in the bubble trap and no current flow could be measured. This air gap remained after the power was turned *on* until the blood pump had started.

Table 11 shows data from eight runs with saline in the blood lines during *normal condition*. Earth leakage current (ELC) was median 143 (range 133-150 µA) while patient leakage current (PLCNC) was 11 µA (range 10-14) at measurement point (MP) MP1 and 0 at point MP6.

Table 11. Leakage current through blood lines in *normal condition* using saline as a fluid

Earth leakage current (ELC) and patient leakage current (PLCN) during normal condition using saline as fluid							
		MP1	MP2	MP3	MP4	MP5	MP6
	uA						
Series	ELC	PLCNC	PLCNC	PLCNC	PLCNC	PLCNC	PLCNC
1	142	11	0	0	0	0	0
2	143	0/*	4	0	0	0	0
3	150	0/*	5	0	0	0	0
4	143	0/*	4	3	0	0	0
5	143	14	3	2	0	0	0
6	143	11	5	3	2	0	0
7	133	10	5	3	2	0	0
8	144	13	6	3	2	0	0
MP1-MP6 indicate measurement points 1-6. * indicates probably due to loss of connection.							

Figure 11 shows data from 8 runs with saline in the blood lines in *single fault condition*. Patient leakage current was median 132 µA (range 127-143) measured at MP1 and median 47 µA (range 4-128) at MP6. The solid line indicates mean values. The dashed line indicates *CF* limit.

Figure 11. Leakage current, blood in bloodlines, *single fault condition*

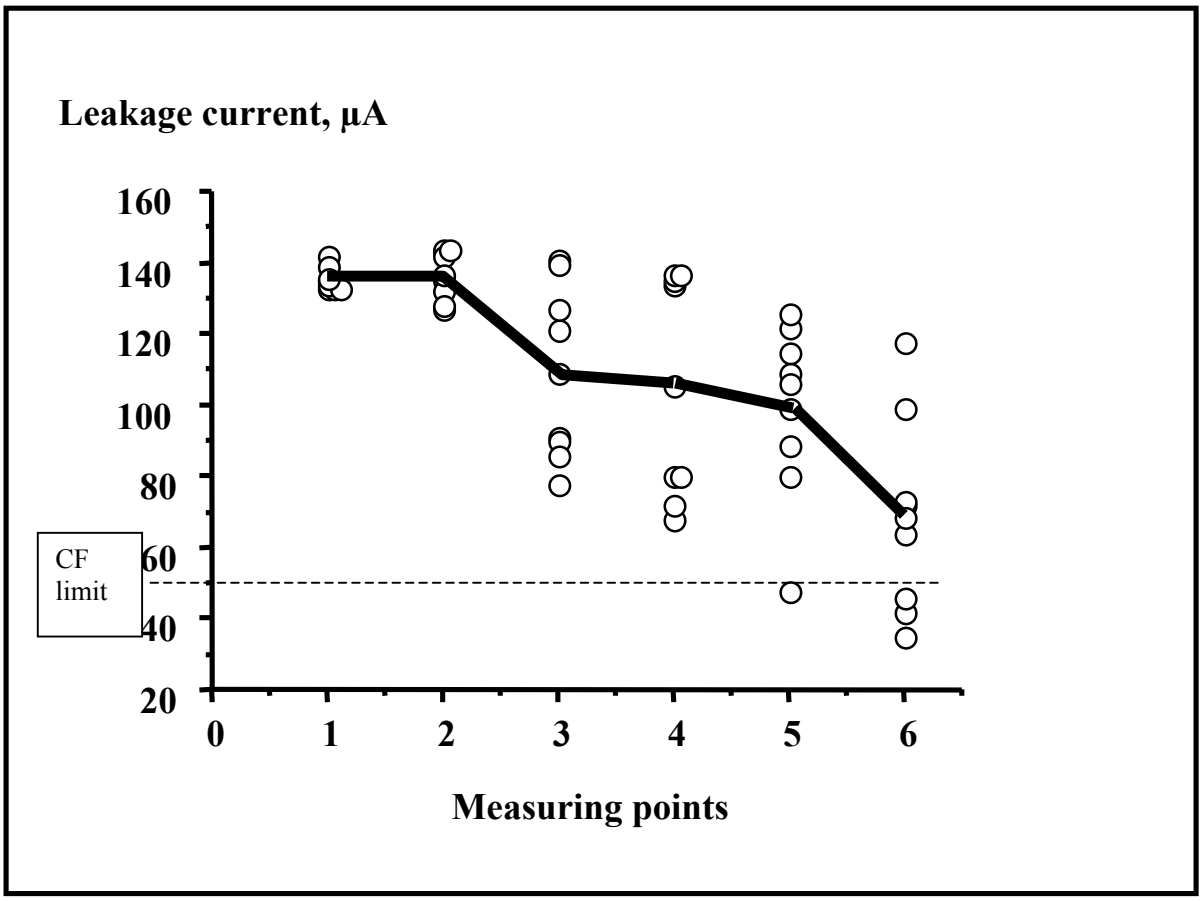


Table 12 shows data from a setting using *normal condition* with 8 runs with blood in the blood lines. Earth leakage current (ELC) was median 147 (range 142-152 µA) while patient leakage current (PLCNC) was median 19 µA (range 16-21) measured at MP1. Patient leakage current (PLCNC) was 2 µA in two and 0 in six of the runs at MP6.

Table 12. Leakage currents through blood lines containing blood during normal condition

Earth leakage current (ELC) and patient leakage current (PLCNC) in µA using blood as a fluid during *normal condition*								
		MP1	MP2	MP3	MP4	MP5	MP6	
	µA							
Series	ELC	PLCNC	PLCNC	PLCNC	PLCNC	PLCNC	PLCNC	%PLCOE
1	142	16	7	3	2	0	0	0
2	146	20	11	4	4	0	2	1
3	144	19	9	4	5	0	0	0
4	147	19	10	4	4	0	2	1
5	147	21	9	4	3	0	0	0
6	148	19	9	4	4	0	0	0
7	152	19	7	3	3	0	0	0
8	150	20	8	3	3	0	0	0
MP1-MP6 indicate measuring points 1-6. The percentage of patient leakage current in relation to earth leakage current is calculated (%PLCOE).								

In *single fault condition* (Fig. 12) patient leakage current was median 134.5 µA (range 133-142) measured at MP1 and median 68 µA (range 35-118) at MP6.

Figure 12. Leakage current through blood lines containing saline during single fault condition

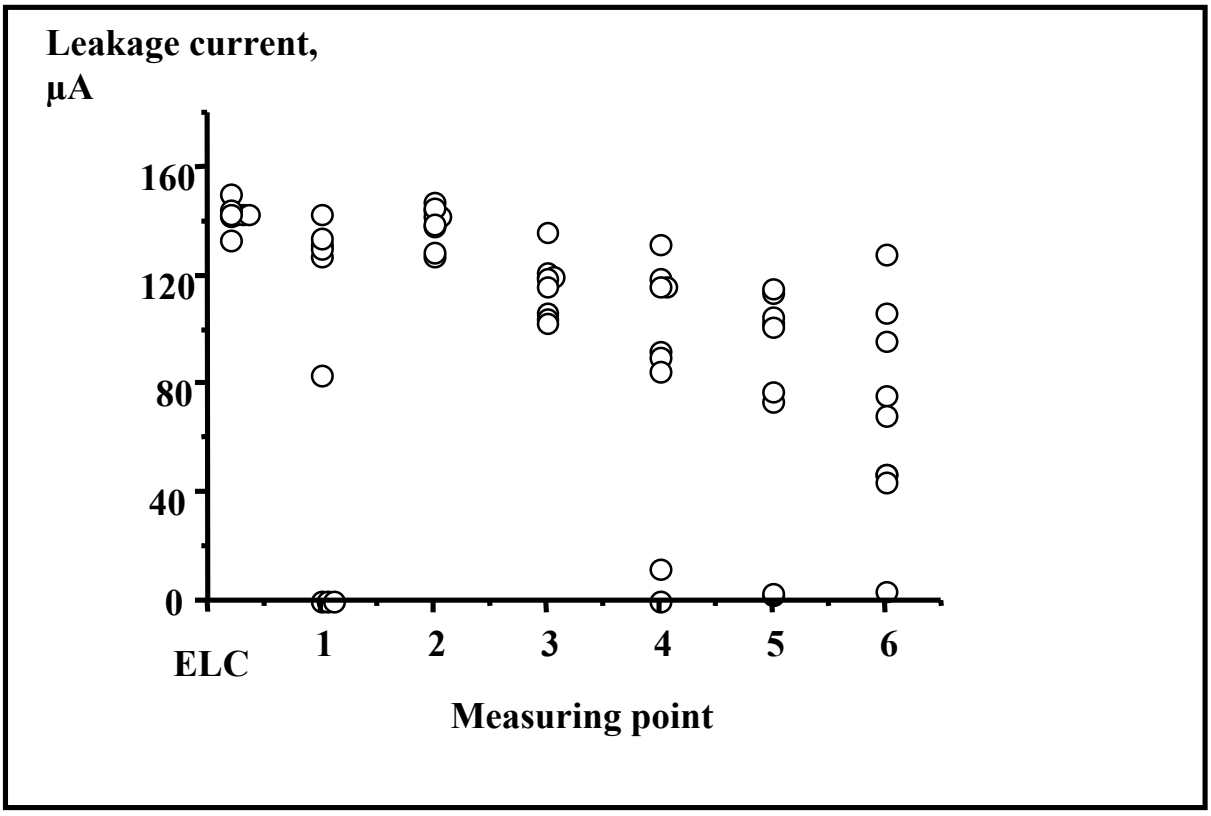


Table 13 and Figures 13 and 14 show data from 8 runs using the test *mains on applied part* (IEC 60-601-1) measured in manual mode (stepwise). This test simulates leakage current generated by other equipment connected to the patient and corresponds to a *single fault condition*. Either blood, Figure 14 or saline, Figure 13, was used to perfuse the "blood lines", the flow was either off (-), on (+) with flow 80 ml/min or 160 ml/min. Measurements were only performed at MP6 for flow 160 ml/min. When using saline in the blood lines the patient leakage current at MP6 was median 1008 µA (range 674-1213) with flow of 80 ml/min.

When blood was used the patient leakage current at MP1 was median 3964 (range 3933-3972 µA) and at MP6 median 610µA (range 441-662). The ratio of retained LC at MP6 was calculated using the LC at MP6 related to the LC at MP1 and adjusted into percentage, which resulted in a median of 15.5% (range 11.1-16.8 %) leakage current.

If the LC at MP6 with a blood flow of 80 ml/min was compared with data when blood flow was increased to 160 ml/min, the LC increased by about 12% (0.7-24%, p=0.012).

When a single fault was simulated on the dialysis device with blood in the tubes the leakage current was lower at M3 than at M2 (p=0.025), lower at M6 than at M5 (p=0.012) but not different between the other sites close to each other (Table 12).

When a fault of mains on applied part was simulated with blood in the tubes, leakage current was significantly lower at the more distal point by comparison from MP1 and MP2, MP2 and MP3 until MP5 and MP6 (p=0.12). Such significant differences were also found using saline (p<0.019).

Data at MP5 show that the leakage current was greater than at MP6. MP5 is the place where a dialysis needle is inserted into the AV fistula (blood line) of a patient. Since these data show that blood conducts leakage current, the risk of having leakage current through an AV fistula (MP5) is not negligible. The other points (MP2-4) are reported to show the conductive dynamics in the blood-line system. To estimate the drop of current, the measurement at the starting point, MP 1, is important.

The blood used was analysed for its concentration of haemoglobin, albumin, sodium, chloride, leukocytes and platelets. When these variables were compared using univariate analysis the leakage current at MP6 during single fault condition was correlated to Na^+ concentration (r^2=0.60, p=0.024) but not to the other parameters. The LC at MP6 during mains on applied part correlated inversely with albumin (r^2=0.81, p=0.0022) and haemoglobin (r^2=0.62, p=0.021).

The impedance in the tubing system (Z(isolation)) was calculated from measured current during mains on applied part. The formula was based on the assuming of clean resistance, no inductive or capacitive component:

U= (Z(isolation)+ R(inner resistance)) x I(leakage current);

U/I=Z+R; (U/I)-R=Z

Saline in blood lines (1008 μA (range 674-1213)): (253/0,001008)-47000=203992 _, approximately ≈ 200 k_ (range 160-330)

Blood in blood lines 610μA (441-662): (253/0,000610)-47000= 368000 _; ≈ 370 k_ (range 340-530). Thus, the total impedance range was 160 - 530 k_ with flow 80 ml/min.

Table

13. Leakage current during the test mains on applied part, flow on/off

Median values of leakage current either with blood (Bl) or saline (Na) in the tubes. In addition, the experiment included a model with dialysate flow off (Dia-, 0ml/min) or on (Dia+, 500ml/min) and blood or saline flow off (Bl-, Na-) or flow on (Bl+, Na+).									
	Blood series				Saline series				
Measurepoint (distance to dialyzer)	Bl- Dia-	Bl- Dia+	Bl+ Dia+	Bl+ Qb 160 Dia+	Na- Dia-	Na- Dia+	Na+ drip Dia+	Na+ Dia+	Na+ Qb 160 Dia+
1 (0)	3574	3945	3959		3252	3795		3936	
2 (50mm)	3072	3324	3358		2972	3451		3421	
3 (812mm)	1582	1635	1728		2018	2291		2206	
4 (1370mm)	1127	1091	1341		61	53.0	481	1854	
5 (3520mm)	598	587	749		113	107	242	1160	
6 (3950mm)	471	461	591	661	121	34.5	179	980	1058
The flow through the tubes (Qb) was set at 80 ml/min or 160 ml/min (Qb160) for measurement at MP 6. When set at 80 ml/min and with saline in the tubes dripping occurred in the venous bubble trap.									

Figure 13 Saline solution in the tubes, mains on applied part

Leakage current through bloodlines containing saline.
Test *mains on applied part* at measuring point 1 – 6 .using priming solution (NaCl) in the tubes.

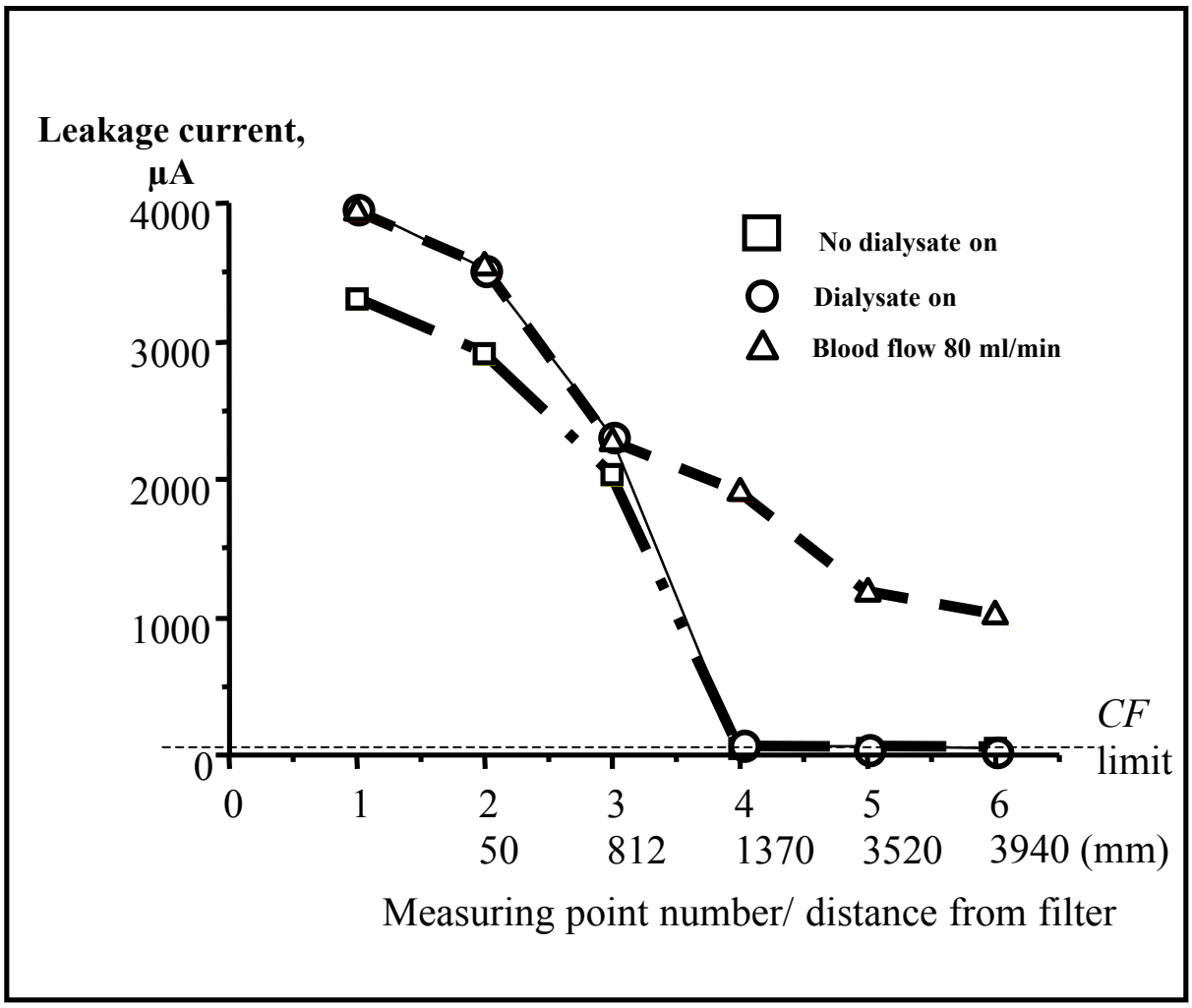
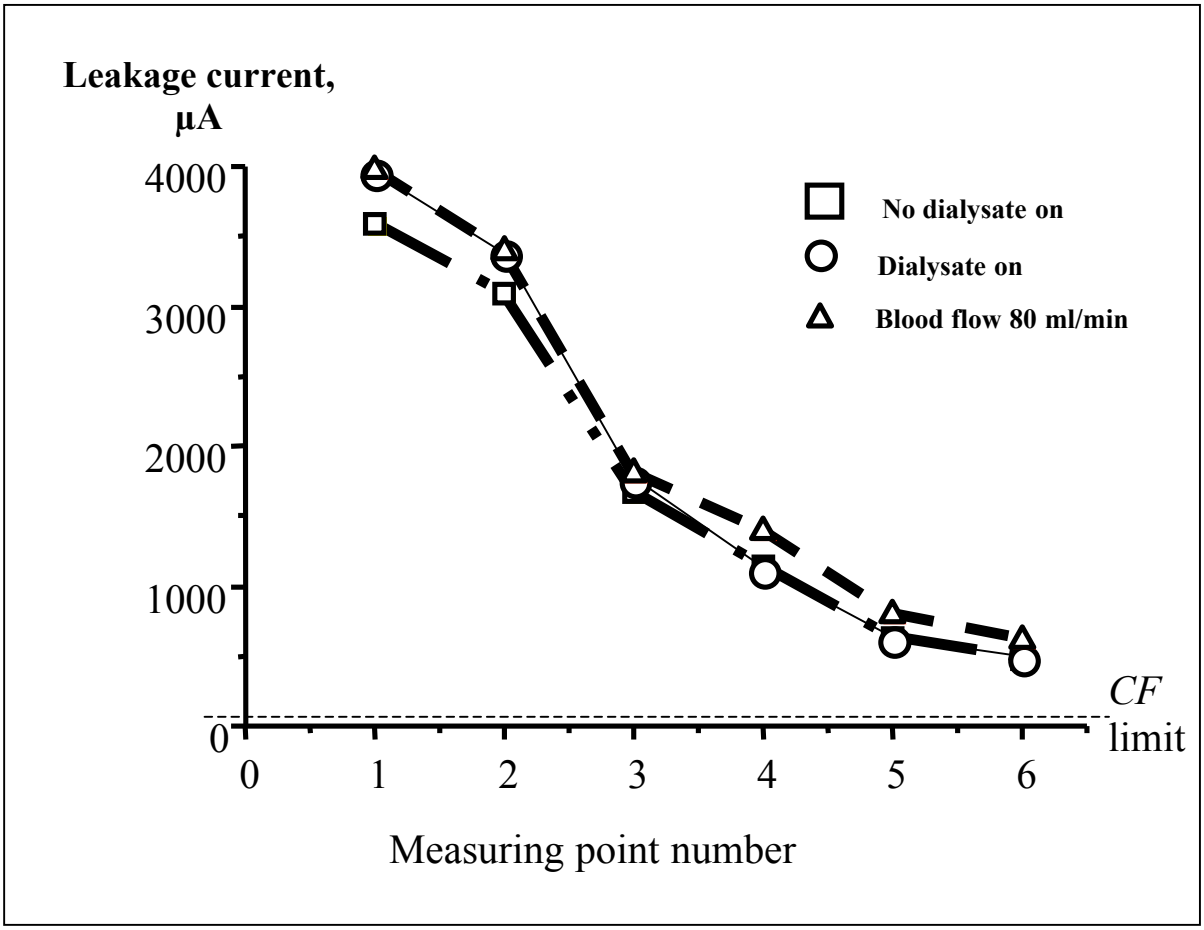
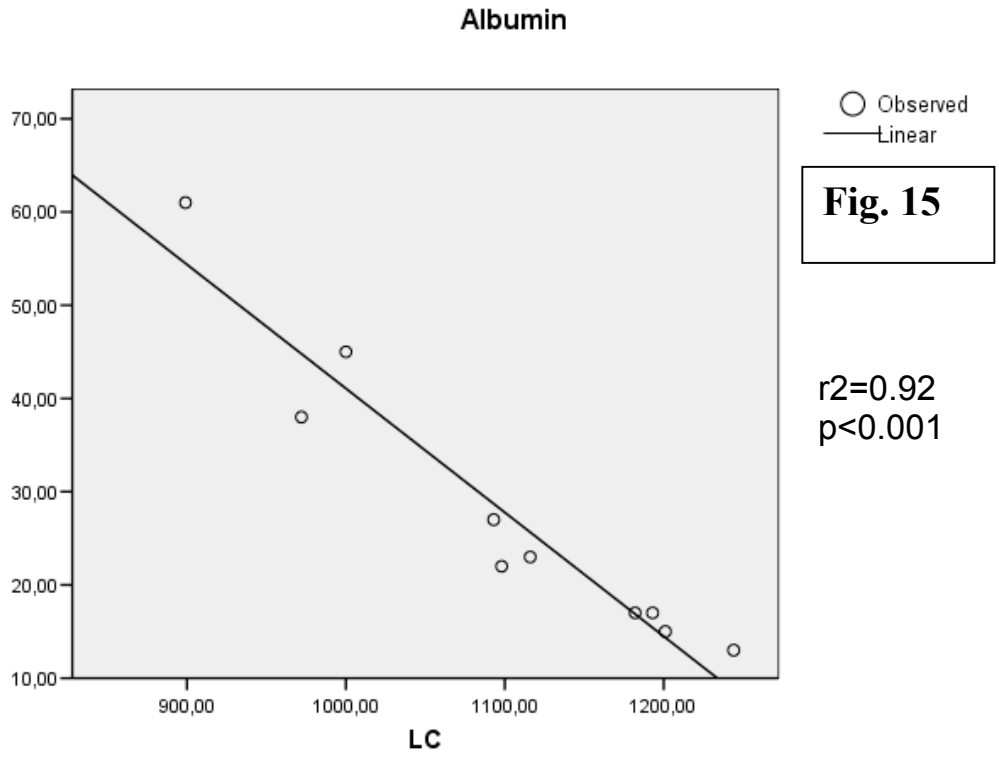


Figure 14. Leakage current using blood in blood lines and testing *mains on applied part*



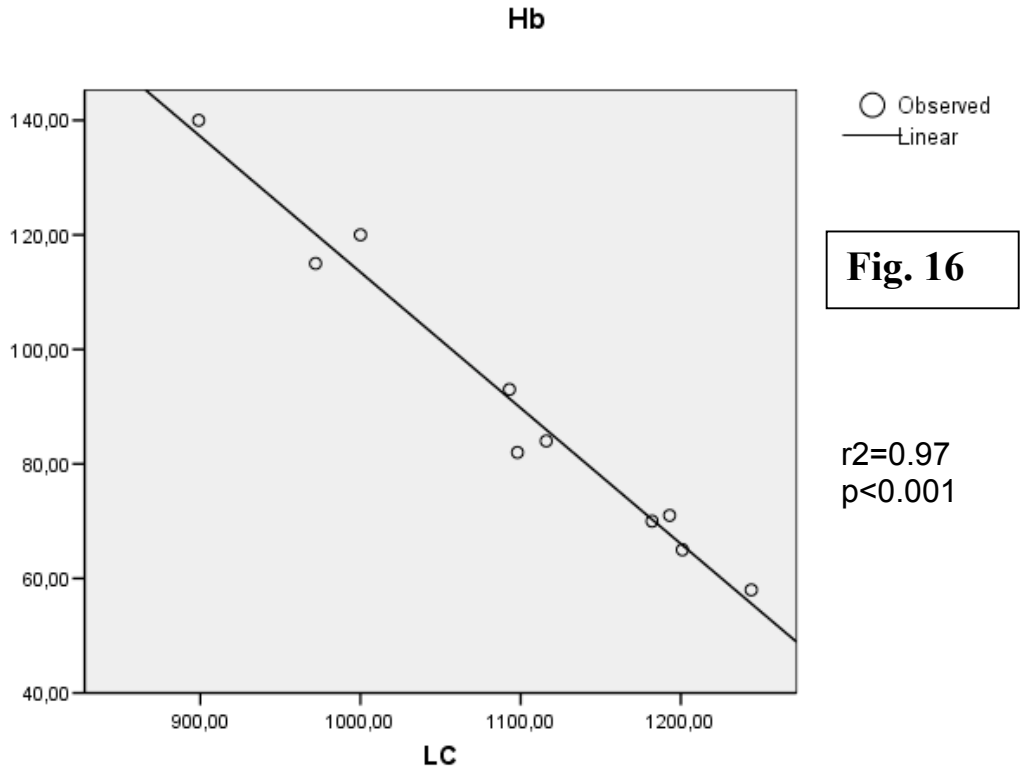
Addendum to Paper II. In vitro measurement of leakage current through diluted or concentrated blood during *mains on the applied part*

Complementary result to Paper II, a single run blood concentration versus *mains on applied part,* (not published). The test for linearity showed that leakage current correlated inversely with the concentration of blood. This is also shown in "Figures 15-18". The leakage current was linearly correlated to the extent of dilution ("Fig. 19").



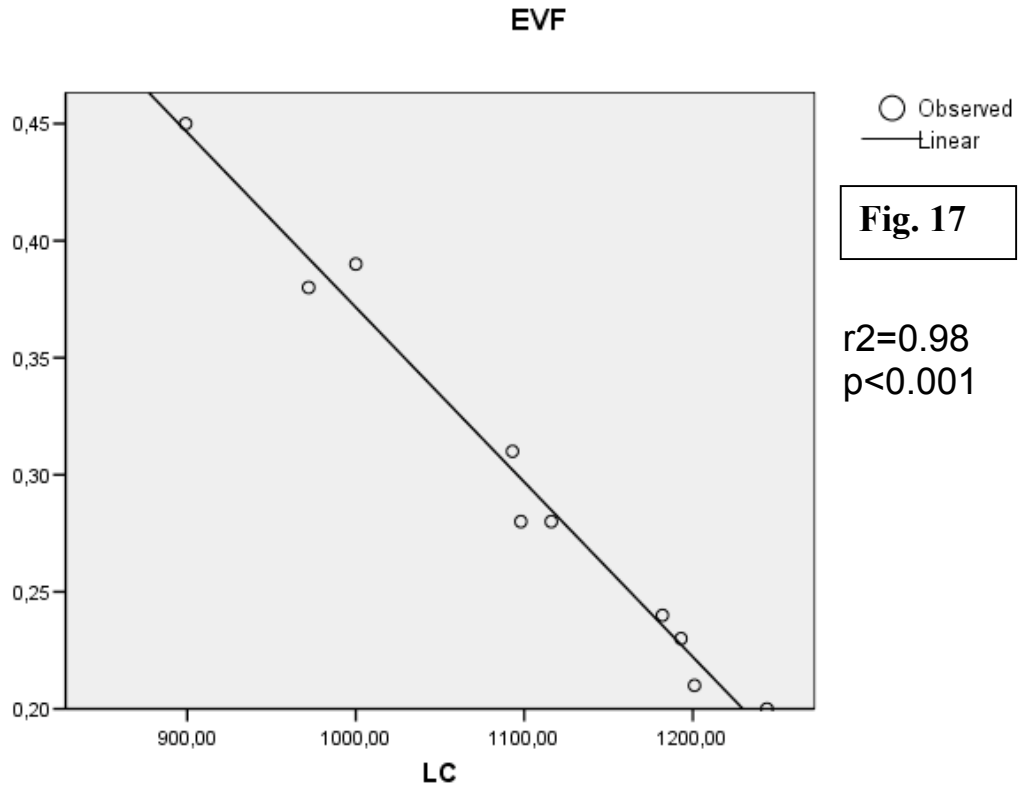
Figures 15 Correlation albumin concentration vs. leakage current.

In-vitro albumin concentration, dialysis with diluted / ultrafiltered blood bag. *Mains on applied part* measured at needle site (MP5).



Figures 16 Correlation Hb concentration vs. leakage current.

In-vitro Blood concentration, dialysis with diluted / ultrafiltered blood bag. *Mains on applied part*, needle site (MP5).



Figures 17 Correlation EVF concentration vs. leakage current

In-vitro Blood concentration, dialysis with diluted / ultrafiltered blood bag. *Mains on applied part*, needle site (MP5).

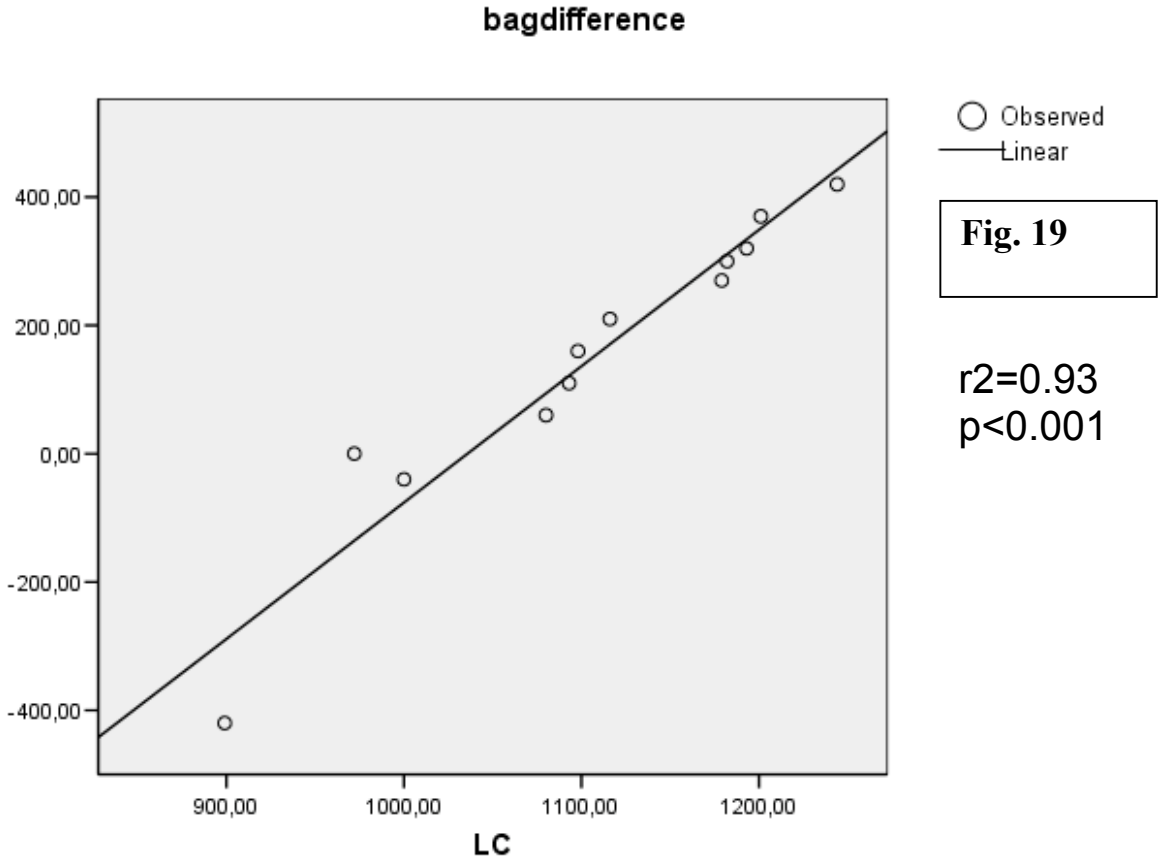


Figure 19. Correlation between blood-volume change

Bag difference, y-axis and leakage current in vitro. Measurements were performed with blood that had been diluted or ultrafiltered, *mains on applied part,* at measurement point 5.

Paper III

Figure 20 show the median percent change in C3d levels versus time. There was a significant increase in C3d throughout the whole time series ($p<0.05$). The increase between 0 and 30 minutes was greater than that between 30 to 60 minutes ($p=0.018$). The increase in C3d was greater between 60 and 90 min than between 30 and 60 minutes ($p=0.018$). There was no difference in the increase at 0 to 30 and 60 to 90 minutes (see Fig. 20).

The erythrocyte volume fraction (haematocrit) did not change significantly during the tests (see Fig. 21 and 22).

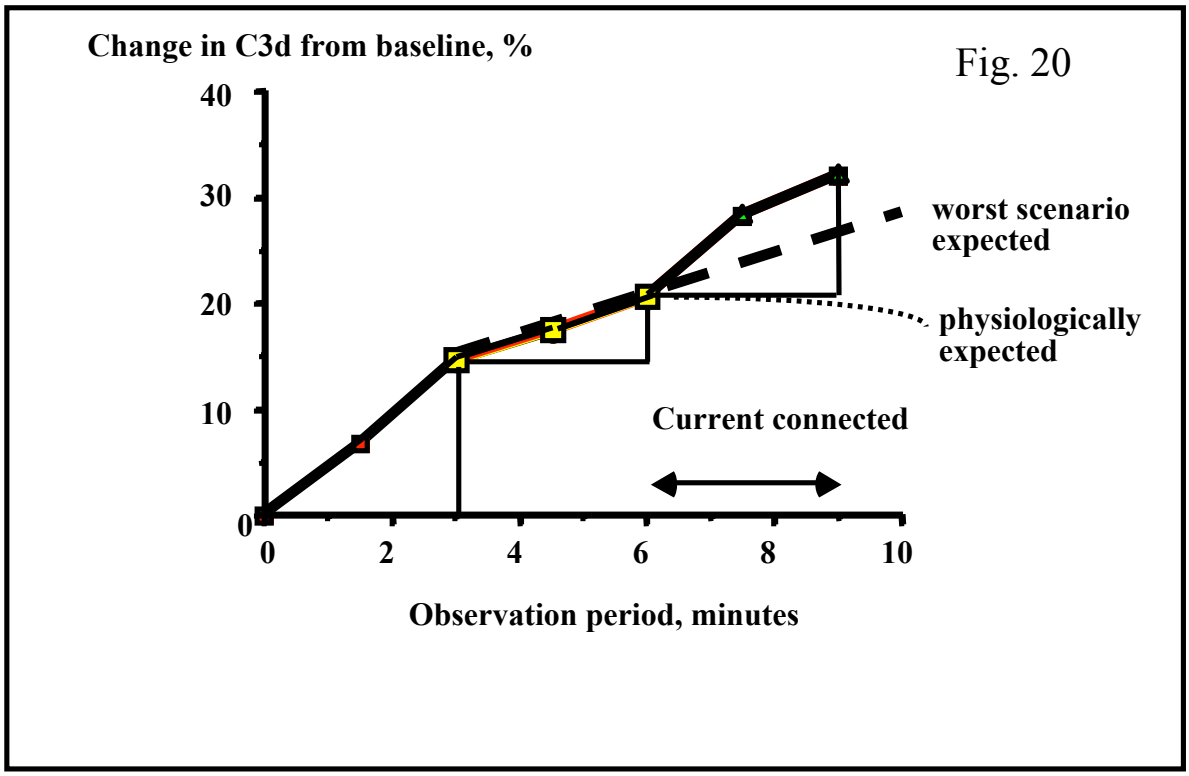


Figure 20 Change in C3d levels versus time

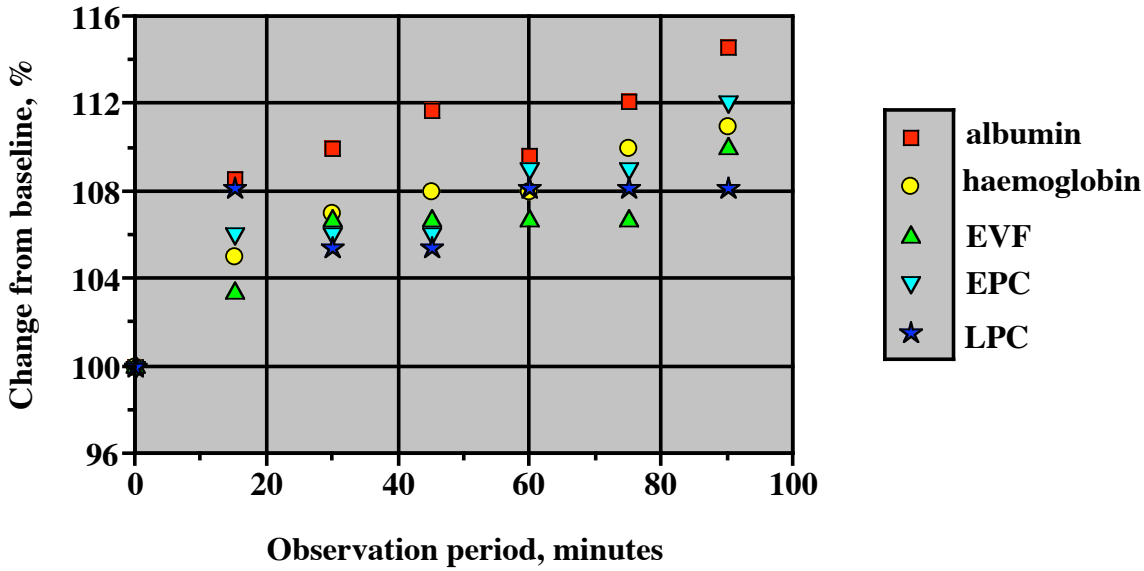


Figure 21. Change in variables during series 6

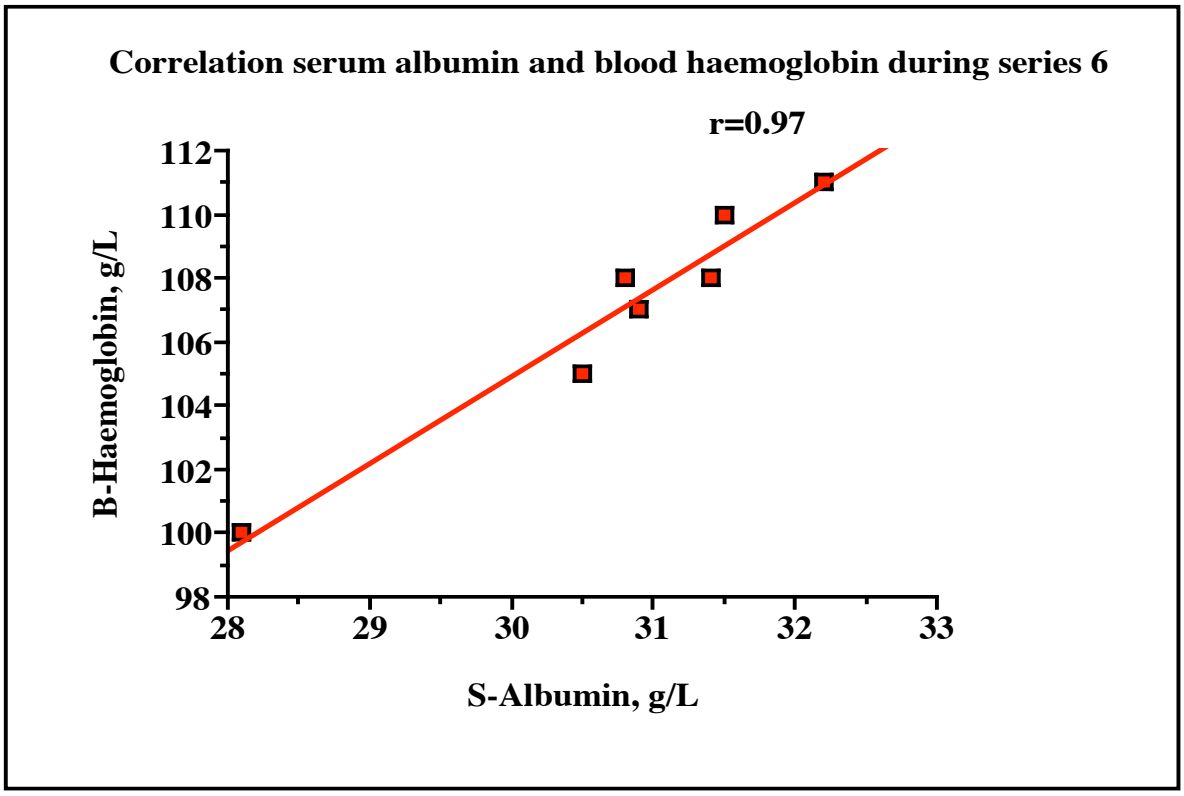


Figure 22. Correlation between serum albumin and blood haemoglobin during series 6

Paper IV

Heart rate decreased significantly after start of dialysis, was thereafter not significantly changed while a significant increase occurred after disconnection of the dialysis. Arrhythmia was more pronounced during the end of dialyses in 13 (35%) of the patients while it was improved in 2 patients and unchanged in 28. Atrial fibrillation developed in 2 patients while 6 had atrial fibrillation already at start of the investigation. No significant differences were seen between those with central dialysis catheter and those with peripheral access. Changes in arrhythmia occurred close to start but also close to finishing the dialysis.

Paper V

The full text article will soon be available:
Jonsson P, Karlsson L, Forsberg U, Gref M, Stegmayr C, Stegmayr B. Air microbubbles pass the security system of the dialysis device without alarming. *Artif Organs, in press,* 2007.

DISCUSSION

This doctoral thesis has focused on safety issues related to the processing of blood during haemodialysis of patients. The amount of leakage current presently allowed for state of the art dialysis devices is based on the *B* level of safety. However, that level does not take into account the use of the central dialysis catheter (CDC). Proximity to the heart should require a *cardiac floating* safety level. The question of leakage current is important because only a small current along a catheter near the heart could be fatal to the patient. The resistance in the b*lood line*s and the presence of air in the blood lines might also affect the possibility for leakage current to reach the patient's heart. Leakage current in the blood lines might also affect the blood itself. Several of the studies in this thesis where not possible to perform directly on patients, since the risk for severe complications was considered too high. Therefore, several experiments were performed in vitro.

Since the 1990s the IEC601 standards are relatively "open standards." This is because if a standard would describe everything in detail there would be no use for the manufacturer to design or construct something better than the standard. In such a case a very detailed safety standard could impair the development of safer procedures. Therefore, in many cases the standards do not state absolute limits. Instead, they include somewhat vague statements that require a system to protect the patient from hazardous outcome according to specific parameters. It is hoped that the manufacturers will constantly compete with each other to improve the safety of their devices and therefore offer machines that are safer, easier to use, and less expensive. However, that requires that the consumers are aware of the risks, how those risks can be measured / compared, and costumers looking for technique that reduce or avoiding this risks. Without background knowledge among the consumers, it would become a competition without rules for the manufacturers, and other considerations during commerce. In that case an open standard does not promote better safety. I hope that the data from this doctoral thesis will add some background knowledge and will promote a improvement of dialysis equipment in the future.

Leakage current Paper I - IV

Paper I describes issues regarding safety against electric shock**.** An AV fistula or graft allows peripheral access to the patient's blood stream. If the haemodialysis treatment is considered as a peripheral connection to the patient, the data showed that leakage currents were within the present safety limits for *body* and *body floating* (IEC 60601-1 #75). That conclusion relates to the measurement of patient leakage current in *normal condition*, *single fault condition* and *mains on applied part* performed according to the IEC standard (IEC #75) –Figure 7-10.

Although the leakage current in *single fault condition* (disconnected ground) is higher, it might be reduced by the resistance in the b*lood line*s and filter according to the conclusion by M. C. Deller in 1974. He wrote that "The dialyzer and lines represent a protective impedance of some 400kohm between the patient and the dialysis machine" and "As far as primary electrical hazards are concerned, dialysis should be considered as being a relatively safe procedure" (Deller, 1979 #74). Is that correct? Is it sufficient protection even with a central dialysis catheter?

A central dialysis catheter (CDC) is not unusual for dialysis patients, and it is usually placed close to or within the heart. The data in Paper I indicated that the leakage current measured in filter couplings could constitute a safety problem if the equipment were used in a *cardiac* application, i. e., with a CDC. The leakage current during *mains on applied part* (fig 10) was at alarming levels in all tested machines as compared to (1) the recommended safety levels for *cardiac* applications and the probabilities for ventricular fibrillation stated in the general standard (IEC #75) and (2) studies performed on hearts of humans and dogs (Starmer, 1973 #79; Watson, 1973 #81). Such high values, except one recording, were recorded after maintenance, and the leakage current could possibly have been even higher before maintenance. For example, salt splashes on the electrical components in the fluid system might increase all types of leakage currents. Dialysis patients with a CDC could be at risk if the dialysis fluid and blood in the tubes lead enough leakage current. Although Deller (1979) had no concerns in this regard, the analyses in Paper II were performed to clarify the risk for leakage current through the b*lood line*s.

The data in Paper II pointed out that the safety level when using a CDC with a modern, state of the art dialysis machine was not within the safety level for class *CF* recommended in IEC 60-601-1 (IEC #75). According to the data in Paper II for the dialysis device tested there is very little risk for ventricular fibrillation during *normal condition* (table 11 and 12) according to the general standards and its references (IEC #75; Starmer, 1973 #79; Watson, 1973 #81). However, the safety limits for *class B* in *normal condition* are not considered safe for a *cardiac* application according to the same references. Paper II showed that leakage current could travel via the b*lood line*s and filter when they contained saline or blood. During the *single-fault condition,* (*broken ground connection)*,

the leakage current increased, and the safety situation worsened (Figure 11 and 12). That dialysis device showed a maximum current of about 130 µA, and that is more than 2_ times the safety limit recommended in the general standard. That amount of current corresponds to >10% probability for ventricular fibrillation according to the probability table in the general standard (IEC 60601-1 #75). An even greater risk occurs if the access point becomes grounded. If the dialysis fluid became grounded the access point would be considered as an electrical ground point in the patient. For a CDC patient this would be within or close to the heart. Leakage currents from all electrical equipment that the patient touched at the same time are likely to more or less sum up at the access point in the patient. This leakage current(s) can be generated by all kinds of electrical equipment with direct or indirect contact with the patient.

According to the general standard (IEC 60601-1 #75) and its references according to microshock (Starmer, 1973 #79), (Watson, 1973 #81) ventricular fibrillation can occur at current below the level of perception. For medical electrical equipment the upper limit for touch current in *normal condition* is 100 µA. Since the patients today can be active and move around the equipment during the dialysis treatment. They can come in contact with other electrical devices. Although many equipments have touch current below 50µA they are allowed to generate 100 µA and in single fault condition 500 µA are tolerated. With grounded dialysis fluid and dialysis access, there is no safety class for electrical equipment with a safety limit for *touch current* that could be considered safe for a dialysis patient with a CDC (below 10 µA in *normal condition* and below 50 µA in *single fault condition*.

During *mains on applied part* (table 13, figure 13 and 14) the measured mean current was 661 µA using blood in the lines. That exposure could be fatal if it were concentrated around a direct *cardiac* application. Using saline, the normal priming solution, the exposure was even greater when the blood pump was set at a flow of more than 80 ml/min. This risk is not within the limits and considerations in (IEC 60601-1 #75) and (IEC 513, 1994 #121). This indicates that the classification of the applied part in a dialysis system intended for use with a central dialysis catheter should be *cardiac floating* (*CF*). The industrial representatives in standardisation committees have been of the opinion that *CF-level* would be difficult and expensive to obtain. However, there already is at least one dialysis machine for intensive care use, for so called continuous renal replacement therapy (CRRT), and it has no ground connection in the dialysis fluid and is classified as *cardiac floating* (Multi Filtrat). Unfortunately, another model of CRRT dialysis system, without ground connection that might had applied with *cardiac floating* limits, was involved in an incident. The CRRT machine generated artefacts on the patient-monitoring system, which resulted in an incorrect diagnosis and unnecessary and potentially harmful treatment when

the artefacts were mistaken for arrhythmias. To avoid recurrence, the fluid pathway of the CRRT machine was grounded. This is an example of a change in construction to avoid one risk (interference due to static electricity) that unintentionally generated a secondary risk (due to leakage current). There the problem that caused the incident was solved (Graansma, 2004 #118), but the solution probably increased the risks related to future leakage currents around the dialysis access.

The 50-µA limit for *cardiac* applications in the general standard (IEC 60601-1 #75) has been disputed during the time I have been doing these studies. Swerdlow et al. studied the effects of current applied in the heart of closed-chest humans. They reported that leakage current caused cardiovascular collapse at levels below the "ventricular fibrillation threshold," and they suggested using 20 µA -- instead of 50 µA -- for leakage currents lasting longer than 5s in the safety standard (Swerdlow, 1999 #80). The mechanisms for cardiovascular collapse at levels below the ventricular fibrillation threshold have been investigated by (Malkin, 2001 #100; Vigmond, 2001 #102).

Paper II also pointed out that the impedance of blood lines and filters, calculated by Deller, is not a constant. The ability for the dialysis system to conduct leakage current can vary considerably with the treatment parameters. The priming solution used at the start and often at the end of treatment provides less impedance than blood. The leakage current through the system during the treatment contains blood with a wide range of concentrations due to ultra-filtration and sometimes dilution during infusion (figure 15-18). Of course, the conductivity of the dialysis fluid and the temperature are also important. During electrical safety analysis of the dialysis access point these parameters should be set to mimic the most dangerous condition (*worst case)* according to the ability of the extracorporeal system to conduct leakage current in a treatment situation. For example, the highest tolerated conductivity and temperature in the fluid system and priming solution or diluted blood in the blood system and no ultrafiltration would conduct the greatest leakage current.

Paper II also pointed out the importance of flow and avoiding air gaps in the system (tubes and filter) during electrical safety analyses which involve measurement of leakage currents in a dialysis access point (Figure 13). If any air gap is present during a measurement the result will not be representative for a treatment situation. Manual safety analysers or manual measuring mode is recommended.

The central dialysis catheter is used with a long time of exposure to the patient. The access point is close to or within the heart of the patient and should be considered as a *cardiac* application. Therefore, it is reasonable that the electrical safety of that applied part for a dialysis system should be classified as *cardiac floating*.

The measuring of leakage current in *blood line*s of a dialysis system should be done with flow in the system.

For dialysis machines classed *B* or *BF* and used together with a CDC, measures are needed to limit potential leakage currents from all electrical equipment that may come in contact with the patient such as. Restrictive use of electrical equipment. Extra redundant protective earth connector have been suggested and separating transformers are available. Frequent electrical safety analyses could be advice. The measures should include all electrical equipment and not only the dialysis machine to reach a safety level, for a dialysis patient with CDC, according to the general standard. Cardiovascular collapses or ventricular fibrillation during haemodialysis using CDC should been handled as an accident or incident and demand a technical investigation of the leakage current. All electrical equipment in the surroundings around the patient should be included in the investigation.

There is also the question about leakage current and a possible effect on the patient's blood (**Paper III**) during dialysis. C3d was chosen as a marker for a possible interaction between leakage current and the blood because it is quite stable and is a reliable marker for complement activation. Complement activation, in turn, then affects many other processes in the blood. To detect any possible effect of current on C3d, even if studied in only a small series of blood samples, a current leakage of DC 1.5 mA was used. This level is within the limit that could be expected for *mains on applied part*. The DC leakage current affected the C3d. Even leakage current of a smaller magnitude would probably enhance the blood-membrane interaction as measured by C3d levels. Paper III found no evidence that haemolysis affected C3d, but the study could not rule out the risk for more side effects for a patient treated with a dialysis device that has an increased level of leakage current as compared to *normal condition*.

In patients exposed to leakage currents in the range up to 34 μA, *normal condition* according to *class B* and *single fault condition* according to *class CF*, **Paper IV** showed a significant change in heart rate, as compared to the *normal condition*, after connection and disconnection of the tubes (electrodes) from the dialysis device to the patient. Normally, one would expect an increase in heart rate when potassium is decreased as well as when fluid is withdrawn from the patient. These data showed the reverse. In addition, some patients experienced more arrhythmia, especially at the end of dialysis. This arrhythmia on some occasions disappeared promptly after disconnection of the dialysis tubes/termination of dialysis. These data do not rule out the possibility that leakage current, even in *normal conditions*, may interfere with the cardiac function, especially in more vulnerable patients.

Distribution of air microbubbles, Paper V

While investigating leakage current the importance of an air gap as resistance was evident. Parallel findings indicated that air could pass the safety

system into the venous blood line together with the blood flowing into the patient. To further clarify this issue, Paper V dealt with the risk for air or gas infusion into the patient from the extracorporeal circulation used in haemodialysis.

For the tested safety systems with the air detector working as a level detector in the venous chamber, the proper installation of the venous chamber according to the manual(s) for the system seems essential. If the venous chamber is mounted with a level detector close to the bottom of the chamber, the probability for adverse events without inducing an alarm is not negligible. Paper V showed that microbubbles of air could pass the safety systems in all tested machines without inducing an alarm because they were small, and not too many occurred at the same time. The fluid level in the venous chamber is of importance for the amount of bubble leakage. A recent in vivo study reports the same situation during standard dialysis treatments (Stegmayr, 2006 #117). This supports the calculations by Polashegg and Levin (Polaschegg, 2004 #54) that small bubbles with less buoyancy follow with the flow down in venous chambers. They also discuss the physics of degassing and redissolution of gas during decompression and compression in a dialysis blood line. Those authors also concluded that small bubbles collapse into the blood before they pass into the patient access, and therefore, according to them, silent passage of air bubbles might not be a direct problem.

The risk for microbubbles and air contamination to the patient is strengthened by Woltman et al. They detected microembolic signals downstream from a dialysis access that could be of gaseous or solid origin using ultrasound (Woltmann, 2000 #14). Rolle et al. also detected microembolic signals (MES) downstream from the dialysis venous access during haemodialysis. The intensity of the MES indicated that they corresponded to synthetic particles or microbubbles, which were not detected by the air-trap (Rolle, 2000 #7). The calibration procedure for the Hatteland equipment used in Paper V showed that, in a deaired system, the tested blood pump and lines did not generate many synthetic particles. In this model no circulation of synthetic material was identified, but a lot of bubbles were identified. In addition, bubbles in blood stay longer “alive” than in water solutions because of coating by protein layers (Barak, 2005 #66). These microbubbles could also cause adverse effects to the endothelia in capillaries and alveoli which might explain the pulmonary morbidity among dialysis patients (Barak, 2005 #66). In case the micro bubble distribution causes adverse effect(s) it will be of importance to prevent or reduce this bubble distribution. This questions has to be further investigated and clarified.

General conclusions

The electrical safety class for dialysis machines intended for use with central dialysis catheters should be classified as *cardiac floating* to achieve an acceptably low risk for of leakage currents. This doctoral thesis provides guidance in verifying compliance.

For *class B* dialysis machines used with central dialysis catheters, other measures are needed to limit these risks. In event of ventricular fibrillation an electrical safety investigation is demanded of all involved electrical equipment. The event should also be reported as an accident or incident according to seriousness. Microbubbles are able to pass the safety system for air infusion without triggering an alarm. This supports earlier calculations by others. The clinical relevance and effect of passage of microbubbles to the patient is disputed (Polaschegg, 2004 #54) (Kurusz, 1995 #41; Barak, 2005 #66). Further investigations are warranted.

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SAMMANFATTNING PÅ SVENSKA

Avhandlingen fokuserar på säkerhetsfrågor som berör blod-dialys (haemodialys) teknik utifrån tekniska frågeställningar. Vid svår njursvikt renas därvid patientens blod i normala fall genom att man via en nål tar blod från ett speciellt förberett blodkärl på armen (AV-fistel eller AV graft). I vissa fall måste man använda en kateter (slang) som läggs in i stora övre hålvenen med spetsen nära hjärtat (Central Dialys Kateter, CDK). Från den nålen eller katetern leds blodet genom dialysslang till en pump som pumpar blodet vidare till en dialysator. I denna (kan jämföras med ett filter) möjliggörs att blod passerar igenom små syntetiska fibrer vilka innehåller ytterst små porer som tillåter att slagg passerar genom dessa till utsidan. På utsidan sköljs dessa slagger vanligtvis bort med en saltlösning så att effekten av rening därmed kan öka. Saltlösningen bereds i dialysmaskinen. När blodet passerat detta filter går det igenom en luftvakt som ska säkra så att patienten ej ska få luft infört i kretsloppet, t.ex. vid skador i systemet. Därefter förs blodet tillbaka till patienten. Denna tekniska utrustning innehåller flera säkerhetssteg som ska garantera att patienterna ej utsätts för hälsorisker. Avhandlingen berör dessa tekniska risker.

I delarbete 1 finner man att dialysmaskinerna alstrar läckström i olika hög grad. Om man förutsätter att dessa endast kommer i kontakt med hud så ligger riktvärdena inom normalområdet. Eftersom patienter kan ha hjärtnära läge genom sin CDK så föreligger andra riktlinjer. Arbetet visar att dessa riktlinjer klarar ej de befintliga dialysutrustningar av vid olika typ av fel.

Delarbete 2 visar att dessa läckström leds från dialysmaskinerna dels genom blodet i slangarna men även den förberedande saltlösningen (priming vätskan). Läckströmen leds i så hög grad att gränsvärdena för hjärtnära utrustning ej tillgodoses vid eventuella fel i utrustningen.

Delarbete 3 studerar om läckström även påverkar blodet menligt så att patienterna kan få bieffekter i kroppen av biologisk karaktär och ej endast av elektrisk. Komplementsystemet är en central funktion i kroppens försvarsmekanismer. Om det aktiveras så är det tecken på en ökad inflammation. Undersökningen visade att en läckström kan medföra en ökad aktivering av komplementsystemet utöver det förväntade.

Delarbete 4 undersökte om läckström under normala dialysbetingelser kan förmodas påverka dialyspatienters hjärtrytm. Undersökning av 45 dialyspatienter utfördes och visade att det sker en ökning av förekomsten av oregelbunden hjärtrytm hos patienterna och särskilt i slutet av dialysen. I vissa fall föreligger en snar förändring i anslutning till att dialysslangarna kopplats till eller från patienten (effekten av elektrisk ledare). Pulsen ändrades hos de som var mer benägna för oregelbunden rytm i samband med start och avslut av dialysen. Undersökningen kunde ej utesluta en negativ effekt av läckström som bidrag till förekomst och ökning av oregelbunden hjärtrytm hos dessa patienter.

Delarbete 5 visar att luftvakten ej är så känslig så att den utesluter mikrobubblor av luft att passera förbi mätutrustningen utan att ge larm. Luften i luftvakten har betydelse dels för elektrisk ledningsförmåga i systemet men kan även ha andra effekter hos patienten om bubblorna ej löses upp snabbt.
Sammanfattningsvis har avhandlingen varit behjälplig till att man inom industrin utvecklar ännu säkrare utrustning och att riktlinjerna för säkerhet skärps ytterligare. Resultaten har även direkt kunnat tillämpas i klinisk praxis för att öka patientsäkerheten.

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