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MEMBRANES FOR HAEMODIALYSIS. WHAT IS MORE IMPORTANT, SIEVING COEFFICIENT OR FLUX?

Key words

Haemodialysis, low- and high-flux membranes, uremic retention solutes, kidney disease.

Abstract

The need for adapting dialysis therapy and technology to special groups is obvious, but it still not realized. Actual observations have proven the notion that avoiding inflammatory stimuli through an improvement of biomaterials, the use of ultrapure water for dialysis fluids has turned out extremely important. Current dialytic strategies do not address the removal of a single molecule but preferentially focus on the elimination of groups or families of molecules from the patient´s blood. The current guidelines for the adequacy of dialysis are all based on the removal of urea and the recommended dose can be achieved with both low and high flux dialysers. The problems associated with inadequate removal of the larger toxins tend to be long term, which makes it much harder to study the benefit of more efficient removal. The more permeable membrane of a high flux dialyser also allows much faster removal of fluid. In haemodiafiltration, rapid removal (and replacement) of fluid is essential, so high-flux dialysers are always used for this type of treatment. There are concerns that easier passage of water through a high-flux could also make it easier for water borne contaminants, particularly endotoxins, to pass from the dialysis fluid back into the blood. This review seeks to define the current scientific and technological factors and how dialysers have changed over the years.

1. Current facts and figures of dialysis

The therapy of kidney patients by haemodialysis with capillary membranes represents a success story for both modern medical device technology and its clinical application. This sounds surprising when referring shortly to historical opinions and statements. When the famous German clinician Franz Volhard, a professor for internal medicine at Halle and Frankfurt, Germany, in the early twenties century became aware of the first clinical experiments on human kidney patients by Georg Haas in Giessen, Germany, he commented: "Dialysis is useless and even dangerous!" Haas, the pioneer of clinical dialysis, later stated, "From the initial idea to the actual realisation of the dialysis method, it was a very long way. I would say, it was a *via dolorosa*!"

Despite these famous statements, haemodialysis with tubular, flat sheet or capillary dialysis membranes has evolved ever since to a routine therapy. Two figures may explain this success. Firstly, the number of dialysis patients undergoing dialysis today adds to a total figure of 2,164,000 patients worldwide in 2012. Secondly, survival of patients suffering from kidney disease and treated by haemodialysis has considerably improved. In the 1980s, the average life expectancy of patients on haemodialysis was less than three years.

Today, and as an example, more than 75,000 patients have a proven record of more than 10 years of therapy in Japan [1]. Following current developments of both, the well-known demographic changes, changes in life style pattern with an increase in diabetes type II, an improved survival of dialysis patients and affordable therapies, we have to assume that the annual increase in the number of dialysis patients adds to a worldwide figure of 7%, whereas the world population increase "only" by 1.1%, annually. Figure 1 depicts the principles of dialysis therapy, its side effects, cost, and the need for capillary dialysis membranes.

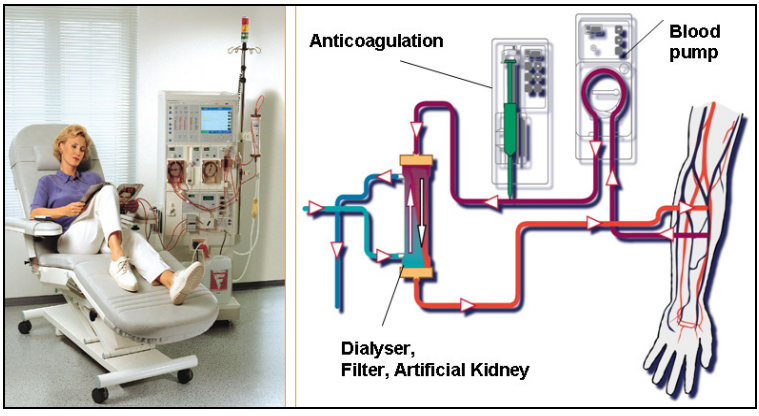

Fig. 1. Scheme for haemodialysis therapy

During the haemodialysis, patients are connected to an extracorporeal blood circuit. An anticoagulant is administered to the blood stream in order to avoid blood coagulation. A routine therapy is performed three times a week for an average time of 4 hours. The longest treatment time is currently observed in Japan with >42 years, similar figures can also be shown for some patients in Europe. The annual estimated cost for dialysis patients in the Western hemisphere is around 60.000 €. The annual production of capillary membranes for dialysis is estimated to surpass 400 million km in 2013.

What has changed throughout the recent years? This question needs to be answered in order to understand current needs for improvement.

1. The main change in dialysis therapy relates to the increasing age of the patient beginning dialysis. In the 1980s and 1990s, the typical beginning dialysis patient was between 40 and 50 years of age. Now, however, the majority of dialysis patients starting this therapy in the Western hemisphere are more than 65 years old. This implies an increase in comorbid conditions, such as atherosclerosis, hypertension, as well as Alzheimer and Parkinson disease. The need for adapting dialysis therapy and technology to this special group is obvious, but not yet realized.
2. Current dialysis techniques primarily focus on the removal of matter across membranes and the regulation of water balance in terms of dry-weight (see below). Actual observations have proven the notion that avoiding inflammatory stimuli through an improvement of biomaterials and the use of ultrapure water for dialysis fluids has turned out extremely important. Standards and norms have been established for the latter by the International Standard Organization (ISO) in 2009 in order to cope with these actual requirements [2–4].

2. Dialysis membranes, performance and flux

Current dialysis procedures focus on the removal of uremic retention solutes, called uremic toxins [5], classified into three categories, such as water-soluble moieties of a low molecular weight, middle molecules, and protein-bound toxins. The molecular weight range of these molecules is between 100 and >60,000. Since entities with higher molecular weights are considered to be of higher importance for removal, many nephrologists have changed their mind and consider high-flux membranes to be the state-of-the-art today. High-flux membranes are defined by an ultrafiltration coefficient to be above 20 [ml/min·mmHg]; whereas, low-flux membranes are characterized by an UFC <20 [ml/min·mmHg].

Thus, high-flux membranes have a world market share of 67% today in 2013. A second observation may be noted. Whilst, dialysis membranes based on the natural polymer cellulose (regenerated cellulose and its derivatives,

Cuprophan®, Hemophan®, and cellulose acetate) dominated the dialysis market in the 1980s and 1990s, the majority of dialysis membranes used in the world is based on synthetic polymers, such as polysulfone (PSu), polymethylmethacrylate (PMMA), and polyacrylonitrile (PAN). Their market share in 2013 is found to be 93% [6].

When discussing the removal of uremic retention solutes, pore size dimensions come into the play. Pore sizes of dialysis membranes have been assessed. Their diameter has been determined to be in the range of >1 nm for low-flux synthetic membranes and of >3 nm for high-flux synthetic membranes. It is assumed that the pore size distribution is rather small, and thus a molecular weight cut-off has been defined, while saying that a dialysis membrane should exclude the passage of the important protein albumin (MW: 66,470 D).

However, the passage or retraction of molecules during haemodialysis is still a matter of debate. With the help proteome-analysis, Weissinger et al. [7] were able to identify more than 1300 different polypeptides in the ultrafiltrate of high-flux membranes and still more than 1000 different polypeptides in the ultrafiltrate of low-flux membranes. If we assume that the composition ultrafiltrate in dialysis should also represent the composition of urine in a healthy patient, it turns out to be extremely difficult to associate uremic toxicity to a single molecule in this context. The question about the identity of the uremic toxin still remains to be answered.

Thus, engineers and membrane scientists are confronted with a dilemma, once they intend to develop new membranes. What should be the optimal removal characteristics, and which molecule should be targeted? The literature refers to about 100 different uremic retention solutes [5], proteomic analyses has determined more than 1300 peptides in the ultrafiltrate [7], and nephrologists are never content with the removal capacity of modern membranes and evidence that kidney failure can be attributed to a single molecule has not yet been provided. Consequently, current dialytic strategies do not address the removal of a single molecule but preferentially focus on the elimination of groups or families of molecules from the patient´s blood.

What is the current consequence of these considerations?

The expert group of the European Dialysis & Transplantation Association (EDTA-ERA) has recently published a series of guidelines for kidney therapy with dialysis membranes [8]. The EDTA expert group recommends maximising middle molecule removal (molecular weight range between 10.000–20.000 D) with the use of high-flux synthetic membranes and applying convective therapies. This leads us to the question of how to improve the transport of large molecules across a dialysis membrane.

Uremic retention solutes with low molecular weights, such as urea, potassium, or phosphate, diffuse across the dialysis membrane following their

concentration gradient. This was first described by Adolph Fick in 1856 and is known as "Fick´s law of diffusion" [9]. It is represented by the following:

$$J = -D \cdot A \cdot \frac{dC}{dx},$$

where J: flux of the solute, D: the diffusion coefficient [cm²/sec], A: the area of diffusion (membrane surface area), dc: the concentration difference of the solutes across the membrane, and dx: the thickness of the membrane.

Therefore, improving solute clearance by diffusion has always aimed at increasing both the membrane´s surface area and the concentration difference, while engineering the membrane thickness as small as possible.

Large molecules merely move along a concentration gradient. There transport is promoted by ultrafiltration. This can be easily understood once we associate this transport to convective forces, bitterly described as "solvent drag." The underlying relation is described by the following:

$$C = SC \cdot Q_F,$$

where C: convective clearance, SC: sieving coefficient of the membrane, and Q_F: ultrafiltrate flow.

Thus, solvent drag can be improved by increasing both the sieving coefficient of the membrane, i.e. using high-flux membranes, and ultrafiltration flow, i.e., by convective therapies, such as haemodiafiltration. Figure 2 depicts the change of sieving coefficient (SC) to larger molecular weight moieties when switching from low-flux to high-flux dialysis membranes. In addition, this SC-curve is further moving towards larger molecular weights, once membranes for liver therapies are used.

There is a positive trend towards the use of high-flux membranes following clinical observation (Fig. 2). Molecules located in the "zone of permeability" are able to pass across the membrane, while the others positioned in the "zone of impermeability" do not have the ability to do so.

Figure 3 shows that Q_F can be risen by means of an increased transmembrane pressure (TMP). When switching from low-flux membranes to high-flux membranes, the ultrafiltration rate is increased using a reduced TMP. Ultrafiltration rates depend on transmembrane pressure (TMP). With the use of high-flux membranes, higher UF-rates can be obtained while using a lower TMP. PSu membranes of comparable surface areas are depicted for both low- and high-flux membranes (Fig. 3).

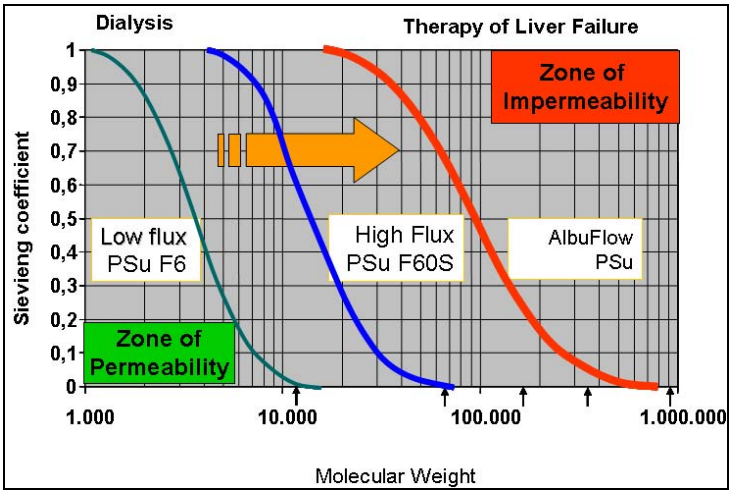

Fig. 2. Sieving coefficient curve for low- and high-flux membranes used for haemodialysis and liver failure therapy

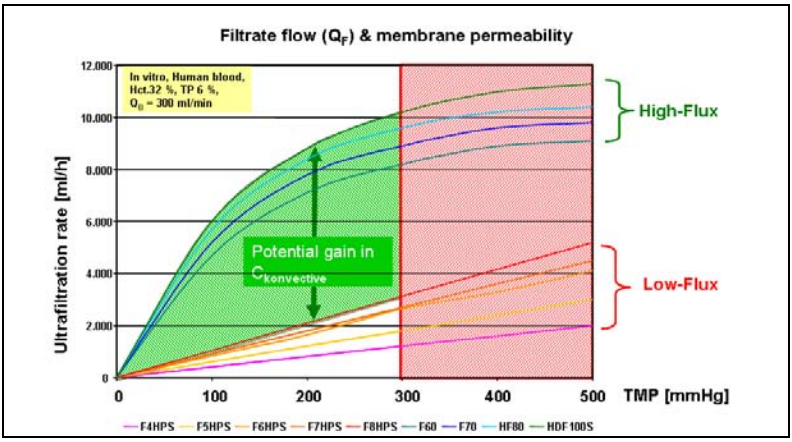

Fig. 3. Filtration profiles for low- and high-flux membranes

The increase in convective flux in clinical haemodiafiltration (HDF) has led to an improved patient survival as shown in a recent publication by Francisco Maduell and colleagues in Spain [10]. In the long term, a randomized and controlled study with more than 900 patients, comparing the survival of dialysis patients treated either with high-flux membranes under standard conditions and high-flux membranes in haemodiafiltration with large substitution volumes (>20L), indicate that survival could be increased within three years by about 30%. Obviously, Paracelsus is still correct, when he outlined in 1538, “Only the dose matters!”

How to obtain large ultrapure substitution volumes at reasonable cost? The answer is "online preparation of dialysis fluid," as shown in Figure 4. The substitution fluid is taken directly from the preparation line of the dialysis fluid following the reverse osmosis unit. Ultrapure water is guaranteed by the use of endotoxin filters. As has been shown by Weber and colleagues [11], membranes based on the polysulfone polymer are able to guarantee that endotoxins are unable to cross the membrane barrier and can, therefore, be used as filters for the preparation of ultrapure substitution fluids (see also below).

Following these observations, efficient dialysis therapies of today must be used with a high dose of ultrafiltration associated with large substitution volumes.

In online HDF, ultrapure substitution fluid is directly obtained from the dialysate circuit. Ultrafilters that contain PSu-membranes guarantee that possible endotoxin contaminations remain below detection limits.

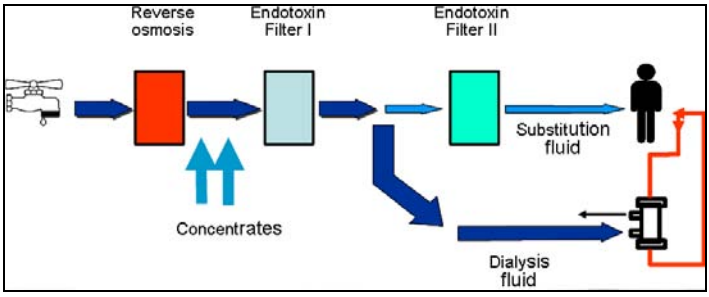

Fig. 4. Online haemodiafiltration (online HDF) with high substitution volumes (>20L) has turned out to be advantageous for patients survival

3. Paradigms for membrane application

Dialysis membranes must not be considered a "one-way-street." Transport always goes in both directions, i.e. from the blood compartment to the dialysate compartment and vice versa. This is extremely important. Once dialysis water may be contaminated by bacterial germs or their degradation products, such as endotoxins, the transfer of these moieties from the dialysate water to the blood stream of the patient provokes inflammatory reactions that might turn out deleterious during long-term application. We have to keep in mind that treatment times have now reached 10 years and longer for many uremic patients.

Fortunately, polymers, such as polysulfone (PSu) or polyamide (PA) offer adsorptive capacities for endotoxins due to their molecular structure. Michael Henrie and colleagues used endotoxins labelled with fluorescent dyes to study the adsorption of these molecules in PSu-membrane walls [12]. They were able to show that this polymer is capable of adsorbing endotoxins and prohibiting their movement to the patient´s blood stream. Similar experiments have been successfully performed in Japan [13].

As described already above, standards for water quality in dialysis have been published as ISO norms, and authorities in Japan and the USA follow these regulations. In 2009, specific regulations have been published for the use of water for haemodiafiltration (HDF) (Table 1).

Table 1. Survey of norms for water quality in haemodialysis

The fluid	Water	Concentrates	Dialysis fluid (ultrapure)	Online HDF Substitution sol.
Standard	European Pharmacopeia 2005	European Pharmacopeia 2005, EN 13867:2002	American Association for Medical Instrumentation, 2004	ISO 11663:2009
Germ count, [CFU/ml]	<100	<100	<0.1	$<10^{-6}$
Endotoxin level, [IU/ml]	<0.25	<0.5	<0.03	<0.01 (below detection level)

Finally, when considering one polymer or the other as the best-suited membrane polymer in haemodialysis, sterilisation issues have become an important parameter. Figure 5 depicts how dialysers are sterilized has changed over the years. Currently, 62% of dialysers marketed in Europe are sterilized by steam, followed by 34% that are sterilized by γ-rays. Ethylene oxide sterilisation technology has become negligible with 4% in Europe. Steam sterilisation has become the major technology in recent years followed by γ-irradiation. Ethylene oxide has lost a considerable market share. Similar figures can be shown for the world market [14].

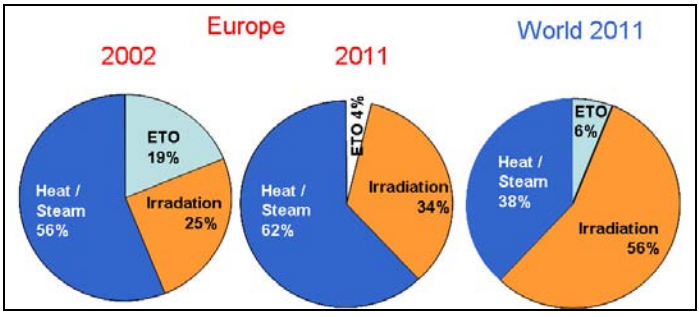

Fig. 5. Sterilisation procedures applied to dialysers in Europe and the world

Conclusion

High-flux membranes allowing large ultrafiltration volumes, such as in online HDF, have considerable advantages for patient survival, given that the membrane polymer has adsorptive characteristics for endotoxins. The

identification of uremic toxins still refers to an unanswered question for membrane improvement and the search for new markers for better prediction of clinical risks and the efficiency of novel treatments should be a central issue for further developments. Ultrapure water is required when using high flux dialysis. Therefore, high flux dialysis should be recommended for patients at high risk and the only factor hampering the use of high flux in all patients is the small difference in cost between high- and low-flux filters in a limited group of patients and the cost of ensuring a supply of ultrapure water. As such, it makes sense to recommend using high flux in all patients, even if the evidence to support the use of high flux in patients with low risk is lacking.

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Membrany do hemodializy. Co ma większe znaczenie – współczynnik przesiewalności czy strumień filtracji

Słowa kluczowe

Hemodializa, membrany typu „high flux", membrany typu „low flux", retencja soli uremicznych, niewydolność nerek.

Streszczenie

Oczywista, chociaż wciąż niezrealizowana, jest konieczność dostosowania procesu dializy do potrzeb poszczególnych grup pacjentów z niewydolnością nerek. Szczególnie ważne jest zapobieganie powstawaniu bodźców zapalnych. Osiąga się to poprzez stosowanie biozgodnych materiałów na membrany i ultraczystej wody do wytwarzania płynu dializującego. Obecna strategia dializy skupia się na eliminowaniu preferowanych grup lub rodzin substancji z krwi pacjenta i pomija usuwanie pojedynczych molekuł. Aktualne wytyczne dotyczące skutecznej dializy oparte są na kryterium usuwania mocznika i mogą być zrealizowane za pomocą dializatorów wyposażonych w membrany niskiej (low flux) lub o wysokiej filtracji (high flux). Usuwanie jedynie toksyn o większych rozmiarach molekuł (high flux) wydaje się mieć znaczenie długoterminowe, co powoduje, iż analiza potencjalnych korzyści wynikających z usuwania także toksyn o małych molekułach (low flux) jest trudna do przeprowadzenia. Stosowanie dializatorów wyposażonych w membrany „high flux", o wyższym strumieniu filtracji, skutkuje także szybszym usuwaniem płynu z organizmu człowieka. W procesie hemodiafiltracji, szybkie usuwanie (i uzupełnianie) płynów z organizmu jest niezwykle istotne, co powoduje, że w dializoterapii z reguły są stosowane dializatory z grupy „high flux". Niemniej istnieje obawa, że ułatwiony transport wody poprzez membranę „high flux" może sprzyjać także transportowi substancji szkodliwych z wody użytej do wytwarzania płynu dializującego do krwiobiegu – dotyczy to w szczególności endotoksyn. W niniejszym artykule, stanowiącym przegląd stanu wiedzy w tym zakresie, podjęto próbę zidentyfikowania kluczowych przesłanek naukowych i technologicznych w zakresie realizacji dializoterapii oraz sformułowania odpowiedzi na pytanie, który ze sposobów dializoterapii, „high flux" czy „low flux", jest skuteczniejszy.