

## Dialysis membrane: from convection to adsorption

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### Abstract

Although patients undergoing dialysis have a complex illness, there are compelling reasons to believe that the inadequate removal of organic waste is an important contributing factor to the illness itself. This paper focuses on the transport phenomena that occur within a dialyser. An attempt is made to clarify how transport phenomena are related to the performance of a dialysis session and how they depend on the membrane characteristics. Our study offers some discussion points on the complex issue of defining what the best parameters could be in comparing the efficiency of different membranes. The new high-flux dialysers have improved larger-molecule clearance and biocompatibility. Membrane performance is a very hard process to evaluate, and different membranes can only be compared by establishing adequate points of comparison. At the same time, the points of comparison themselves may change depending on the type of co-morbidities of the specific patient who is considered for membrane selection. This editorial (together with all the papers presented in this issue) seeks to focus on the membrane's own merits in improving the dialysis therapy.

**Keywords:** adsorption; convection; dialysis membranes; diffusion

### Introduction

Although patients who undergo dialysis suffer from a complex illness, there are compelling reasons to believe that the inadequate removal of organic waste is an important contributing factor to the illness itself [1,2]. Nevertheless, randomized trials examining the impact of increased clearance of traditional uraemic solutes have yielded disappointing results [3,4]. The Haemodialysis Study (HEMO) failed to show any significant reduction in mortality with an increased dialysis dose [3]. In contrast, in a *post hoc* analysis, the level of  $\beta_2$ -microglobulin (representative of middle molecules) was found to be predictive of the relative mortality risk [5]. Furthermore, the results from a recent prospective, randomized and controlled study [6] comparing online haemofiltration (HF) and haemodialysis (HD) have shown a significant difference in mortality in favour of HF, in spite

of a very low Kt/V in the convective procedure ( $1.07 \pm 0.06$  with HF vs  $1.42 \pm 0.06$  with HD).

This further confirms a series of observational studies that had already demonstrated that, in terms of patient survival, techniques capable of increasing middle-molecule clearance, such as haemodiafiltration (HDF), hold an advantage over the conventional HD [7,8]. In recent years, scientists have been increasingly convinced that a large number of high-molecular-weight toxins increase their plasma concentration during uraemia and are responsible for a number of dialysis co-morbidities, such as an immune system imbalance, itching and so on. Hence, the interest of clinicians, followed by that of industry, in a new class of dialysis membranes aimed at enhancing the transport capabilities (clearance) of middle, large and even protein-bound molecules by using all the available membrane separation phenomena: diffusion, convection and adsorption, by designing and developing both high-performance 'high-flux' dialysers and 'protein-leaking' dialysers. By 'protein-leaking dialyser', we mean the dialyser capable of removing large molecules on the basis of convection enhancement (super-flux) or adsorption capabilities.

### From Low- to Middle-Molecular-Weight Toxin Removal: The Convective Transport

The main aim of a dialysis filter is to better reproduce the physiological process of glomerular ultrafiltration. Dialysis membrane clearance, however, is based on concentration differences rather than the convective separation of solutes and low-molecular-weight proteins from large serum proteins and blood elements. In an attempt to replicate glomerular ultrafiltration and the removal of 'middle molecules' in high-flux dialysers, a significant increase in porosity has been obtained in order to remove large-molecular-weight solutes. Hand in hand with the increase in porosity and the efficiency of mass transfer, there is a concomitant increase in the membrane ultrafiltration coefficient. The optimization of these properties has produced dialysers that allow for rapid solute fluxes and clearance profiles akin to those achieved across human glomeruli. The other significant feature of high-flux membranes, particularly

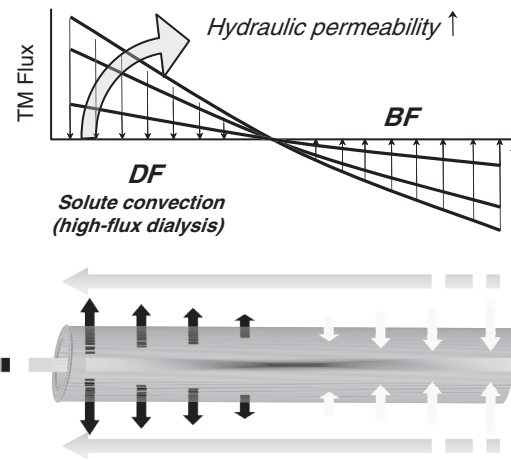
the synthetic membranes, is that they tend to be more biocompatible.

The properties of a dialyser, on the physical or biocompatible level, are related to its microstructural and macrostructural characteristics [9]. Microstructural aspects refer to the characteristics acting on the molecular scale (i.e. the chemical modification of the side chains, thickness of the hollow fibre wall, membrane porosity). Macrostructural properties refer to the properties acting on a length scale greater than molecular dimensions (i.e. surface area, packing density, boundary layers adjacent to the membrane–solution interfaces, shape and configuration of the hollow fibres, spacing and sterilization techniques).

The so-called ‘high-flux’ membranes are prepared with hydrophilic base materials, including polyacrylonitrile, polysulphone, polyaryethersulphone, polyamide and polymethylmethacrylate with various hydrophilic components. Nevertheless, there are some examples of cellulose-based high-flux membranes, such as cellulose triacetate [10].

In view of the large hydraulic permeability of synthetic membranes, the bidirectional water flux across the dialysis membranes is maximized (Figure 1). Under conditions of diffusive HD, at the proximal end of the dialyser, the sum of hydrostatic osmotic and oncotic pressure results in a large water movement from the blood to the dialysate. At the distal end of the hollow fibres, the net water movement is from the dialysate into the blood—the so-called ‘backfiltration’. Nowadays, most dialysis machines are equipped with an automatic ultrafiltration control system. Hence, the large volume of water leaving the blood and crossing into the dialysate at the proximal side is offset by the water backfiltration from the dialysate to the blood on the distal side. This ‘internal filtration’ process may enhance the small- and large-molecule clearances. However, a larger and more important amount of small- and middle-molecule removal can be obtained in HDF [10]. In HDF, with the further use of dialysate, a relatively free ultrafiltration is allowed, and there is a large volume of ultrafiltrate with no significant backfiltration from the dialysate. The amount of ultrafiltrate that offsets the fluid loss that the patient has to shed must be replaced by the direct intravenous substitution fluid infusion. In HF, all the water movements are from the blood to the dialysate compartment, and solute clearance is by convection alone. Moreover, the removal with large-pore (i.e. high-flux) membranes is related to diffusion, convection and, in some cases, as discussed in the following, adsorption [11]. This mechanism adds capacity to remove components with a pathophysiological potential, such as  $\beta_2$ -microglobulin, cytokines and protein-bound uraemic toxins (PBUT).

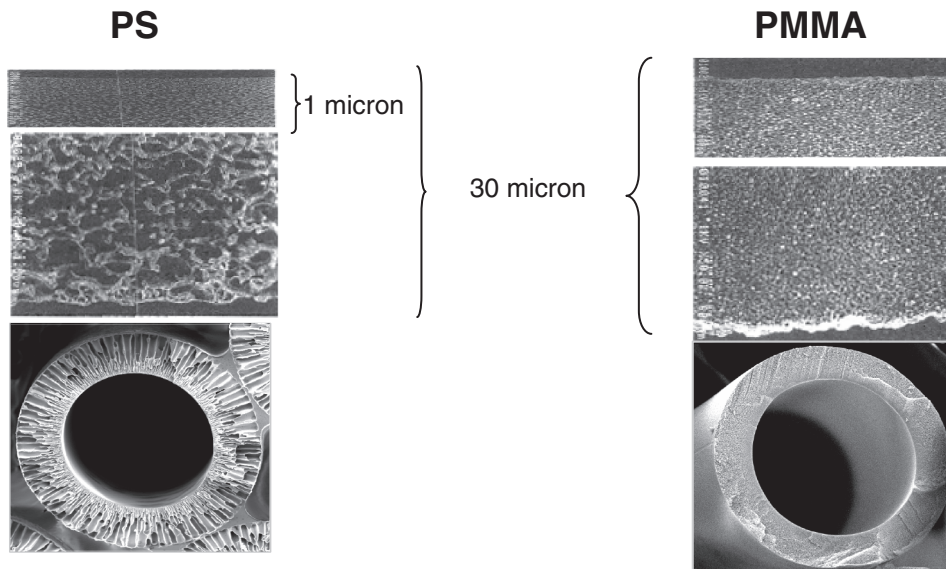
High-flux dialysers have an improved larger-molecule clearance and biocompatibility [1,2]. The latter is reflected in the lower activated serum complement levels, a lower intradialytic reduction in white cell counts, a lower oxygen radical production, and a reduction in the release of interleukin-1 and tumour necrosis factor in the course of dialysis [12]. On the other hand, these membranes may remove generated cytokines from circulation, either by convection or adsorption. This reduced cytokine production along with decreased bioincompatibility has been used to account for the fewer dialysis-related symptoms, in particular



**Fig. 1.** Diagram of the internal backfiltration (A) and backdiffusion (B) phenomenon in a high-flux dialyser. A schematic description of the pressure plays that leads to the onset of the backfiltration phenomenon. At the filter blood inlet, there is a water movement from the blood to the dialysate, due to the interplay of the hydrostatic, osmotic and oncotic pressures, as well as the dialysate pressure. At the outlet, the equilibria are inverted: the dialysate pressure and oncotic pressure grow, while the blood hydrostatic pressure is reduced. Thus, the fluid is transferred from the dialysate to the blood.

less intradialytic hypotension observed with high-flux techniques [13]. Preliminary studies with high-flux dialysers have shown varying results upon the haemoglobin response, the increased  $\beta_2$ -microglobulin clearance, and a reduction in advanced glycation end products, peroxidation products and homocysteine levels [10,11,13,14]. However, only a few of these studies are randomized, none of them is blind and the comparison is often made with older-generation low-flux membranes [15]. Moreover, there are no clear and unequivocal data showing that improved biocompatibility and excellent larger-molecule clearance translate into improved patient symptoms and better survival. The same can be said of techniques such as HF or HDF based on the use of high fluxes attainable with high-flux dialysers. On the latter issues, however, a whole strand of literature is coming out in favour of the convective techniques, which is not only based on observational studies, as in the past, but on randomized controlled trials. The recent Membrane Permeability Outcome (MPO), a study in which 647 incident dialysis patients were randomly allocated to high-flux or low-flux dialysis membranes, demonstrated that the improved  $\beta_2$ -microglobulin clearance led to an improved survival in those with albumin  $<4$  g/dl, with a 37% reduction in the mortality risk with the high-flux membrane [16]. The European acetate-free biofiltration (AFB) study [17] has shown better survival in patients with mild hypertension treated for 4 years by means of an acetate-free biofiltration as compared with conventional dialysis. Even the online HF performed by a high-flux dialyser does not only appear to have a superior cardiovascular stability but also a better survival as compared with HD [6].

Recently, the idea that the removal of a distinct class of uraemic toxins, such as  $\beta_2$ -microglobulin, factor D, leptin and adrenomedullin, while minimizing albumin loss, could improve treatment outcome in end-stage renal disease (ESRD) patients has led to the development of a series



**Fig. 2.** Synthetic membranes such as polysulphone are usually asymmetric, which means that, on a membrane thickness of 30 microns, a layer of 1 micron only is responsible for the separation process, while 29 microns have structural functions only. PMMA, conversely, is a symmetric membrane, in which the whole thickness is involved in the separation process allowing middle-molecule adsorption.

of dialysers known by the name of ‘super-flux’. Super-flux dialysers have been designed to maximize convective transport by increasing the pressure drop along the membrane fibres.

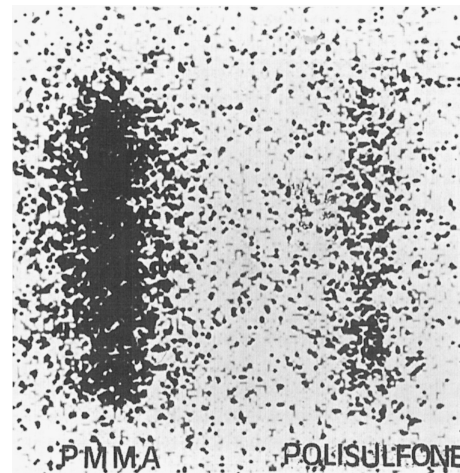
### High-Molecular-Weight Toxin Removal: Adsorption

The same toxic substances directly bind with protein (PBUT), originating from high-weight complexes (50–200 kDa) potentially involved in important uraemia comorbidities such as itching and altered immune response [18–21]. Removing PBUT from the blood by means of diffusion and convection (containing the albumin loss) is virtually impracticable; however, PBUT can be removed by using the adsorptive properties of particular biomaterials.

A number of adsorption techniques are well known in the world of blood purification: with selectivity or without selectivity, working with plasma or whole blood, consisting of fibres or solid spheres. In this context, only dialysers made with a synthetic membrane having adsorption capabilities should be taken into account.

Synthetic membranes, such as polysulphone, are usually asymmetric (Figure 2—left); this means that, on a membrane thickness of 30 microns, just a 1-micron layer is responsible for the separation process, while 29 microns have structural functions alone. Thus, we can improperly define such membranes as ‘2D membranes’ that can separate solutes by convection and diffusion alone.

Another class of synthetic membranes, i.e. polymethylmethacrylate (PMMA), is characterized by a symmetric structure (Figure 2—right). In this case, the pores are larger, longer and winding, designed to trap different substances. Moreover, in some cases, an ionic treatment of the inner surface may enhance this adsorption mechanism. PMMA adsorption capabilities have been demonstrated



**Fig. 3.** Scintigraphic image (from Campistol *et al.*[22]) of the dialyser (PMMA vs polysulphone) after the end of the dialysis session, using  $^{131}\text{I}$ -labelled  $\beta_2$ -microglobulin.

both *in vivo* and *in vitro*. Among others, Campistol and co-workers [22] have shown that PMMA BK removes  $\beta_2$ -microglobulin by adsorption, while high-flux polysulphone does so by filtration, using radiolabelled  $\beta_2$ -microglobulin and scintigraphic analysis (Figure 3). Kawanishi [23] measured interleukin (IL)-6 removal from different membrane mini-modules isolating convection and adsorption contributions.

### Enhanced Convection and Adsorption in the Clinical Setting: Present and Future Scenarios

Super-flux dialysers based on enhanced convection or adsorption, at least on the theoretical plane, could be widely

used in clinical situations in which, apart from toxins of small molecular size, large quantities of mediators and toxic products are also produced, with a negative biological effect at a middle–high molecular weight, or which are rapidly bound to the proteins. These filters make it possible to treat septic patients with acute renal failure and simultaneously provide the control of uraemia and fluid status as along with cytokine removal [24]. In the field of haematological diseases, particularly in myeloma, early yet encouraging results have already been obtained in the light chain removal [25]. HD with super-flux dialysers has been shown to be more effective than high-flux dialysis in reducing plasma homocysteine [26].

However, an important side effect of super-flux dialysers, or at least some of them, might be plasma protein loss, and not only that of albumin but also coagulation factors, growth factors and hormones [27]. Hence, before opening the door to these new filters, it will be necessary to develop strategies in use to achieve a good clearance of waste and harmful products, while minimizing the risk of a huge loss of substances, such as proteins, useful for our organism's biochemical homeostasis.

*Conflict of interest statement.* G.G. is the Sales and Marketing Director of Estor S.p.A, a company involved in the promotion and commercialization of Toray medical devices.

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