Hemodialysis Membranes

Ronco C and Clark WR. Hemodialysis membranes. *Nat Rev Nephrol*. 2018; 14:394-410. doi: 10.1038/s41581-018-0002-x.

BACKGROUND

Hemodialysis is an extracorporeal process in which the blood is cleansed via removal of uremic retention products by a semipermeable membrane. Traditionally, dialysis membranes have been broadly classified based on their composition (cellulosic or non-cellulosic) and water permeability (low flux or high flux). Incorporation of innovative manufacturing processes have led to consideration of other parameters for classification including new permeability indices, hydrophilic vs hydrophobic balance, adsorption capacity, and electrical potential.

AIM

To provide clinicians with an updated analysis of dialysis membranes and dialyzers, highlighting online hemodiafiltration and new therapies such as expanded hemodialysis, and considerations governing the clinical acceptable balance between large-solute clearance and albumin loss for extracorporeal therapies.

OVERVIEW

History of Dialyzers

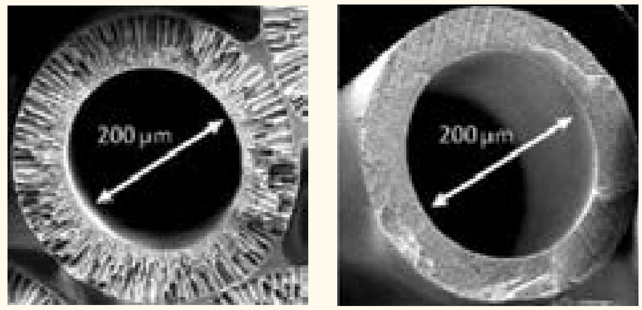
The availability of devices like the rotating drum kidney, coil dialyzer, and Kiil dialyzer allowed the use of dialysis to grow but it had many limitations. Of note were the high blood compartment volumes required and the inefficient mass transfer characteristics. In the late 1960s the hollow-fiber artificial kidney revolutionized dialysis by providing improved geometry in terms of blood rheology and solute mass transfer. Specific advantages included an improved surface-area:volume ratio in the blood compartment and decreased boundary layer effects with acceptable end-to-end pressure drops. These made the hollow-fiber configuration the main choice in dialysis. At present (2018) approximately 300 million hollow-fiber hemodialyzers are utilized worldwide.

History of Hollow-fiber Membranes

Categorization of dialysis membranes have traditionally been based on their material composition, either cellulosic or synthetic membrane groups. The use of unmodified cellulosic membranes has dropped precipitously over the past decades, to the point of effective absence from the market (i.e. no longer manufactured). Dialyzers with synthetic high-flux membranes now dominate clinical practice.

Synthetic membranes were originally developed for a dialysis application more than 40 years ago to address the relative bioincompatibility and limited permeability of unmodified cellulosic membranes. The first highly permeable membrane, sulfonated polyacrylonitrile (**AN69**), was introduced in the late 1960s. Subsequent development included polysulfone membranes, which had very thick walls (75-100 µm), and despite higher permeability, were not conducive to diffusion-based therapies. Their use was originally limited to convection-based hemofiltration. Modern synthetic membranes (e.g. polyethersulfone (PES)) have thinner walls (20-50 µm) and higher permeability, permitting diffusion and convection to be employed simultaneously. Please see Figure 1.

Polysulfone Wall thickness 75-100 µm | **Polyethersulfone Wall thickness 30 µm**



Polysulfone:
- > Synthetic polymer-asymmetric
- > Hydrophobic structure
- > High hydraulic permeability
- > HIgh sieving properties
- > Exclusively used for convective therapy (hemofiltration)

Polyethersulfone:
- > Synthetic polymer-microporous
- > Hydrophobic-hydrophilic
- > High hydraulic permeability
- > HIgh sieving properties
- > Combination diffusive-convective therapy (high-flux hemodialysis and hemodiafiltration)

Figure 1. Physical Characteristics of Synthetic Membranes. Adapted from Ronco and Clark.

The majority of synthetic membranes (e.g. PES) used for contemporary dialysis have an asymmetric structure. In contrast, synthetic membranes similar to cellulosic membranes (e.g. **AN69** and poly (methyl methacrylate) (PMMA)) are structurally symmetric.

New Membrane Classification

Focus on Solute Permeability Properties

Conventional membranes that are used in hemodialysis generally provide high clearance for small solutes such as urea (60.055 Da)[1] and creatinine (113.12 Da)[2]. However, membranes in current use provide limited clearance of compounds >10 kDa. Although these membranes have relatively large mean pore sizes (compared to unmodified cellulosic membranes), they still offer mass transfer resistance to the diffusive removal of large solutes. Furthermore, (membrane) fouling has a considerable effect on convective solute clearance, especially for molecules >10 kDa.

In typical hemodialysis operating conditions, the water permeability characteristics for a standard high-flux dialyzer result in a fairly large drop in the blood compartment axial pressure during treatment. The pressure drop is sufficiently large that the blood compartment pressure is less than the dialysate compartment pressure in normal operating conditions.

There is a point at which the ultrafiltrate begins to be driven from the dialysate to the blood as opposed to the 'standard' (blood-dialysate) direction. This combination of filtration and backfiltration, termed internal filtration, is considered to be the predominant mechanism by which larger compounds are removed during standard high-flux dialysis. Maximizing the extent of internal filtration during high-flux dialysis through a combination of increased membrane permeability (increased pore size) and higher axial blood compartment resistance (decreased hollow fiber inner diameter) can provide clinically meaningful increases in large solute clearance.

Classification schemes that focus even more on solute permeability properties have been proposed. These new classification systems acknowledge the importance of larger molecules and the need to incorporate additional membrane classes that have extended removal spectra. High-flux and ‘protein leaking’ membranes have been defined based on a combination of water permeability, beta-2 microglobulin (β2m) (12 kDa)[3] removal factors (sieving coefficient (SC) or clearance) and albumin (65 kDa)[3] parameters (SC or amount cleared). In this system, the high-flux class is defined by a water permeability of 20–40 m/h/mmHg/m², a β2m SC of 0.7–0.8 and albumin loss of < 0.5 g (on the basis of a 4 h hemodialysis treatment), whereas the same parameters defining a protein-leaking membrane are >40 m/h/mmHg/m², 0.9–1.0, and 2–6 g, respectively. Although not explicitly stated, these values correspond to ‘virgin’ membrane performance and do not reflect potential diminutions during treatment as a result of secondary membrane effects.

Medium Cut-Off and High Cut-Off Membranes

Two new membrane classes, (**MCO** membrane) and (**HCO** membrane), have been proposed, extending the earlier classification scheme.

The **HCO** class is characterized by a substantial increase in water permeability (relative to both high-flux and the protein-leaking classes) and a virgin β2m SC of 1.0. However, the high albumin loss rates associated with this membrane class generally preclude their long-term use for patients with end stage renal disease (ESRD). In addition, this membrane has been used for fairly limited time periods in clinical conditions in which the potential risks due to albumin loss are considered reasonable to the potential benefits (e.g. for patients with myeloma-associated acute kidney injury to target augmented removal of free antibody light chains (kappa interleukin light chain (22.5kDa)[3]; lambda interleukin light chain (45 kDa)[3]). The role of HCO membranes in clinical practice remains unclear.

In comparison to high cut-off membranes, the medium cut-off class is intended to preserve the β2m sieving characteristics and to improve the clearance of other large-molecular-weight solutes (for example, free antibody light chains) while demonstrating a marked reduction in albumin permeability. The **MCO** membrane represents the basis for a new diffusion-based therapy called ‘expanded hemodialysis’.

Molecular Weight Retention Onset (MWRO)

A new solute removal parameter for the characterization of modern highly permeable membranes has been proposed. This new parameter, the ‘molecular weight retention onset’ (MWRO) index, is generated from a standard solute sieving coefficient versus molecular weight profile, as with the classic molecular weight cut off (MWCO). The MWRO is defined as the molecular weight at which the SC value first reaches 0.9 (whereas the MWCO corresponds to a SC of 0.1). This approach was rationalized by suggesting that the MWRO index, which provides insights about pore size distribution, supplements information provided by the MWCO, which is primarily correlated with mean pore size. The steepness of the sieving coefficient versus molecular weight profile is determined mostly by the proximity of these parameters. A classification scheme has been proposed in which the MWCO and MWRO are utilized in combination to define different dialyzer classes.

Insights

Although extending the removal spectrum of modern dialysis membranes beyond the capabilities of standard of high-flux devices is highly desirable, the design challenge is to maximize the removal of large uremic toxins while also maintaining albumin losses for long-term treatment of patients with ESRD. The updated classification system includes the previously mentioned **MCO** membrane that incorporates high-retention onset (HRO) properties. This membrane class may hold promise in achieving acceptable albumin losses.

Pore size distribution curves (Fig. 2 a-c) and the corresponding sieving coefficient profiles (Figure 2d) and the corresponding sieving coefficient for three classes of membranes (high flux, **MCO** membrane, and **HCO** membrane) reveal that as the separation between MWRO and MWCO decreases, the profile of the curve becomes steeper, resulting in increased removal of large uremic toxins and decreased loss of albumin. As shown in Figure 2d, the **MCO** membrane curve is the steepest of the four curves, stopping before the molecular weight (MW) of albumin, while the **HCO** membrane extends beyond albumin's MW.

By virtue of larger pore sizes, increased membrane diffusivity is one mechanism by which the removal of large solutes is augmented with the **MCO** membrane class of dialyzers relative to standard high-flux membranes. Although hemodialysis using this type of dialyzer is technically diffusion-based, most large-solute removal still occurs by convection through the mechanism of internal filtration. For **MCO** membrane and other dialyzers, the effect of this mechanism is intentionally augmented through increases in the mean pore size and reductions in the inner diameter of hollow fibers. Preliminary data suggest that this class of dialyzers has depuration capabilities that approach those of online post-dilution hemodiafiltration without the need for (exogenous) substitution fluid administration.

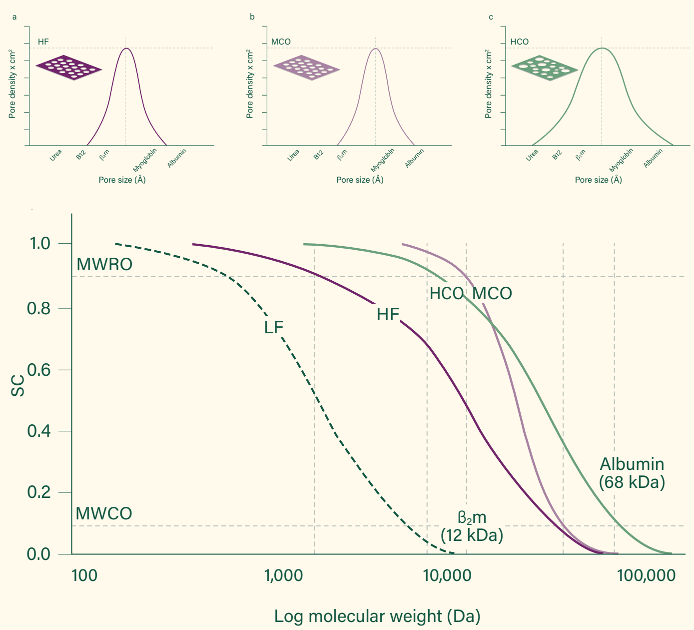


Figure 2. Performance characteristics of hemodialysis membranes derived from a suggested new classification system. Pore size distribution curves are schematically depicted for three classes of membranes, high flux (HF; part a), medium cut-off (**MCO** membrane; part b) and high cut-off (**HCO** membrane; part c), as well as their sieving coefficient (SC) profiles (part d). As the interval between molecular weight retention onset (MWRO) and molecular weight cut-off (MWCO) decreases, the profile of the curve becomes steeper, increasing the removal of large uremic toxins (such as β2-microglobulin (β2m)) while decreasing the loss of albumin (part d). A low-flux (LF) membrane is shown for comparison. Figures adapted from Ronco and Clark.

CONCLUSIONS

The bidirectional process of mass separation between the blood and the dialysate involves several mechanisms of interaction between the fluid phases and the membrane barrier. The nature of the fluid phases, the characteristics of the solutes and the structure of the membrane represent a combination of elements that are involved in the final process of mass separation and dialysis.

The development of a unifying classification system for dialysis membranes is extremely complex and must be multidimensional. Proposed in the classification system is inclusion of membranes that have substantial differences of potential clinical importance, like **MCO** membranes. The **MCO** membrane class is intended to improve the clearance of large molecular-weight solutes, while demonstrating a marked reduction in albumin permeability, influenced primarily by the decreased interval between MWRO and MWCO and resulting steep sieving curve. This membrane class may hold promise in achieving acceptable albumin losses, representing the basis for a new diffusion-based therapy called 'expanded hemodialysis.'

The MCO membrane features an increased pore density with tight pore-size distribution, enhancing ultra-filtration and permeability via a steep sieving-curve — resulting in clearance of larger uremic toxins, while retaining essential proteins.

References:

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