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Contemporary Topics in Critical Care MEDICINE

Asia Pacific Association of Critical Care Medicine



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JAYPEE

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CHAPTER

4 Are Super High-Flux Membrane Dialyzers the Future of RRT?

Nilesh Purushottam Mahale, Divya Choudhary, Pradip Balasaheb Dalvi

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INTRODUCTION

There is an incessant increase in the incidence and prevalence of patients with end-stage kidney disease requiring renal replacement therapy (RRT) worldwide.[1,2] Among renal replacement therapy (RRT) modalities, hemodialysis is the main treatment modality. Uremic toxins that accumulate in patient's body are removed by hemodialysis and they are classified as small-sized (<500 Da) such as urea and creatinine, middle-sized (500 Da–50,000 Da), such as β2-microglobulin (β2MG) and cystatin C or protein bound such as p-cresol and retinol-binding protein.[3] Starting in the 1980s, middle-sized toxins and large molecular weight substances (>5,000 Da) were targeted for removal.

In these previous years, the most dialyzers have been low-flux membrane dialyzers which have an ultrafiltration rate of <15 mL/mm Hg/h and β2MG clearance of <15 mL/min, solutes are removed through diffusion, but only small amounts of middle-sized solutes are removed.[4,5] In a posthoc analysis, the concentrations of middle-sized molecules were found to be an independent predictor of mortality with the relative risk of death increased by 11% for every 10 mg/L increase in predialysis β2MG concentrations.[6] Thus, high-flux membrane dialyzers, which have an ultrafiltration rate of ≥15 mL/mm Hg/h and β2MG clearance rate of ≥15 mL/min were developed.[4] High-flux membranes have higher permeability for middle-sized solutes than low-flux membrane dialyzers. In 2005, to address the problem of albumin leakage, super high-flux membranes with a large pore size were developed in Japan.[7]

Recently, membrane permeability outcome study showed that in 647 dialysis patients who were randomly divided into low-flux (LF) or high-flux (HF) dialyzer membranes, found that improved β2MG clearance with HF membranes led to a 37% risk reduction in mortality in patients with albumin concentrations <4.0 g/dL.[8]

Thus, there is a rising interest in the development of technologies aimed at increasing the removal of these larger molecules few of them include online hemodiafiltration, resin-coated or absorbent membranes, and increased frequency or prolonged duration of dialysis.[9] Another potential strategy is conventional hemodialysis using one of a new class of dialysis membranes known as super-flux (SF) or protein leaking membranes, engineered to have a larger pore size and hence molecular-weight cutoff value and designed to maximize middle-molecule clearance while minimizing albumin loss. This effect is achieved, at least in part, by increased convection caused by an increase in back filtration and internal filtration.[10]

CLASSIFICATION

In Japan, dialyzers are classified into five types based on their clearance of β2MG with a blood flow rate of 200 mL/min and a dialysate flow rate of 500 mL/min.[7]

1. Type I are classified as low-flux membrane dialyzers (<10 mL/min clearance)
2. Type II and III as high-flux membrane dialyzers (≥10 to <30 mL/min and ≥30 to <50 mL/min clearance, respectively)
3. Type IV and V as super high-flux membrane dialyzers (≥50 to <70 mL/min and ≥70 mL/min clearance, respectively).
4. Type IV and V dialyzers are also classified as high-performance membrane (HPM) dialyzers due to their high-flux rate, permeability, and biocompatibility.

Table 1 enumerates the classification of dialyzers.

TABLE 1: Types of dialyzers.

Flux	*Type*	*Clearance*
Low-flux	Type I	<10 mL/min
High-flux	Type II	≥10 to <30 mL/min
	Type III	≥30 to <50 mL/min
Super high-flux	Type IV	≥50 to <70 mL/min
	Type V	≥70 mL/min

PRINCIPLE AND STRUCTURE

The essential element is the use of dialyzers that have larger pores for the removal, both of uremic toxins and of fluid. Membranes are thin, have large pores and very lower resistances. With high-flux dialysis, blood urea nitrogen (BUN) clearly is removed more quickly. But there is also now evidence that larger molecules may also play an important role in causing the uremic symptoms that are both annoying and dangerous to dialysis patients. Such molecules are too big to be removed by conventional dialysis but are removed with high-flux and super high-flux dialyzers.[11]

A typical adult dialyzer has around 15,000 hollow fibers tightly packed, forming a compact bundle placed inside a 20 cm plastic tube. The sum of the inner area of these fibers varies usually from 1.4 to 2.1 m^2, creating the blood-dialysate barrier. The fibers are made of synthetic polymers and the process of producing them in essence is the same utilized in the textile industry to produce modern synthetic fabrics. Ideally, all the pores should have the same size to allow the adequate transport of uremic toxins, while sparing the loss of essential proteins such as albumin, soluble receptors, immunoglobulins, and proteins involved in the coagulation physiology. Characteristics such as pore size, uniformity in pore size, pore distribution, and density across the surface of the membrane will define its efficiency.[12]

Three physicochemical mechanisms define the clearance of solutes from the blood during hemodialysis (HD)—diffusion, convection, and adsorption. Routinely employed filters for chronic HD defined as high-flux (HF) allow diffusive and convective clearances, having polyarylethersulfone (PAES) as its main compound. The mean pore radius of these filters is 3.9 nm, and they can be applied in conventional HD [high-flux HD (HF-HD)], or hemodiafiltration [high-flux hemodiafiltration (HF-HDF)]. The high-flux HD modality can remove solutes with a molecular weight >15 kDa only. The online high-flux hemodiafiltration (HF-HDF) modality removes efficiently a broader range of molecules up to 25 kDa, utilizing the same membrane of high-flux-HD because of high ultrafiltration volumes of around 100 mL/min, which allows convective clearance of such molecules. An inherent consequence of high convective volumes is the increment in the transmembrane pressure, associated with higher deposition of proteins in the inner surface of the hollow fibers, partial obstruction of pores, and loss of membrane efficiency during the treatment, a phenomenon termed clogging.[13] **Table 2** enumerates the widely available dialyzers.

High-volume postdilution online hemodiafiltration (ol-HDF), defined as a convective volume of at least 23 L/session, could provide greater removal of both uremic toxins and improve patient survival. However, high-volume postdilution ol-HDF is generally not available in most HD centers and needs additional dialysis hardware technology to be included in the extracorporeal blood circuit such as substitution pump and tubing as well as sterile substitution fluid preparation system compared to high-flux HD. With limitations of high-volume postdilution ol-HDF, HD with the new type of dialyzer, which has a larger pore size than standard high-flux dialyzer, might provide better removal of protein-bound and middle-molecule uremic toxins. Medium cut-off (MCO) from Europe and super high-flux (SHF) such as PES 17D α (PES) from Japan are two new large pore size dialyzers.[13]

The high cutoff (HCO) and the medium cutoff (MCO) membranes have wider pores and more uniformity in pore size, allowing an increased clearance of uremic toxins. Owing to the mechanism of back filtration/internal filtration, middle molecules are dragged by the convective forces, and no substitution solution is needed.[12] The technology employed for the development of medium cutoff (MCO) and high cutoff (HCO) dialyzers is disruptive since it provides equivalent or even higher removal of middle molecules in the conventional HD modality than HF-HDF modality without the need for a devoted hemodiafiltration (HDF) machine and the production of online reinfusion solution. Albeit using a similar blend of PAES and polyvinylpyrrolidone as utilized in HF filters, the mean pore radius for the MCO filter (5.0 nm) and HCO filter (10 nm) are higher than those of HF filters (3.9 nm) as depicted in **Figure 1**.

TABLE 2: Characteristics of dialyzers.

Dialyzer	*Type*	*Purpose*	*Mean pore size*	*Inner diameter/ wall thickness*	*Company*	*MWRO*	*MWCO*
EMiC2®	HCO	CKRT	10 nm	220 µm/35 µm	Fresenius*	15 kDa	170 kDa
SepteX®	HCO	CKRT	10 nm	215 µm/50 µm	Gambro/Baxter§	15 kDa	170 kDa
Theralite®	HCO	HD dysproteinemias	10 nm	215 µm/50 µm	Gambro/Baxter§	15 kDa	170 kDa
Theranova®	MCO	HD	5 nm	180 µm/35 µm	Gambro/Baxter§	9 kDa	56 kDa

(CKRT: continuous kidney replacement therapy; HCO: high cutoff; HD: hemodialysis; MCO: medium cutoff; MWCO: molecular weight cutoff; MWRO: molecular weight retention onset)

*Fresenius Medical Care GmbH, Bad Homburg, Germany.

§Gambro Dialysatoren GmbH, Hechingen, Germany. Baxter Healthcare Corporation, Deerfield, IL, USA.

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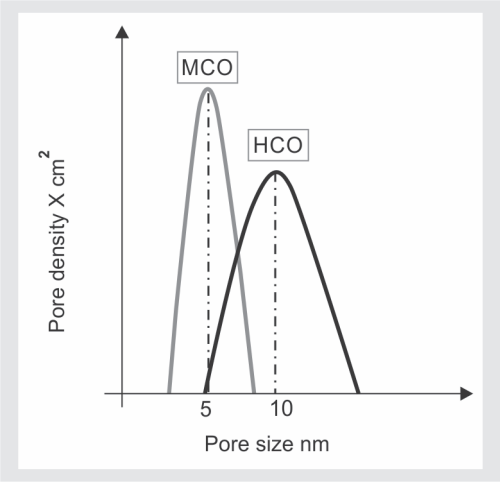


Fig. 1: Pore size distribution of MCO and HCO membranes. (MCO: medium cutoff; HCO: high cutoff)

The MCO membranes have a pore size of 5 nm, SD of 0.1 nm and HCO membranes have a pore size of 10 nm, SD of 2 nm.

ADVANTAGES

High-flux membranes compared to low-flux have larger pores and allow diffusion of greater amounts of uremic toxins and middle molecules such as β2-MG and therefore they may decrease the risk of dialysis-related amyloidosis.

For example, a molecule called *β2-MG*, which can have a role in causing arthritis in dialysis patients, is removed only by high-flux dialysis. There are already reports of patients with less joint pain when switched from conventional to high-flux dialysis.

Allows the accurate removal of very small volumes, as well as, volumes up to 4 L/h, which can never be achieved with conventional dialysis.

DISADVANTAGES

- *General:* Dialysis catheter insertion, dialysis and anticoagulation related.

  The major disadvantage of high-flux hemodialysis relates to the use of dialysis fluid, which is commonly not pure and may endanger patients treated with high-flux hemodialysis. Pyrogen reactions, characterized by high temperatures in patients during dialysis treatments. Caused by small pieces of dead bacteria that can be found in the dialysate. Because high-flux dialyzers have larger pores, the bacterial particles can pass more easily into the patient's bloodstream, and that patients have more frequent pyrogen reactions. Endotoxin fragments and other bacterial substances derived from bacteriologically contaminated dialysis fluid may enter from the dialysate into the patient's blood either by convective transfer (backfiltration) or by movement down the concentration gradient (backdiffusion). Repeated exposure of high-flux hemodialysis patients to backtransport of dialysate contaminants aggravates the uremia-associated inflammatory response syndrome and contributes to long-term morbidity. Presently either by use of endotoxin/bacteria retentive filters or dry powder cartridges are used to produce ultrapure dialysate fluid, which reduces inflammation.[14]
- *Albumin loss:* The preponderance of data state that use of protein leaking membranes for conventional hemodialysis tends to result in a small decrease in serum albumin concentration of, so far, unknown consequence, at least in well-nourished patients. Use of protein-leaking membranes for hemodiafiltration results in an albumin loss of up to 7 g/treatment. To date, there are no long-term studies to show whether this level of albumin loss has an impact on serum albumin. The level of protein loss is still well below the 10–12 g/treatment reported to occur after dialyzers that contain a polysulfone membrane are cleaned multiple times with bleach. However, the average albumin loss experienced by these patients may have been much <10–12 g/treatment because it took 20–25 uses of the dialyzer to achieve that level of loss.[10]

APPLICATIONS

Research have shown multiple applications of super high-flux dialyzers/MCO membrane dialyzers.

- There have been trials stating that high-flux hemodialysis in patients with diabetes was also found to have significantly longer survival as compared to low-flux hemodialysis, showing a relative risk reduction of 38%.[8]
- *Treatment with the MCO dialyzer:* Theranova 400 dialyzer on maintenance HD patients, maintained serum albumin level while providing superior removal of larger middle molecules as compared with a similar size high-flux dialyzer over 24 weeks.[15]
- HD with HCO dialyzer showed evidence to improve anemia and chronic inflammation due to much more removal of uremic toxin larger than 30–70 kD range but unfortunately causes a large amount of dialysate albumin loss ranging 2–6 g/session.[10]
- 3 years mortality was significantly dependent on dialyzer performance, which was classified according to β2MG clearance in prevalent dialysis patients.[7]
- Dialyzer types might affect mortality risk in hemodialysis patients and super high-flux membrane dialyzers might improve outcomes as when mortality was compared between the five types of dialyzers after final adjustment for multiple predicting factors, the hazards ratio for the

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type I group was significantly higher and the type V group was significantly lower compared with the type IV reference group.[7]

- HD with HCO dialyzer for a 3-week duration yielded a significant decrease in proinflammatory markers such as soluble tumor necrosis factor (TNF)-receptor. Nevertheless, serum albumin level was significantly decreased from. (3.6 ± 0.4 to 3.1 ± 05 g/dL 16)
- In the head-to-head comparison of HF-HD vs. MCO-HD, the RR of middle molecules such as β2-MG (12 kDa), cystatin C (13 kDa), myoglobin (17 kDa), prolactin (23 kDa), kappa FLC (23 kDa), complement factor D (24 kDa), α1-acid glycoprotein (41 kDa), lambda FLC (45 kDa) was robustly higher in MCO-HD.[5,15,16]
- The REMOVAL-HD trial showed not only a higher RR but also a sustained reduction in the predialysis concentration of free light chains favoring MCO-HD over HF-HD in myeloma patients.[17]
- Belmouaz et al. demonstrated that myoglobin and prolactin have higher RR in MCO-HD vs. HF-HD.[5]
- Finally, the possibility of utilizing the MCO filter for CKRT seems appealing as it merges the advantages of CVVHD (increased filter life span) and CVVH/CVVHDF (higher clearance of inflammatory mediators).[12]

It is highly debatable if the better clinical outcomes achieved with HF-HDF can be extrapolated for MCO-HD, since the removal of middle molecules is similar for both modalities.

CURRENT LITERATURE AND FUTURE PROSPECTS

In 2021, A crossover RCT study done by Khajohn et al., in Thailand on 10 hemodialysis patients found HD + super high-flux + hemoperfusion could not provide superior efficacy in removing uremic toxins to high-volume postdilution online Hemodiafiltration.[18]

A Japanese study done by Akira et al., in 2013 found super high-flux HD showed a slightly higher reduction rate for small water-soluble compounds although even in pre-dilution HDF, satisfactory removal of small compounds was achieved. Super high-flux (type V) HD produced a 73.4% reduction of β2MG and a 16.7% reduction of α1-MG with 1,800 mg loss of albumin. Therefore, these super high-flux dialyzers can display greater solute elimination performance than low-efficacy HDF, in which ultrafiltration is insufficient or an inappropriate filter is used.[19]

Another Japanese prospective cohort study done in 2022 on 2.42 lakh patients looking at associations of use of each dialyzer type with 3 years all-cause mortality by Masanori et al., found that mortality was significantly higher for type I, II, and III dialyzers compared with type IV after adjustment for basic factors and further adjustment for dialysis-related factors. The hazard ratio was significantly higher for type I, but significantly lowers for type V, after further adjustment for nutrition- and inflammation-related factors suggesting super high-flux HD is associated with lower mortality.[7]

A 6-week, Randomized, Double-blind, Crossover Trial done in Australia by Rebecca et al., found the removal of β2-MG was more efficient with the Helixone super-flux FX-E membrane, with only a small decrease in albumin concentrations despite increased albumin loss. Large trials with longer treatment periods are required to evaluate the impact of the FX-E membrane on clinical outcomes.[9]

A study done in Thailand by Theerachai et al., in their prospective cross-over randomized controlled trial found super high-flux-HD provides non-inferior effectiveness to high-volume post-dilution ol-HDF in removing various uremic toxins with significantly increased serum albumin levels despite higher albumin loss. SHF-HD might be an effective alternative treatment when high-volume postdilution ol-HDF is not available.[13] **Table 3** summarizes the details of a few earlier clinical studies using MCO-HD and the present SHF-HD study when compared with high-volume postdilution ol-HDF.

LIMITATIONS

Major limitations of the studies so far are as follows:

- Selection bias in some studies.
- Short duration of treatment, a smaller number of participants and the use of surrogate markers for clinical outcomes and nutritional status.
- Clinical relevance of adsorption of these middle molecules is unknown.
- Paucity of data on chronic dialysis patients.

CONCLUSION

This novel class of super high-flux membranes have recently been designed and incorporated into clinical practice to remove middle and large molecules during hemodialysis treatment. Despite some positive results with high-flux dialysis, caution must be advised with interpretation of these results as they were obtained from posthoc analyses. In light of HEMO, MPO studies, selected subgroups such as diabetes, hypoalbuminemic patients who have been on hemodialysis for a long period of time may benefit from dialysis with high-flux membranes.

Further long-term well-designed studies with more participants, longer term of follow-up with appropriate clinical endpoints are required to establish the potential benefits of removal of these middle molecules.

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TABLE 3: Clinical studies using MCO-HD and the present SHF-HD study when compared with high-volume postdilution ol-HDF.

Studies	***Kirsch et al.***	***Garcia-Prieto et al.***	***Garcia–Prieto et al.***	***Theerachai et al.***
Study design	Prospective, open-label, and randomized, controlled cross-over trial	Prospective, open-label, randomized, and controlled cross-over trial	Prospective, open-label, and observational study	Prospective, open-label, noninferiority, and randomized controlled trial
N	20	18	21	12
Population	ESRD on HD or ol-HDF >3 months	ESRD on ol-HDF >3 months	ESRD on HD >3 months	ESRD on ol-HDF >3 months
Intervention (I) [dialyzer name]	• MCO-HD (HDx) (Theranova 400) • high-volume	• MCO-HD (HDx) (Theranova 400) • High-volume	• MCO-HD (HDx) (Theranova 400) • High-volume	SHF-HD (PES17D α)
Control (C) (convective volume, L) (dialyzer name)	High-volume postdilution ol-HDF (24) (FX CorDiax 800)	High-volume postdilution ol-HDF (28) (FX CorDiax 1000)	High-volume postdilution ol-HDF (28) (FX80 CorDiax)	High-volume postdilution ol-HDF (24.4) (HF 80)
Duration of study	1 week/each treatment	1 week/each treatment	1 sessions/each treatment	12 weeks/each treatment (4-week run-in period and 4-week wash-out period)
• Results Small solute removal • Middle-molecule removal	• Comparable small solute removala • I <C, β2MG RR, I >C, α1MG RR	• Comparable URR • I >C, β2MG RR, myoglobin RR, prolactin RR, a-1 glycoprotein RR	• Comparable URR, Kt (L) • I <C, β2MG RR, I = C, α1MG RR	• Comparable small solute removal • I = C, β2MG RR, α1MG RR
• Protein-bound removal • Albumin loss	• NA • I, 3.2 g/session; C, 0.4 g/session	• NA • I, 0.03 g/session; C, 3.1 g/session	• NA • I, 2.2 g/session; C, 2.7 g/session	I = C; IS RR I, 4.2 g/session; C, 0.6 g/session

(α1MG: α1-microglobulin; β2MG: β2-microglobulin; IS: indoxyl sulfate; MCO-HD: hemodialysis with medium cut-off dialyzer or HDx, expanded hemodialysis; NA: nonapplicable; ol-HDF: online hemodiafiltration; RR: reduction ratio; SHF-HD: hemodialysis with super high-flux dialyzer; URR: urea reduction ratio)

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