Flow Dynamic Analysis by Contrast-Enhanced Imaging Techniques of Medium Cutoff Membrane Hemodialyzer

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BACKGROUND

The introduction of medium cutoff membrane has spurred new interest in potential improvements in medium- and long-term outcomes in patients undergoing chronic hemodialysis. **MCO** membrane presents increased solute permeability with improvement of molecular weight retention onset (MWRO) while maintaining cutoff values adequate to limit albumin losses. **MCO** membrane is utilized in a dialysis technique defined "expanded hemodialysis" that provides significant improvement in removal of large (PM > 25 and < 58 kDa) middle molecular weight solutes (LMM) responsible for symptoms and complications. While solute clearances, sieving coefficients, and hydraulic permeability have been extensively studied, flow dynamic characteristics of hollow fiber hemodialyzers utilizing such membranes have not been studied in detail. This information may be required to correctly prescribe **HDx** therapy and to optimize its operational parameters.

OBJECTIVE

To evaluate the flow dynamic and cross-filtration characteristics of the new **MCO** hemodialyzer (**Theranova** 400; Vantive, Deerfield, IL, USA), and aiming to gather specific information useful for the correct and safe delivery of expanded hemodialysis with the **MCO** membrane, specifically:

> Define the flow dynamic conditions inside the blood compartment and the flow distribution inside the dialysate compartment

> Define the hydraulic permeability and its sieving properties

> Analyze the segmental cross flow (direct filtration and backfiltration) along the length of the hollow fiber bundle

METHODOLOGY

Characteristics of Dialyzer Evaluated

The **Theranova** 400 dialyzer is a dialyzer designed specifically for **HDx** therapy with a surface area of 1.7 m^2. The membrane has an asymmetric 3-layer structure composed of polyarylethersulfone and polyvinylpyrrolidone blend, BPA free. It is characterized by uniform pore distribution and specific sieving properties: high MWRO and molecular weight cutoff (MWCO) value lower than albumin.

Study Techniques

Blood and dialysate flow distribution and internal transmembrane cross-filtration were studied with two separate imaging techniques: CT helical scanning and sequential and static scintigraphic imaging. Two different experimental setups were used in the CT imaging technique for blood and dialysate flow dynamic analysis. See Figures 1 and 2.

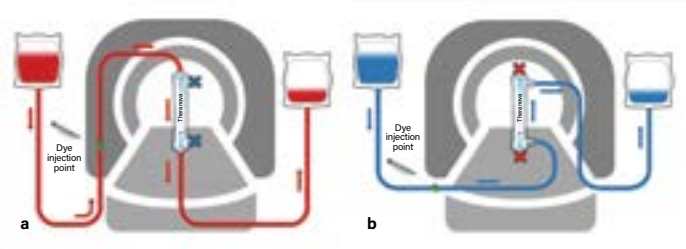

FIGURE 1. Schematic representation of the first experimental setup. The dialyzer was held in vertical position and placed in the middle of the gantry. Blood and dialysate compartments were analyzed separately. **a** Dye solution was injected in the blood inlet line, and flow was directed from the top to the bottom; the dialysate compartment was prefilled and sealed. **b** Dye solution was injected in the dialysate inlet line, and flow was directed from the bottom to the top; the blood compartment was prefilled and seal. Figure adapted from Lorenzin, et al.

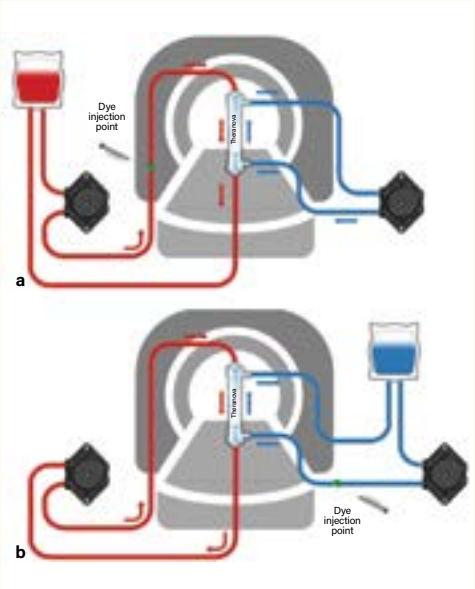

FIGURE 2. Schematic representation of the second experimental setup. The dialyzer was held in vertical position and placed in the middle of the gantry. Two peristaltic pumps flowed blood and dialysate in counter-current at 300 and 500 mL/min, respectively, and no net filtration. **a** Dye solution was injected in the blood inlet line, and flow was directed from the top to the bottom; the dialysate circulated in a closed loop. **b** Dye solution was injected in the dialysate inlet line, and flow was directed from the bottom to the top; blood circulated in a closed loop. Figure adapted from Lorenzin, et al.

A third analysis was conducted employing a scintigraphic method to assess the internal filtration/backfiltration. See Figure 3.

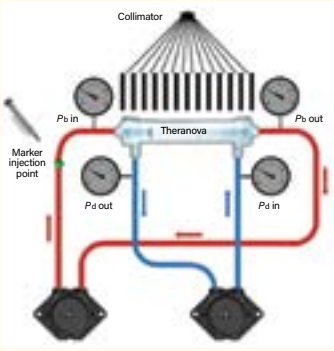

FIGURE 3. The scintigraphic experimental setup. Dialyzer was laid on the gamma camera. Blood (300 mL/min) and dialysate (500 mL/min) were circulated in a closed loop configuration ensuring zero net filtration. The tracer was injected in the blood line, upstream the inlet of the dialyzer. Pressures at inlet and outlet of the 2 compartments were monitored. Pb: pressure blood; Pd: pressure dialysate. Figure adapted from Lorenzin, et al.

RESULTS

Figure 4 displays the dye distribution pattern in blood and dialysate compartments during the first experimental setup: blue/green areas are free from dye solution, pink areas point out the presence of the dye solution, and red/yellow areas are transition zones. In the blood compartment (300 mL/min), flow distribution appears homogeneous. Minimal difference in velocity was observed between peripheral and central fibers. In the dialysate compartment (500 mL/min), no dead space or irregularities are noticed from the images of the filled compartments, except for a black spot in the blood one, due to n air bubble artifact (see Figure 4c).

In the blood compartment, the velocity profile changes its shape along the length of the dialyzer. In the inlet blood port, the dye solution displays a homogeneous progression featuring a kind of plug flow configuration with an average velocity of 1.4 cm/s (See Figure 4a). A small increase in differential velocity among the fibers was observed as the dye proceeds toward the outlet port. Peaks of velocity are displayed in the central (1.1 cm/s) and in the extreme peripheral regions (1.5 cm/s) of the dialyzer, while velocities as low as 0.6 cm/s are observed in rare groups of intermediate fibers.

The wall shear rates are 458, 666, and 276 s−1, respectively. These differences are absolutely acceptable and compatible with a well-designed blood compartment and a good flow distribution in the fiber bundle. Furthermore, the wall shear rate values are always above the limit where blood viscosity starts to increase significantly. The very short length of the Mass Transfer Zone (MTZ) (1.5 cm) in the proximal part of the dialyzer (See Figure 5a) confirms the plug flow; at half length of the dialyzer, MTZ is slightly longer but still within optimal values (3 cm) confirming the excellent utilization of all fibers of the bundle and a good distribution of flow with optimized flow velocity per single fiber (See Figure 5b).

In the dialysate compartment, dye solution flows initially along the case and through the outlying fibers with a velocity of 1.8 cm/s. When the solution begins to seep in the center of the fiber bundle, the velocity in the central region rises to 1.7 cm/s. Proceeding to the outlet port, the front of the velocity profile becomes more homogeneous with the optimal utilization of the whole cross-sectional area available for the flow (See Figure 4f). The dialysate MTZ presents a value of 8.1 cm. While a moderate dispersion of local velocities is observed, the value is far below half of the length of the dialyzer confirming optimal flow distribution of the dialysate (See Figure 5c).

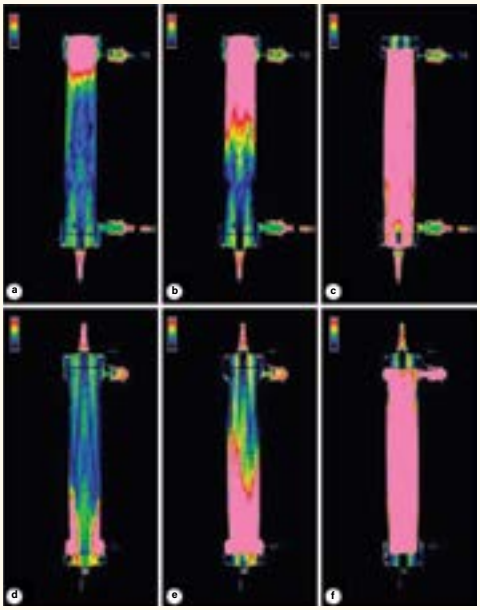

FIGURE 4. Dye progression in blood (a, b, c) and dialysate (d, e, f) compartments after 4 and 12 seconds and at total filling (33 seconds for blood and 28 seconds for dialysate), for the first experimental setup. Blue/green areas are free from dye solution, pink areas point out the presence of the dye solution, and red/yellow areas are transition zones. Figure adapted from Lorenzin, et al.

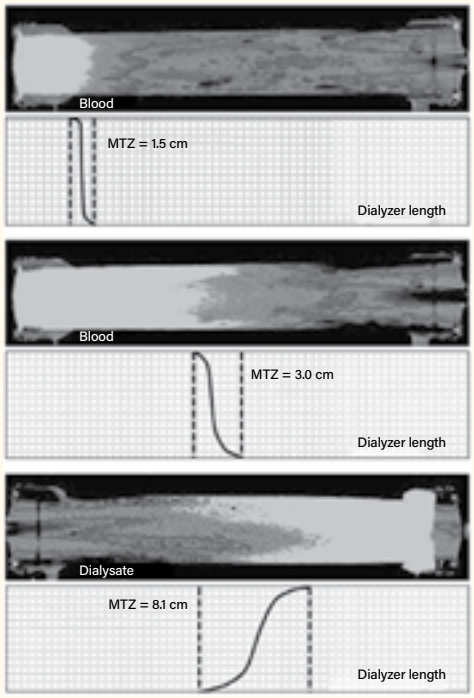

FIGURE 5. MTZ in blood (a, b) and dialysate (c) compartments obtained from the first acquisition. MTZ represents the distance between the point of maximal dye saturation and the point of absolute absence of dye. MTZ: mass transfer zone. Figure adapted from Lorenzin, et al.

Figures 6a and 6c report the images obtained from the second experimental setup, in which blood and dialysate circulated counter-current, simultaneously. Compared with the first experiment (Figures 6b, 6d), images display a perturbation of the dialyzer perfusion likely induced by the local transmembrane cross flow of dialysate and plasma water. The blood flow distribution (blood flows from the top to the bottom) is homogeneous in the proximal half of the dialyzer while in the distal part, yellow areas describe the effect of backfiltration from the dialysate compartment into the hollow fibers. Dialysate compartment describes an analog effect (dialysate flows from bottom to top in counter-current with blood). Dye solution saturates the portion of the dialyzer close to the inlet (pink), while toward the middle of the dialyzer, the flow distribution pattern becomes slightly dishomogeneous due to ultrafiltration (plasma water cross flow from the blood into the dialysate compartment).

This complementary behavior testifies the internal filtration and backfiltration phenomena. Considering the orientation of blood stream, in the proximal part of the dialyzer, plasma water crosses the membrane, and the effect of the internal filtration causes a dilution of the dye solution in the dialysate compartment (See Figure 6c); in the distal part, instead, the reduction in dye intensity in the blood compartment is a consequence of backfiltration, the cross flow of the dialysate through the membrane into the fibers (see Figure 6a).

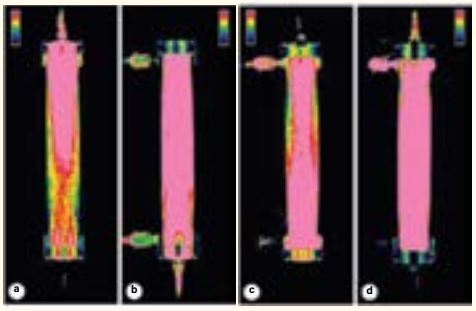

FIGURE 6. On the left, CT images acquired after reaching the total filling in the blood **(a)** and dialysate **(c)** compartment in the countercurrent flow experiment. Visible differences are noticed if compared with the same images acquired in the first experiment **(b, d)**. The reduction of dye intensity in the images on the left is the consequence of the internal/backfiltration phenomenon that occurs in counter-current flow configuration. Figure adapted from Lorenzin, et al.

Internal Filtration/Backfiltration

The kinetics of transmembrane cross flow are confirmed in the third experiment. Scintigraphic images (See Figure 7) display significant variation in radioactive count along the length of the dialyzer, due to local transmembrane cross flow of plasma water through the membrane in both directions. The increase in concentration of the marker molecule in the proximal part is ascribed to the direct filtration of plasma water from blood into the dialysate while the dilution in the distal part to backfiltration of the dialysate into blood. The turning point is observed at 53% of the dialyzer length. At steady state, the concentrations at inlet and outlet of the fiber bundle are identical, confirming the condition of zero net filtration. The calculation of relative changes of the marker molecule allows for the cumulative estimation of the amount of filtration and backfiltration inside the dialyzer under the selected experimental conditions.

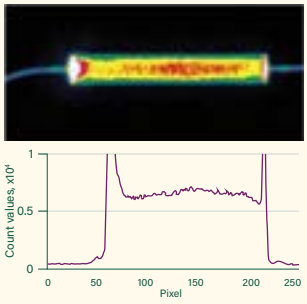

FIGURE 7. Scintigraphic image of the dialyzer at the steady state and radioactivity count. The change in color corresponds to the relative variation in radio labeled marker molecule activity in a numerical scale. Radioactive count is proportional to the marker concentration in blood. In the proximal part, the internal filtration causes the increase in marker counts while the backfiltration in the distal part brings back the radioactive counts to the inlet value, restoring the zero net filtration condition. Figure adapted from Lorenzin, et al.

The concentration of the marker molecule increases reaching a peak value (Cmax) at half length of the filter and then decreases until the end of the fiber bundle reaching the same concentration observed at the inlet. This behavior demonstrates a proximal direct filtration (IF) and a distal backfiltration (BF). Calculated IF was 32.75 mL/min while BF was 32.46 mL/min. The slight difference is compatible with the error of the method. Filtration and backfiltration rates can increase or decrease depending on blood and dialysate flows and dialyzer surface area.

DISCUSSION

The clinical performance of **Theranova** dialyzer as used in **HDx** therapy is based on a signficant convective exchange by enhanced mechanism of internal filtration/backfiltration. This study demonstrated the flow dynamics leading to the dialyser performance. The homogeneous pattern of blood distribution at the inlet port and along the fiber bundle represents a proof of an optimal design of the distributor and the entire blood compartment of the dialyzer. This ensures a good performance of the filter in the diffusion mode and guarantees the optimal utilization of the available surface area. Adequate flow distribution and high wall shear rates contribute to minimize the formation of a protein layer at the blood membrane interface. The occurrence of a significant concentration polarization phenomenon with consequent reduction of membrane permeability is mitigated by the utilization of the dialyzer in the hemodialysis mode (**HDx** therapy).

Excessive convective rates such as those achieved in the hemodiafiltration (HDF) mode would contribute to impair membrane permeability by the formation of a protein cake onto the internal surface of the fibers. This phenomenon leads to the formation of a new contact surface whose thickness is added to that of the original membrane and interferes with the final permeability of the membrane in vivo. This unwanted effect is prevented by high wall shear rates in all fibers which contribute to reduce the thickness of the protein boundary layer and improve membrane hydraulic and sieving permeability.

The distribution of the dialysate flow outside the fibers is also optimized as demonstrated by the dynamic images where the dye appears to be homogeneously distributed in the entire cross-sectional area of the dialysate compartment. Thus, any blood-to-dialysate flow mismatch is avoided, and the surface area available for the exchange is maximized.

Considering the cross flow kinetic results obtained with the nuclear scintigraphic method, these observations are important. Results confirm a significant amount of filtration and backfiltration inside the dialyzer at zero net filtration > 30 mL/min. This means that in presence of higher blood flows, higher surface areas, and higher net filtration rates (15–20 mL/min), direct fluid cross flow may reach values around 50 mL/minute. This is achieved in presence of a wall shear rate in all fibers sufficiently high to maintain blood viscosity at minimal levels and a significant cleaning effect at the blood membrane interface with negligible concentration polarization of plasma proteins. Such effect results in a maintenance of the sieving properties of the membranes throughout the dialysis session. Internal filtration between 30 and 50 mL/min combined with the sieving characteristics of **MCO** membrane allows for convective clearance values of medium-large molecules equal or even superior to those achieved in high-volume online HDF, without need of fluid replacement and very high filtration fractions inside the hemodialyzer.

CONCLUSION

This study demonstrates the basis for the use of **MCO** membrane in expanded hemodialysis maximizing the benefits of internal filtration while maintaining the simplicity and safety of high-flux dialysis configuration and blood flows in the range of 300 mL/min.