CHAPTER 150

Solute and Water Transport in Hemodialysis: Dialyzers, Flow Distribution, and Cross-Filtration

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OBJECTIVES

This chapter will:

1. Discuss the determinants of the two main dialysis mass transfer mechanisms, diffusion and convection, along with the factors influencing ultrafiltration.
2. Explain the concept of solute clearance and the various ways in which it is expressed.
3. Describe the basic characteristics of hollow fiber dialyzers and highlight the major features influencing ultrafiltration properties and small and larger solute removal capabilities.

Conventional hemodialysis remains an important renal replacement modality for critically ill patients with acute kidney injury. Because prescription of hemodialysis requires establishing goals for the rate and extent of solute and fluid removal, an understanding of the mechanisms by which solutes and fluid are removed during hemodialysis is necessary. This chapter provides an overview of basic mechanisms of solute and fluid transfer during conventional hemodialysis. The major characteristics of hollow fiber membranes influencing solute and water removal are discussed. Within this section, the chemical composition and physical characteristics of commonly used dialysis membranes and the features determining their solute and water permeability properties are reviewed. Flow distribution inside the dialyzer, internal filtration, and backfiltration phenomena are discussed in the last part of the chapter.

DIFFUSION AND CONVECTION

The basic physical mechanisms leading to removal of solute and water through a semipermeable membrane have been discussed already in other sections of this book. Diffusion is the dominant mass transfer mechanism mediating small solute removal in conventional hemodialysis.

Diffusion is a process in which molecules randomly move in all directions. Statistically this phenomenon results in net movement of solutes from a more concentrated area to a less concentrated one. In addition to the concentration gradient *(dc),* the solute diffusive flux per unit of area *(J_d)* through a semipermeable membrane depends directly on the diffusivity *(D)* of the solute (which is a function of temperature, viscosity of the fluid, and an approximate solute radius) and is inversely proportional to the membrane thickness *(dx),* as shown by the following equation:

$$J_d = D\left(\frac{dc}{dx}\right)$$

Equation 1

On the contrary, convection is related to ultrafiltration of plasma water and involves solute transfer through fluid movement in response to a transmembrane pressure gradient based on a process termed "solvent drag." Therefore the solute convective flux (removal rate per unit area, J_c) depends on the ultrafiltration flux (ultrafiltration rate per unit area, Q_{UF}), the solute concentration in plasma water *(C_{Pi}),* and the solute sieving coefficient *(SC),* as shown in the following equation:

$$J_c = \frac{Q_{UF}}{A} \times C_{Pi} \times SC$$

Equation 2

These definitions of diffusion and convection (together with ultrafiltration) imply the two phenomena are separate. In fact, since the dawn of dialysis, they have been combined in an attempt to replace renal function. The knowledge of diffusion came from industrial chemistry, and dialyzers were designed to be ideal countercurrent exchangers, whereas the potential clinical advantages of convection were recognized later. In current clinical practice, the combined effect of diffusion and convection is exploited commonly. Although it is impossible to define precisely the contribution of these individual processes in the removal of solutes because of their continuous interactions, this principle applies not only to hemodiafiltration but also to standard high-flux hemodialysis.

Blood flow greatly affects the clearance of small solutes such as urea, whereas the influence of ultrafiltration rate is relatively greater for the removal of larger solutes. An increase in dialysate flow rate becomes important only with large surface area dialyzers and mostly affects the clearance of small solutes. In addition to the above aspects related to modality and flow rates, the type of membrane used and the hydraulic conditions within the hemodialyzer also must be considered.

MEMBRANES AND FILTERS FOR INTERMITTENT HEMODIALYSIS

Membranes used in dialysis are of natural or synthetic origin. Table 150.1 shows a simple but comprehensive comparison between membrane properties in these two classes. Different membranes have been generated from numerous basic materials and have been used subsequently in extracorporeal therapy over several decades. Table 150.2 presents an overview of existing membrane materials with the defining characteristics for each.

An obvious difference between synthetic and cellulosic membranes is chemical composition. Unlike naturally occurring cellulose membranes, synthetic membranes are manufactured polymers that are classified as thermoplastics. As reported previously in Table 150.1, another feature differentiating cellulosic and synthetic membranes is wall thickness (Fig. 150.1). Synthetic membranes have wall thickness values of at least 20 μm and may be structurally symmetric (e.g., AN69, PMMA) or asymmetric (e.g., polysulfone, polyamide, polyethersulfone, polyarylethersulfone/polyamide). For asymmetric structures, a very thin "skin" (approximately 1 μm) contacting the blood compartment lumen acts primarily as the membrane's separating element with regard to solute removal. The structure of the remaining wall thickness ("stroma"), which determines the thermal, chemical, and mechanical properties, varies considerably among the different synthetic membranes.[1]

TABLE 150.1

Basic Comparison Between Classes of Membranes for Renal Replacement Therapy

PARAMETER	NATURAL	SYNTHETIC
Structure	Homogeneous	Mainly asymmetric
Porosity	Hydrogel	Microporous
Interaction with water	Hydrophilic	Hydrophobic
Thickness	Small	Large
Biocompatibility	Low	High
Electrical charges	Mixed	Negative
Hydraulic permeability	Low-flux	High-flux

Cellulosic Membranes

The relatively long duration of popularity of cellulosic membranes can be explained largely by their particular

TABLE 150.2

Membrane Materials for Renal Replacement Therapy

MATERIAL	MEMBRANE CHARACTER
Cellulosic	
Cellulose	
Cellulose diacetate	Hydroxyl groups replaced with acetate
Cellulose triacetate (CTA)	Hydroxyl groups replaced with acetate
Hemophane	Hydroxyl groups replaced with diethylaminoethyl radicals
Synthetic Membranes	
Ethylvinyl alcohol (EVAL)	Hydrophilic
Polysulfone (PS)	Hydrophobic
Polymethylmethacrylate (PMMA)	Hydrophobic
Polyacrylonitrile (PAN)	Hydrophobic
Polyamide (PA)	Hydrophobic
Polyethersulfone (PES)	Hydrophobic
Polyarylethersulfone (PAES)	Hydrophobic
Polyesther polymer alloy (PEPA)	Hydrophobic

Modified from Saito A KH, Yamashita AC, Mineshima M. *High-Performance Membrane Dialyzers.* Basel: Karger; 2011.

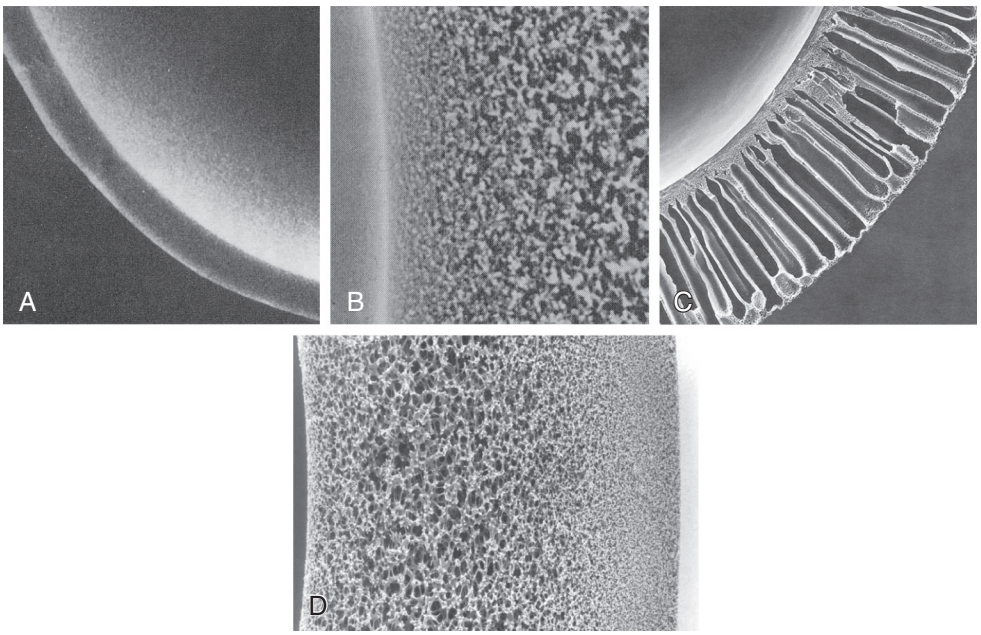

FIGURE 150.1 Structure of different membranes used for clinical hemodialyzers. A, Cellulose-based membrane with no visible porosity. B, Foamlike synthetic membrane. C, Macroreticular anisotropic synthetic membrane. D, Three-layer foamlike synthetic membrane.

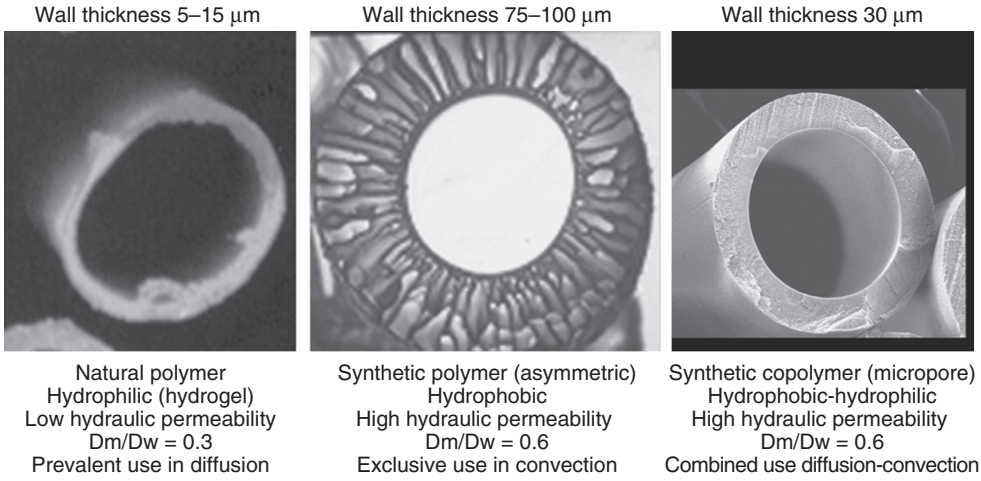

FIGURE 150.2 Dialysis membranes can be characterized according to different parameters. Among them are composition (natural or synthetic) and permeability (high-flux and low-flux). The ratio between diffusivity in membrane and diffusivity in water (Dm/Dw) also describes the capacity of the membrane to perform in diffusive treatments. The last parameter is the thickness of the membrane, which may interfere with the process of diffusion. Low-flux membranes are used mostly in hemodialysis, in which the prevalent solute transport mechanism is diffusion. High-flux membranes are used in hemofiltration, in which the mechanism is convection, and hemodiafiltration, in which the mechanism is mixed diffusion and convection.

suitability for a diffusion-based procedure such as hemodialysis.[2] The underlying hydrogel structure of these membranes and their tensile strength allow the combination of thinner walls (from 5 to 15 µm Fig. 150.2) and high porosity to be achieved in the fiber spinning process.[3] These characteristics allow the attainment of high rates of diffusive membrane transport and efficient removal of small, water-soluble uremic solutes, such as urea and creatinine. Another characteristic feature of these membranes is symmetry with respect to composition, implying an essentially uniform resistance to mass transfer over the entire wall thickness.

The most commonly used cellulosic dialyzers contain cellulose acetate (rigorously, cellulose diacetate) membranes,[4] in which approximately 75% of the hydroxyl groups on the cellulosic backbone are replaced with an acetate group. As compared with a hydroxyl group, an acetate group does not bind avidly to a C3 molecule to initiate activation of the complement cascade. Consequently, in dialysis using cellulose acetate membranes, complement activation is attenuated, as is the leukopenic response, in comparison with dialysis using unmodified cellulosic membranes. Because production of cellulose triacetate membranes involves complete hydroxyl group substitution with acetate groups, further attenuation of complement activation and leukopenia is achieved.[5]

Synthetic Membranes

Synthetic membranes were developed essentially in response to concerns about the narrow scope of solute removal and the pronounced complement activation associated with unmodified cellulosic dialyzers. The AN69 membrane, a copolymer of acrylonitrile and an anionic sulfonate group, was employed first in flat sheet form in a closed-loop dialysate system in the early 1970s.[6] Since that time, a number of other synthetic membranes have been developed, including polysulfone,[7] polyamide,[8] polymethylmethacrylate (PMMA),[9] polyethersulfone,[10] and polyarylethersulfone/polyamide.[11]

Largely in relation to the interest in hemofiltration as a therapy for end-stage renal disease, along with the inability to use low-flux unmodified cellulosic dialyzers for this therapy, synthetic membranes initially were formulated with high water permeability.[12] The large mean pore size and thick wall structure of these membranes allowed the high ultrafiltration rates necessary in hemofiltration to be achieved at relatively low transmembrane pressures.

However, dialyzers with these highly permeable membranes were used subsequently in the diffusive mode as high-flux dialyzers. This latter mode continues to be the most common application of these membranes, although they increasingly are being employed for long-term hemodiafiltration.[13]

Properties of Hemodialyzer Membranes That Influence Dialyzer Performance

Although not strictly correct, hollow-fiber dialyzer membrane function can be approximated with a model having straight cylindric pores, all of the same radius *(r)* and all with a directionality perpendicular to the flow of blood and dialysate.[2]

The major determinants of plasma ultrafiltrate flow rate through the pores are the number of pores (i.e., number per unit area of membrane surface area), transmembrane pressure, and pore size. With regard to pore size, the rate of ultrafiltrate flow depends on the fourth power of the pore radius *(r^4),* consistent with application of the Hagen-Poiseuille equation to an individual pore. Mean pore size also directly influences water permeability.

Membrane wall thickness is one important determinant of diffusive transport. The relatively thin-walled structure of cellulosic membranes (usually 5–15 µm) is largely responsible for their particular suitability in the setting of diffusive hemodialysis. The other major determinant of diffusive transport is porosity, also known as pore density. Membrane porosity is directly proportional to the number of pores and the square of the pore radius *(r^2).* Therefore the smaller dependence of membrane porosity on pore size,

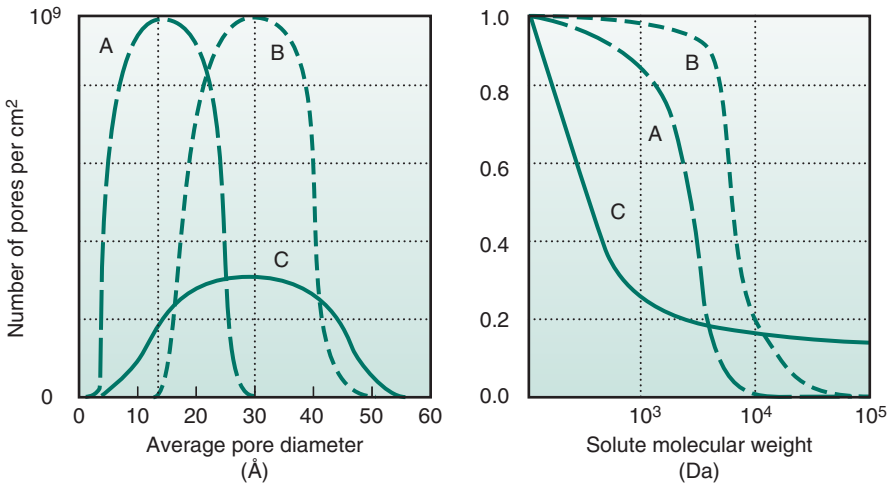

FIGURE 150.3 Pore size distribution and sieving coefficient profiles for three hypothetical membranes. *Left,* The relationship between number of pores and pore size. *Right,* Sieving coefficient as a function of solute molecular weight. (From Ronco C, Ballestri M, Gappelli G. Dialysis membranes in convective treatments. *Nephrol Dial Transplant.* 2000;15[Suppl 2]:31–36.)

relative to the case of water permeability, implies a relatively greater importance of pore number in determining diffusive permeability.

In fact, flux and diffusive permeability can be independent of each other for a particular hemodialysis membrane, because of their differing major determinants (r^4 for the former and number of pores, r^2 and wall thickness for the latter). Such is the case for cellulosic high-efficiency dialyzers, which typically have very high diffusive permeability values for small solutes but low water permeability.

A membrane represented by the cylindric pore model previously described deviates from an actual membrane used for clinical hemodialysis, in that the latter actually has a distribution of pore sizes. Ronco et al.[14] have discussed the manner in which pore size distribution may differ among hemodialysis membranes and the resultant influence on a membrane's sieving properties. In Fig. 150.3, which has been reproduced from their study, the membrane represented by curve A on the left diagram has a large number of relatively small pores, whereas the membrane represented by curve B has a large number of relatively large pores. On the basis of the relatively narrow pore size distributions, the solute sieving coefficient versus molecular weight profiles for both membranes (right diagram) have the desirable sharp cutoff, similar to that of the native kidney. However, the molecular weight cutoff for membrane A (approximately 10 kDa) is consistent with a high-efficiency membrane (high diffusive permeability but low hydraulic permeability), whereas that of membrane B (approximately 60 kDa) is consistent with a high-flux membrane (membrane ultrafiltration coefficient K_{UF}>25 mL/hr/mm Hg/m^2). In addition, primarily because of the large number of pores, both membranes would be expected to demonstrate favorable diffusive transport properties. On the other hand, the membrane represented by curve C exhibits a pore size distribution that is unfavorable from a diffusive transport and sieving perspective. The relatively small number of pores accounts for the poor diffusive properties. In addition, the broad distribution of pores explains not only the "early" drop-off in sieving coefficient at relatively low molecular weight but also the "tail" effect at high molecular weight (right diagram). This latter phenomenon is highly undesirable, because it may lead to unacceptably high albumin losses across the membrane. In practice, all highly permeable membranes have measurable albumin sieving coefficient values so that the design of this type of membrane involves striking a balance between optimized removal of high-molecular-weight toxins and minimal loss of albumin.

As suggested earlier, the most common classification scheme for membranes used in hemodialysis traditionally has included low-flux, high-efficiency, and high-flux groups. High cutoff membranes are the most recent addition to this scheme. Although these membranes are used commonly in CRRT, they also have been employed in hemodialysis, most commonly for patients with myeloma-associated AKI ("cast nephropathy"). In the virgin state, these membranes may allow passage of molecules as large as approximately 300 kDa, thus providing significant clearance of free light chains. Although the effective molecular weight cutoff is much lower after blood exposure, relatively substantial albumin loss (as much as 30 g per treatment) still occurs with use of these membranes. Thus a risk/benefit determination is important when these membranes are employed for myeloma-associated AKI or other disorders.

CHARACTERIZATION OF DIALYZER PERFORMANCE: CLEARANCE AND ULTRAFILTRATION COEFFICIENT

Clearance

Whole Blood Clearance

By definition, solute clearance *(K)* is the ratio of mass removal rate per unit of time *(N)* to blood solute concentration *(C_B)* as follows:[15]

$$K = \frac{N}{C_B}$$

Equation 3

For a hemodialyzer, the mass removal rate is simply the difference between the rate of solute mass per unit of time (i.e., product of flow rate and concentration) presented to

the dialyzer in the inlet blood line and the rate of solute mass leaving the dialyzer in the outlet blood line. This mass balance applied to the dialyzer results in the following classic whole-blood dialyzer clearance equation:

$$K_B = \frac{(Q_{Bi} \times C_{Bi}) - (Q_{Bo} \times C_{Bo})}{C_{Bi}} + Q_{UF} \times \frac{C_{Bo}}{C_{Bi}}$$

Equation 4

with (in the absence of adsorption):

$$Q_{UF} = Q_{Bi} - Q_{Bo}$$

Equation 5

where K_B is whole blood clearance, Q_B is blood flow rate, C_B is whole blood solute concentration, and Q_{UF} is net ultrafiltration rate. (The subscripts *i* and *o* refer to the inlet and outlet blood lines.)

The formula for the clearance aforementioned underscores the diffusive (K_{DIFF}) and convective (K_{CONV}) contributions made to total clearance.

Blood Water and Plasma Clearance

An implicit assumption in the determination of whole blood clearance is that the volume from which the solute is cleared is the actual volume of blood transiting through the dialyzer at a certain time. This assumption is incorrect for two reasons. First, in the erythron and plasma components of blood, a certain volume is composed of solids (proteins or lipids) rather than water. Second, for solutes such as creatinine and phosphate, which are distributed in the erythron and plasma water, slow mass transfer from the intracellular space to the plasma space (relative to mass transfer across the dialyzer) results in relative sequestration (compartmentalization) in the former compartment.[16] This reduces the *effective* volume of distribution from which these solutes can be cleared in the dialyzer. As such, derivation of whole blood dialyzer clearances from plasma water concentrations in conjunction with blood flow rates—a common practice in dialyzer evaluations—results in a significant overestimation of actual solute removal. The more appropriate approach is to employ blood water clearances, which account for the previously described hematocrit-dependent effects on effective intradialyzer solute distribution volume, as follows:[17]

$$Q_{BW} = 0.93 \times Q_B[1 - Hct + K(1 - e^{-\alpha t})Hct]$$

Equation 6

where Q_{BW} is blood water flow rate. In this equation, for a given solute, K is the red blood cell (RBC) water–plasma water partition coefficient, α is the transcellular rate constant (units: time^{-1}), Hct the hematocrit, and t is the characteristic dialyzer residence time. The factor 0.93 in this equation corrects for the volume of plasma occupied by plasma proteins and lipids. Estimates for these parameters have been provided by numerous prior studies and have been summarized by Shinaberger et al.[18] Finally, K_{BW} can be calculated by substituting Q_{BW} for Q_B in Eq. 4.

Although the distribution volume of many uremic solutes approximates that of total body water, it is much more limited for other toxins, particularly those of larger molecular weight. For example, the distribution space of β_2-microglobulin and many other low-molecular weight proteins is the plasma volume. Consequently, when Eq. 4 is used to determine β_2-microglobulin clearance, plasma flow rates (inlet and outlet) should replace blood flow rates in the first term of the right side of the equation.

The distinction between whole blood, blood water, and dialysate-side clearances (see below) is very important in the interpretation of clinical data. However, clearances provided by dialyzer manufacturers are typically in vitro data generated from experiments in which the blood compartment fluid is an aqueous solution. Although these data provide useful information to the clinician, they overestimate the actual dialyzer performance that can be achieved clinically (under the same conditions). This overestimation is related to the inability of aqueous solution–based experiments to capture the effects of RBCs and plasma proteins on solute mass transfer, especially over time.

Dialysate-Side Clearance

As indicated in Eq. 3, solute clearance is the ratio of mass removal rate per unit of time to blood solute concentration. Although blood-side measurements typically are used to determine solute mass removal rate, clearance also can be estimated from dialysate-side measurements, as follows:

$$K_D = \frac{Q_{Do} \times C_{Do}}{C_{Bi}}$$

Equation 7

where Q_{Do} is dialysate flow rate and C_{Do} is the outflow dialysate solute concentration. In this equation, dialysate-side solute clearance (K_D) is determined by measurement of the rate of mass appearance in the effluent dialysate stream ($Q_{Do} \times C_{Do}$). Dialysate-side measurements provide more accurate mass transfer information than blood-side determinations and generally are considered the gold standard for evaluating dialyzer performance. Relative to dialysate-side values, whole blood clearances substantially overestimate true dialyzer performance. Blood water clearances also moderately overestimate dialyzer performance, although the agreement between these values and simultaneously determined dialysate-side values (for nonadsorbing solutes) is usually within 5% of each other under rigorous test conditions. The major disadvantage of dialysate-based clearance techniques is the need to assay solute concentrations at very low concentrations. For some solutes (e.g., phosphate), these dilute concentrations may be difficult to assay with standard automated chemistry devices.

Clearance Versus Mass Removal Rate

Clearance is *not* a measure of actual mass removal of a particular solute by dialysis. As Eq. 3 indicates, clearance is the ratio of mass removal rate to blood concentration for a given solute; it can be defined also as the amount of solute removed from the blood per unit of time, divided by the solute concentration in the incoming blood. In hemodialysis, the mass removal rate of small solutes such as urea is very high during the early stage of an intermittent hemodialysis treatment, owing to a favorable transmembrane concentration gradient for diffusion at this time. As the treatment proceeds, proportional decreases in blood urea nitrogen value and urea mass removal rate, which is determined by the instantaneous blood urea nitrogen value, occur.[15] Eq. 4 predicts that a proportional decrease in these parameters is associated with a constant dialyzer clearance during the treatment (provided that dialyzer function is preserved) (Fig. 150.4).

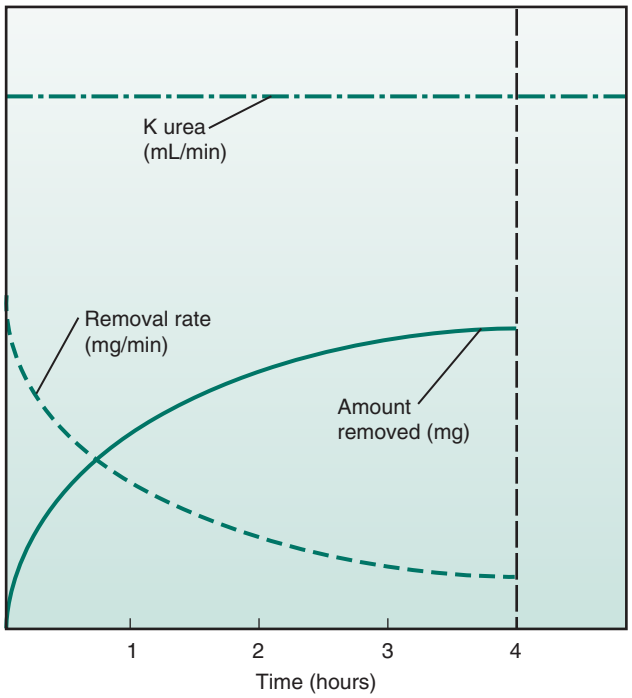

FIGURE 150.4 Relationship among solute clearance, mass removal rate, and cumulative removal during a 4-hour hemodialysis treatment. Even with constant dialyzer clearance, mass removal rate falls during the treatment because of a reduced concentration gradient. (From Clark WR, Henderson LW. Renal vs continuous vs intermittent therapies for removal of uremic toxins. *Kidney Int.* 2001;59[Suppl 78]:S298–S303.)

Despite not being a measure of actual dialytic solute removal, clearance remains a very reasonable parameter to assess dialyzer function. The distinction between solute clearance and mass removal rate described above is a much more relevant consideration when a whole body clearance (e.g., Kt/V) rather than dialyzer clearance is used.

Concept of Kt/V

The parameter Kt/V is a measurement of the efficacy of a hemodialysis session. It identifies the effective removal of a specific solute (clearance K) resulting from a given treatment (characterized by time t) in a given patient (with a specific volume of distribution V for the solute considered). Operationally, Kt/V is a dimensionless number.

As an efficacy measurement in chronic hemodialysis patients, urea Kt/V is considered a valid adequacy parameter with respect to small solute clearance. In such patients, this measurement of efficacy generally correlates with survival, and a delivered single-pool Kt/V of 1.4 at minimum currently is recommended for patients treated three times weekly.[19] On the other hand, the current recommendation for AKI patients treated with intermittent therapies is a weekly Kt/V of 3.9.[20]

DETERMINANTS OF DIFFUSIVE SOLUTE CLEARANCE

Diffusion is the dominant mass transfer mechanism mediating small solute removal in hemodialysis. Diffusive solute removal involves sequential mass transfer from the dialyzer blood compartment, through the membrane, and into the dialysate compartment. To quantify a dialyzer's diffusive capabilities, the concept of mass transfer resistance frequently is employed, as shown in the following equation[21]:

$$R_O = R_B + R_M + R_D$$

Equation 8

where R_O is the overall resistance to diffusive mass transfer of a particular solute by a dialyzer, R_B is blood compartment resistance, R_M is resistance because of the membrane itself, and R_D is dialysate compartment resistance. In turn, R_O is the inverse of the overall mass transfer coefficient (K_0), which is a component of the overall mass transfer-area coefficient (K_0A).

As previously described, diffusive solute clearance depends (among other features) on blood and dialysate compartment characteristics.

Blood Compartment

A fundamental relationship exists between diffusive clearance and blood flow rate for all solutes in conventional HD. For a given solute, a graph of clearance versus blood flow rate (Q_B) has two domains.[22] In the relatively low Q_B regimen, an effectively linear relationship exists between these two parameters. For all solutes, the line defined by this relationship falls below the line of identity, thus indicating that dialyzer clearance can never exceed the blood flow rate. For a given dialyzer, the slope of the line defining this flow-limited regimen is related inversely to solute size. Beyond a certain Q_B, the curve defining the clearance versus Q_B relationship for a given solute-dialyzer combination demonstrates a plateau. This plateau defines the K_0A-limited region. For a given solute-dialyzer combination, the K_0A parameter can be regarded as the maximal clearance attainable under a given set of flow conditions. The Q_B at which the transition from the blood flow–limited to the K_0A-limited region and the plateau clearance value are specific for a given solute-dialyzer combination.[22] For a given solute, an increase in either membrane diffusivity (K_0) or area (A) has the effect of increasing the transition Q_B and the plateau clearance value.

Minimizing the mass transfer resistance in the blood compartment is achieved primarily through the use of relatively high flow rates (i.e., shear rates), which minimize effects related to boundary (unstirred) layers. A *boundary layer* can be conceptualized as a stagnant film of fluid residing on the membrane surface.

However, another important factor influencing blood compartment resistance is hematocrit. Blood is a complex fluid in which RBCs are suspended in plasma. Plasma is an aqueous solution, but it does have a solid component (approximately 7% by volume) consisting of proteins and lipids. The erythron is also primarily aqueous, with water making up approximately 70% of the total erythron and the remaining solid component primarily comprising cellular membranes. Although many uremic solutes are distributed in the aqueous phase of the RBC and plasma fractions of blood, solute removal during hemodialysis can occur only from plasma water.

Before actual dialytic removal of solutes with this type of distribution can be achieved, mass transfer from the RBC water to the plasma water must occur. In turn, the rate at which this latter process occurs is solute specific. During

hemodialysis, urea in the plasma water leaving the dialyzer is in equilibrium with urea in the RBC water, with the ratio of these concentrations (approximately 0.76) being determined by the ratio of the water fractions of the aqueous and RBC compartments.[23] On the other hand, the transcellular rate of movement for other uremic solutes, such as creatinine and phosphate, is small (or negligible) relative to the rate of dialytic removal.[24] For a given unit volume of whole blood, a rise in hematocrit causes a relative increase in the distribution of solute in the RBC water, resulting in a relative sequestration of solutes with low RBC membrane diffusivity.

The application of rheologic principles to the flow of blood in a dialyzer also raises concerns that blood compartment mass transfer may be impaired by increasing hematocrit. For a given solute, diffusive mass transfer resistance in the blood compartment of a dialyzer is the ratio of effective diffusive path length *(x)* to effective solute diffusivity *(D),* both of which may be influenced by hematocrit.[24] Because the volume of RBC mass per unit volume of blood increases with rising hematocrit, solutes diffusing to the membrane surface are relatively more likely to encounter an RBC, causing an effective lengthening of the diffusion distance. In addition, solute diffusivity may decrease as a function of rising hematocrit because of the latter's effect on viscosity, which is a determinant of mass transfer resistance.[17] Finally, hematocrit also may influence flow distribution within the blood compartment of a dialyzer.[24]

Dialysate Compartment

Higher efficiency of blood compartment and transmembrane small solute mass transfer has been attained through the use of high blood flow rates and improved membrane designs, respectively. Consequently, efforts recently have been focused on dialysate-side mass transfer. On the basis of the K_0A concept, the dialysate-side mass transfer coefficient and membrane surface area may influence mass transfer. The dialysate-side mass transfer coefficient is determined largely by boundary layer phenomena, as in the blood compartment. Moreover, effective mass transfer area (A) is not necessarily equal to the manufacturer-reported (nominal) value.

Dialyzer characteristics that influence dialysate-side mass transfer include packing density, fiber undulation (also known as crimping), and the presence or absence of spacer yarns. *Packing density* is defined as the ratio of the area composed of hollow fibers to the area of the dialyzer housing, based on a cross-sectional cut through the dialyzer. Recent magnetic resonance imaging and computed tomography studies suggest that nonoptimized packing density may be the cause of channeling of dialysate at standard flow rates.[24,25] From a physical perspective, the interior of a fiber bundle packed too tightly represents a path of relatively large resistance, and the peripheral pathway is the path of least resistance. Obviously, an inwardly situated hollow fiber cannot participate in diffusive mass exchange if it is not perfused with dialysate. Packing density values beyond the optimum may account for the finding that large surface area dialyzers (i.e., greater than 1.7 m^2) generally are associated with less efficient mass transfer of dialysate small solutes, relative to dialyzers of smaller surface area.[26]

Another dialyzer characteristic that influences hollow fiber perfusion with dialysate is fiber bundle spacing. Dialysate may not be able to perfuse the area between adjacent fibers that are too close to one another. As is the case for nonoptimized packing density, this situation reduces the effective membrane surface area available for mass exchange. Two approaches have been developed to address this fiber spacing problem. First, *spacer yarns* are multiple-filament, linear structures interspersed longitudinally in a specific spatial distribution within the fiber bundle.[24] Second, all hollow fibers are manufactured with a relatively specific periodicity (amplitude and frequency).

In a clinical evaluation, Ronco et al.[24] measured the effect of microcrimping and spacer yarns on small solute removal and dialysate flow distribution. The microcrimped polysulfone fibers contained in the dialyzers used in this study have a relatively low amplitude and high frequency. In comparison with conventional dialyzers (i.e., that have fibers with standard undulation and no spacer yarns), urea clearances were found to be significantly higher for dialyzers with microcrimped fibers and spacer yarns. Using a computed tomography–based technique, these investigators also found that dialysate flow distribution was most homogeneous in dialyzers with microcrimped fibers, least homogeneous in conventional dialyzers, and intermediate in dialyzers with spacer yarn technology (Fig. 150.5). These data suggest that both of these approaches improve dialysate flow distribution and thus increase effective membrane surface area.

In addition to this influence on effective surface area, microcrimping also may reduce dialysate-side mass transfer resistance, essentially by disrupting ("agitating") the boundary layer. Another way in which boundary layer effects may be attenuated is through creation of a turbulent flow regimen with a relatively high Q_D.

Two important points about Q_D-related effects on small solute mass transfer require comment. First, for Q_D to have a significant effect on K_0A, a minimal Q_B value must be achieved. Specifically, if the blood flow rate is much less than 50% of the dialysate flow rate at baseline, an increase in the latter cannot be expected to confer much benefit.[27] Second, the beneficial effect of increasing Q_D on small solute mass transfer also may be due to a reduction in channeling with improved perfusion of the inner fiber bundle. Thus the mass transfer benefit of microcrimping and increased dialysate flow may be due to dissipation of boundary layer effects, an increase in effective membrane surface area, or both.

Diffusion and Convection as Competing Phenomena

Although convection and diffusion are described as two separate phenomena, their single contributions cannot be distinguished in practice. Moreover, especially in treatments that involve the combined use of diffusion and convection, there is a continuous interference between the two transport mechanisms.[28] In such circumstances, enhancement of one type of transport can produce effects on the other, which may be beneficial or detrimental.

In hemodiafiltration, solutes are carried across the membrane at the same concentration as in plasma water in association with high rates of ultrafiltration. This phenomenon takes place principally in the proximal side of the filter and reduces the driving force for diffusion. In this case, convection negatively affects diffusion, a fact that becomes more important on the distal side of the filter, where the ultrafiltration rate approaches zero. This effect emphasizes the importance of the surface area for diffusive performance in hemodiafiltration. However, the back-diffusion of substances such as buffers from dialysate into the blood also may be affected negatively, at least in the proximal side of the filter, where ultrafiltration is higher.

In high-flux dialysis, a typical filtration-backfiltration profile occurs (see later in chapter).[29,30] The minimal

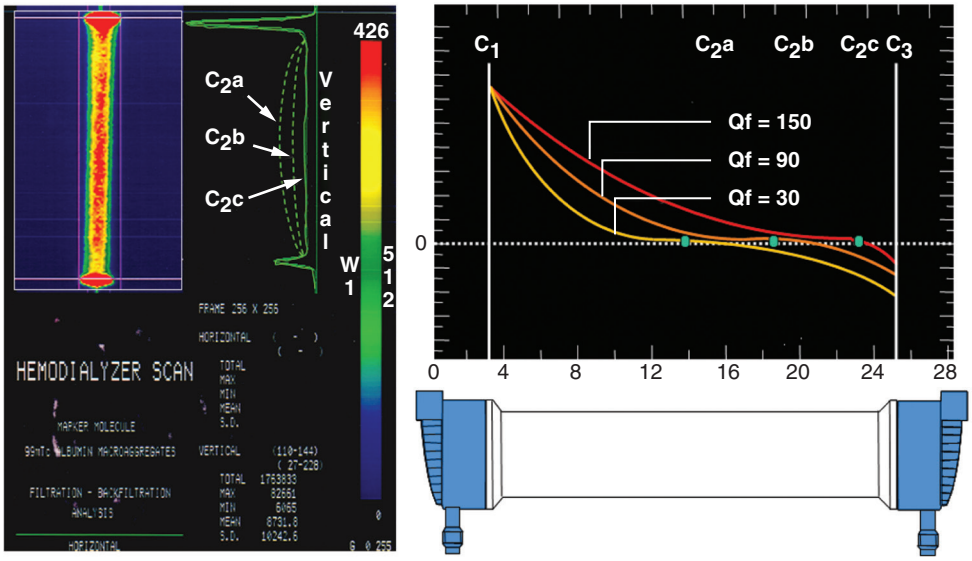

FIGURE 150.5 See also color plates. *Left,* Images of a dialyzer filter analyzed with the gamma camera after injection of a specific marker molecule in blood. The increased concentration of the labeled nondiffusible marker molecule in the central portion of the hemodialyzer can be visually captured from the change in color. The curve of the radioactive count is displayed on the right side of the filter image. The peak changes in concentration C_2a, C_2b, C_2c differ according to the net filtration rates. The lower the filtration rate is, the higher the peak concentration change and the higher the internal filtration-backfiltration (*right*). The different lines describe the local cross-filtration along the length of the fiber bundle. In the proximal portion (*left*) the cross-filtration is positive and in the distal portion (*right*) the cross-filtration is negative (backfiltration).

interference between convection and diffusion is achieved in the central part of the dialyzer, at which point the water flux in both directions is near zero. In the region near the blood ports, convection may interfere with diffusion in the filtration and backfiltration modes.

INTERNAL FILTRATION AND BACKFILTRATION

Hemodiafiltration enhances middle molecule clearances, but the need to replace the ultrafiltrate with sterile solutions makes this modality more complex and costly than conventional HD. Volumetrically controlled hemodialysis with high-flux membranes (high-flux dialysis) also achieves better middle molecule clearances than standard hemodialysis, and without the need for substitution fluid. In this latter modality, however, the convective removal of middle molecules is limited by the rate of internal filtration.

Internal filtration is governed by the hydraulic and oncotic forces acting along the length of the dialyzer on each side of the membrane. At each point of the dialyzer, the local pressure gradient across the membrane is called *transmembrane pressure* (TMP), which varies with the length l along the whole filter according to the following equation:

$$TMP(l) = P_B(l) - P_D(l) - \pi_B(l)$$

Equation 9

where P_B is the hydrostatic pressure in the blood compartment, P_D is the hydrostatic pressure in the dialysate compartment, and π_B is the plasma oncotic pressure.

When TMP is positive, the water flux occurs from the blood compartment to the dialysate compartment. When TMP is negative, backfiltration occurs (Fig. 150.6). Thus removal of middle molecules can be enhanced by raising the positive-pressure differential in the proximal part of the dialyzer, thus increasing internal filtration. Adequate net filtration is maintained by the ultrafiltration control system through a parallel increase in the negative-pressure differential in the distal part of the dialyzer. This results in greater proximal filtration and distal backfiltration without affecting the "net" filtration rate.

When high rates of backfiltration are used, high-quality dialysate is needed to prevent side effects related to pyrogen transfer into the patient's circulation. For this treatment, use of the latest-generation hemodialysis machines is suggested strongly. New machines are equipped with a built-in pyrogen filter to prepare ultrapure dialysate. The reinfusion via backfiltration provides an additional safety barrier because the fluid is filtered again across the hemodialysis membrane before it reaches the blood compartment.

Several possible ways to increase the rate of internal filtration have been investigated, including modifications of the geometry of the dialyzer and the application of an O-ring in the middle portion of the hemodialyzer.[31,32] The most practical modification has been shown to be a reduction of the inner diameter of the hollow fiber. This is an interesting way to increase the positive-pressure differential across the membrane in the proximal and distal regions of the hemodialyzer without introducing major changes in dialyzer design.

The difference in pressure drop between a "normal" filter and a filter with reduced inner diameter of the hollow fibers is significant, as it is predicted by the Hagen-Poiseuille equation, as follows:

$$\Delta P = Q_B \times \frac{8\eta L}{\pi r^4}$$

Equation 10

where ΔP is the end-to-end pressure drop, Q_B is blood flow, η is blood viscosity, L is the length of the fiber, and r is the internal radius of the fiber. Because the pressure drop in a fiber correlates inversely with r^4, it seems logical to attempt

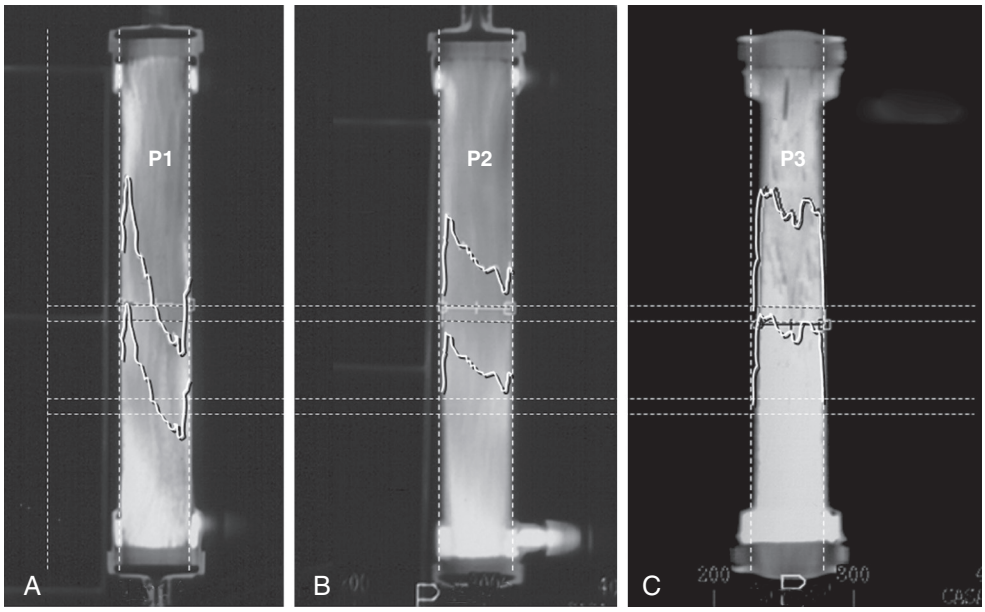

FIGURE 150.6 Distribution of dialysate in three different hemodialyzer configurations: **A,** standard fibers; **B,** fibers with spacer yarns; **C,** hollow fibers with moiré structure, which corresponds to microcrimping. It is evident that the most homogeneous distribution is obtained with the micro-undulation design of the hollow fibers (**C**).

solutions that involve modifications of the fiber geometry. In this case, even small changes in the inner diameter of the fiber may cause dramatic changes in its performance. With net filtration rates near zero, the increases in filtration and backfiltration can be doubled with specific dialyzer and fiber designs.

Reduction of the inner diameter of the hollow fiber also may result in an increase in the average blood flow velocity per fiber and a consequent rise in wall shear rates. This additional factor may result in a "cleaning" effect at the blood-membrane interface. In fact, higher shear rates attenuate the negative impact of the "secondary membrane" of nonspecifically adsorbed proteins on membrane permeability. Therefore reducing the inner diameter can improve performance of the filter in terms of not only filtration rates at a given local transmembrane pressure gradient but also improve use of the sieving capacities of the membrane.

In vivo analysis of middle molecules removal has demonstrated the benefits of increased internal filtration resulting from the reduction in hollow fiber diameter. Although urea, creatinine, and phosphorus clearances were not changed as expected from their high diffusion coefficients (minimally affected by changes in convection), clearances of vitamin B_{12} and inulin were improved by more than 30% by use of the modified dialyzers.

Therefore modifications in the design of hollow fibers may lead to new and interesting improvements in hemodialyzer performances. Newly conceived dialyzers therefore may appear in the future with enhanced convective transport, leading to simplified hemodiafiltration techniques that do not require replacement solutions, but simply use internal filtration as a major way to improve convective transport.

CONCLUSION

The major mechanisms mediating solute removal by hollow-fiber membranes (diffusion and convection) and water removal (ultrafiltration) in conventional hemodialysis have been discussed, along with the features determining their intrinsic solute and water permeability properties. The major dialyzer and membrane properties that affect solute and fluid transfer also have been discussed. Among them are composition (natural or synthetic), permeability (high flux and low flux), thickness, mean pore size, and distribution of pore size. These characteristics determine the diffusive properties, sieving profiles, and water permeability, ultimately determining its overall performance.

Solute clearance can be expressed in different ways: whole blood, blood water, plasma, dialysate-side, and whole body. It is important to understand which one is the most pertinent to be used in specific clinical situations.

Hemodialyzers are designed with consideration of diffusion and convection processes. The blood and dialysate compartments are optimized to maintain the best concentration gradient for diffusion, whereas convection and internal filtration depend mostly on operational conditions, such as adequate blood and ultrafiltration flows.

Once these aspects are understood, the appropriate prescription can be chosen to achieve the desired results with the treatment.

Key Points

1. Although many convective modalities and therapies are used increasingly in clinical practice, diffusion is still the main solute removal mechanism in conventional hemodialysis.
2. Dialysis membranes can be characterized according to material and geometric characteristics, which determine the performance characteristics of a dialyzer.

3. Solute clearance can be expressed in the following ways: whole blood, blood water, plasma, dialysate-side, and whole body.
4. Blood flow is paramount with respect to the diffusive and convective removal capacity of a dialyzer. Special blood ports are created to achieve a uniform distribution of the flow inside the blood compartment and to obtain full utilization of the membrane surface.
5. All of the components described play a role in the final efficiency of the system and help explain the mechanisms operating in different techniques, such as hemodialysis (prevalently diffusion-based with low-flux membranes), high-flux dialysis (mixed diffusion and convection with internal filtration and backfiltration), and hemodiafiltration (mixed diffusion and convection with reinfusion external to the filter).

Key References

11. Ronco C, Crepaldi C, Brendolan A, et al. Evolution of synthetic membranes for blood purification: the case of the Polyflux family. *Nephrol Dial Transplant*. 2003;18(suppl 7):vii10-vii20, discussion vii55.
12. Rockel A, Hertel J, Fiegel P, et al. Permeability and secondary membrane formation of a high flux polysulfone hemofilter. *Kidney Int*. 1986;30:429-432.
23. Ronco C, Brendolan A, Crepaldi C, et al. Blood and dialysate flow distributions in hollow-fiber hemodialyzers analyzed by computerized helical scanning technique. *J Am Soc Nephrol*. 2002;13(suppl 1):S53-S61.
28. Ronco C, Brendolan A, Crepaldi C, et al. Dialysate flow distribution in hollow fiber hemodialyzers with different dialysate pathway configurations. *Int J Artif Organs*. 2000;23:601-609.
32. Saito AKH, Yamashita AC, Mineshima M. *High-Performance Membrane Dialyzers*. Basel: Karger; 2011.

A complete reference list can be found online at ExpertConsult.com.

References

1. Ward RA, Leypoldt JK, Clark WR, et al. What clinically important advances in understanding and improving dialyzer function have occurred recently? *Semin Dial*. 2001;14:160-174.
2. Lysaght MJ. Evolution of hemodialysis membranes. *Contrib Nephrol*. 1995;113:1-10.
3. Lysaght MJ. Hemodialysis membranes in transition. *Contrib Nephrol*. 1988;61:1-17.
4. Hoenich NA, Woffindin C, Cox PJ, et al. Clinical characterization of Dicea a new cellulose membrane for haemodialysis. *Clin Nephrol*. 1997;48:253-259.
5. Ronco C, Brendolan A, Everard P, et al. Cellulose triacetate: another membrane for continuous renal replacement therapy. *J Nephrol*. 1999;12:241-247.
6. Funck-Bretano JSA, Man NK, et al. A new hemodialysis treatment associating a membrane highly permeable to middle molecules with a closed circuit dialysate system. *Proc EDTA*. 1972;9:55-66.
7. Streicher E, Schneider H. The development of a polysulfone membrane. A new perspective in dialysis? *Contrib Nephrol*. 1985;46:1-13.
8. Gohl H, Buck R, Strathmann H. Basic features of the polyamide membranes. *Contrib Nephrol*. 1992;96:1-25.
9. Bonomini M, Fiederling B, Bucciarelli T, et al. A new polymethylmethacrylate membrane for hemodialysis. *Int J Artif Organs*. 1996;19:232-239.
10. Jaber BL, Gonski JA, Cendoroglo M, et al. New polyether sulfone dialyzers attenuate passage of cytokine-inducing substances from pseudomonas aeruginosa contaminated dialysate. *Blood Purif*. 1998;16:210-219.
11. Ronco C, Crepaldi C, Brendolan A, et al. Evolution of synthetic membranes for blood purification: the case of the Polyflux family. *Nephrol Dial Transplant*. 2003;18(suppl 7):vii10-vii20, discussion vii55.
12. Rockel A, Hertel J, Fiegel P, et al. Permeability and secondary membrane formation of a high flux polysulfone hemofilter. *Kidney Int*. 1986;30:429-432.
13. Ledebo I. Principles and practice of hemofiltration and hemodiafiltration. *Artif Organs*. 1998;22:20-25.
14. Ronco C, Ballestri M, Cappelli G. Dialysis membranes in convective treatments. *Nephrol Dial Transplant*. 2000;15(suppl 2):31-36.
15. Clark WR, Henderson LW. Renal versus continuous versus intermittent therapies for removal of uremic toxins. *Kidney Int Suppl*. 2001;78:S298-S303.
16. Skalsky M, Schindhelm K, Farrell PC. Creatinine transfer between red cells and plasma: a comparison between normal and uremic subjects. *Nephron*. 1978;22:514-521.
17. Lim VS, Flanigan MJ, Fangman J. Effect of hematocrit on solute removal during high efficiency hemodialysis. *Kidney Int*. 1990;37:1557-1562.
18. Shinaberger JH, Miller JH, Gardner PW. Erythropoietin alert: risks of high hematocrit hemodialysis. *ASAIO Trans*. 1988;34:179-184.
19. Eknoyan G, Beck GJ, Cheung AK, et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med*. 2002;347:2010-2019.
20. Lameire N, Kellum JA. Contrast-induced acute kidney injury and renal support for acute kidney injury: a KDIGO summary (Part 2). *Crit Care*. 2013;17:205.
21. Huang Z, Clark WR, Gao D. Determinants of small solute clearance in hemodialysis. *Semin Dial*. 2005;18:30-35.
22. Leypoldt JK, Cheung AK. Optimal use of hemodialyzers. *Contrib Nephrol*. 2002;129-137.
23. Cheung AK, Alford MF, Wilson MM, et al. Urea movement across erythrocyte membrane during artificial kidney treatment. *Kidney Int*. 1983;23:866-869.
24. Ronco C, Brendolan A, Crepaldi C, et al. Blood and dialysate flow distributions in hollow-fiber hemodialyzers analyzed by computerized helical scanning technique. *J Am Soc Nephrol*. 2002;13(suppl 1):S53-S61.
25. Poh CK, Hardy PA, Liao Z, et al. Effect of flow baffles on the dialysate flow distribution of hollow-fiber hemodialyzers: a nonintrusive experimental study using MRI. *J Biomech Eng*. 2003;125:481-489.
26. Leypoldt JK, Cheung AK, Agodoa LY, et al. Hemodialyzer mass transfer-area coefficients for urea increase at high dialysate flow rates. The Hemodialysis (HEMO) Study. *Kidney Int*. 1997;51:2013-2017.
27. Sigdell JE, Tersteegen B. Clearance of a dialyzer under varying operating conditions. *Artif Organs*. 1986;10:219-225.
28. Ronco C, Orlandini G, Brendolan A, et al. Enhancement of convective transport by internal filtration in a modified experimental hemodialyzer: technical note. *Kidney Int*. 1998;54:979-985.
29. Ronco C, Brendolan A, Crepaldi C, et al. Dialysate flow distribution in hollow fiber hemodialyzers with different dialysate pathway configurations. *Int J Artif Organs*. 2000;23:601-609.
30. Rangel AV, Kim JC, Kaushik M, et al. Backfiltration: past, present and future. *Contrib Nephrol*. 2011;175:35-45.
31. Ronco C. Backfiltration: a controversial issue in modern dialysis. *Int J Artif Organs*. 1988;11:69-74.
32. Ronco C, Brendolan A, Feriani M, et al. A new scintigraphic method to characterize ultrafiltration in hollow fiber dialyzers. *Kidney Int*. 1992;41:1383-1393.