CHAPTER 139

Principles of Extracorporeal Circulation and Transport Phenomena

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OBJECTIVES

This chapter will:

1. Present a brief overview of the main components of the extracorporeal circulation for renal replacement therapies.
2. Explain the safety features involved in the delivery of these therapies.
3. Describe the implications of the principal mechanisms of water and solute transport as the basis of renal replacement therapies.

During renal replacement therapy (RRT), blood circulates through an extracorporeal circuit, in which the site of purification is a filter. This chapter describes first the main components of the extracorporeal circuit and its principal safety features. In the second part, the transport phenomena of water and solutes involved in blood purification are explained.

PRINCIPLES OF EXTRACORPOREAL CIRCULATION

This section defines functions, components, and safety features of the extracorporeal circuit for blood purification therapy.

Therapeutic Functions of Extracorporeal Circuit

The extracorporeal circuit is designed to remove blood from the patient's circulation, deliver it to some form of blood purification device, and then return the purified blood to the patient. These tasks must be performed without damaging blood components, losing blood to the environment, or exposing the patient to potentially harmful contaminants from the extracorporeal circuit or the environment.

Main Components of Extracorporeal Circuit

A typical extracorporeal circuit is shown in Fig. 139.1; the main elements that are involved in blood circulation are described below.

Blood Access

Most patients receiving RRT in an acute setting do not have an established vascular access. In these patients, access to the circulation usually is provided by a catheter placed in an appropriate blood vessel. A single catheter with two lumens may be used for withdrawal and return of the blood. Less commonly, two single-lumen catheters may be used. If the patient does have an established blood access, such as a fistula or a synthetic graft, 15- to 16-gauge needles may be used. More details on blood access are given in Chapter 167.

Blood Tubing

Blood is conveyed to and from the blood purification device by a disposable tubing set. It consists of two segments: an inflow ("arterial") segment that connects the blood access to the inlet port of the purification device, and an outflow ("venous") segment that connects the outlet port of the blood purification device to the return blood access. Blood tubing sets usually are manufactured from plasticized polyvinylchloride and may be sterilized with ethylene oxide or gamma irradiation. Some systems specifically designed for continuous RRT applications combine the tubing set and the purification device in a system-specific integrated unit. The blood tubing set typically includes ports for the administration of fluids (replacement, dialysate) and anticoagulants, as well as a chamber in the venous line for capturing any air that may enter the blood circuit inadvertently. Specific segments of the lines are designed to be connected to pressure sensors on the machine.

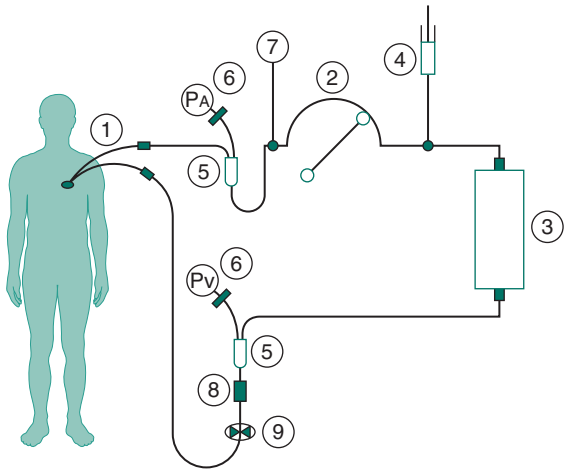

FIGURE 139.1 Typical extracorporeal circuit for hemodialysis. Convective therapies, such as hemodiafiltration and hemofiltration, use a similar circuit with the addition of lines for the infusion of replacement solution before or after the hemodialyzer or hemofilter. The major components of the extracorporeal circuit are as follows: *1,* a blood access device (shown as a central venous catheter); *2,* a blood pump; *3,* a blood purification device (hemodialyzer, hemofilter, or sorbent cartridge); *4,* an anticoagulant infusion pump; *5,* air-capture chambers; *6,* pressure-monitoring systems (shown as a pressure transducer isolated from the blood path by a pressure-transmitting sterile barrier); *7,* a side line for priming the extracorporeal circuit with saline; *8,* an ultrasonic air and foam detector; and *9,* a line clamp.

Blood Pump

The central venous pressure of the patient is usually insufficient to provide the desired flow rate of blood through the extracorporeal circuit. Therefore extracorporeal circuits for RRT use a blood pump to provide a controlled flow to the blood purification device. Peristaltic pumps (also known as roller pumps) usually are employed, because they guarantee no direct contact with blood and accurate control of blood flow. A typical peristaltic pump uses a rotating arm fitted with diametrically opposed spring-loaded rollers (two or three) that occlude the tubing accommodated in the pump housing and force the blood in the section of tubing before the point of occlusion to the outlet of the pump as the arm rotates. The rotational speed of the pump depends on the blood flow prescription and is proportional to the stroke volume, defined by the geometry of the pump and the inner diameter of the blood tubing.

Blood Purification Device

Nearly all contemporary blood purification devices used in critical care nephrology are hollow-fiber membrane devices (filters or dialyzers) that allow exchange of solutes by diffusion and/or convection and removal of water by ultrafiltration (see section below). The mechanisms involved in solute removal depend on the selected therapy. Hemodialysis relies mostly on diffusion, particularly for small waste products, electrolytes, and non–protein-bound drugs, whereas hemofiltration, achieved through convection, allows the removal of larger molecular-weight-solutes. Other therapies, such as hemodiafiltration, rely on a combination of diffusion and convection. More details on these processes are given in Chapter 165.

Another type of blood purification device achieves depuration specifically by adsorption of solutes and consists of a cartridge containing various types of adsorption resins (see also Chapters 193 and 194).

Anticoagulation System

All extracorporeal circuits activate coagulation pathways because of contact of blood components with foreign surfaces and air within the circuit. Furthermore, low wall shear stress in the fibers of the filter enhances the risk of this activation. For these reasons, extracorporeal therapy usually requires infusion of an anticoagulant into the extracorporeal circuit. The anticoagulant may have a systemic effect

(involving the patient and the circuit) or local ("regional") effect (involving only the circuit, specifically the filter). Common anticoagulants used for extracorporeal circulation in critical care RRT are heparin and citrate (see Chapter 168). Heparin may be administered as an intermittent bolus or as a continuous infusion through a dedicated syringe pump (in the machine or external) that allows highly accurate control of the volume infused. Citrate anticoagulation is regional, involving infusion of a citrate solution into the inflow line and a calcium solution into the outflow line through dedicated pumps.

Other Pumps

RRT achieves depuration by administration of fluids, the nature of which are dictated by the specific therapy prescribed. Administration and balance of these fluids are controlled through a dialysis machine having incorporated pumps with dedicated lines. The replacement/infusion pump controls the rate of replacement fluid infused into the blood inflow line (predilution) and/or into the blood outflow line (postdilution). The dialysate pump controls the rate of dialysate flow into the dialysate compartment of the filter. The effluent/ultrafiltrate pump controls the removal rate of fluid leaving the filter.

Main Safety Features of the Extracorporeal Circuit

Extracorporeal circuits should be designed to minimize the risk of adverse events during their utilization. The incorporation of active protective systems should form part of this design process. In general, a protective system independently monitors some operational parameters of a device (such as pressure profiles and fluid balance) and causes the device to assume a safe state if a parameter enters a hazardous range. The major hazards associated with the extracorporeal circuit are loss of blood to the environment after a break in the integrity of the lines, loss of blood and therapeutic efficacy resulting from clotting in the extracorporeal circuit, and air embolism.

System Integrity

To avoid accidental separations, the extracorporeal circuit should be designed so that all connections between the blood access, the tubing set, the blood purification device, and any other ancillary tubing are made with locking connectors. Although the use of this kind of connector reduces the likelihood of inadvertent line separation, this protection is not absolute. For this reason, connections in the extracorporeal circuit should remain visible throughout the treatment.

Pressure Monitoring

The extracorporeal blood circuit can be envisioned as a series of resistances to flow. As such, the flow of blood creates a pressure profile along the length of the extracorporeal circuit that is dependent on flow rate, geometry of the circuit, and blood properties.[1] A typical pressure profile is shown schematically in Fig. 139.2. The change in pressure along each segment of the extracorporeal circuit is governed by the laws of fluid mechanics, including the Hagen-Poiseuille law and Bernoulli equation.[1] These laws

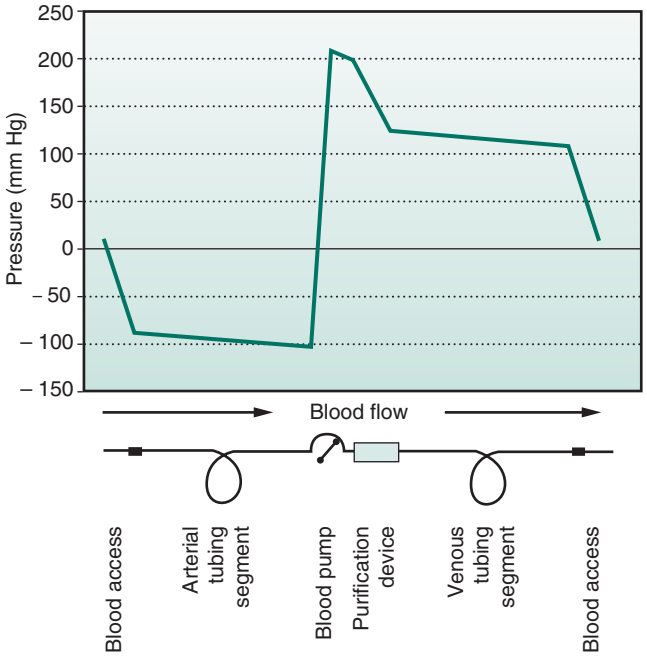

FIGURE 139.2 Typical pressure profile along the extracorporeal circuit. For a given treatment, actual pressures depend on the nature of the circuit used and the operational parameters. In particular, pressures are affected by the blood flow rate, the patient's hematocrit, and the type and internal diameter of the blood access devices.

relate changes in pressure to the dimensions of the flow path, blood flow rate, and physical properties of blood, such as viscosity and density. In general, the pressure drop along a segment of the extracorporeal circuit increases as the flow rate and viscosity increase and as the diameter of the flow path decreases. Because viscosity increases exponentially with hematocrit over the range of values encountered in extracorporeal circulation for RRT,[2] it may change markedly along the length of the extracorporeal circuit and with time of treatment, depending on ultrafiltration and fluid infusion. Although the prescribed operating parameters, such as blood flow rate and ultrafiltration rate, establish the pressures in the extracorporeal circuit, these pressures may, in turn, affect the operating parameters.

INFLOW PRESSURE. Because the pressure in the inflow blood tubing proximal to the blood pump is almost always less than atmospheric pressure, air can be drawn into the blood tubing if any connection in this segment does not have a tight seal or an arterial access; blood line disconnection occurs. Any air drawn into the system has the potential to cause clotting in the blood purification device or to result in an air embolus (if the air and foam detector fail simultaneously). Pressure monitoring in this segment serves as the basis for a protective system to guard against these hazards. Because the pressure in this segment is subatmospheric, a break in tubing integrity will lead to an increase in pressure so that the upper alarm limit is exceeded. The same protective system also guards against occlusion of the blood tubing proximal to the pressure sensor, which can occur if the blood tubing becomes kinked or there is a problem with the blood access. In this instance, pressure will decrease and breach the lower alarm limit. If either alarm limit is breached, the protective system alerts the operator and places the machine in a safe mode.

PREFILTER PRESSURE. Monitoring of pressure between the blood pump and the inlet to the blood purification

device (also referred as prefilter pressure) can alert the user to the possibility of clotting or mechanical occlusion downstream of this pressure sensor. An increase in the prefilter pressure, together with an increase in the difference between this pressure and the pressure in the outflow segment of the blood tubing (i.e., filter pressure drop), usually signifies clotting in the blood purification device. Conversely, an increase in the prefilter pressure with little or no change in the pressure drop usually signifies clotting of the blood access device or occlusion of the tubing beyond the outflow pressure monitor. Prefilter pressure also is used to monitor the transmembrane pressure, particularly in convective modalities such as hemofiltration and hemodiafiltration.

OUTFLOW PRESSURE. The outflow pressure is the positive pressure between the blood purification device and the patient's vascular access. This parameter is used for the calculation of transmembrane pressure and pressure drop along the purification device. An increase in the outflow pressure could be related to line or catheter occlusion or clotting downstream of the detection point. A decrease in the value of this pressure could be a consequence of blood line separation downstream of the pressure sensor or filter clotting.

EFFLUENT AND ULTRAFILTRATE PRESSURE. This parameter reflects the pressure in the effluent compartment of the filter. The pressure sensor is placed along the effluent line, upstream of the associated pump that controls the fluid removal rate. If the membrane is relatively "clean" with minimal clotting and pore occlusion ("clogging") resulting from protein deposition in the inner surface (e.g., at the beginning of RRT session), this value is positive. However, as treatment progresses, the likelihood increases that the above phenomena become important, resulting in increased resistance within the fibers. In this context, the effluent/ultrafiltrate pressure falls, possibly reaching negative values. In conjunction with other pressures, this parameter also allows the calculation of the transmembrane pressure (see later in this chapter).

FILTER DROP PRESSURE. This pressure is calculated as the difference between prefilter pressure and outflow pressure. Its increase usually signifies clotting in the blood purification device.

TRANSMEMBRANE PRESSURE. Transmembrane pressure (TMP) is defined as the pressure gradient across the blood purification device membrane. It depends on several different pressures and varies along the filter length as:

$$TMP = \left[\frac{P_{Bi} + P_{Bo}}{2} - \frac{P_{Di} + P_{Do}}{2} - P_{onc} \right]$$

where P_{Bi} is blood compartment inlet pressure, P_{Bo} is blood compartment outlet pressure, P_{Di} is dialysate/ultrafiltrate compartment inlet pressure, P_{Do} is dialysate/ultrafiltrate compartment outlet pressure, and P_{onc} is oncotic pressure of the blood.

An approximate value of TMP can be obtained as the difference between the mean pressure value in the blood compartment and the effluent/ultrafiltrate pressure:

$$TMP = \frac{P_{PRE} + P_{OUT}}{2} - P_{EFF}$$

where P_{PRE} is the pre-filter pressure, P_{OUT} is the outflow pressure, and P_{EFF} is the pressure measured in the effluent line.

Monitoring of pressures in the extracorporeal circuit serves as the basis for protective systems to guard against blood line separation or occlusion. High and low alarm limits usually are set automatically by the machine at some predetermined amount above and below the measured operating pressure at the start of the treatment. However, some machines allow the operator to adjust the magnitude of these preset high and low alarm limits. The difference between the limits and the operating pressure should be small enough to detect a hazardous condition but not so small as to cause frequent nuisance alarms when small excursions in operating pressure occur (e.g., during patient movement). If a pressure reading falls outside the established operating range, audible and visible alarms are activated. In addition, the blood pump is stopped, the automatic safety clamp is activated, and the dialysis device's fluid balancing system is set to a neutral condition so that no fluid exchange occurs.

Pressure-based protective systems are not perfect. Depending on pressures in the extracorporeal circuit, disconnection of blood tubing from the blood access device or dislodgement of a blood access needle may not result in a pressure change sufficient to activate the protective system. This situation is most likely to occur at low blood flow rates when the pressure drop across the blood access device is small, or when relatively wide alarm limits are set. For this reason, connections to the blood access device, as well as to the access site, always should be kept visible, and the low pressure alarm limit should be set as close as possible to the operating pressure.

Air Embolism

Separation of the inflow line from the blood access catheter, presence of small air bubbles coming from replacement fluid bags, and incomplete air removal from the filter during the priming procedure are the primary reasons for air entry into the extracorporeal circuit. To mitigate the risk of an air embolus to the patient, the dialysis machine has two protective aspects. The first is a chamber, located downstream of the blood purification device, in which entrained air can be separated from the blood to a large extent.

As this mechanism cannot guarantee complete air removal, the machine is equipped with an additional protective system. This system consists of an ultrasonic sensor and a safety clamp, associated with the outflow tubing downstream of the air chamber. If the ultrasonic sensor detects air in the blood tubing, the clamp occludes the line to prevent air from reaching the patient; at the same time, the pump system stops and audible and visible alarms are activated.

Blood Loss

The blood leak detector (BLD) is an optical sensor placed in the effluent line. It identifies blood leaks from the blood compartment of the filter resulting from fiber rupture.

Fluid Imbalance

During the delivery of a RRT, the effective balance between administration and removal of fluids is an important consideration. Excessive removal of fluid (net negative fluid balance) may lead to a hypovolemic condition in the patient, possibly precipitating hemodynamic instability, whereas inadequate fluid removal (net positive fluid balance) may result in clinically significant hypervolemia.

Fluid imbalance related to the RRT system is related primarily to pump-related flow inaccuracies and human error (e.g., erroneous clamping of a line through which fluid outflow or inflow should be occurring). Importantly, from the specific perspective of *patient* fluid balance, the failure to account for fluid administration or removal that is not part of the RRT prescription (e.g., fluid boluses for hypotension, urine output) also may be included in this latter category of human error.

Monitoring of the treatment fluid balance can be achieved through gravimetric, volumetric, or fluxometric methods or by a combination of these mechanisms.

TRANSPORT PHENOMENA

The mechanisms involved in RRT are based on the principles of water and solute transport whereby the composition of a solution (blood) is modified by exchange across a semipermeable membrane.[3–5] This dynamic exchange process is driven by the use of specific fluids, which in turn are dependent on the particular therapy prescribed. Fluid transport is driven by *ultrafiltration* and *osmosis*. Solute transport occurs mainly by two phenomena, namely *convection* and *diffusion*. *Adsorption* influences solute removal by attachment of solute to the membrane.

Water Transport

Ultrafiltration

Fluid transport across the porous membrane of a filter during treatment is defined as ultrafiltration. This process is governed by the plasma oncotic pressure and, more importantly, the presence of a hydrostatic pressure gradient between the blood and effluent/ultrafiltrate compartments. Mathematically, the ultrafiltration flow rate can be expressed in terms of membrane permeability (or membrane ultrafiltration coefficient K_{UF}), membrane area, and pressure gradient across the membrane:

$$Q_{UF} = K_{UF} \cdot A \cdot TMP$$

where the product of membrane ultrafiltration coefficient (K_{UF}) and area (A) gives the dialyzer ultrafiltration coefficient (DK_{UF}). As the treatment proceeds, particularly over an extended period of time, this relationship will be nonlinear because of the permeability decay that accompanies progressive protein and fibrin deposition on the membrane surface (Fig. 139.3).

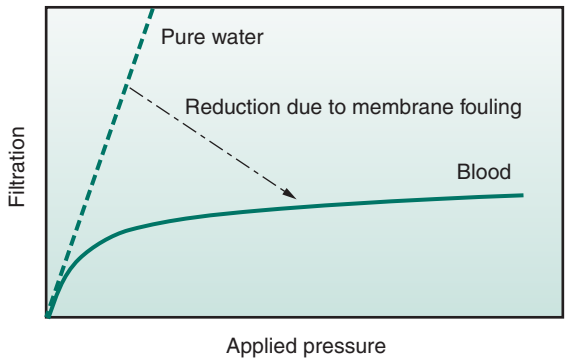

FIGURE 139.3 The influence of fluid composition on filtration.

The dependence of ultrafiltration on the fluid dynamic conditions within devices is complex. Its role is particularly important in filters, where the ultrafiltration flow is dependent on the shear rate or the velocity gradient at the blood-membrane interface. In turn, shear rate is influenced importantly by blood flow rate and hematocrit.

Osmosis

Osmosis is a biophysical phenomenon occurring commonly in biologic systems, in which cells of fluid compartments are separated by semipermeable membranes. Osmosis describes the diffusion of the solvent through a semipermeable membrane. The driving force of the solvent shift is the concentration difference of solutes in the solutions separated by the semipermeable membrane. In contrast to solvent, solutes cannot pass this barrier. Water, the usual solvent in biologic systems, migrates from the compartment with lower concentration to the compartment with higher concentration of solutes. The net fluid flux ends when the concentration of osmotic active molecules is equal in the two compartments. Therefore the distribution of water is a matter of osmosis and not transport of solutes.

Solute Transport

Convection

Convection occurs when water flow, driven by either a hydrostatic or an osmotic pressure gradient across a semipermeable membrane, is accompanied by the transport of solutes having dimensions that allow passage through the membrane pores. This is also referred to as "solvent drag." Solutes having unrestrained passage through the membrane have filtrate concentrations similar to those in the original solution. On the other hand, larger molecules may have constrained passage (i.e., are sieved), resulting in filtrate concentrations that are lower than those in the original solution. Filtration occurs in response to the TMP gradient.

The combined effects of ultrafiltration and convection result in the transport of solutes across the membrane at various rates according to their membrane rejection coefficient (RC), with σ being near 1 for albumin and near 0 for small solutes such as urea. The sieving coefficient for a solute (SC) is correlated inversely with the membrane rejection coefficient ($SC = 1–RC$). In clinical practice, SC is approximated as the ratio of the concentration of solute in the ultrafiltrate and its concentration in plasma water. In purely convective treatments (for nonadsorbing solutes) therefore the transport (J_c) of a solute *x* is governed by the formula:

$$J_c = \frac{Q_{UF}}{A} \cdot C_{UF} = J_F \cdot C_{UF}$$

where J_c is the convective mass flux of solute x ($mg/hr/m^2$), J_F is the ultrafiltration flux ($mL/hr/m^2$), and C_{UF} is the concentration in the ultrafiltrate of solute x.

Diffusion

Diffusion is a process in which molecules move randomly across a semipermeable membrane. Solute movement occurs from a more concentrated to a less concentrated area, until

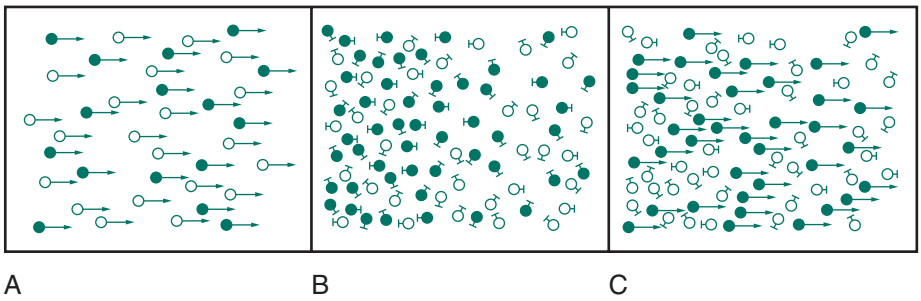

FIGURE 139.4 Diffusion is the result of microscopic molecular movements. A, Convection without diffusion moves all molecules equally and does not result in separation. B, Unhindered ordinary diffusion causes initially separated molecules to move together. C, Forced diffusion, provided by an external force, separates molecules when the force acts differently on different molecular types.

equilibrium concentration between the two compartments is reached. The concentration gradient ($C_1 - C_2 = dc / dx$) is the driving force and the unidirectional solute diffusive flux (J_d) through the semipermeable membrane follows Fick's law of diffusion. It depends on the diffusivity coefficient (D) of the solute and is inversely proportional to the distance between compartments (dx).[6,7]

$$J_d = -D \cdot \frac{dc}{dx}$$

This phenomenon is illustrated in Fig. 139.4B, in which the larger proportion of blue molecules on the left will lead ultimately to their uniform distribution in the mixture as a result of random motion.

Although diffusion in solutions depends on properties of the solution and sizes of the different molecular species, this dependence is not strong. Most small molecules (such as glucose, urea, and ionized salts) have D values near 10^{-5} cm^2/sec in physiologic solutions at ambient and physiologic temperatures. For molecules that are large relative to those comprising the medium, D varies with the molecular radius R, as described by the Stokes-Einstein equation:

$$D = \frac{k_B T}{6\pi\mu R}$$

This analysis is based on the usual assumption that most molecules are globular, having an effective radius for diffusion (R) proportional to molecular weight.[7] In this equation, k_B is the Boltzmann constant, T is the absolute temperature, and μ is the viscosity of the medium.[7,8] Thus the diffusion coefficient of albumin is only about 15 times smaller than that of urea, even though its molecular weight is about 1000 times larger.

Fig. 139.5 shows a membrane through which transport is occurring from right to left. The pore structure of the membrane (lines in the figure) allows passage of small molecules *(small circles)* but not large molecules *(large circles)*. Instead, the large molecules are rejected and accumulate at the membrane surface, resulting in a relatively high concentration at the blood-membrane interface. Because this "submembranous" concentration is higher than the "bulk" concentration away from the blood/membrane interface, one possibility is that these rejected molecules diffuse from the surface back into the bulk stream in response to the concentration gradient established. (Note that some molecules still can move simultaneously in the opposite direction toward the membrane from the bulk phase due to the random nature of diffusion.) The other potential fate of the accumulated molecules is to be transported

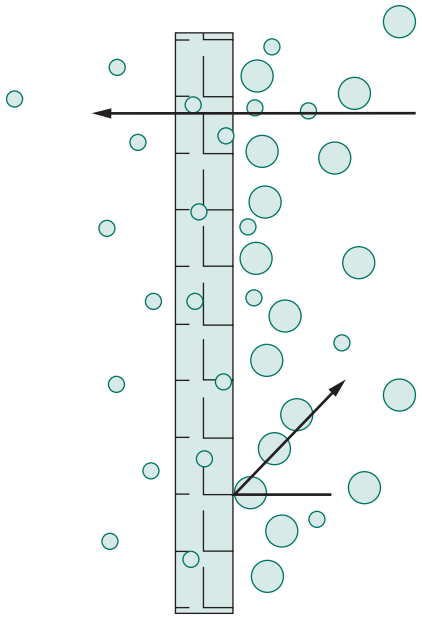

FIGURE 139.5 Hindered ordinary diffusion, typically provided by a membrane, separates molecules. The hindering structure must act differently on the different types of molecules to be separated.

"sidewards" (upward or downward in the figure) by a crossflow mechanism that is dependent on shear forces acting at the blood/membrane interface (this analysis assumes the larger molecules only accumulate at the membrane surface but are not physically adsorbed). Thus solute rejection by the membrane is a dynamic process and molecular size is only one, albeit important, determinant of its selectivity.

Adsorption

Adsorption (membrane binding) is another mechanism by which hydrophobic compounds such as peptides and proteins may be removed during extracorporeal therapy. Although this process is a relatively poorly understood phenomenon, certain membrane characteristics play an important role. First, adsorption occurs primarily within the pore structure of the membrane rather than at the nominal surface contacting the blood.[9] Therefore the open-pore structure of high-flux membranes affords more adsorptive potential than the pores of low-flux membranes. Second,

synthetic membranes, many of which are fundamentally hydrophobic, generally are much more adsorptive than hydrophilic cellulosic membranes.[10]

CONCLUSION

The devices applied for performing extracorporeal renal replacement therapies are designed to provide a very high level of safety for the patient, minimizing the risk of damage of blood components, blood loss to the environment, and exposure to potentially harmful contaminants. Contemporary, renal replacement devices are equipped technologically with adequate control systems for monitoring these therapies. The knowledge of these devices and related disposables is essential for the clinical care team to perform an adequate and safe treatment.

At the same time, the filter is the most important component of the extracorporeal circuit with respect to achieving therapeutic goals. Therefore it is imperative for clinicians to understand the basic principles of solute and water transport phenomena so that personalized therapy meeting the specific needs of each patient is prescribed.

Key Points

1. Machines and related extracorporeal circuits for renal replacement therapies are technologically well equipped to perform the treatments in safety; a deep knowledge of components and operating parameters is crucial.
2. The mechanisms involved in renal replacement therapy are based on the principle of water and solute transport according to three fundamental principles: ultrafiltration for fluids, convection, and diffusion for solutes.

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