CHAPTER 141

Continuous Renal Replacement Therapy Machine Technology

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OBJECTIVES

This chapter will:

1. Provide a brief history of the development and evolution of continuous renal replacement therapy (CRRT) systems.
2. Describe the basic features of CRRT machines, including the user interface, pumps, pressure monitoring, safety features, and anticoagulation capabilities.
3. Understand the basic principles of CRRT membranes and filters, especially with regard to the influence of modality, membrane characteristics, and blood/fluid flows on solute transport.
4. Describe recent developments in CRRT membrane technology.

CONTINUOUS RENAL REPLACEMENT THERAPY MACHINES: HISTORICAL PERSPECTIVE

Between 1965 and 1975, Lee Henderson et al. reported clinical results from therapies using hollow-fiber filters for hemofiltration and ultrafiltration in patients with end-stage renal disease (ESRD).[1,2] Although these therapies used a blood pump, Kramer et al. subsequently reported an adapted, machine-free method using a similar hollow-fiber device for the treatment of critically ill, fluid-overloaded patients resistant to diuretics.[3] This simple system consisting of arterial and venous catheters connected to a capillary hemofilter by tubing; filtrate pressure was produced by the difference

between blood pressure and environmental pressure. This approach was termed continuous arteriovenous hemofiltration (CAVH), although the original description[3] did not mention the use of replacement fluid in the system, whereas a later report did.[4] Along with continuous arteriovenous hemodialysis (CAVHD)[5] and arteriovenous slow continuous ultrafiltration (SCUF),[6] the development of CAVH established continuous renal replacement therapy (CRRT) as a set of treatment modalities for critically ill patients with acute renal failure.

Arteriovenous CRRT modalities had several limitations, especially the unpredictability of blood flow rate and ultrafiltrate production (because of the dependence on the patient's blood pressure) along with the requirement for placement of large-bore catheter in a major artery. As such, interest turned toward developing systems incorporating a blood pump. The first-generation venovenous CRRT machines subsequently developed were simple devices derived from components of standard hemodialysis equipment used for maintenance dialysis. From a safety perspective, monitoring of the extracorporeal circuit typically included standard pressure sensors along with an air/foam detector and blood leak detector on the filtrate/spent dialysate line. In general, these systems either had no or relatively unsophisticated fluid balancing systems, required many procedures (e.g., circuit priming) to be performed manually, and incorporated only rudimentary user interfaces. A major step was the 1994 market introduction of the Prisma system by Gambro (later acquired by Baxter) (Fig. 141.1).[7] This device was developed specifically for continuous treatment in the intensive care unit (ICU), allowing hemodialysis, hemofiltration, and hemodiafiltration (CVVHD, CVVH, and CVVHDF, respectively) with intravenous-quality replacement fluid and/or dialysate. In addition to four pumps for blood, dialysate, replacement fluid, and effluent, this machine had three scales for dialysate, replacement fluid, and effluent. Fluid balancing was achieved by minute-to-minute comparison of actual weights versus expected values based on the prescription, with corrections made to pump speeds based on servo-type software. Another significant achievement with this device was the air-free disposable cassette system having an integrated filter. Finally, the user interface was improved substantially, guiding the user through the various steps required for setting up the machine and rectifying problems. However, the maximum allowable blood flow rate was only 180 mL/min, and total effluent was limited to 5.5 L/hr. The Prisma machine triggered the development of integrated, specialized CRRT machines all over the world.[8] These newer machines included three to five pumps and three to four scales able to handle 12 to 20 L of replacement fluid or dialysate and capable of producing blood flows up to 400 to 600 mL/min. The general trend has been toward more fully automated machines that allow all renal support treatment modes at higher blood flow and fluid exchange rates. In addition, these recent devices have been developed with more emphasis on human factors, especially at the user interface, in an attempt to improve safety and the quality of delivered therapy. Another feature of many of the new machines is the ability to perform adjunctive therapies, including liver and respiratory support.[9,10] Finally, specific functionalities, such as those enabling regional citrate anticoagulation, have been included in some newer devices.

The remainder of this chapter provides more specific technical details regarding the latest generation of CRRT machines. Much of this information ultimately can be traced to the Charta of Vicenza,[11] which led to the organization of a recent consensus conference termed the Nomenclature Standardization Initiative (NSI).[12] For this initiative, members of the clinical community and industry collaborated to develop standardized terminology for dialysis therapies used in the management of critically ill patients with acute kidney injury (AKI) and other disorders.

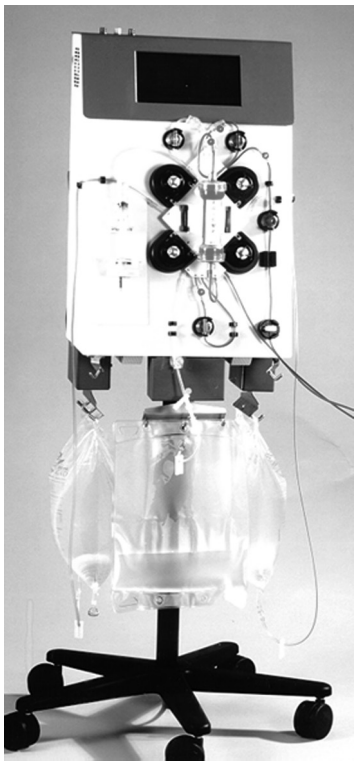

FIGURE 141.1 The Prisma machine.

CONTINUOUS RENAL REPLACEMENT THERAPY HARDWARE

A diagram demonstrating the major features of the typical contemporary CRRT machine appears in Fig. 141.2. The following provides commentary on the different aspects of these devices; several commercially available devices are shown in Fig. 141.3. Although different CRRT modalities are mentioned in this chapter, a more detailed discussion of them occurs in other sections of this book.

User Interface or Screen

Although early generations of CRRT machines provided relatively limited treatment information to the user, the interface between the user and contemporary devices is now much more sophisticated.[13] In addition to basic treatment information, such as actual flow rates, elapsed time, and circuit pressures, modern machines also provide instantaneous and cumulative values for critical parameters, especially those related to fluid balance on an ongoing basis. In addition, discrepancies between prescribed and delivered (actual) values for treatment time and effluent volume allow assessments of treatment adequacy. Current machines also provide a number of timely alerts, including those related to a potentially adverse circuit pressure trend (suggesting impending circuit clotting) and the need for a bag change.

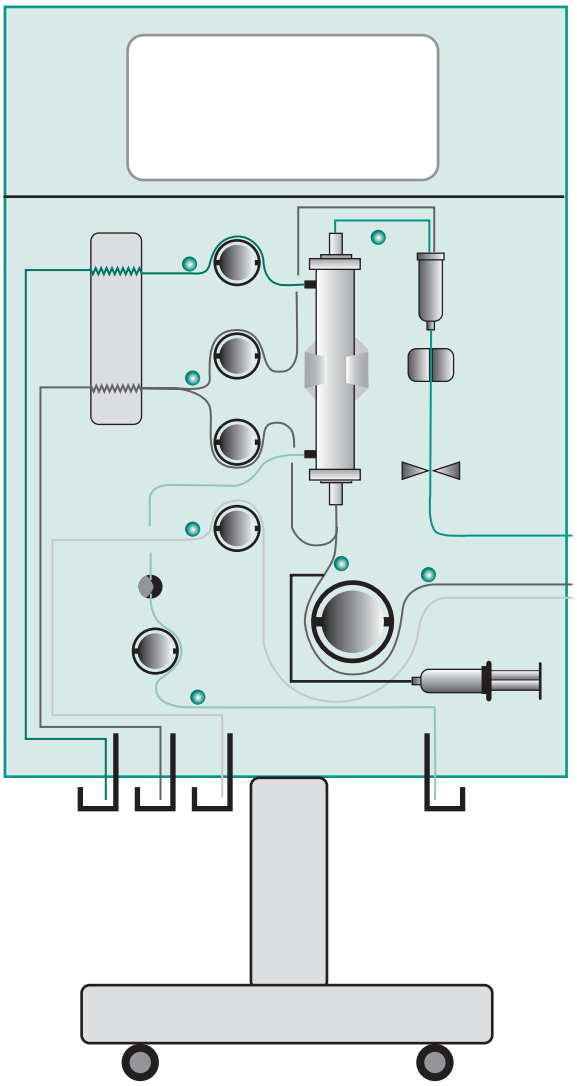

FIGURE 141.2 Basic components of a standard gravimetric continuous renal replacement machine. Prominent components include the user interface, infusion/effluent pumps and lines, blood pump, pressure monitors, and scales. Safety aspects include an effluent blood leak detector, venous drip/deaeration chamber, and venous clamp. (Adapted from Villa G, Neri M, Bellomo R, et al. Nomenclature for renal replacement therapy and blood purification techniques in critically ill patients: practical applications. *Crit Care.* 2016;20[1]:283.)

From a safety perspective, an important addition in the past decade has been the incorporation of device software that controls the deviation from prescribed fluid removal rates.[14] Newer features also remind the user to assess the cause of an alarm signifying such as a deviation and the magnitude of the fluid imbalance that may arise. Finally, many machines now have the operator's manual and tutorials directly available to the user at the screen. Of course, a prerequisite for the user to achieve the maximum benefit from these new safety features is adequate training, primarily at the institutional level but also from the manufacturer when necessary.

Circuit Pumps and Pressure Monitoring

A series of pumps controlling the flow rates of blood along with effluent, replacement fluid, and/or dialysate is integral to any CRRT device. Although blood flow rates of 100 to 125 mL/min or less were typical in the early years of CRRT, the demonstration in a 2000 publication by Ronco et al.[15] of improved survival with an effluent-based dose of 35 mL/kg/hr or more (vs. 20 mL/kg/hr) in postdilution CVVH compelled manufacturers to offer systems with higher blood flow rate capabilities. The particular importance of blood flow rate in delivery of the prescribed dose of hemofiltration, whether in the predilution or postdilution mode, has been highlighted.[16]

Fluid Mechanics of Blood Flow in the Extracorporeal Circuit

As blood flow rate increases, higher absolute pressures within the blood compartment along with larger pressure drops along the length of the circuit are created. Blood flow through blood lines and filter of the extracorporeal circuit can be characterized by the Hagen-Poiseuille equation,[17] in which a direct relationship exists between flow rate and pressure drop for flow through a tube. The resistance to blood flow is directly proportional to blood viscosity and inversely proportional to the fourth power of the tube radius (whether for the blood lines or the hollow fiber capillaries in the filter). In essence, pressure drop is directly proportional to resistance at a given blood flow rate. The dimensions of manufacturers' tubing and filter fibers fall in a relatively narrow range to balance the desire to achieve adequate solute and water transport characteristics while avoiding excessive pressure drops and the associated risk of turbulent flow and hemolysis. On the other hand, blood viscosity can be variable, being influenced by the dilution mode used for convective therapies and the patient's hematocrit (see below).

Pressure Measurements

For modern CRRT circuits, pressure is monitored at several critical locations, providing absolute pressures and pressure differences. In the blood compartment, pressure is monitored by sensors at the following locations (see Fig. 141.2):

- Between the patient's vascular access and the blood pump (inflow line): measures the degree of negative pressure generation resulting from the suction effect of the blood roller pump in withdrawing blood from the access. For catheters, excessive negative pressure can be created by occlusion of the arterial limb with fibrin or thrombus and a malpositioned catheter against a vessel wall.
- Between the blood pump and filter (inflow line): in conjunction with outflow line pressure, allows for the determination of (end-to-end) filter pressure drop and transmembrane pressure (TMP).
- Between the filter and the vascular access (outflow/return line): in conjunction with inflow line pressure, allows for determination of filter pressure drop and transmembrane pressure. An increase in this pressure may signify a mechanical obstruction in the venous limb of a catheter, related to thrombus/fibrin formation or malpositioning against a vessel wall.

Measurement of effluent pressure, in conjunction with the inflow and outflow blood compartment pressures, allows calculation of TMP. (Effluent volume comprises the volumes of replacement fluid, dialysate, and the net ultrafiltrate desired from a fluid balance perspective.) Effluent pressure can be positive or negative, depending on the specific modality, flow rates, and filter conditions. Although effluent

FIGURE 141.3 Examples of commonly used and recently developed continuous renal replacement therapy machines. Beginning at the upper left and moving clockwise: Prismaflex (Baxter); multiFiltratePro (Fresenius Medical Care); Omni (B Braun); System One (NxStage Medical); Aquarius (Nikkiso); Carpediem (Medtronic); Amplya (Medtronic); Kibou (Asahi); PrisMax (Baxter). (Carpediem is specifically designed as a pediatric CRRT device and is discussed elsewhere in this book.)

pressure typically is measured at a single location as the effluent leaves the filter, some devices used in the CVVHD mode measure the inflow (dialysate) pressure and outflow (dialysate plus net ultrafiltrate) pressure for a more accurate estimation. Clinical experience suggests a substantial increase in the filter pressure drop during treatment is due primarily to filter thrombosis (i.e., fiber occlusion), whereas a substantial TMP increase during treatment is related primarily to blood-membrane phenomena, especially protein deposition. For postdilution CRRT modalities (especially CVVH), hemoconcentration is an important consideration with respect to both of these pressure measurements.[18] Filtration fraction, generally defined as the ratio of the filter effluent rate to the plasma flow rate delivered to the filter, is an indicator of hemoconcentration. Postdilution CVVH operated at a filtration fraction greater than 20% to 25% increases the risk of excessive increases in the hematocrit of the blood as it flows from filter inflow to outflow. In addition to concentrating red blood cells, blood viscosity also increases with a proportional increase in the resistance to flow. Moreover, concentration of plasma proteins occurs, facilitating protein-membrane interactions and reducing membrane permeability.[19] For these reasons, many contemporary machines provide estimates of filtration fraction so that excessive hemoconcentration can be avoided.

These considerations are represented diagrammatically in Fig. 141.4. As blood flow rate increases, filtration fraction decreases (because of a higher rate of plasma flow to the filter at a given hematocrit). Moreover, the physical effect of increased blood flow rate is increased "shear" at the blood/membrane interface, which mitigates the detrimental impact of protein adsorption on membrane function.

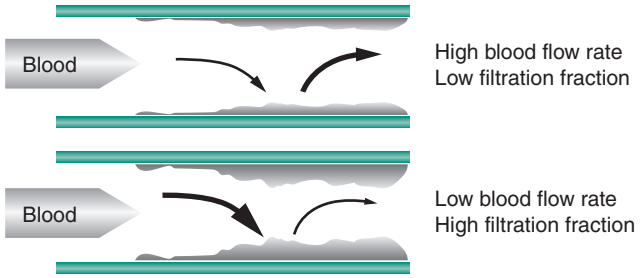

FIGURE 141.4 Diagrammatic representation of the factors influencing secondary membrane formation during continuous renal replacement therapy. In general, conditions of low filtration fraction and/or high blood flow rate attenuate this process while high filtration fraction and/or low blood flow rate promote it.

Most devices provide trend analyses of filter pressure drop and TMP during treatment and alert users upon attainment of threshold values that necessitate a circuit change to avoid significant blood loss associated with a frankly coagulated circuit. Moreover, relative to baseline values established early in the use of a particular circuit, changes in access negative pressure (more negative) or return pressure (more positive) that reach certain threshold values also provide warnings to the user.

A final caveat about pressure monitoring relates to the potential for catheter disconnection. For different pressure

measurements in the extracorporeal circuit, alarm "windows" signifying acceptable operating ranges are established for a particular treatment; the user is notified if a pressure falls outside its window. However, although not reported widely in the literature, it is well known that partial disconnection of a catheter from the return blood line may not result in a sufficient decrease in the return pressure for it to fall outside its operating window. Without any user notification of this development, significant blood loss can occur, even to the point of exsanguination. This risk is mitigated by protocolized catheter connection procedures and strict avoidance of visually obscured catheters (e.g., by bed sheets).

Fluid Balance

A basic component of the CRRT prescription is the desired degree of net fluid removal from the patient, the estimation of which requires a volume assessment of the patient along with hemodynamic status. A point worth emphasizing is that *machine* fluid balance is determined simply by the difference between CRRT-related inputs (replacement fluid and/or dialysate) and CRRT-related output (effluent), whereas *patient* fluid balance incorporates all fluid inputs and outputs. This is an important distinction when evaluating hourly or cumulative fluid balance data. Although CRRT machines use different technical approaches for fluid balancing, some common considerations apply. In all fluid balancing systems, the component instruments (pumps, scales, volumetric chambers) all have an inherent error ("tolerance"). Manufacturers typically provide these tolerances as deviations (+/-) from a certain prescribed value. The fluid accuracy ("specification") of a CRRT system reflects the cumulative effect of the tolerances associated with the various components of the system. A fluid balance error is defined as an imbalance (either positive or negative) outside a device's specification. Although most conventional hemodialysis machines employ volumetric balancing (see below), a gravimetric (scale-based) system is used most commonly for CRRT. Based on reported fluid accuracy specifications, a gravimetric system is the most reliable technique specifically during long treatment intervals, during which the risk of cumulative fluid balance errors is potentially high. (However, as discussed below, actual fluid balance is influenced by not only the accuracy specification for the system but also the manner in which the user applies the system to the patient.) A fundamental aspect of this type of system is the continuous weighing of the effluent along with replacement fluid and/or dialysate, with the rate of mass accumulation or disappearance for a particular scale acting as a surrogate for fluid flow rate. The machine software continuously analyzes these scale data, and any discrepancies between prescribed and actual (measured) values lead to adjustments in pump speed rates based on a servo-feedback mechanism, as mentioned previously. This functionality has evolved further for at least one system (Aquarius; Nikkiso), which has the capability to compensate automatically for any fluid balance discrepancies, in accordance with the patient's prescribed net fluid balance.

Although the benefits of gravimetric fluid balancing seem to be widely accepted, drawbacks include specific scale-related issues (calibration, sensitivity to environmental factors) along with the need for users to manage large volumes of fluids in bags. Furthermore, users must be constantly vigilant about potential flow obstructions (e.g., clamped fluid line) and respond to alarms in a decisive and timely manner. As suggested above, modern machines strictly address the extent of fluid imbalances created in these situations by limiting the allowable cumulative fluid imbalance over specific time intervals for a given disposable set.

A typical volumetric fluid balancing system consists of a series of balance chambers and valves. The fluid accuracy specification for a volumetric system typically includes a parameter that represents a certain percentage of the total volume of fluid exchanged. Over long treatment times, cumulative errors of significant volumes can occur because there is no feedback system that continuously compares prescribed and actual fluid volumes. On the other hand, the advantage from the user's perspective is freedom from the need to manipulate large volumes of bagged fluids. Moreover, relative to gravimetric systems, the number of fluid-related interventions is reduced. A volumetric CRRT system used commonly in the United States is the NxStage System One.[20]

Other Safety Features

Hypothermia commonly develops during CRRT, and its management can be difficult.[21] Even though current machines offer the possibility to heat dialysate/replacement fluid or blood, a significant percentage of patients nevertheless develop hypothermia. It is possible that future CRRT machine technology may incorporate technologies capable of estimating thermal energy balance and preventing hypothermia, as has been proposed for chronic hemodialysis.[22] Other standard safety features incorporated into all modern CRRT devices include bubble detectors, venous clamps, and blood leak detectors. These features are adapted largely from chronic hemodialysis technology.

Anticoagulation

Over the past decade, a series of publications have raised questions about the safety of heparin as an anticoagulant for CRRT.[23,24] Nevertheless, heparin continues to be used in a substantial percentage of patients, even some who are at high risk of bleeding. Nearly all CRRT machines have syringe pumps capable of providing heparin or other anticoagulants (e.g., nafamostat) in the form of bolus and continuous infusions. In light of the concerns about heparin, a migration to regional citrate anticoagulation (RCA) has occurred, possibly accelerated in the past few years by recommendations from the Kidney Disease: Improving Global Outcomes (KDIGO) consensus group.[25] Earlier versions of CRRT devices generally were not equipped adequately for this method and the citrate (usually in hypertonic form) and calcium solutions typically were infused by external pumps. As such, the CRRT machine's fluid balance system did not account for the fluid administered to or removed from the circuit in this approach. Moreover, users had to ensure that these external pumps were operated synchronously with the CRRT machine's pumps.

Some of the latest generation CRRT devices have features allowing for safer and more efficacious delivery of RCA.[26] In particular, such latest generation systems have an infusion pump integrated into the CRRT machine, which delivers fluid before the blood pump. Although this pump can infuse any solution, it is employed most commonly for infusion of hypertonic and isotonic ("dilute") citrate anticoagulant solutions. Based on the concentration of such citrate solution, the infusion rate is coupled to blood flow rate by machine software to achieve a target citrate concentration in the blood.

For the Prismaflex system (as an example), use of a dilute anticoagulant solution is particularly common and the

typical infusion rate (at least 1 L/hr) required to achieve the desired anticoagulant effect augments the total fluid volume (blood plus anticoagulant solution) delivered to the blood pump.[27] In this respect, the citrate solution acts also as a replacement fluid.[28] Older CRRT technology does not account for this mixing phenomenon; the flow rate delivered by the pump to the filter is simply the prescribed blood flow rate and reflects the degree to which the blood is diluted. On the other hand, the Prismaflex system software automatically increases the blood pump speed by an amount equivalent to the rate of pre-blood pump infusion. With this pump compensation functionality, the blood flow rate prescribed by the clinician actually is delivered to the filter. Another important feature of the preblood pump infusion site is its location very close to the connection of the catheter to the blood inflow line, allowing for anticoagulation of nearly the entire prefilter blood segment. Finally, the Prismaflex RCA system has integrated calcium reinfusion for which the rate is modulated by device software to balance calcium losses to effluent, according to several therapy, filter, and patient parameters.

As an alternative to dilute citrate solution, other systems such as the multiFiltratePRO rely on a hypertonic citrate anticoagulation solution when delivering CVVHD or CVVHDF treatments. Again, these systems have algorithms embedded into the software that control the ratio of citrate flow rate to blood flow rate and support the user in an analogous manner. As citrate solution flow rate is low in comparison with the blood flow rate, the impact of predilution on clearance is negligible. Calcium replacement distal to the filter is provided by an additional integrated pump. This latter aspect is controlled by the software to ensure a correct ratio between the effluent and calcium flows on a continuous basis. Finally, the relatively large buffer load provided by the hypertonic citrate solution is compensated by a low bicarbonate concentration in the dialysate. Prescribing the fluids in suitable proportion achieves the desired control of acid-base status.[29] The multiFiltratePRO system provides control by monitoring the ratio of the blood and dialysate flow rates, making the user aware of settings outside the expected range. A recent study has demonstrated this approach can be applied safely in ICUs having relatively little experience with RCA.[30] Finally, the Aquarius system has additional integrated citrate and calcium pumps synchronously linked to the blood pump. Software algorithms remove the additional fluid administered through these two solutions. A more recent adaptation ensures not only this automated coupling but also maintenance of the desired citrate dose if the blood pump rate is changed.

CONTINUOUS RENAL REPLACEMENT THERAPY DISPOSABLES

Disposables ("sets") are defined as the single-use components of the extracorporeal circuit. These devices are specific to a certain CRRT machine and typically have integrated high-flux filters, although some "open" systems allow interchangeability. The specific type of filter, especially with regard to surface area, is dictated by the chosen modality. Before the widespread prescription of higher CRRT doses, replacement fluid and/or dialysate rates along with blood flow rates were relatively low (frequently less than 1 L/hr and 125 mL/min, respectively). Based on such parameters, filters could be operated efficiently and under acceptable operating conditions with membrane surface areas less than 1.0 m^2.[31] However, in response to the routine prescription now of higher CRRT doses established by the Ronco et al., dose trial[15] and other prospective trials,[32] manufacturers now offer filters of substantially larger surface areas. Specifically, filters with surface areas of at least 1.5 m^2 allow for operation at acceptable TMP values in convective modalities employing high ultrafiltration rates and maximize the likelihood of solute saturation of the dialysate in CVVHD.[33]

As opposed to surface area, membrane material in standard CRRT filters has not changed appreciably through the years, with AN69 and various versions of polysulfone still most common. Membrane composition along with pore size and structure have little effect on small solute clearances, which are determined primarily by blood flow rate, fluid flow rate(s), and membrane surface area. On the other hand, membrane material and pore characteristics assume an important role in the removal of larger molecular weight compounds, especially peptides and proteins.[34] Certain membranes, particularly AN69 and PMMA, achieve removal of such solutes primarily by adsorption. However, previous studies have demonstrated a distinct time-dependence of this phenomenon and the efficacy of adsorptive clearance beyond the first few hours of filter use is unclear.[35] For a newly developed version of AN69 (oXiris),[36] the membrane has adsorptive capacity for not only low-molecular-weight proteins (because of large surface area) but also endotoxin and other negatively charged compounds resulting from a specific polymeric coating incorporated in the manufacturing process (Fig. 141.5).

For other membranes, including standard polysulfone, removal of larger molecular weight compounds occurs predominantly by convection or diffusion. Another relatively recent development is the incorporation of polysulfone-based membranes having mean pore sizes that are substantially

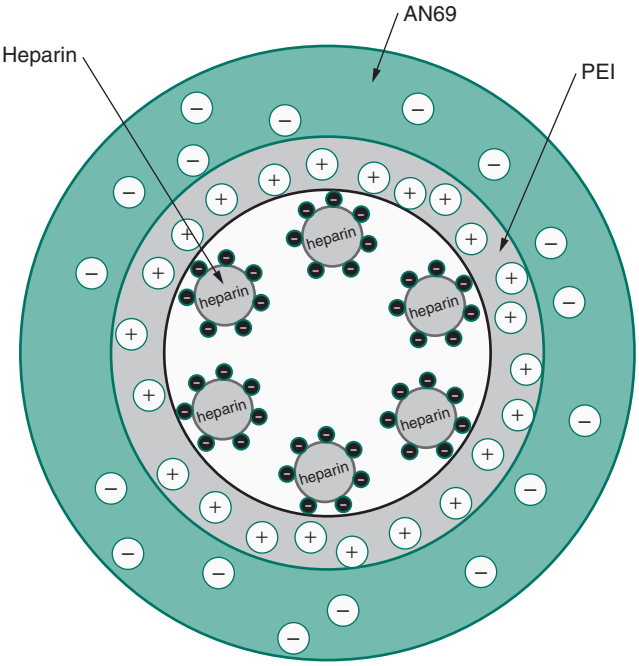

FIGURE 141.5 Representation of an oXiris hollow fiber. The base material is AN69, which has a high adsorptive affinity for peptides and proteins through ionic binding and hydrophilic interactions. Surface treatment with a positively charged polymer (PEI) allows for the chemical binding of heparin during the manufacturing process and the possibility of more targeted adsorptive removal of negatively charged compounds (e.g., endotoxin) from the bloodstream during treatment. Image courtesy of Baxter International.

larger than those found in standard high-flux versions[37–39] (Fig. 141.6). Even with the reduction in permeability after blood contact, these membranes have pore size distributions that may result in clinically relevant losses of albumin, especially when used in the convective mode.[40] Accordingly, manufacturers recommend their use only in the diffusive mode (CVVHD). The rationale for the use of such a filter is enhanced elimination of proinflammatory and antiinflammatory mediators, consistent with the "peak concentration hypothesis."[41] The clinical significance of enhanced mediator elimination by large-pore filters, along with the general issue of adsorptive versus transmembrane removal of large molecular weight compounds, continues to be debated.

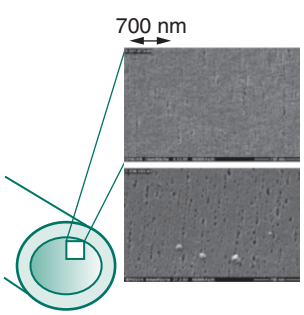

FIGURE 141.6 Representation of large pore ("high cutoff") filters. A comparison is made between this type of filter and a standard high-flux filter with respect to pore dimensions and electron micrograph appearance. (Adapted with permission from Villa G, Chelazzi C, Morettini E, et al. Organ dysfunction during continuous veno-venous high cut-off hemodialysis in patients with septic acute kidney injury: A prospective observational study. *PLoS One.* 2017;12[(2]:e0172039.)

CONCLUSION

From its relatively rudimentary beginning, CRRT has evolved substantially over the past 40 years from a clinical and technologic perspective. Machines now are designed with human factors and user-friendliness as important considerations and safety is the highest priority. CRRT membranes and filters also have evolved to meet the changing clinical requirements of the therapy and new developments continue to occur. Further evolution most likely will focus on software advances and the application of information technology to allow for delivery of multiple and increasingly complex treatments[13,42] (Fig. 141.7).

Key Points

1. Continuous renal replacement therapy (CRRT) systems have evolved from technology adapted largely from the chronic dialysis realm to devices designed specifically for critically ill patients.
2. Contemporary CRRT machines have several components, including sophisticated user interfaces, pumps, pressure monitoring, and other features, that allow for safe and efficient delivery of therapy.
3. The routine use of filters having membrane surface areas of 1.5 m^2 or more has been one of the biggest changes in CRRT clinical practice over the past 10–15 years, other characteristics (especially surface area) have changed to meet new clinical requirements.

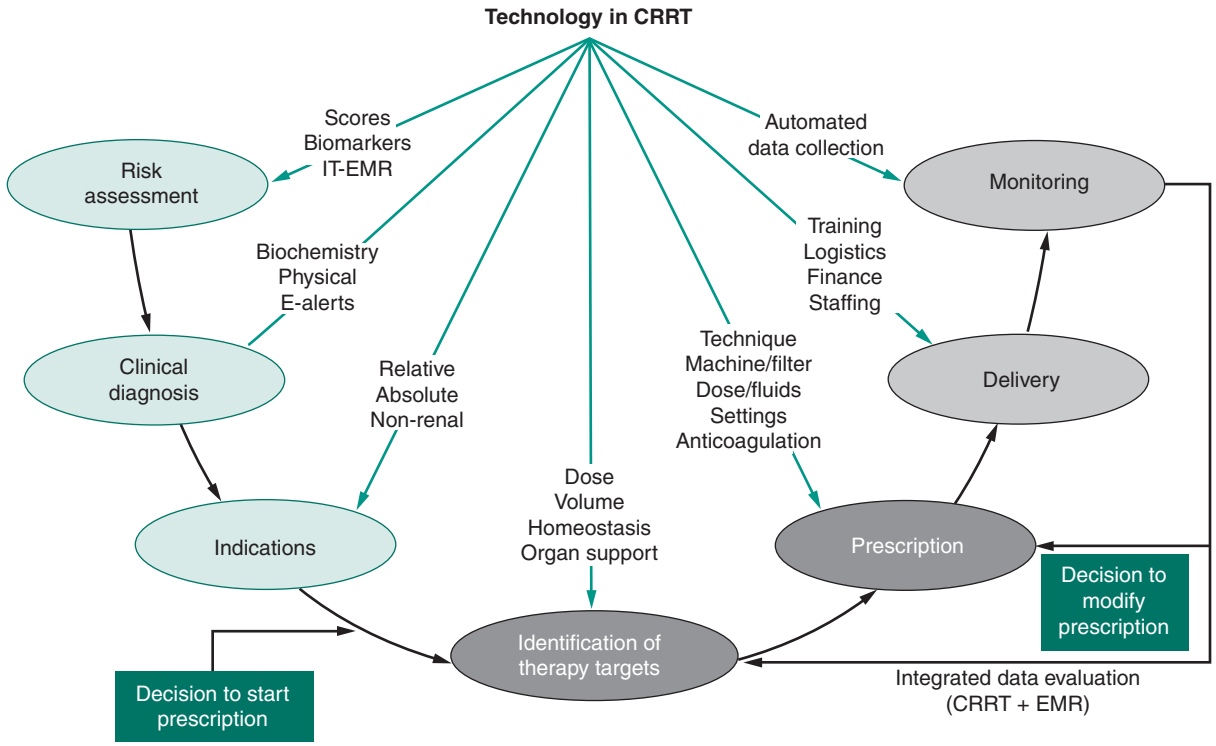

FIGURE 141.7 Information management in CRRT. (Reprinted from Cerdá J, Baldwin I, Honore PM, Villa G, Kellum JA, Ronco C. ADQI Consensus Group: Role of Technology for the Management of AKI in Critically Ill Patients: From Adoptive Technology to Precision Continuous Renal Replacement Therapy. *Blood Purif.* 2016;42[3]:248–265.)

4. New developments in CRRT membrane technology involve surface modifications and increased pore size to allow for expanded removal capabilities.

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