

## 2.1 Introduction

The goal of renal replacement therapy is primarily to restore the chemical and fluid balance in uremia (milieu interior). In hemodialysis (HD), the processes of diffusion and convection are combined to achieve solute exchange and water removal across a semipermeable membrane to provide the necessary blood purification. Diffusion takes place through random movement of molecules that lead to a net solute transfer from higher to lower concentration between compartments separated by the semipermeable membrane. The diffusive capacity depends on the concentration gradient, the diffusive coefficient of the solute, and membrane properties [1]. Convection involves transfer of fluid volumes accompanied by the removal of dissolved larger solutes across the dialysis membrane (ultrafiltration). This process is dependent on the ultrafiltration rate and the solute sieving coefficient for the membrane [2]. In a typical HD session, both these exchange processes occur simultaneously and their contribution to overall purification can be difficult to quantify separately. The HD system is comprised of the blood compartment, the dialysate compartment, and the membrane interface. These components of dialysis technology and their application to renal replacement therapy are discussed below.

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## 2.2 The Extracorporeal Blood Circuit

The extracorporeal circuit provides the necessary conduit for transporting blood from the patient's vascular system (via arteriovenous access) to the artificial kidney at a defined flow rate and then returning the dialyzed blood back to the patient. This must be achieved without damage to the blood cell components, coagulation of blood, or loss of integrity that can result in blood loss or contamination with microorganisms from the external environment. The closed extracorporeal setup consists of a blood access device (needles or catheter) connected by tubing to the dialyzer or the artificial kidney. All the circuit components in contact with blood are made of inert or highly biocompatible material and sterilized prior to packaging [3–5]. An extracorporeal blood volume of approximately 80–250 ml circulates outside an adult patient at any one time [6]. During HD, blood from the patient's vascular access (arterial needle) flows into the dialyzer and then back to the patient's access (venous needle). These afferent and efferent parts of the extracorporeal circuit are differentiated by color coding of two sections of the blood tubing: arterial (pre-dialyzer, red) and venous (post-dialyzer, blue).

### 2.2.1 Pre-dialyzer (Arterial Limb)

This entire part of the blood circuit (pre-dialyzer) constitutes the “arterial limb” of the circuit. The blood is propelled into the arterial tubing by a negative pressure (suction pressure) mechanically generated and maintained by a peristaltic blood pump (to draw the blood and propel it through the circuit). The pump could deliver blood to the dialyzer at rates that can vary from 0 to 600 ml/min but typically set between 300 and 550 ml/min, restricted by the pressures generated within the extracorporeal circuit. The machine displays the achieved blood flow rate ( $Q_b$ , ml/min), calculated from the number of revolutions of the pump per minute and the volume of tubing segment within the pump [6]. The latter is

calculated from the predefined internal diameter of the blood pump segment. The arterial pump effect is measured as the “arterial pressure,” which is a negative value. As the arterial pressure becomes more negative the tubing insert becomes flatter and the tubing calculated  $Q_b$  is higher than the actual flow rate. Some machines automatically correct the displayed blood flow on the machine for the measured arterial pressure to derive the effective or delivered  $Q_b$  (or effective blood flow rate (EBFR)) [7]. At pressures  $-150$  mmHg or lower, EBFR deviates significantly from calculated  $Q_b$  and can lead to loss of treatment efficiency. Excessive negative pressures could indicate poor arterial inflow due to vascular access problems and should be avoided [6].

The arterial pump rollers press against the blood column to drive the blood through the circuit; hence, tight rollers can damage blood cells causing hemolysis. If the rollers are too loose this may reduce the EBFR. Modern rollers use springs to create occlusion, so the pump tubing segment must be inserted properly. In case of emergency, all machines are provided with a handle to rotate the pump manually (hand cranking) and at a rate just fast enough to keep venous pressure in the distal circuit at the pre-alarm level.

While the blood circulates through the extracorporeal circuit and the artificial kidney, its natural disposition is to coagulate. Anticoagulation is necessary to prevent formation of microthrombi, blood coagulation, and resulting loss of circuit. A heparin-infusion driver, positioned after the blood pump and prior to the dialyzer inlet, adds a measured dose of the anticoagulant via an infusion port into the circulating blood. The location of the port facilitates the heparin to be pushed towards the dialyzer inlet and avoid the negative force of the blood pump drawing up air from the heparin line.

There is often an additional port for saline infusion, located on the arterial blood tubing in the pre-pump segment, so saline bags can be set up for priming or fluid infusions. If the saline infusion line is not clamped correctly, too much fluid or air can enter the extracorporeal blood circuit. Saline port connection errors between the arterial and venous part of the circuit can lead to potentially catastrophic consequences [8]. Traditionally, saline bags are set up to run fluid infusions. However, modern machines capable of producing ultrapure water enable the use of online-generated high-quality fluid to prime, rinse, and infuse a measured fluid bolus into the patient, obviating the need for saline bags.

The anticoagulated blood column is then propelled into the dialyzer via the mechanical force generated by the blood pump and a positive pressure inside the artificial kidney, which facilitates a hydrostatic gradient across the dialyzer membrane required for ultrafiltration.

Some machines can estimate the total blood volume processed (liters) within the dialyzer for a single treatment by count of blood pump turns. It is not a measure of delivered

dialysis dose but can be a useful tool for quality assurance especially if there are significant treatment interruptions for a single session.

### 2.2.2 Post-dialyzer Venous Limb

After the blood is subjected to the processes of diffusion and convection within the dialyzer, it enters the “venous limb” of the circuit, returning blood back into the patient. Although the pressure in the venous limb distal to the dialyzer gradually falls, it remains sufficiently positive in order to enable return of the blood to the body. The pressure within this part of the circuit is monitored by the venous blood pressure monitor, which is located typically just before the air bubble chamber. High venous pressures indicate an obstruction in the venous limb distal to this point, and an alarm window can be set up to bring this to the attention of the dialysis staff. High-pressure alarms warrant, at first, a check of the lines for kinks and clamps. Additionally, venous needle blow out or clots in the air trap ought to be excluded. In the absence of any obvious cause, often the needle position may need to be adjusted or rotated [6]. Persistently high venous pressures, however, can be harmful and lead to potential loss of circuit. It could also indicate a stenosis within the vascular access [9]. Trends in such pressure changes can be employed as a screening tool for vascular access monitoring [10]. A low venous pressure is most commonly associated with low arterial pressure due to poor arterial flow or, alternatively, a wet venous isolator.

### 2.2.3 Air Trap (Bubble Chamber) and Air Detector

There is a distinct apparatus that sits in the venous limb between the dialyzer and the patient’s venous access and acts as a gateway for safe return of the blood back into the patient. The air detector, an ultrasonic device, continuously checks for air or foam in the blood pathway at this location throughout the dialysis treatment by detecting changes to ultrasonic signal induced by the presence of air bubbles. The air trap will prevent entry of large air bubbles into the returning needle of the AV fistula.

An air detector’s alarm sensitivity limits are preset by the manufacture but can be recalibrated by qualified technicians. When the air detector senses air, it will trigger audible and visual alarms, stop the blood pump, and clamp the venous blood tubing to stop return of the blood to the body and prevent air getting into the bloodstream. Of course, air leak beyond the detector can go undetected by this setup. The air detector and the venous line clamps must always be

checked prior to the start of every dialysis session, as per manufacturer's instructions. The air trap chamber also serves to prevent blood clots (microthrombi) generated within the extracorporeal circuit from reaching the patient, by using a fine mesh screen.

Air in bloodlines and dialyzer typically occur due to underfilled air trap chamber, inadequate priming, empty saline bag, loose connections, or dialysis needle removal/dislodgement while blood pump is still running. Saline priming of the dialyzer and blood tubing and deaeration of the fluid pathway are important preparatory steps prior to each dialysis session to effectively remove trapped air from the circuit.

Extracorporeal circuit can also generate microbubbles [11]. The current trapping mechanism fails to recognize or limit transfer of such microemboli. In such cases, air emboli may cross through the shunt from venous to systemic circulation and cause varying degrees of damage to the brain and other organs (paradoxical embolism). Thus, it is reasonable to believe that a patient with a patent foramen ovale is at a higher risk for having neurologic morbidity as a result of recurrent venous air embolism during HD [12].

### 2.2.4 Transducer Protectors

Transducers are devices inside the machine that converts pressure into an electronic signal that can be displayed. They serve an important role in monitoring the pressures within arterial and venous circuit. Transducer protectors [13] act as a barrier between blood in the tube and the transducer in the machine. They connect to the machine's venous and/or arterial ports via a small tubing segment on top of the drip chamber. Transducer protectors use membranes with a nominal pore size of  $0.2\ \mu\text{m}$  that are hydrophobic when wetted, to stop fluid from passing through. Moisture would damage the transducer. If these filters get wet, they prevent airflow. Wet or clamped transducer protectors cause pressure-reading errors. On the other hand, a loose or damaged transducer protector on a pre-pump arterial drip chamber port could also allow air into the bloodline circuit. Wet transducer protectors must be changed immediately, and the machine side of the protector should be inspected for contamination or wetting [13]. If a fluid breakthrough is found on the removed transducer protector, the machine's internal transducer protector (backup) must be inspected by a qualified technician, for safety, quality, and infection control purposes.

### 2.2.5 Pressures in the Extracorporeal Circuit

The extracorporeal circuit can be viewed as an extension of the patient's own circulation during the HD process, and its monitoring, therefore, is essential for patient safety. Pressure

in the extracorporeal circuit is dependent on the blood flow rate and the resistance to flow which is primarily exerted at the levels of the arteriovenous fistula or catheters, dialysis needles, the dialyzer, and the tubing. Some machines may also have a dialysate compartment pressure monitor. These are more common for flow control-based ultrafiltration management systems. The pressure in the dialysate compartment should not exceed that of the blood compartment to prevent high levels of backfiltration throughout the dialyzer and risk of dialyzer membrane rupture. An outline of the pressure profiles through the different components of the extracorporeal circuit is provided in Fig. 2.1.

Minor changes in the geometry of tubing, for example, kinking can lead to very high pre-stenotic pressure leading to hemolysis [14]. This can be as a result of manufacturing or packing techniques. The site of kink determines which pressure alarms are affected and whether hemolysis ensues.

### 2.2.6 Blood Volume Monitor

Blood volume monitors (BVM) are continuous sensors built into specific blood lines for noninvasive monitoring of plasma volumes [15]. They use either ultrasound to measure density of plasma or optical scattering to measure the hematocrit. BVM can be used to guide ultrafiltration rates in individuals that are prone to intradialytic hypotension [16, 17]. Although BVM can be quite useful in some individuals with intradialytic blood pressure instability, its wider benefits in all types of patients including those with anemia and low serum albumin, require further clarification [15].

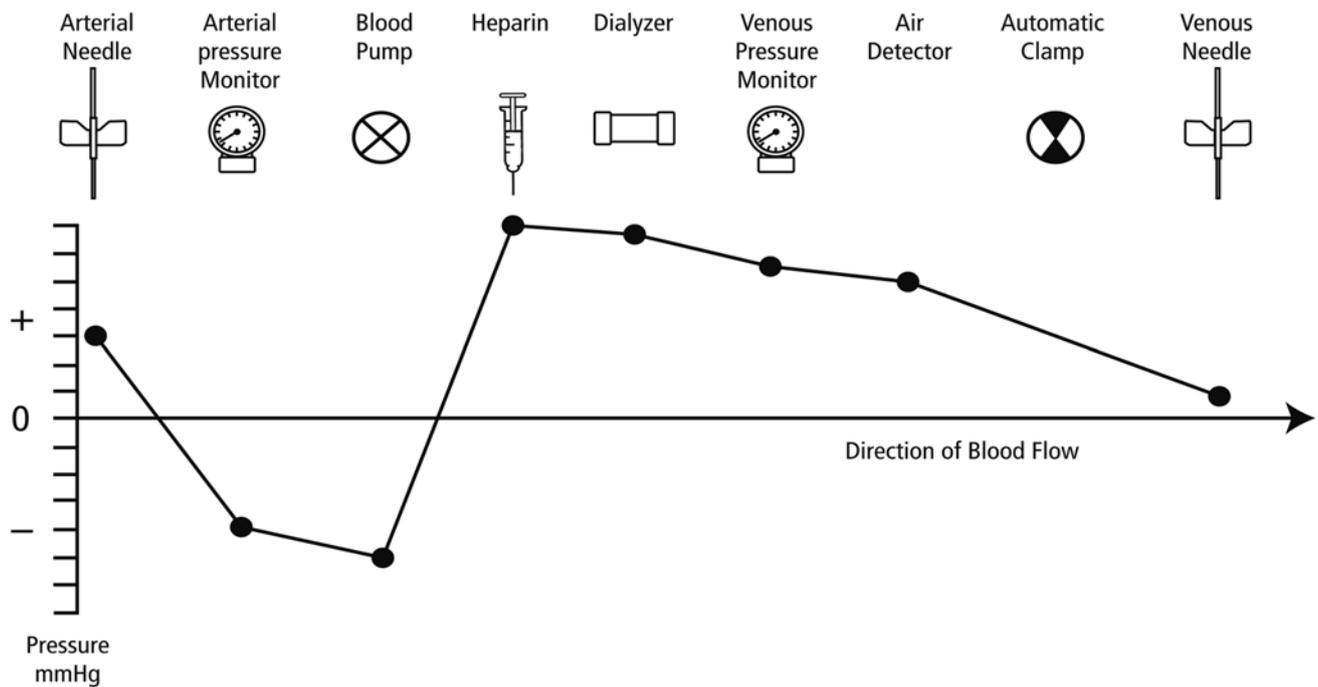
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## 2.3 The Artificial Kidney (Dialyzer Membrane)

### 2.3.1 Structure and Setup

The artificial kidney (dialyzer) consists of a cylindrical rigid structure internally packed with the semipermeable membrane configured as hollow fibers (cellulose, modified cellulose, or synthetic polymers), which provide a blood channel and a separation barrier between the blood and dialysate compartment. They vary in size with a range of membrane surface area ( $0.8\text{--}2.2\ \text{m}^2$ ) and internal compartmental volumes [18]. There is a pair of inlet and outlet for each compartment.

Through its transit in the dialyzer, the blood comes in contact with the dialysate solution of a specified composition and experiences variable hydrostatic gradients. Typically for an average patient size of 70 kg with good vascular access, optimal performance of the dialyzer can be maintained with an EBF of between 300 and 400 ml/min and a surface area of  $1.8\text{--}2.0\ \text{m}^2$  [19]. The blood and dialysate fluid columns



**Fig. 2.1** Pressure profile within the extracorporeal circuit. The pressure profile is demonstrated at specified points in the circuit as indicated above the profile. The *horizontal axis* represents the direction of blood flow. The *vertical axis* represents the pressure generated within the circuit (mmHg millimetres of mercury)

can flow in the same direction within the dialyzer (concurrently) or in opposing directions (countercurrent). The latter provides a more uniform diffusive gradient across the whole length of the dialyzer compartment and is therefore preferred where less rapid shifts in toxins and electrolytes are required, for example, in those with extremely high urea levels, during first dialysis session, or in children. The pressure in the dialyzer is monitored by a dialysate inflow pressure monitor. Very high inflow pressures could mean a clotted dialyzer. Transmembrane pressure alarms are a measure of the altered pressure inside the dialyzer and maybe due to kinked lines, incorrect ultrafiltration, high venous pressure, or clotting. Although the rate at which the blood and dialysate pumps operate is a controlled variable, the distribution of blood and dialysate through the dialyzer can be uneven which can impact the efficiency of dialysis. The hollow fiber design offers the least resistance to the flow of both blood and dialysate, but the flow of blood tends to be higher in the centre of the cylindrical arrangement while that of dialysate higher in the periphery [20–22]. A more homogeneous flow distribution in the dialysate pathway has been achieved by using spacer yarns to separate the fibers or by the use of wave-patterned (Moiré structured) hollow fibers, which improve the fiber spacing within the device [22].

### 2.3.2 Dialyzer Efficiency

Dialyzer efficiency is denoted by its mass transfer coefficient ( $K_0A$ ) for urea at infinite blood and dialysate flow, where  $K_0$  is the transfer coefficient of the membrane and  $A$  is the surface area.  $K_0A$  is equivalent to the maximal clearance of urea (ml/min) that can be achieved [19]. High-efficiency dialyzers [19] can achieve greater urea clearances than low-efficiency dialyzers at comparable blood flow rates. Conventional cellulose, with good diffusive properties, have poor biocompatibility and limited pore size [23]. Modified cellulose and synthetic polymer microfibrils significantly enhance the efficiency and biocompatibility of the membrane. Ultrafiltration coefficient ( $K_{uf}$ ) of the membrane is used to denote its permeability (ml of ultrafiltrate/hr/mmHg) and high flux dialyzers typically have a  $K_{uf}$  between 20 and 80 ml/hr/mmHg [18, 24]. Factors such as entrapment of large negatively charged particles within the dialyzer could change its properties (Gibbs–Donan effect) [1, 25]. In addition to dialyzer properties, several other factors such as solute characteristics of the molecule, its charge, protein binding and patient hydration status, blood hematocrit, and viscosity may influence the overall performance of the system [1].

Super-high-flux and sorbent-coated membranes with very high cutoff (>60 kDa) provide an opportunity for enhanced

removal of the uremic profile, but their clinical benefit and safety remain largely unproven [26, 27].

### 2.3.3 Dialyzer Biocompatibility and Reactions

Membrane incompatibility can result in either complement activation or activation of the coagulation cascade and cellular mediated pathways resulting in an acute phase reaction with pyrexia and hemodynamic instability or a chronic inflammatory state. The latter can lead to erythropoietin resistance, increased production of  $\beta_2$  microglobulin, and failure to thrive. Poor biocompatibility can also lead to procoagulability and clotting of both the dialyzer and blood circuit. Severe anaphylactic reactions to the artificial kidney have been reported especially during first use, typically manifested by wheezing, breathlessness, back pain, chest pain, hemolysis, or even sudden death [28]. These can be caused either by residual sterilant or the membrane material itself [5]. The use of gamma irradiation, steam sterilization, or electron-beam radiation and the use of materials with higher biocompatibility have reduced the incidence of anaphylactic reactions. A series of dialysis reactions, including deaths were reported due to heparin contaminated during the manufacturing process with oversulfated chondroitin sulfate [29]. New dialyzer materials or processing methods ought to be investigated in unexplained allergic reactions.

### 2.3.4 Dialyzer Reprocessing (Reuse) Systems

Dialyzer reuse over several treatment sessions for a particular patient has been a prevalent practice in some parts of the world for several years. Preparation of the dialyzer after each treatment session (dialyzer reprocessing) requires systems, which are effective and in good condition for optimum cleaning and maintenance of the dialyzer membrane surface area repeatedly used for HD. This optimizes the amount of useable membrane interface to come in contact with blood volume in order to provide adequate HD. Operational issues include scheduling and crucial quality-assurance procedures such as monitoring of applicable reuse chemicals, procedures for flushing and testing dialyzers for residual chemicals, rigorous monitoring on appropriate patient-specific dialyzer usage, and verification procedures for “volume pass” and “reuse number pass” [30, 31].

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## 2.4 Dialysis Fluid and Its Pathway

This section of the dialysis machine has been the focus of major technological progress over the past few decades. The principle function of the dialysis fluid pathway is to prepare

dialysate (combining treated water, acid concentrate, and a buffer) and deliver this fluid to the dialyzer at a prescribed flow rate under optimal conditions. Additionally, the circuit is designed to remove a prescribed amount of fluid from the patient (ultrafiltration). The spent dialysate with the removed fluid (effluent) is then drained out. The majority of this pathway is located inside the machine. The machine components that are reused and part of the fluid pathway must be sterilized as per manufacturer recommendations. The first step in the whole process, however, is dependent on treated water, prepared by water purification systems, being fed directly into the machine.

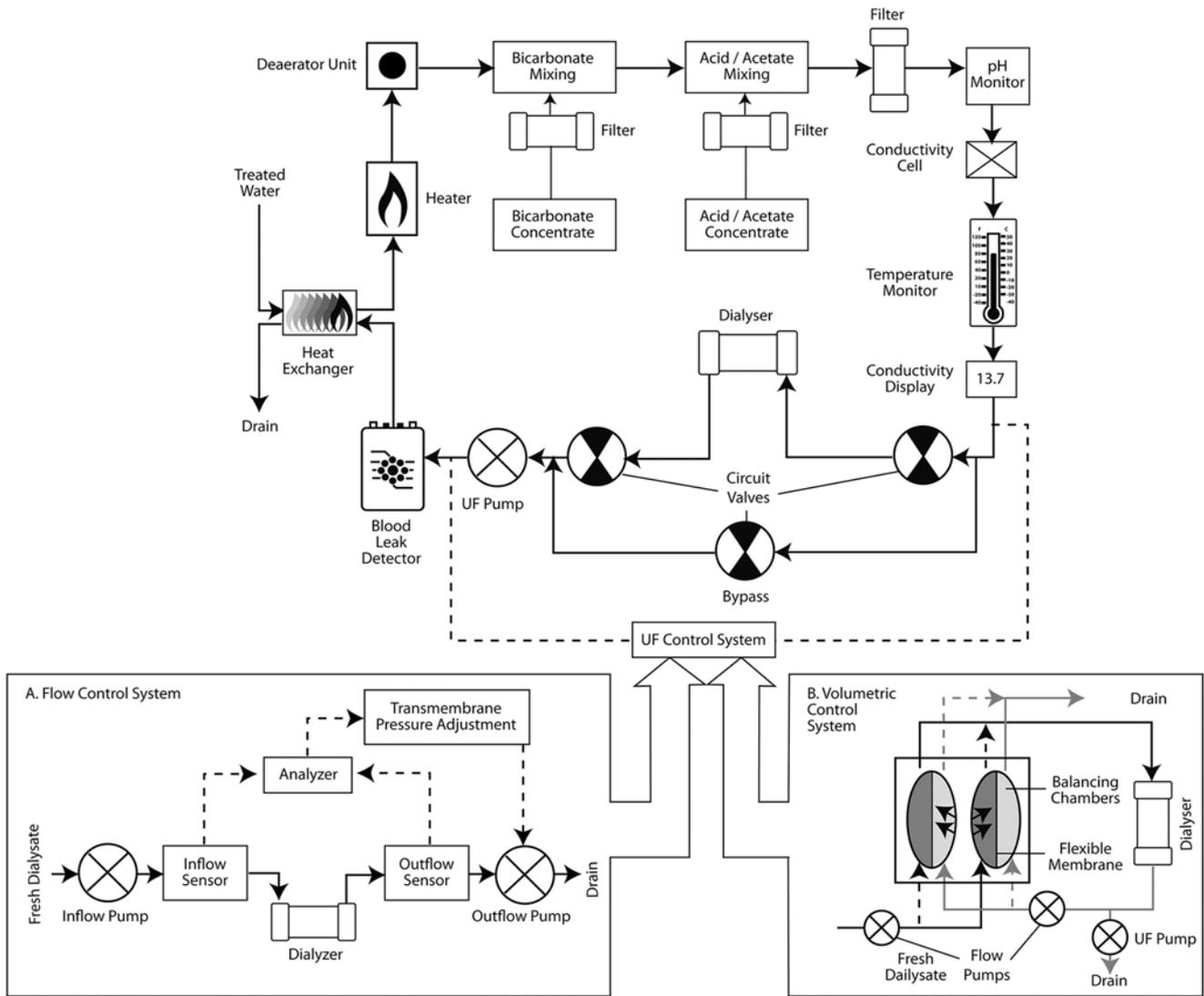
### 2.4.1 Water Treatment Systems

A single HD treatment can require upto 500 l of water. The water from the main supply goes through a series of steps of pre-filtration to remove particulate material, softening to remove calcium and magnesium, carbon filtration to remove chloramine, organic contaminants and chloride, and microfiltration followed by reverse osmosis. This involves the filtration of water through a membrane with pore size of 300 Da under high pressures. This could be done through single or a double reverse osmosis module and often coupled with electroionization or photoradiation treatment. The resultant water is devoid of most microorganisms and 90% of dissolved ions [32]. The water passes through cold sterilizing ultrafilters prior to its entry into the dialysate fluid pathway.

A standard HD session of three times weekly for 4 h at 500 ml/min dialysate flow could potentially expose a patient to 18,720 l of water contaminants per year. The quality of the water used for preparing the dialysate for HD must therefore meet recommended guidelines and standards [33–35]. Ultrapure water is defined as water with a bacterial count below 0.1 colony-forming unit/ml and endotoxin below 0.03 endotoxin unit/ml and is recommended for use in high-flux HD and hemodiafiltration. Both chemical and microbiological qualities are mandatory and provide an essential quality assurance of the treatment. An adequate water treatment system combined with ultrafilters at the inlet of the dialysis fluid pathway and a robust monitoring and governance process can help maintain high standards of water purity in HD.

### 2.4.2 Preparation of the Dialysate

Treated water enters the dialysis circuit and is heated to a specified temperature. Any air trapped in the water is removed by a deaerator unit where the water is submitted to negative pressures in a closed loop consisting of a pump, a



**Fig. 2.2** Machine circuit for dialysate preparation and ultrafiltration. Inset pictures a and b represent the two commonly used automated ultrafiltration control systems, flow control, and volumetric control. UF Ultrafiltration

constricting valve, an air trap, and a vent. The proportioning chamber, at a specified ratio, mixes the purified water with the base and acid solutions. Although the pretreated water and acid component can be premixed to generate online dialysis fluid to be circulated in the main ring of the fluid distribution system in dialysis units, the base component (bicarbonate), supplied in powder cartridges, has to be freshly prepared and mixed at the point of treatment delivery to prevent bacterial growth [36].

The dialysate then undergoes self-check through a series of monitors and then enters the dialyzer compartment where the pressures are regulated by an automated ultrafiltration control system (UFCS). The dialysate effluent then passes through a deaeration system and blood leak monitor before providing further feedback to the UFCS. Both parts of UFCS

form closed loops and aim to maintain an equal inflow and outflow of dialysate with a specific ultrafiltrate (UF) volume removed from the loop, the rate of which is determined by the UF prescription and the UF pump. Figure 2.2 provides an overview of a typical machine circuit for the preparation of dialysate demonstrating the two different automated UFCSs.

Variations to standard dialysate preparation include the single-pass batch system (Genius®) where a fixed volume of premixed dialysate (75 L) is typically utilized for the whole treatment session. Lack of need for water purification, ultra-pure dialysate, and convenience are major advantages, especially in the intensive care setting and for home patients, although the fixed dialysate volume could limit HD efficiency for large patients.

### 2.4.3 Ultrafiltration Control system

Precise and automated regulation of fluid removal has enabled the safe performance of convective treatments during HD (ultrafiltration, high-flux HD, and hemodiafiltration). The two UF mechanisms typically employed are either volumetric or flow sensor control systems.

#### 2.4.3.1 Volumetric Ultrafiltration Control System

Volumetric control systems [6, 37] are the most widely used and utilize balancing chambers located inside the machine. Each balancing chamber is split in half by a membrane. One half of each chamber gets filled by fresh dialysate en route to the dialyzer while the other by spent dialysate en route to the drain. The inlet and outlet of the chamber are controlled by two valves. As one half of the chamber fills with spent dialysate, it pushes an equal amount of fresh dialysate out of the chamber. Inversely as one half of the chamber fills with fresh dialysate, it forces an equal amount of spent dialysate out and towards the drain. There are two pumps controlling the inflow and outflow from the balancing chambers. The ultrafiltration pump removes fluid from the spent dialysis prior to it entering the balancing chamber (Fig. 2.2).

#### 2.4.3.2 Flow Sensor Ultrafiltration Control System

A flow control system [6, 37] is based on flow sensors located on the inlet and outlet of the dialyzer to control the rate of inflow and outflow pumps to achieve balance. A separate analyzer system can guide an increase in the transmembrane pressure to act as a post-dialyzer ultrafiltration pump, which can remove excess fluid before the spent dialysate passes through the outflow sensor (Fig. 2.2). This system can limit the dialysate flow rates that can be applied.

### 2.4.4 Dialysate Composition

The dialysate is a combination of water mixed with specific portions of acid concentrate and a buffer solution to produce a near physiological solution to allow removal of soluble toxins and electrolytes from the bloodstream and replenish deficient electrolytes and buffer back into the circulation. The acid component, supplied directly to each machine from a central source or provided in individual containers, is a concentrate of acetate 5–6 mmol/l (or citrate 1 mmol/l), chloride salts of sodium, potassium, calcium, magnesium, and glucose. The salt concentrations can be varied for clinical use, particularly with regard to calcium and potassium. The final concentration of electrolytes is generated by a process of proportioning inside the machine. Several ratios of concentrate to water are in common use depending on the dialysis system to deliver a specified dialysate composition. Each proportioning ratio will therefore require its own

particular acid and bicarbonate concentrates. Some machines are designed for use with a single proportioning ratio, whereas other machines can be set to use different proportioning ratios. Dialysate composition is monitored mainly by conductivity; hence, use of the wrong concentrates may lead to dialysate of the correct conductivity but the wrong composition. Failure to use the correct machine setting or appropriate concentrates with a given machine can lead to serious patient harm [6].

The typical dialysate sodium level is between 137 and 141 mmol/l to minimize diffusive sodium losses during UF. Low (<137) or high (>141) sodium setting on the machine are often used to achieve a net sodium gain or loss, respectively, but could be associated with osmotic symptoms during HD. Their long-term clinical benefit remains unproven. The usual dialysate potassium content is 2 mmol/l. Lower levels of dialysate K have been associated with increased mortality and should be avoided. Dialysate calcium levels are usually maintained at 1.25 or 1.5 mmol/l in standard HD. Glucose-free fluid may have less inflammatory effect but risk osmotic symptoms and hypoglycemia, particularly in diabetics on insulin therapy and in acute settings. Glucose-containing dialysates (100 mg/dl) are most widely used. Higher concentrations (200 mg/dl) are rarely used but may be beneficial in relieving headaches associated with osmotic shifts or to achieve enhanced fluid removal and caloric gain temporarily in specific patient groups. Additional phosphate supplementation in the fluid may be required in hypophosphatemia [38] (e.g., frequent nocturnal HD). Magnesium-containing fluids (5 mmol/l) are rarely used but may be required for patients with magnesium-losing states such as those with severe malabsorption syndrome, high-output stoma, or needing intravenous Mg supplementation.

### 2.4.5 Dialysate Circuit Monitoring

After dialysate mixing and proportioning, a series of monitoring checks are undertaken for the safety of the patient.

#### 2.4.5.1 Dialysate Temperature Monitor

Temperatures of above 42°C can cause hemolysis and protein degeneration in the blood compartment, as well as raising the temperature of the patient leading to vasodilatation and hemodynamic instability. Temperatures of 35°C or lower may be too cold to be tolerated and cause shivering. Most dialysis units will set the dialysate temperature between 35 and 36.5°C.

The HD process has been shown to increase body temperature and predispose to intradialytic hemodynamic instability. Using lower dialysate temperature (35–36°C) improves hemodynamics and reduces cardiovascular strain [39, 40].

### 2.4.5.2 Conductivity Monitor

Conductivity is defined as the conductive potential of a solution to an electrical current and reflects the balance of positively charged to negatively charged particles in it. In dialysate fluid, this is made up of the electrolyte concentrations, and positively charged ions such as sodium, potassium, calcium, and magnesium are its main determinants. Conductivity can also be affected by temperature. Dialysate conductivity is typically maintained between 12 and 16 mS/cm (millisiemens per centimeter) [6]. The conductivity monitor remains in contact with the dialysate and consists of two electrodes placed 1 cm apart, across which a constant voltage is applied. Changes in electrolyte concentration therefore would cause changes in the voltage. The conductivity monitor is reasonably accurate but is reliant on successful calibration. However, the conductivity of a solution has a nonlinear relationship with temperature, salt concentration, and glucose composition of the fluid. The conductivity monitor is connected to an alarm, which is triggered when the fluid ionic composition has changed significantly outside the set limits. The type of concentrate and composition, the level of the probe in the fluid, the buffer cartridge, and temperature should be examined in these situations. If any significant alteration to the flow, pressure, or composition of the dialysate occurs the conductivity alarm would open the bypass valve to drain away the unsafe dialysate. After the necessary corrections are made, it may take several minutes for the conductivity readings to return to the normal range.

### 2.4.5.3 pH Monitor

The recommended dialysate pH is 6.8–7.6. Extremes in pH can lead to oxidative stress and hemolysis.

### 2.4.5.4 Blood Leak Detector

Blood should not be able to cross the dialysis membrane; any red cells present in the dialysate would alter the light signal in the sensor which might trigger an alarm that automatically stops the blood pump. The blood leak detector [6] is made up of an infrared or photoelectric sensor, and it is positioned immediately downstream of the dialysate outlet of the dialyzer. Persistent or severe blood leak alarms require cessation of the treatment, disconnection, and discard of the lines and dialyzer without washback.

## 2.5 Treatment Modes

The HD apparatus is configured not only to deliver a standard HD treatment session but also has design features that allow modifications to the treatment delivery under specific circumstances and clinical need.

### 2.5.1 Standard Hemodialysis Session

The steps for the initiation of HD involve a disinfection cycle taking approximately 40 min followed by compulsory test program. During this phase the machine will mix the dialysate fluid to achieve the correct concentration. The machine is then lined using the appropriate blood lines and the prescribed dialyzer. The line pack will contain arterial, venous, and, if appropriate, a substitution line if using HDF. Lines are also available for other modes, for example, single needle HD, or for specific monitoring purposes, such as the BVM. Priming of the blood circuit including the dialyzer is the next step (automated settings for priming cycles are in-built and vary according to the dialyzer and consumable in use for the treatment, for example, tubing volumes and pump speeds). The aim is to deaerate all lines and dialyzer and adjust any levels of fluid in the bubble trap. Once the required priming volume has been achieved most machines go into pre-circulation mode. Information can now be put into the machine, for example, the dialysate prescription and the UF volume, etc. Prescribed anticoagulation can now be drawn up. This may include not only a stat dose but also an infusion, which can now be attached to the infusion pump on the machine. A sterile area is prepared for vascular access preparation. Cannulation of the arteriovenous access follows a strict aseptic non-touch technique. Once the vascular access has been successfully cannulated, the next step is to connect this to the blood lines on the machine. Clinical observations (e.g., blood pressure) ought to be documented pretreatment, during treatment, and post-treatment. At completion of treatment, reinfusion takes place by choosing a preset method and pump speeds. Arteriovenous fistula needles can now be removed and hemostasis achieved. The machine can now be stripped down by removing the blood lines and dialyzer, followed by activation of the disinfection cycle as per manufacturer recommendations.

### 2.5.2 Profiled Dialysis

With the development of sensor capabilities, it is becoming increasingly possible to provide continuous, real-time monitoring of patients during HD treatment. This provides an opportunity to design a responsive mode that can detect the signals and, where clinically relevant, adjust or alter the dialysis prescription (biofeedback) to allow a more personalized treatment. The term profiled dialysis [41, 42] refers to the automated real-time adjustments to a specific prescription variable in order to match the patients changing biological parameters. It is aimed primarily at reducing circulatory stress and hemodynamic symptoms and is most beneficial in patients who suffer from repeated intradialytic hypotension and hemodynamic instability. The most widely used profile

regimens [39, 41, 43, 44] are variations of the ultrafiltration rate (using BVM, to minimize sharp changes in blood volume), dialysate temperature (specific modules, thermo-neutral or cool HD), or conductivity profiles (isonatric HD refers to maintaining a near constant conductivity gradient between blood and dialysate to minimize diffusive sodium losses). Biofeedback devices that vary the UF rate and conductivity in response to the relative BVM change may reduce serious hemodynamic instability on HD. However, the benefit and clinical impact of such technology are not yet fully understood [16, 41].

### 2.5.3 Single-Needle Hemodialysis (SNHD)

When difficult or inadequate vascular access does not allow two needle access (such as following repair surgery, incomplete maturation, or due to bruising from needle dislodgement), SNHD mode [45, 46] can allow continuation of dialysis treatment with a single needle, albeit with reduced HD efficiency. Specially adapted machines with dual blood pumps are required where both the arterial and venous tubing can be connected to a single vascular access needle. In SNHD, the arterial tubing carries blood to the dialyzer via the action of an arterial pump while a venous pump return the blood to the patient, coordinated in sequence to allow inflow and outflow from a single needle. SNHD will reduce the risk of blood loss in the event of needle dislodgement as both the arterial and venous ends would be disconnected and the blood pump would stop. Patients on frequent nocturnal home HD often utilize this mode for routine treatment.

### 2.5.4 Recirculation and Machine Bypass

HD machines offer a dialysate circuit bypass option. This allows dialysate flow to bypass the dialyzer (therefore not delivering fresh dialysate). During this time on bypass, the blood circuit can be isolated from the patient and allowed to circulate (recirculation) typically for 5–20 min. During this period staff can troubleshoot any problems with patient interruption or vascular access issues for a brief period of time without having to discontinue the entire setup and process. If blood is allowed to circulate on bypass mode for a long time, its composition might be altered significantly and not be safe to be returned to the patient.

### 2.5.5 Isolated Ultrafiltration (IsoUF)

The IsoUF mode is typically used for rapid or urgent fluid removal in emergencies such as pulmonary edema or refractory fluid overload states such as severe cardiac failure

[47]. IsoUF used at the beginning of a dialysis session can be achieved by maintaining a transmembrane pressure gradient across the dialyzer generated by negative pressure in the dialysate compartment [48], while the dialysate delivery is in bypass mode. IsoUF preserves hemodynamic stability better during ultrafiltration.

## 2.6 Alarms and Treatment Hazards

HD is an invasive treatment process, and patient safety remains the most important consideration in the design of the technology. A variety of inbuilt monitors can detect faults and limit harm. Alarms are designed to alert users when a warning is needed or a fault has occurred and can be set to either shut down the dialysis circuit or alert the dialysis staff. Machines alarm configurations can vary.

For most alarms, a flashing light and an audible alarm usually accompanied by stoppage of the blood pump will occur. It is useful to remember that the “mute button” on the machine when pressed for silencing the alarms do not recommence the treatment. Most machines will have an emergency mode, which allows an automated switching off of the ultrafiltration pump and reduction of blood pump speed to 50 ml/min with or without an automatic bolus of fluid infusion.

The combination of integral safety features, adequate alarm settings or configurations and operator vigilance, are necessary to assure safety. Two groups of errors have been recognized (a) machine faults or parts malfunction or (b) user errors [49]. The majority of the hazards in the treatment today relate to user-related errors. It is therefore an integral part of the training accreditation that the operator is able to troubleshoot various components of safety and alarms. These individuals can be adequately trained dialysis staff, nephrologists, or technicians. Individual alarms in the blood and dialysate pathway and their troubleshooting has been discussed earlier in their respective sections.

### 2.6.1 Disconnection or Leakage

Dialysis systems are found lacking in the event of a disconnection or leakage from the bloodline [50, 51]. The lack of an alarm in this setting may be due to a complete or partial venous needle dislodgement, small pressure drops, incorrect alarm limits, or small leaks through faulty connectors. Extreme blood loss in HD is rare but can occur in venous needle dislodgement, rupture of access (aneurysm or anastomosis), and dialyzer crack or loose connections in circuit. For venous line dislodgement, back pressure created by the needle resistance prevents the machine’s venous pressure monitors from sensing the loss of pressure created by the dislodgment. In this situation the venous pressure at the

needle site will remain positive, and the alarm will not trigger. Smaller-gauge needles combined with high blood flows create significant back pressures, such that even if the needle is fully or partially dislodged from the patient, the venous pressure monitor continue sensing the pressure created by the needle's resistance, and the smaller drop in pressure associated with the disconnection may be insufficient in triggering an alarm.

The problem is exacerbated by the fact that users may sometimes widen the alarm limits to minimize nuisance alarms. These are usually caused by high venous pressures in the system due to roller pump generated oscillations in pressure and maneuvers that can naturally change the venous pressure such as coughing or even change in posture during HD. The resulting variations can often exceed even the customary  $\pm 50$  mm Hg venous pressure monitor limits. All these limitations can make venous needle dislodgements and its life threatening consequences go undetected during HD. This problem is not unique to any specific machine model. Securement of access guided by a well-defined unit policy, avoidance of unnecessary widening of venous pressure alarm limits, and adequate visibility of the connection points for the extracorporeal circuit with greater vigilance can minimize risks significantly. Although efforts have been made to design innovative solutions to address this problem, detection of blood loss that can activate the venous clamp and stop the blood pump is not yet available in routine clinical practice.

### 2.6.2 Air Embolism

Air embolism [11, 52] is a rare event but may occur when a bolus of air enters the venous blood line below the air trap. This can lead to symptoms of chest pain, breathlessness, confusion, and headaches with potentially fatal consequences. If an air bolus is suspected, the venous line should be clamped and the patient turned onto the left side with feet elevation and seek further help.

### 2.6.3 Hemolysis

Hemolysis can occur either through mechanical (shear forces through kinks and obstructions to the circuit, defective blood pump, high negative pressure in the circuit), chemical (contaminated dialysate with disinfectant such as chlorine, bleach, formaldehyde, copper, nitrates, nitrites, or low-osmolar dialysate), or thermal factors (dialysate temperature  $>42$  C) [4, 14, 36, 52].

### 2.6.4 Power Failure or Disruption

Power failure or disruption will set the machine alarms off and trigger venous line clamp. The backup battery will allow some time (approx 15–20 min) to reinfuse and terminate the treatment. Beyond this time period, manual intervention of freeing up the venous line and hand cranking the blood pump will be required (according to specified machine policy). If the water pressure falls or is turned off, the machine will not be able to prepare the dialysate and the treatment will have to be terminated.

In the event of any crisis on HD, where the etiology is unclear, in addition to all the necessary supportive measures the following steps should be undertaken: (a) stop dialysis, (b) take samples from venous and arterial lines and disconnect the patient, (c) collect dialysate sample and the used dialyzer, and (d) remove the machine from further use so that all evidence is well preserved for further investigation.

## 2.7 Configuration and Connectivity

The goal of technological reliability is primarily to avoid treatment disruptions related to technical faults, quick turnaround, and restoration of such faults and robust governance around safety checks and monitoring procedures.

The treatment parameters for each session can be captured electronically in modern machines through USB, Ethernet, and a variety of serial interfaces. Wireless interfaces may also be available for direct connection to hospital networks. Data card slots on some machines allow personal medical information and dialysis prescription to be stored on it to allow automatic setup of the machine parameters.

Dialysis machines are medical equipment regulated by the Food and Drug Administration (FDA). Complex design and manufacturing of dialysis machines incorporate pumps and multiple valves with electronic actuation to allow different mixing ratios, and employ sensors for monitoring pressure, temperature, pump speed, and transmembrane pressure gradient at specified points in the blood extracorporeal and dialysate circuits, during routine treatment. Advanced features, such as comprehensive self-test and fault-indication capabilities, require additional circuits and components. The technical governance of such complex life-saving technology requires a rigorous schedule of maintenance, hardware support, and software updates.

Dialysis equipment is powered [6] by AC but may also include batteries (or ultracapacitors), for example, to supplement the power supply's output when heating water for sterilization in home-use machines. Safety regulations require power supply self-monitoring for voltage, temperature, and current flow.

## 2.8 Technology and Human Factor Limitations

The advances in HD technology have significantly improved its performance and reliability but remains limited nevertheless by the need for a skilled operator, a dedicated setting, and restrictions imposed on the patient lifestyle. The cliché of an HD machine is based predominantly on the financial criteria and performance characteristics, as defined by effectiveness and efficiency. In future, user acceptance (staff and patients) and integration with different care delivery models could significantly enhance the value and differentiation of the technology.

The improved reliability and safety features may have desensitized us from the clinical dangers of the HD process itself [52], particularly factors that govern the interaction of the patient with the machine. The HD treatment could be viewed as single system that integrates the patient's cardiovascular system and the extracorporeal circuiting series and facilitates interaction with the dialysis technology across the membrane interface. With an increased number of elderly and frail individuals commencing HD, it is apparent that we need technology to address such patient complexities. Hemodynamic stability and intradialytic hypotension have been identified as significant factors that need to be addressed to improve outcomes [41]. Vascular access is another major factor that affects outcomes and remains the commonest cause of HD treatment failure [53, 54]. The treatment of uremia and removal of a range of uremic toxins is critically reliant on our understanding of the equilibration of the circulatory system with the toxin reservoirs (total body water and circulatory compartments) and its implications in various disease states and comorbidities.

Technological progress in dialysis is necessary but one that aims for paramount clinical safety combined with simplicity and reliability for the user. Capabilities of self-use of the technology will allow for wider adoption of the technology outside traditional settings such as in patient homes or self-care units. This will enable greater user engagement and empowerment, which has been linked to better outcomes in chronic illnesses. Adapting the technology to allow patients to participate or self-manage their treatment will be a major advancement in the adoption of extended dialysis schedules.

Future innovations will need to address technological and human factor limitations in HD therapy to bring about improvements in both the quantity and quality of life for the patient.

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