Chapter (19)

Techniques and Kinetics of Hemodiafiltration

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CHAPTER OUTLINES

- Historical Notes
- Membranes for hemodiafiltration
- Water and solute transport in on-line HDF
- HDF Techniques and infusion modalities
- Kinetic modeling in hemodialysis and hemodiafiltration
- Biological Effects of HDF
- Clinical effects of HDF
- Effect of HDF on outcome
- Conclusion

CHAPTER OBJECTIVES

- To review present knowledge of materials, devices and technique of hemodiafiltration.
- To describe the most common mathematical models to simulate the solute kinetics during hemodiafiltration and to evaluate the efficiency of the treatment
- To review present evidence in favor of hemodiafiltration

KEY TERMS

- Hemodiafiltration
- Kinetic Models
- Mass transport
- High-flux membranes
- Diffusion
- Convection
- Adsoprption
- Dialyzer performance
- Ultrafiltration
- Patient outcome

ABSTRACT

Medium–long-term application of on-line high-efficiency HDF compared to low- and high-flux HD results in enhanced removal and lower basal levels of small, medium and protein-bound uremic solutes, some of which are retained as markers or causative agents of several uremic derangements, mainly inflammation, secondary hyperparathyroidism, dyslipidemia and cardiovascular disease. Probably, many of the benefits attributed to HDF potentially result from a general reduction of the uremic toxicity. This might be the link with the clinical benefits reported in patients undergoing chronic

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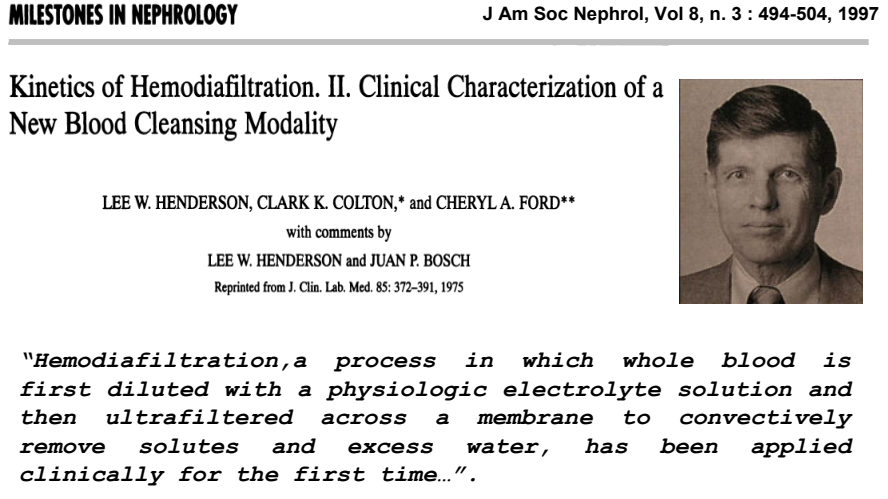
HDF which eventually contribute to improving patients survival, as suggested by published observational studies. However, In the absence of large randomized, prospective studies, it is reasonable to conclude that online HDF is a logical and safe therapy effective in maintaining the life and well-being of dialysis patients. Knowledge of the performance of materials, apparatus and devices used in HDF, and study of the solute transport mechanisms with the aid of modelling simulation will help to optimize this technique and obtain additional clinical benefits.

19.1 HISTORICAL NOTES

After the pioneering experiments conducted in dogs in 1947 (Malinow and Korzon 1947), a new blood-cleansing modality based on convection as a mechanism of uremic toxins removal was first applied in patients with end stage renal failure (ESRD) at the University of Pennsylvania and its rationale was published in 1967 by Henderson and colleagues (Henderson et al. 1967). The concept was inspired by the observation that ultrafiltration (UF) across the peritoneal membrane results in convective transport of urea and other small solutes (Henderson 1966), and the new technique was called ‘diafiltration’ to recognize the role of both diffusion and convection as transport mechanism. Parallel investigation on convective transport was also carried out in 1968 (Dorson and Markovitz 1968), and in 1972 (Quellhorst et al. 1972), but the original term 'hemodiafiltration' (HDF) was used by H.W. Leber from Germany, who was the first investigator to propose HDF as a new alternative treatment for ESRD (Leber et al. 1978).

Preliminary human studies on the new technique were started with great caution in the USA, hindered by regulatory requirements and the concern that some medium molecular weight compounds, critical for life, would be lost in the ultrafiltrate. As no adverse events were encountered, larger human application led the authors to deepen the focal points of their technique and to formulate the principles and the fundamental mathematical relationships for HDF (Colton et al. 1975; Henderson et al. 1975) (see Fig. 19.1). At the same time, HDF was applied clinically in Europe and the promising results of a series of studies in patients over a long time period were reported in 1983 by Quellhorst (Quellhorst 1983). From that time, continuous evolution of HDF took place until the more recent modalities of its application. Fundamental steps of this evolution were: 1) the introduction of bicarbonate-based dialysis fluid and replacement solution in substitution of the original fluids containing acetate or lactate, cause of relevant side-effects to the patients; 2) the application to dialysis machines

of UF control systems, primarily based on devices measuring differential flow between the outlet and inlet dialysate flow, which control body weight (BW) loss, balance UF and fluid replacement rates and adjust the trans-membrane pressure (TMP) in the filter; 3) on-line production of indefinite amount of ultrapure dialysate/infusion fluid al low cost, which avoided the cumbersome and expensive use of replacement fluids in sterile bags; 4) the availability of synthetic highly biocompatible and permeable membranes with selective cut-off, extended to small molecular weight proteins and beyond, and 5) the impressing technological development of dialysis machines, now specifically oriented towards convective techniques and equipped with advanced software devices, which are able to prescribe and monitor the achievement of the adequate dose of therapy with the use of conductivity apparatus, to enhance treatment efficiency by optimizing convective solute removal with ultrafiltration/trans-membrane pressure feed-back devices, to ensure better intradialytic stability also in critical patients with the use of software-guided profiles for UF, plasma sodium concentration and body temperature and to improve the safety of the sessions, automatically managed by the machine and easily controlled through a friendly user interface.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Kinetics of Hemodiafiltration. II. Clinical Characterization of a New Blood Cleansing Modality

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"Hemodiafiltration,a process in which whole blood is first diluted with a physiologic electrolyte solution and then ultrafiltered across a membrane to convectively remove solutes and excess water, has been applied clinically for the first time…".

Fig. 19.1 Lee W. Henderson and his landmark publication in 1975, in which the principles and the fundamental mathematical relationships for HDF were formulated. The event was celebrated with a reprint of the article in the Journal of the American Society of Nephrology in 1997.

Nowadays, on-line HDF with high-flux membranes, combining diffusion and maximal convection, is the extracorporeal renal replacement technique which may ensure maximal solute removal in a wide spectrum of molecular weights.

19.2 MEMBRANES FOR HEMODIAFILTRATION

Cellulosic membranes have been used for many years on hemodialysis (HD). These symmetrical hydrophilic membranes granted efficient removal of small solutes by diffusion due to their thin-walled structure, usually in the range of 6-15 μm, and their porosity, more related to the high number of pores than to their size. However, the small diameter of pores limited their hydraulic permeability and achievement of high water fluxes, and the chemical structure of these membranes, including hydroxyl groups, was responsible for frequent incompatibility reactions (Clark et al. 1999a). This led to later chemical modifications of these membranes with reduction of their hydrophilic properties which resulted in substantial improvement of their biocompatibility and permeability to water fluxes. At the same time, synthetic highly biocompatible and permeable membranes took place, largely related to the interest in hemofiltration in the late 1970s. The first synthetic membranes (Amicon), made from precipitated polyelectrolyte and asymmetrical in structure, had a thin 1-2-μm skin supported by a thick spongy stroma which permitted very high UF and convective middle molecule (MM) removal but presented a significant barrier to diffusion due to their thickness (200 μm) (Colton and Lysaght 1966). Polyacrylonitrile (AN69®, Hospal) was also employed at that time (Funck-Brentano et al. 1972). This synthetic highly permeable membrane, symmetric in structure, coupled remarkable diffusion and convection properties and, in addition, favored the adsorptive process thanks to the net negative charge carried on its surface (Leypoldt et al. 1986).

Since that time, a number of other synthetic membranes have been deve1oped, mainly asymmetric, inc1uding polysulfone (Streicher and Schneider 1985), polyamide (Gohl et al. 1992), polymethylmethacrylate (Bonomini et al. 2004), polyethersulfone (Jaber et al. 1998) and polyarylethersulfone/polyamide (Ronco et al. 2003). These membranes were hydrophobic and had a very thin skin layer (approx. 1 μm) contacting the blood compartment lumen and surrounded by a microporous structure with a total thickness of 75-100 μm. Their large mean pore size and thick wall structure allowed the high ultrafiltration rates necessary in hemofiltration (HF) to be achieved at relative1y low TMP, but the marked thickness of the hollow fiber wall limited small solutes transfer by diffusion. This was

one of the reasons why, in the mid-1980s, the interest in HF fell as a chronic replacement therapy and highly permeable membranes started to be used in the diffusive mode as high-flux dialyzers. For this purpose, a new generation of synthetic polymers was produced with a combined hydrophilic-hydrophobic structure and a reduced wall thickness (30-35 μm). These membranes, constituted of the same polymers mixed in various proportions with hydrophilic compounds such as polyvinylpyrrolidone, realized an optimization of the combination of diffusion and convection and maximized the bidirectional water flux across the membrane (see Table 19.1).

Table 19.1 High-flux membranes. Performance of some dialyzers for HDF

Membrane	Dialyzer	Area, m^2	$K_{UF}D$ ml/h/mmHg	Sieving Coeff.		Clearance, ml/min		
				β2-m	albumin	urea	creatinine	P
polyamide	Polyflux S	1.7	71	0.63	< 0.01	254	229	223
	Polyflux S	2.1	83	0.63	< 0.01	267	245	240
purema	PF-170H	1.7	74	0.8	< 0.01	274	259	240
	PF-210H		80	0.8	< 0.01	285	272	253
rexbrane	Rexeed 18A	1.8	71	0.85	0.002	280	265	250
	Rexeed 21A	2.1	74	0.85	0.002	284	272	257
helixone	FX80	1.8	59	0.8	< 0.01	276	250	239
	FX100	2.2	73	0.8	< 0.01	278	261	248
polyethersulfone	MD 190H	1.9	90	0.8	0.005	276	264	257

Data from manufacturer's specification sheets. $K_{UF}D$, ultrafiltration coefficient, measured with bovine blood. K_D, whole-blood clearance, measured at Q_B = 300 ml/min, Q_D = 500 ml/min Q_{UF} = 0.

More recently, Helixone, a new polysulfone based membrane assembled with sophisticated spinning nanotechnology procedures (Ronco and Bowry 2001) (see Fig. 19.2), was shown to promote greater MM removal by convection favored by a more regular and larger size of its pores (33 nm), while preventing significant albumin loss due to an extremely narrow distribution of the pore-size (Bowry and Ronco 2001) and minimal number of large pores. Moreover, the ability of this membrane to remove phosphate (P) was enhanced by modifying the composition and distribution of the polymer of the support region, critical for P transport, and improving the affinity between the low molecular weight (MW) compounds and the polymer matrix (Ronco et al. 2006).

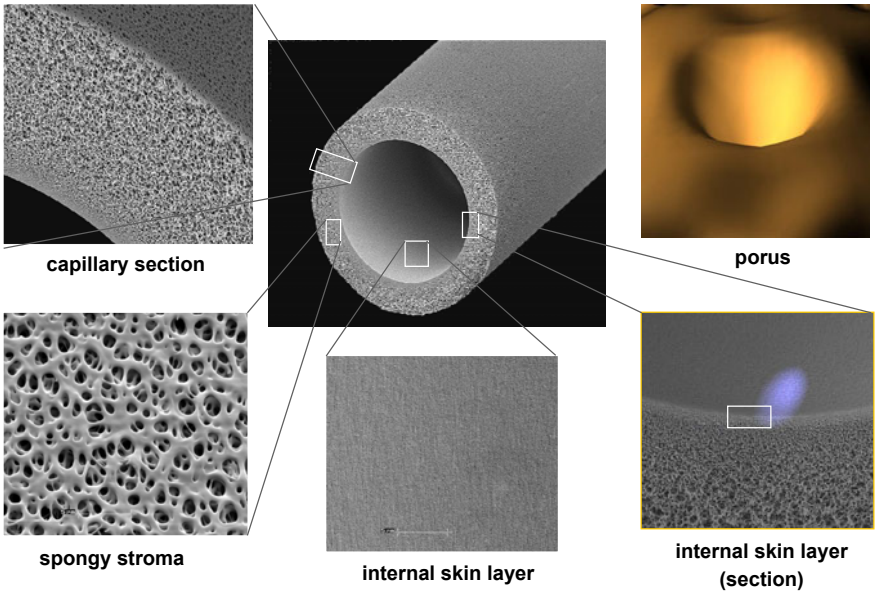


Fig. 19.2 Polysulfone (Helixone) hollow fiber Fresenius. Different magnification (x 250, 800, 3000). Nano-controlled structure of the internal skin layer.

An alternative new class of dialysis membranes known as super-flux (SF) or protein-leaking membranes has been developed for HD in the last years (Ward 2005). These membranes have a larger pore size and hence provide greater clearances of low MW proteins and small protein-bound solutes than do conventional high-flux membranes by coupling diffusion with increased convection with the mechanism of back-filtration and internal filtration (DeSmet et al. 2007; Pellicano et al. 2008). Combined use of SF membranes and chemotherapy in patients with myeloma kidney and dialysis-dependent acute renal failure has been shown to reduce serum free light chain concentration and favour renal recovery (Hutchison et al. 2009). It is yet unproven whether SF membranes offer benefits beyond those obtained with high-flux membranes used in HDF or HF, and whether the considerable amount of albumin lost in the dialysate through their large pores can be tolerated by chronic patients in the long-term (Ward 2005).

19.3 WATER AND SOLUTE TRANSPORT IN ON-LINE HDF

19.3.1 Water Transport: Ultrafiltration (UF)

Plasma water ultrafiltration occurs as a consequence of a pressure gradient established across the dialyzer membrane. At every point of the

capillary length the driving force for water filtration is the resultant of the hydraulic pressure inside the fiber (P_B) and in the dialysate (P_D) and the oncotic pressure exerted by plasma proteins (π). An equation (Henderson 1989; Hoenich 2007) that relates the volumetric water flux (J_f) to the transmembrane pressure difference is:

$$\frac{J_f}{A} = L_P\left(\Delta P - \Delta\pi\right) \tag{19.1}$$

where L_p is the hydraulic permeability of the membrane for water, i.e. the water flow rate per unit area of membrane (A) per unit pressure gradient (ml/min/cm^2/mmHg).

The average pressure gradient across a dialyzer membrane TMP is expressed with the Eq. (19.2):

$$TMP = \frac{\left(P_{Bin} + P_{Bout}\right)}{2} - \frac{\left(P_{Din} + P_{Dou}t\right)}{2} - \frac{\left(\pi_{in} + \pi_{out}\right)}{2} \tag{19.2}$$

where the suffix *in* and *out* indicate the inlet and outlet ports of the two dialyzer compartments.

In clinical practice, the ability of a dialyzer membrane to ultrafiltrate plasma water is defined with the ultrafiltration coefficient of the dialyzer ($K_{UF}D$, ml/hour/mmHg of TMP). The term $K_{UF}D$ expresses the hydraulic permeability of the overall membrane surface of the dialyzer and defines its class in terms of flux. A nominal $K_{UF}D > 40$ ml/hour/mmHg is a requisite for high-flux dialyzers.

$K_{UF}D$ is calculated in vitro by applying increasing TMP values in a defined experimental setting: the resulting ultrafiltration rate (Q_{UF}) is related linearly to the TMP up to a certain value (200-300 mmHg for high-flux membranes), and $K_{UF}D$ corresponds to the slope of the regression equation (Henderson 1989). Its value largely depends on the surface and characteristics of the membrane (mainly the pore radius), and on the dialyzer geometry. Lower than nominal $K_{UF}D$ values are found in vivo as a consequence of the protein layer formation on the inner face of the membrane (secondary membrane). Loss in hydraulic permeability is negligible and quite constant along low-flux HD sessions (Bosch et al. 1985) conducted at moderate Q_{UF}. Progressive and even substantial reduction in $K_{UF}D$ may be observed along HDF and HF sessions when higher Q_{UF} and filtration fraction (FF) are usually applied, as an effect of the solute and protein polarization on the inner membrane surface and thickening of the secondary membrane (Rockel et al. 1986; Vilker et al. 1981). In addition, the colloid osmotic pressure exerted by the concentrated plasma proteins counteracts

the filtration pressure (Vilker et al. 1984). As a consequence, the relationship between TMP and Q_{UF} becomes curvilinear and progressively increasing TMP is necessary to maintain the programmed filtration, until a plateau is reached, beyond which further increments in TMP are no more effective (Henderson 1989). The level of the plateau is mainly a function of the blood flow rate (Q_B) permeating the capillaries of the dialyzer. Therefore, high Q_B is preferential for successful application of all convective therapies.

19.3.2 Solute Transport

Solute transport across the dialyzer membrane can occur in HDF via diffusion, convection and adsorption.

19.3.2.1 Diffusion

Diffusion is the solute transport which occurs according to a first-order kinetics in the presence of a concentration gradient between blood and dialysis fluid. It is governed by Fick's law, expressed mathematically with Eq. (19.3):

$$\frac{J_D}{A} = -K_o \frac{dC}{dx} \tag{19.3}$$

where J_D is the rate of solute diffusive flux per unit area (A), proportional to the concentration gradient (dC/dx), and K_o is the solute diffusion coefficient (or, overall mass transfer coefficient) which characterizes the overall resistance to the solute flux across the membrane and is determined primarily by the property of the membrane and the solute.

Removal by diffusion is mainly influenced by Q_B and dialysate flow (Q_D) and by the dialyzer surface, and the relative role of each factor depends on K_o. At constant Q_{UF}, increasing dialyzer surface results in moderate enhancement of the diffusion transport according to a curve that achieves its plateau faster for the small molecular solutes. The level of the plateau is a function of the diffusive permeability of the membrane. An increase in Q_B up to 500-600 ml/min progressively increases diffusive removal of small solutes, while middle-high molecular weight solutes removal is scarcely affected by Q_B values beyond 200-250 ml/min (Wizemann et al. 2001). An increase in Q_D from 500 to 800 ml/min results in moderate enhancement of small solute removal by diffusion but not of the larger solutes (Hauk et al. 2000).

19.3.2.2 Convection

Solute transport by convection results from bulk movement of the solvent through the membrane in response to a hydrostatic pressure gradient. All solutes that are sieved by the membrane are carried along by the filtered fluid. In contrast to diffusive transport, convective transport is constant over a wide range of molecular weight solutes but decreases as the hydrated molecular size approaches that of the pores. The sieving property of a membrane determines what is removed, and its ability to remove a solute from plasma by convection is defined with an index, the sieving coefficient (S_C, dimensionless) for that solute. Sc, measured in vitro in a defined experimental setting and in the absence of diffusion, is the ratio between the solute concentration in the ultrafiltrate (C_{uf}) and its average plasma concentration within the dialyzer (Henderson 1989):

$$S_C = \frac{2C_{uf}}{\left(C_{in} + C_{out}\right)} \tag{19.4}$$

Thus, the mathematical equation that relates convective transport of a solute (J_C) to the rate of fluid transfer across the membrane Q_{UF} and the solute plasma concentration (C) may be written as:

$$J_C = Q_{UF} \times C \times Sc \tag{19.5}$$

S_C is a function of the membrane characteristics (electro-chemical properties and structure, pore radius and conformation) (Floege et al. 1989; Kim 1994; Morti and Zydney 1998; Ronco et al. 1997). Its value is inversely related to the solute molecular weight and varies between 0 for a freely permeable molecule and 1 for a completely impermeable molecule. The in vivo S_C value (apparent sieving) for middle-molecular solutes such as beta2-microglobulin (β2-m) changes in accordance with the operating conditions similarly to $K_{UF}D$ and may approach zero in post-dilution hemofiltration (HF) at very high Q_{UF} (David and Cambi 1992) as a consequence of the same events that affect the hydraulic permeability of the membrane. In general, the degree to which convection increases total solute removal is proportional to Q_{UF} and to the molecular weight of the solute (Lornoy et al. 1998). The pore diameter, structure, and chemical properties of the membrane also play an important role (Floege et al. 1989; Kim 1994; Morti SM and Zydney 1998; Ronco et al. 1997).

19.3.2.3 Adsorption

Adsorption may be an additional mechanism which contributes to the overall solute removal from blood when membranes carrying electrical

charges are used. Electrochemical interaction between these membranes and certain hydrophobic compounds like peptides and proteins may cause them to adhere on the inner surface of the membrane within the pore structure (Clark et al. 1994). Therefore, the open pore structure of high-f1ux membranes affords more adsorptive potential than do low-f1ux membranes, and synthetic hydrophobic membranes are generally much more adsorptive than hydrophilic cellulosic membranes (Clark et al. 1995). Albumin coats the membrane immediately after exposure to blood, with the effect to reduce its in vivo permeability. Adsorption assumes relevance as a removal mechanism particularly in the case of some high-flux membranes, such as polyacrilonitrile and polymethyl-metacrilate (Bouman et al. 1998; Lonnemann et al. 1988) and may significantly enhance the dialyzer clearance of β2-m and of several cytokines. Adsorption capacity of cellulose triacetate and polyamide membranes is fairly small in face of the high diffusivity of the former, which extends to middle-molecular compounds (Bouman et al. 1998; Floege et al. 1989) and the combined effects of diffusion and convection of the latter (Bouman et al. 1998). Polysulfone membranes show minor absorptive capacity and remove middle molecule compounds mainly by convection (Clark et al. 1999a).

19.3.3 Dialyzers Performance

Mass removal capacity of a dialyzer can be quantified on the basis of the instantaneous mass balance in blood and dialysate compartments. At any time, the amount of a solute removed from blood must be found in the dialysate:

$$Q_{Bin}C_{Bin} - Q_{Bout}C_{Bout} = Q_{Dout}C_{Dout} - Q_{Din}C_{Din} \tag{19.6}$$

where Q_{Bin} , Q_{Bout} , Q_{Din} , Q_{Dout} , are whole-blood and dialysate flow rates at the inlet and outlet blood and dialysate compartments of the dialyzer, and C_{Bin} C_{Bout} C_{Din} C_{Dout} are the relative solute concentrations. If Q_{UF} is the ultrafiltration rate, then:

$$Q_{Bout} = Q_{Bin} - Q_{UF} \tag{19.7a}$$

$$Q_{Dout} = Q_{Din} + Q_{UF} \tag{19.7b}$$

The dialyzer dialysance of a solute (D, ml/min) is the ratio of mass removal rate and incoming concentration driving force and determines the removal rate of a solute from blood. In all techniques, HD, HDF or HF, D

at a given time of the session can be calculated by rearrangement of equation 6 and integration with Eq. (19.7a):

$$D = Q_{Bin} \frac{(C_{Bin} - C_{Bout})}{(R_D C_{Bin} - C_{Din})} + \frac{Q_{UF} C_{Bout}}{(R_D C_{Bin} - C_{Din})} \tag{19.8}$$

Where R_D (Donnan factor), the ratio between the ionic concentration in dialysate and blood must be taken into account.

The term dialyzer clearance (K_D, ml/min) applies to non-charged solutes not present in the dialysate and, in analogy with D, is the ratio of mass removal rate and incoming whole-blood concentration:

$$K_D = Q_{Bin} \frac{(C_{Bin} - C_{Bout})}{C_{Bin}} + \frac{Q_{UF} C_{Bout}}{C_{Bin}} \tag{19.9}$$

The concept of whole-blood clearance, assuming that the total volume of blood is cleared from the solute, overestimates the actual solute removal rate which only occurs from the aqueous part of blood. Moreover, larger solutes present in both red cells and plasma water are not freely diffusible across the cell membrane and may be retained in the intracellular space (Skalsky et al. 1978). The more appropriate approach is to consider the effective blood flow-rate (Q_E) of the solute under evaluation (Sargent and Gotch 1996), which can be calculated with knowledge of the hematocrit (Hct) and the fractions of plasma and red cell water (F_P and F_R) as:

$$Q_e = Q_{Bin} \left[F_P - \frac{Hct}{100} (F_P - F_R \gamma R_D) \right] \tag{19.10}$$

where γ is a coefficient which expresses the resistance of a solute to transcellular transfer (being 1.0 for freely diffusible solutes and 0 for impermeable solutes). Theoretically, K_D is constant during the treatment only under unchanged operating conditions of flow and membrane permeability. In vivo, minor reduction in K_D may occur during HD sessions, while substantial reduction is possible during HDF, especially if very high Q_{UF} are applied, due to reduction of the hydraulic and solute permeability of the membrane as a consequence of the secondary membrane forming on the surface of the membrane at a rate dependent on Q_{UF} (Henderson et al. 1975).

19.3.4 Interactions between Diffusion and Convection

Solute removal occurs in HDF according to two simultaneous transport mechanisms, convection and diffusion, but the overall mass transport is

not the sum of the two separate components because of an interaction between them, which is more prominent at the high Q_{UF} of HDF. Thus, the effects of the two transport mechanisms cannot be separated precisely, but several mathematical models have been proposed to determine their combined effect in term of solute removal. The simplest model is described by Eq. (19.11):

$$K_{HDF} = K_{diff} + Q_{UF}T \tag{19.11}$$

where K_{diff} is the solute clearance in the absence of UF and T the transmittance coefficient, a parameter which is a function of the flow conditions and membrane properties.

Jaffrin et al (1990) proposed an expression for T that is universal for all solutes:

With $Q_{UF} < 70$ ml/min

$$K_{HDF} = K_{diff} + 0.46 Q_{UF} \tag{19.12}$$

With $Q_{UF} > 70$ ml/min

$$K_{HDF} = K_{diff} + 0.43 Q_{UF} + 0.00083 Q_{UF}^{2} \tag{19.13}$$

19.4 HDF TECHNIQUES AND INFUSION MODALITIES

19.4.1 Internal Filtration

When high-flux membranes are used in HD (high-flux HD), large water transfer occurs from blood to the dialysate compartment at the proximal end of the dialyzer according to a pressure gradient which results from the sum of hydrostatic, osmotic and oncotic pressures acting within the dialyzer compartments across the membrane. Water acts as solvent drag and favors removal of middle molecular compounds by convection. As a consequence of high UF, blood flow rate and hydraulic pressure within the capillaries drop progressively along the fiber length, while oncotic pressure increases with plasma protein concentration until, at a certain point of the dialyzer length, the pressure gradient across the membrane reverses its direction and, accordingly, water transfer occurs from the dialysate to the blood compartment (see Fig.19.3). This phenomenon, called 'back-filtration' or 'internal filtration' is the underlying principle of high-flux HD and its effect is an enhancement of small- and middle-molecular solute removal. Internal filtration flux taking place during high-flux HD may be

quantified by means of a mathematical model designed to supply the clinician with useful information about the contribution of convection to the efficiency of this treatment modality (Fiore et al. 2006).

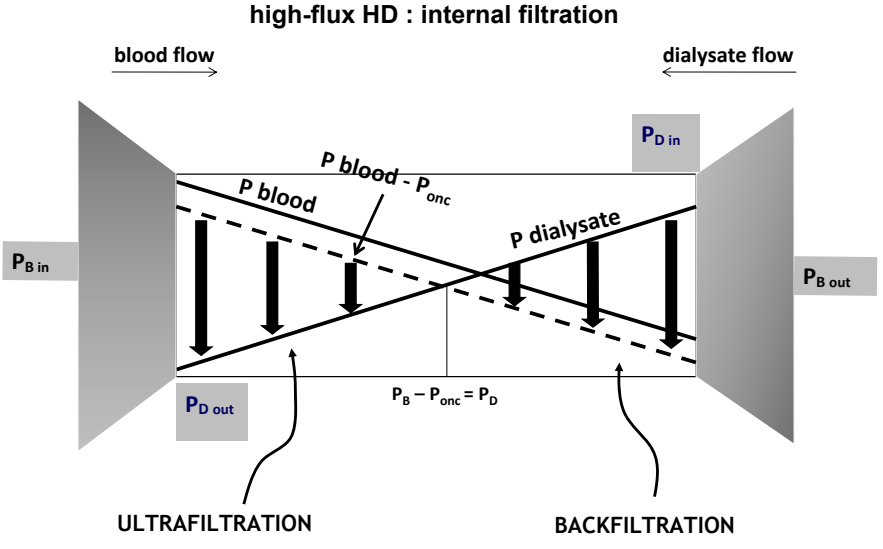


Fig. 19.3 Schematic representation of internal filtration as a convective transport mechanism acting during high-flux HD.

In HDF, higher Q_{UF} may be obtained in the absence of significant back-filtration. As a result of water filtration, solutes with diameter up to that of the membrane pores are dragged (convection) across the membrane independently of their molecular size. Pure convection (HF) promotes a higher rate of medium- and large-molecules removal than conventional HD but lesser removal of small-molecular compounds, which mainly occurs by diffusion. Combining both removal mechanisms into a single treatment (HDF) is undoubtedly the strategy enabling the high potential of hydraulic and solute permeability of synthetic membranes to be most properly exploited.

19.4.2 Post-dilution HDF

Post-dilution HDF (see Fig. 19.4A) is commonly held as the infusion mode in HDF that most efficiently removes middle molecules (Ahrenholz et al. 1997; Lornoy et al. 1998; Pedrini et al. 2000; Wizemann et al. 2001). Up to 5-6 liter of UF per hour may be obtained with appropriate pressure

regimen, thus maximizing removal by convection of uremic toxins, and the excess fluid loss of the patient is replaced with a sterile solution produced on-line from the dialysate and infused after the filter. However, when very high Q_{UF} are applied in post-dilution HDF, hemoconcentration increases blood viscosity and resistance to flow inside the fibers, especially when high rates of weight loss are necessary to achieve the dry body weight and when the individual capacity to recruit fluid from the extra-vascular space during dehydration (refilling) is scarce. In these conditions, a critical reduction of the membrane permeability is likely to occur. In fact, progressive protein concentration contributes to a thickening of the secondary membrane layer so limiting its hydraulic and solute permeability (Rockel et al. 1986; Vilker et al. 1981). Moreover, plasma proteins exert an increasing oncotic pressure that resists UF (Vilker et al. 1984). As a consequence, increasingly higher TPM gradients are often reached in the attempt to maintain the planned Q_{UF} but, beyond a certain limit, Q_{UF} reduces and even stops. In order to better preserve the membrane permeability when high Q_{UF} are applied, high Q_B should be applied in order to increase the shear rate that stirs the protein layer formed on the blood side of the membrane.

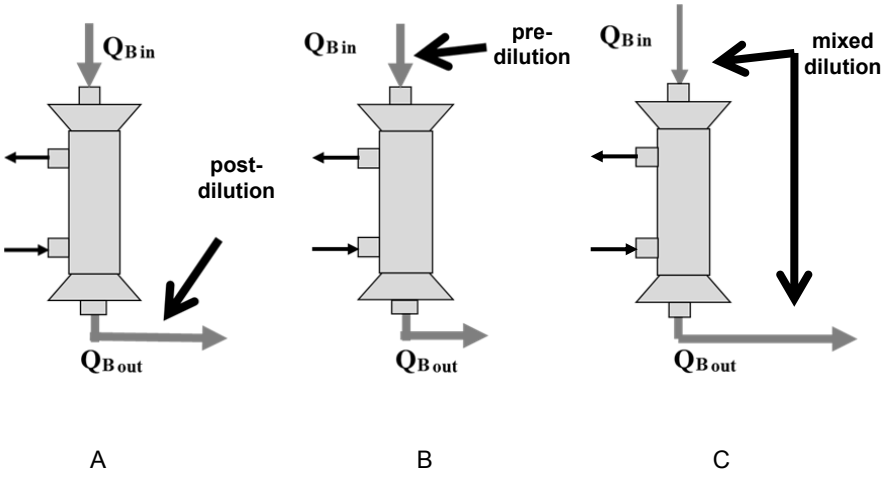


Fig. 19.4 Infusion modalities in HDF. A, post-dilution HDF; B, pre-dilution HDF; C, mixed HDF.

19.4.3 Pre-dilution HDF

Pre-dilution HDF (see Figure 19.4B) partially prevents these drawbacks, by ensuring safer rheological and pressure conditions, and, thus, the possibility of higher infusion and Q_{UF}. In this modality, the replacement fluid solution is added to blood before the dialyzer, and the increased rate of diluted flow within the capillaries better preserves the permeability of the membrane by stirring the secondary protein layer. However, this advantage in terms of convective removal may be offset by the dilution of the plasma solutes concentration available for diffusion and convection, with consequent reduction of their cumulative transfer (Ahrenholz et al. 1997; Pedrini et al. 2000; Pedrini and Zerbi 2007; Wizemann et al. 2001), in spite of an accelerated extraction of the diffusible small solutes from the intracellular space, due to a more favorable transcellular gradient (Cheung et al. 1983; Colton et al. 1975). Loss in efficiency of pre-dilution HDF due to the above conditions may be limited by setting the infusion rate to a value approximately double with respect to post-dilution HDF (Ahrenholz et al. 1997; Wizemann et al. 2001).

19.4.4 Mixed (Pre and Post-dilution) HDF

Mixed HDF (see Figure 19.4C) is a newly developed modality of HDF in which the replacement fluid is simultaneously infused to a variable ratio at the inlet and outlet port of the dialyzer. The aim of this technique is to overcome limits and risks implicit in the traditional infusion modes in HDF while coupling their advantages (Pedrini et al. 2000, 2002, Pedrini and DeCristofaro 2003). The basic concept is that splitting the infusion between pre- and post-filter guarantees better rheological and hydraulic conditions within the dialyser and preserves the characteristics of water and solute transport of the membrane. Consequently, the highest fluid exchange rate may be achieved with enhanced solute removal by convection. In mixed HDF, variable amount of infusion is added in pre-dilution and balanced with that in post-dilution in order to ensure the highest possible filtration fraction, while simultaneously avoiding dangerous hydrostatic pressures within the dialyzer and excessive dilution of the inlet solute concentrations. Preliminary studies have shown that mixed HDF, performed under the control of a TMP/Q_{UF} feedback system, achieved removal of small and large size solutes which was similar to post-dilution HDF when Q_{UF} was matched for the two infusion modes (Pedrini et al. 2000). A more

recent study demonstrated that greater β2-m and phosphate removal may be safely obtained in on-line mixed HDF than in post-dilution HDF by further increasing the total infusion rate and forcing Q_{UF} to achieve the most efficient convective transport (Pedrini et al. 2006; Pedrini and Zerbi 2007).

Mixed dilution may be of special advantage in patients with high predialysis hematocrit and an increased risk of filter clotting with post-dilution HDF due to hemoconcentration (Kuhlmann 2010).

19.4.5 Mid-dilution HDF (MD-HDF)

MD-HDF (see Figure 19.5A), a recently proposed HDF technique aimed at increasing convective solute transport (Krieter et al. 2005a), is based on the use of particular dialyzers (OLpur™ MD190 and MD220, Nephros, New York, USA) which include a U-shaped blood capillary bundle with a middle infusion port at the point where blood flow reverses direction. Blood and dialysate flow counter-current in the descending U branch of the capillaries where post-dilution is performed and co-currently in the ascending, pre-dilution U branch.

This infusion technique has been claimed to be of greater efficiency when compared to traditional pre- or post-dilution HDF (Krieter et al. 2005b). On the other hand, MD-HDF carried with it serious risks when applied as proposed in the original study because considerably high TMP in the post-dilution section of the filter was necessary to achieve the planned ultrafiltration of about 10 liter/hour (Feliciani et al. 2007). This problem was overcame by reversing the configuration of the blood tubing (Santoro et al. 2007). (reverse MD-HDF), but safer hydraulic conditions in MD-HDF was only shown with the use of the filter with the larger surface area (MD-220, 2.2 m^2) in reverse MD-HDF configuration (Pedrini et al. 2009). This system still lacks an efficient pressure control system with modulation of the infusion rate according to the operational conditions of the treatments, necessary to improve safety and performance in the routine clinical application of this technique.

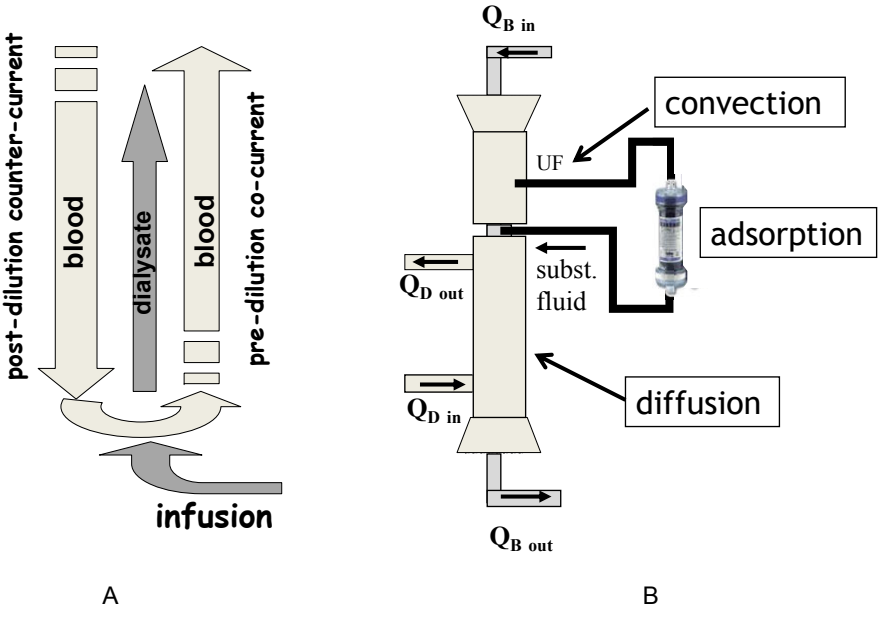


Fig. 19.5 Schematic representation of Mid-dilution HDF (A) and HDF with endogenous reinfusion (B). Explanation in the text.

19.4.6 HDF with Endogenous Reinfusion (HFR)

HFR (see Figure 19.5B) is an HDF technique performed by means of a 2-chamber filter with a high-flux polyethersulfone membrane in the first chamber and a low-flux polyethersulfone in the second one (Ghezzi et al. 1991). The two filtration stages allow separation of the convective from the diffusive process. The ultrafiltrate produced in the first chamber is 're-generated' by a sorbent cartridge in a closed circuit and then used as an endogenous replacement solution infused in the second one. This system is claimed to prevent any problem of sterility and apyrogenicity (Tetta et al. 2002) of dialysis fluids and any loss of bicarbonate and amino acids (Borrelli et al. 2010). The sorbent cartridge contains a hydrophobic styrenic resin which has high affinity and adsorbs several uremic toxins and MM, such as β2-m, homocysteine, parathyroid hormone, and several cytokines, while electrolytes and small solutes such as urea, creatinine and uric acid are not adsorbed and are managed in the second, diffusive section of the dialyzer (Marinez de Francisco et al. 2000; Ghezzi et al. 1991).

19.4.7 Ultrafiltration Control in On-line HDF

On-line HDF has been shown to obtain substantial clinical benefits when performed with high volume exchange, thus fully exploiting its potential of convective solute removal (Canaud et al. 2006). Indeed, proportional increase in β2-m removal is achievable in post-dilution HDF with increasing Q_{UF} (Lornoy et al. 1998; Wizemann et al. 2001). For this reason, operating conditions should be set in order to achieve this goal by maximally exploiting the permeability of high-flux membranes. At any given blood flow the maximal efficiency in convective removal is obtained at the highest filtration fractions (Pedrini et al. 2000). The highest achievable FF may only be achieved in the post-dilution mode, but its value is often unpredictable, due to the events described above. At any given blood flow, TMP is exponentially related to the filtration fraction, and the slope of the curve is a function of the hydraulic permeability of the dialyzer (Pedrini et al. 2000). Above a certain level of TMP the system becomes unstable (Jenkins et al. 1992) and sudden dangerous pressure peaks are likely to result from small changes in blood flow or viscosity, venous pressure, or for clinical reasons (see Fig. 19.6), particularly in patients with cardiac failure, diabetes or hemodynamic instability. In such circumstances residual irreversible reduction in the performance of the dialyzer was observed, even after restoring safer pressure conditions. Historically, the limit beyond which the adverse events of high TMP levels and hemoconcentration may occur was set empirically at a FF of 0.5 (Henderson 1989). Setting the infusion rate purely on the basis of the in vitro $K_{UF}D$ may be misleading for several reasons. The present technology of HDF machines helps to automatically plan a session in order to accomplish this task safely with the use of feedback devices which modulate the infusion rate through the control of TMP. In mixed HDF a newly developed feedback system is able to automatically maintain TMP within the highest range of safety during the session, while at the same time ensuring a constant and maximal infusion rate, by optimizing the ratio between pre-filter and post-filter infusion (Pedrini et al. 2000, 2006, Pedrini and DeCristofaro 2003) (see Fig. 19.7A, B). It has been reported that with the use of the new TMP-UF feedback control an infusion rate similar to the plasma water flow rate, split between pre and post-dilution in order to achieve a FF as high as possible, resulted in β2-m removal that was significantly higher than that obtained in both post-dilution HDF and pre-dilution HDF

performed at the highest infusion rate (Pedrini and DeCristofaro 2003). In post-dilution HDF, TMP the infusion rate is set and maintained at the maximum level compatible with safe TMP values and is modulated through the session according to a preset algorithm that reduces the infusion rate if TMP increases beyond its maximum limit as a consequence of the progressive decline of the membrane permeability through the session (see Fig. 19.7C).

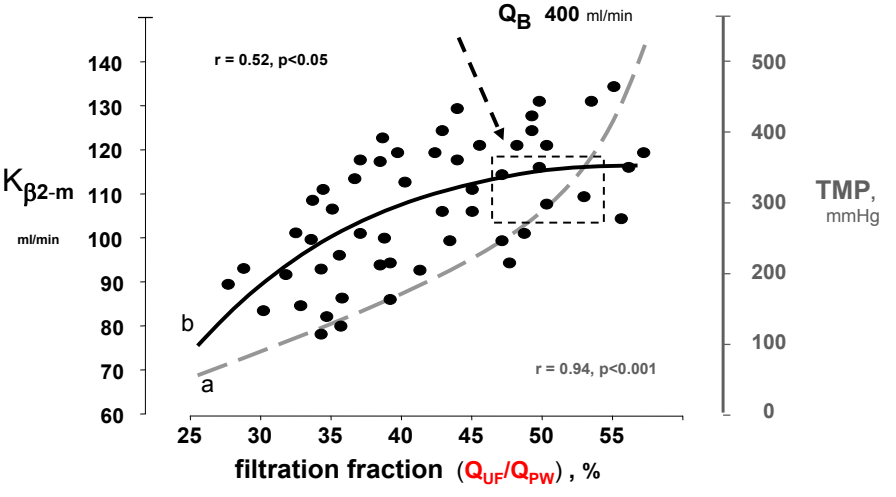


Fig. 19.6 Dependence of the trans-membrane pressure (TMP, right y-axis, curve a) and β2-m clearance ($K_{\beta 2\text{-}m}$, left y-axis, curve b) on the filtration fraction (FF = Q_{UF} /Q_{PW}, x-axis). Steep increase in TMP and stable $K_{\beta 2\text{-}m}$ values occur at a certain FF value between 50 and 55%. The domain included in the dotted square indicates the operating conditions of flow and pressure suitable to achieve safely maximal MM removal by convection in HDF. Data from Pedrini et al (2006).

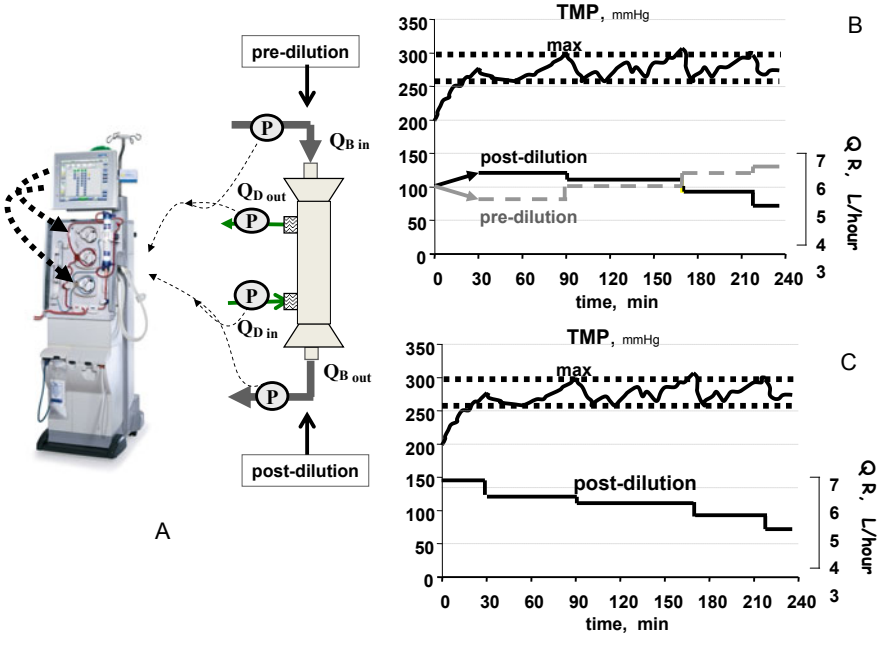


Fig. 19.7 Schematic representation of the hardware for mixed HDF (A) implemented on the 5008 Fresenius system. Four pressure probes (P) placed at the inlet and outlet blood and dialysate compartments provide serial measurements (1200 per minute) from which the instantaneous mean TMP is calculated. Two infusion pumps work at variable speed to modulate and proportion the infusion rate at the inlet and outlet port of the blood compartment. The diagrams represent the mechanism by which the TMP/UF feedback system controls TMP in mixed dilution HDF (B) by modulating the total infusion and the ratio between post- and pre-dilution infusion, and in post-dilution HDF (C) by modulating the total infusion. More details in the text.

19.5 KINETIC MODELING IN HEMODIALYSIS AND HEMODIAFILTRATION

Kinetic modeling is an analytic technique based on the principle of conservation of matter and used to describe the time course of a solute concentration during and between dialysis treatments, which results from changes in the solute content of its distribution volume over

time (Gotch and Keen 2005; Sargent and Gotch 1996). A marker solute for toxins of similar molecular weight or kinetic behavior may be used to simulate the rate of change in concentration of all solutes of the group in the various compartments of the body, and to prescribe the dialysis dose regarded as "adequate" to control the clinical symptoms of the uremic syndrome (Gotch and Keen 2005).

A model formulation requires a rigorous mathematical definition of its parameters in order the relative effect of each of them and their interactions to be precisely assessed (Sprenger et al. 1983). Precise characterization is needed for: 1) the solute distribution volume in the body and, in the case of multiple compartment models, the relative volume of each compartment, the net rate of volume change with time, the inter-compartmental mass transfer coefficient of the solute, its distribution coefficient within each compartment, 2) the solute mass gain of the system, expressed by the rate (and site) of solute generation, 3) the rate of solute mass removal from the system through residual renal clearance and metabolic transformation (extra-renal clearance), and 4) the solute mass exchange through the dialyzer membrane (removal or gain), which depends on the transport properties of the dialyzer (dialysance or clearance) and the nature and concentration of the solute.

19.5.1 Single Pool Model

The single-pool model has been applied to simulate the kinetics of small molecules (mainly urea) during different dialysis techniques (Gotch and Keen 2005;Sargent and Gotch 1980; Sausse et al. 1974). A schematic representation is depicted in Fig. 19.8A. Its simplest version, the fixed-volume single-pool (FVSP) Urea Kinetic Model (UKM), assumes that urea is uniformly distributed in a single, homogeneous fluid compartment (V) coextensive with the total body water (TBW). The variable-volume (VVSP) UKM accounts for volume changes during the dialysis cycle. V changes occur at constant rate, estimated from the weight loss per unit of time during dialysis, and from the rate of weight gain between dialyses.

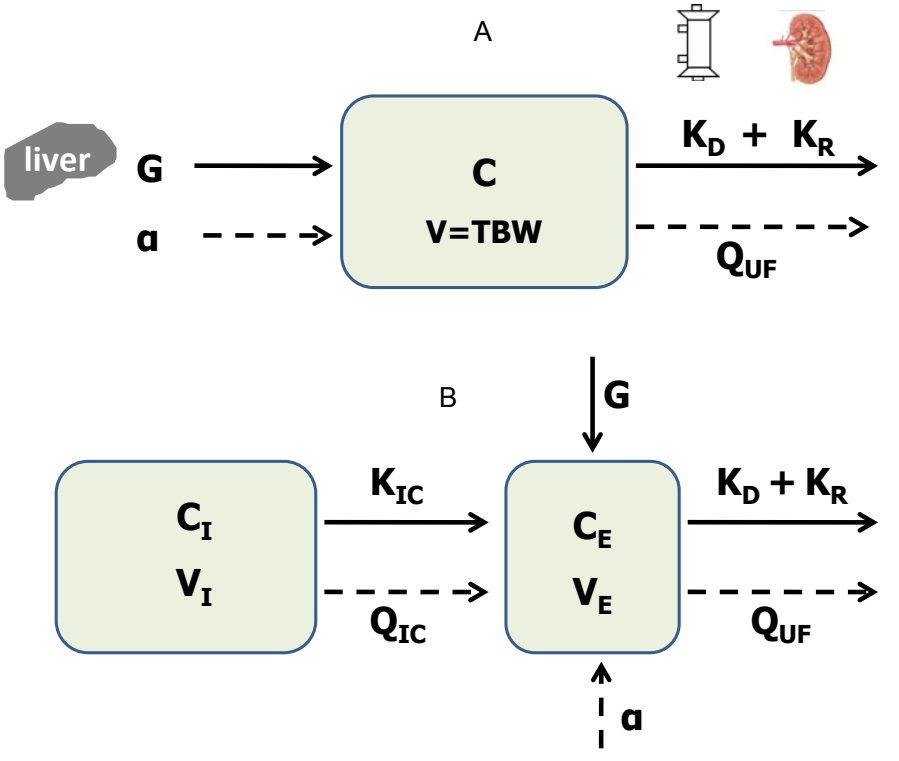


Fig. 19.8 Schematic representation of the VVSP (A) and VVDP (B) kinetic models. Explanation in the text.

The solute mass gain of the system is expressed by the rate of urea generation (G, mg/min). Urea, the end product of protein catabolism, is added to the distribution pool V at a constant rate throughout the dialysis cycle and G may be quantified as the increase in urea content in V between sessions (Δ V C_B) divided by the length of the interdialytic interval (t_{id}), as:

$$G = \frac{\left[V_{o2} C_{BO2} - VtC_{Bt} - K_R \frac{(C_{BO2} + C_{Bt})}{2} \right]}{t_{id}} \qquad (19.14)$$

where the suffix o, t and $_{O2}$ refer to the start and the end of the session and the start of the following session, respectively, and K_R is the residual renal clearance of the solute.

The rate of solute mass removal from the system (J_T) is the product of the total solute clearance K_T by its concentration (C_B):

$$J_T = C_B K_T = C_B \left(K_D + K_R \right) \tag{19.15}$$

K_D (ml/min), as above defined, is the dialyzer clearance of a solute, i.e. the ratio of mass removal rate and incoming concentration and determines the removal rate of a solute from blood. In all techniques, HD, HDF or HF, K_D at a given time of the session can be calculated with Eq. (19.9) substituting Q_e for Q_{Bin} as in Eq. (19.10).

Knowledge of K_oA, the overall mass transfer coefficient (per area) of the solute, provides an alternative method to estimate K_D (Sargent and Gotch 1996). K_oA is typical for a given dialyzer and constant at any blood and dialysate flow rate and solute concentration. The relationship between the diffusive K_D, K_oA and flow rates is expressed by the Eq. (19.16):

$$K_D = Q_B \frac{\left\{ \exp\left[\frac{K_o A}{Q_B} \left(\frac{1 - Q_B}{Q_D} \right) \right] - 1 \right\}}{\left\{ \exp\left[\frac{K_o A}{Q_B} \left(\frac{1 - Q_B}{Q_D} \right) \right] - \frac{Q_B}{Q_D} \right\}} \tag{19.16}$$

The equation is valid for counter current flow and only with Q_{UF} null or minimal. Q_{UF} typical on HD (up to 10 ml/min) has a trivial effect on K_D of urea and highly diffusible solutes, while it may substantially increase K_D of larger solutes.

K_R (ml/min) contribution to removal should not be neglected because even very low values may significantly affect blood concentration of solutes, particularly in the middle molecular weight range. K_R is usually calculated by collecting and measuring urine volume (V_u) and its concentration (C_u) over an entire interdialytic interval and taking the average of blood urea concentration at the beginning and the end of urine collection, with the assumption of a linear increase in C_B:

$$K_R = \frac{\left(C_u \times V_u \right)}{\left[\frac{\left(C_{Bt} + C_{Bo2} \right)}{2} \times t_{id} \right]} \tag{19.17}$$

With these premises, the rate of change in body content of urea during a dialysis treatment is described mathematically from the following general equation of the FVSP-UKM (Sargent and Gotch 1996):

$$VC_B\left(\frac{d}{dt}\right) = -K_T C_B + G \tag{19.18}$$

While, the general equation of the VVSP-UKM is:

$$\left(\frac{d}{dt}\right)\left[V(t)C_B(t)\right] = -K_T(t)C_B(t) + G \tag{19.19}$$

Integration and rearrangement of the VVSP model equation Eq. (19.19) allows calculation of V and G on the basis of measured values for K_D, C_{Bo}, C_{Bt}, C_{Bo2}, t_d, t_{id} and the constant rate of change in V during dialysis (Q_{UF}) and the interdialytic period (α):

$$V_t = Q_{UF} \times t_d \left\{ \left[1 - \left(\frac{G - C_{Bt}(K_T - Q_{UF})}{G - C_{Bo}(K_T - Q_{UF})} \right)^{\frac{Q_{UF}}{K_T - Q_{UF}}} \right]^{-1} - 1 \right\} \tag{19.20}$$

$$G = \frac{(K_r + \alpha)\left[C_{BO} - C_{Bt}\left(\frac{V_t + \alpha t_{id}}{V_t} \right)^{-\frac{K_r + \alpha}{\alpha}} \right]}{1 - \left(\frac{V_t + \alpha t_{id}}{V_t} \right)^{-\frac{K_r + \alpha}{\alpha}}} \tag{19.21}$$

Equations (19.20) and (19.21) may be solved iteratively for the end-session V (V_t) and G until unique solution for V_t and G is found. Once individual estimate of the variables V_t, and G has been achieved, then the actual time course of the concentration changes during dialysis and the end-session concentration (C_{Bt}) may be obtained on the basis of the initial solute concentration (C_{Bo}) by solving the Eq. (19.19) for C_{Bt} (Sargent and Gotch 1996):

$$C_{Bt} = C_{Bo}\left[\frac{V_o - Q_{UF} t_d}{V_o} \right]^{\frac{(K_T - Q_{UF})}{Q_{UF}}} + \left[\frac{G}{K_T - Q_{UF}} \right] \times \left[1 - \frac{V_o - Q_{UF} t_d}{V_o} \right]^{\frac{(K_T - Q_{UF})}{Q_{UF}}} \tag{19.22}$$

while, plasma solute concentration at the start of the following session (C_{BO2}) may be obtained as :

$$C_{BO2} = C_{Bt}\left[\frac{(V_t + \alpha t_{id})}{V_t}\right]^{-\frac{(K_R+a)}{a}} + \left\{\frac{G}{(K_R+a)} \times \left[1 - \frac{(V_t + \alpha t_{id})}{V_t}\right]^{-\frac{(K_R+a)}{a}}\right\} \quad (19.23)$$

Since equations (19.22) and (19.23) are discontinuous when Q_{UF} or $\alpha = 0$, assumption of a very small value for V changes is necessary to solve the equations in this case without affecting the final result.

The weekly course of the solute concentration simulated by the VVSP model for thrice/weekly HD schedule is represented in Fig. 19.9

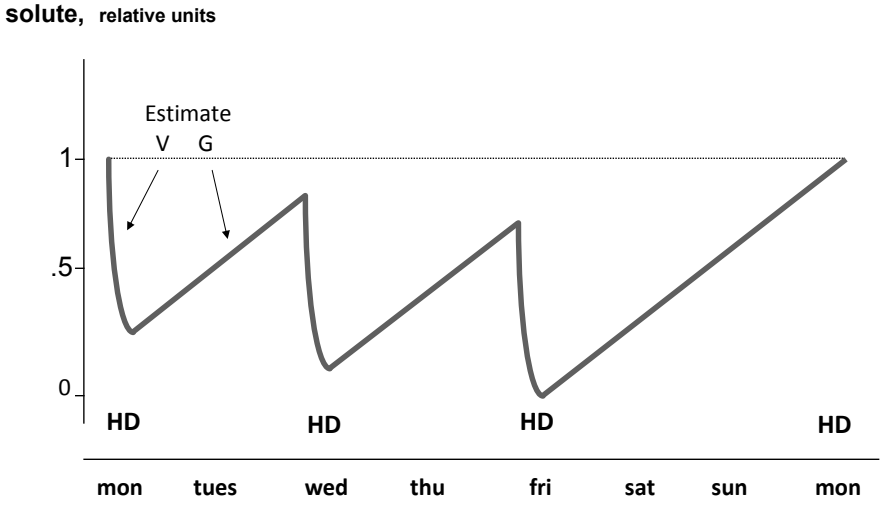


Fig. 19.9 Weekly time course of urea concentration simulated by the VVSP-UKM model in steady state condition.

Clinical application of this model requires three determinations of urea concentration from two consecutive dialyses. A simpler method, which only requires knowledge of Co and Ct from a single dialysis (Depner and Cheer 1989; Gotch and Keen 2005)., is based on iterative solution of the model equations over a weekly dialysis schedule and adjustments of Vt and G values until a unique solution for Co is found.

The SPVV-UKM provides a method for quantifying the amount of delivered dialysis dose and for monitoring the quality of the prescribed therapy with an index, the K_D t / V_t , which expresses the fractional urea clearance of the session.

19.5.2 The Variable Volume Double-Pool Model (VVDP)

The VVSP model assumes a single body compartment as a solute distribution volume and does not simulate precisely the intradialytic kinetics of solutes which do not cross freely the body compartment barriers. The actual distribution volume of low MW compounds, such as urea, creatinine and phosphate includes the intracellular (V_I) and the extracellular space (V_E), the latter divided in turn into interstitial (V_i) and intravascular (V_P) space. The capillary bed is highly permeable to most small solutes and concentration equilibrium between V_P and V_i is achieved instantaneously. Hence, in this case the two compartments are retained as a single extracellular pool V_E (Schindhelm and Farrell 1978). A schematic representation of the VVDP model is depicted in Fig. 19.8B.

A concentration disequilibrium between V_I and V_E may be generated during dialysis when a solute is cleared from plasma water at a faster rate than its transfer rate across the cell wall membrane. This imbalance between concentrations triggers a solute movement between V_I and V_E according to a diffusion concentration gradient. The magnitude of transfer depends on the resistance opposed by the cell membrane, which is expressed by the solute inter-compartment mass transfer coefficient (K_{IC}, inter-compartmental clearance) and is typical for the solute (null for large impermeable molecules and large for freely diffusible small molecules). At the end of the session solute removal from blood ceases, but its transfer from the inner to the outer compartment continues until the respective concentrations re-equilibrate. This phenomenon appears as a rapid increase of plasma concentration immediately after the end of dialysis (post-dialysis rebound) (Pedrini et al. 1988) and its magnitude and duration are inversely proportional to the solute K_{IC} (see Fig. 19.10).

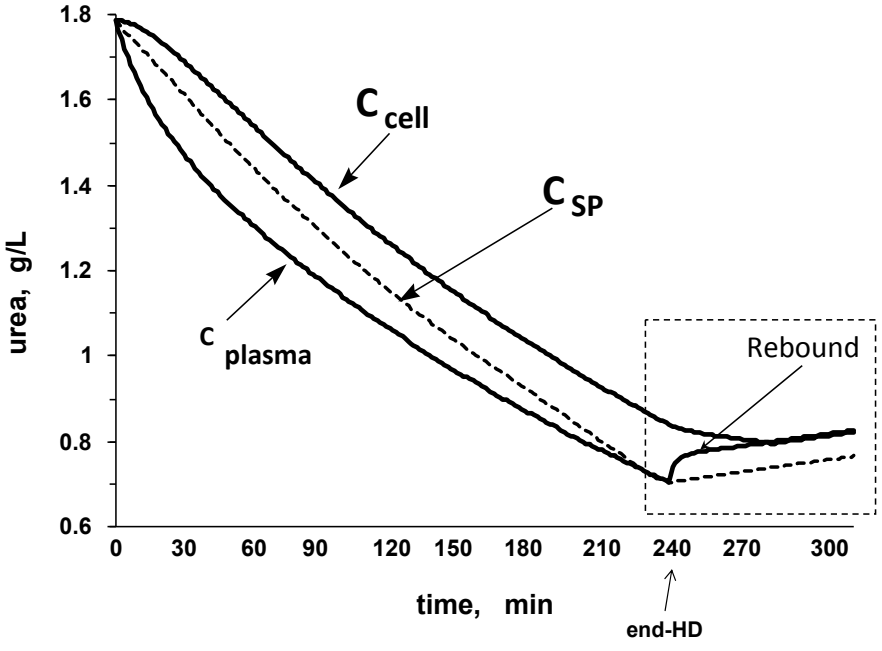


Fig. 19.10 Time course of plasma and intracellular urea concentration during a session of HDF and during the rebound period, as simulated by the VVDP-UKM model. The dotted line represents the VVSP-UKM simulation obtained at the same operating conditions.

Not accounting for these events, the single pool model does not simulate accurately the kinetic behavior of most solutes, but the error is small when urea or other solutes freely diffusible are modeled (Rastogi et al. 1968). HDF has the main objective to remove middle molecular compounds, which are retained in the inner body compartment to a variable extent according to their molecular weight and may exhibit a post-dialysis rebound of up to 50% (Popovich et al. 1975). Thus, two- or multiple pool models simulate more reliably the kinetics of small solutes not freely permeable, such as creatinine and phosphate, and their application is mandatory for reliable simulation of the kinetics of larger molecules such as β2-m.

19.5.2.1 The Variable Volume Double-Pool Urea Kinetic Model (VVDP-UKM)

The most consistent VVDP-UKM provides simultaneous modeling of urea, sodium (Na) and fluid volume changes (Gotch and Keen 2005; Gotch et al. 1980; Sargent and Gotch 1980, 1996). In this model, urea V corresponds to

the TBW, which is divided in two compartments, V_I and V_E. Sodium distribution space is V_E but its osmotic power regulates the water content of both V_E and V_I compartments by driving water shifts across the cell membranes. Therefore, a consistent assumption for modeling purposes is that the distribution volume of Na activity extends to the TBW, and that extracellular Na activity is counterbalanced in V_I by the cation osmotic activity (C+), assumed to be constant and corresponding to the intracellular K+ concentration (Edelman et al. 1958).

Solute removal from the system occurs from V_E at a rate determined by K_T (ml/min), as in VVSP model. Urea is assumed to be generated in V_E (Gotch and Keen 2005) or in both compartments according to other authors (Rastogi et al. 1968). The original formulation of the VVDP-UKM is based on the following mass balance equations for urea (C, concentration), Na and water (Gotch 1995):

For Urea:

$$\frac{d}{dt}\left(V_E C_E\right) = K_{IC}\left(C_I - C_E\right) + G - \left[K_T\left(1 - \frac{Q_{UF}}{Q_E}\right) + Q_{UF}\right] C_E \quad (19.24)$$

$$\frac{d\left(V_I C_I\right)}{dt} = -K_{IC}\left(C_I - C_E\right) \quad (19.25)$$

The initial intracellular urea concentration C_I can be estimated from C_E and the distribution coefficient χ, that is the ratio of a substance in two compartments at equilibrium ($C_E = \chi\, C_I$).

For Na:

$$\frac{\mathrm{d}}{\mathrm{dt}}\left(\mathrm{V_E Na_E}\right) = \mathrm{D}\left(1 - \frac{\mathrm{Q_{UF}}}{\mathrm{Q_E}}\right)\mathrm{Na_{Di}} - \left[\mathrm{D}\left(1 - \frac{\mathrm{Q_{UF}}}{\mathrm{Q_E}}\right) + \mathrm{Q_{UF}}\right]\mathrm{Na_E} \quad (19.26)$$

$$\frac{d}{dt}\left(V_I C^{+}{}_I\right) = 0 \quad (19.27)$$

where D is Na dialysance [see Eq. (19.8)] and Na_{Di} is the inlet dialysate Na concentration. Trans-compartmental water flow is driven by the osmotic

gradient which results from the combined difference in concentration/activity of urea and anions between VI and VE and is limited by the trans-cellular transfer coefficient for water (K_{CW}):

For Water:

$$\frac{d}{dt}V_E = K_{CW}\left[\left(C_E - C_I\right) + \left(Na_E - C^+{}_I\right)\right] - Q_{UF} \tag{19.28}$$

$$\frac{\mathrm{d}}{\mathrm{dt}}\left(\mathrm{V_E Na_E}\right) = \mathrm{D}\left(1 - \frac{\mathrm{Q_{UF}}}{\mathrm{Q_E}}\right)\mathrm{Na_{Di}} - \left[\mathrm{D}\left(1 - \frac{\mathrm{Q_{UF}}}{\mathrm{Q_E}}\right) + \mathrm{Q_{UF}}\right]\mathrm{Na_E} \tag{19.29}$$

Mathematical solution of the VVDP-UKM requires the exact definition of at least five parameters (G, V_I, V_E, K_{IC} and K_{CW}), which could only be calculated individually on the basis of serial blood sampling for urea and Na and numerical integration of the model equations (Gotch and Keen 2005), for instance with the Runge-Kutta method. Thus, estimate of parameters for clinical model application are often assumed from the literature, with the drawback that inaccurate simulation may result from incorrect assumptions.

The relative magnitude of V, V_I and V_E spaces has been estimated with various kinetic models and radioisotopic injection methods in accordance with physiological measurements, usually in patients with normally functioning kidneys (Popovich et al. 1975; Rastogi et al. 1968; Schindhelm et al. 1978; Watson et al. 1980). Urea K_{IC} may be calculated with a series of measurements of blood concentrations during dialysis and post-dialysis rebound. Values reported by several authors are ranging from 500 to 860 ml/min (Clark et al. 1999b; Frost and Kerr 1977; Gotch and Keen 2005; Pedrini et al. 1988; Popovich et al. 1975;Schindhelm and Farrell 1978). In general, K_{IC} decreases with increasing MW of different solutes. K_{IC} is the limiting factor in mass transport because of its magnitude which is least an order lower than that of the trans-capillary transfer coefficient. An estimate of 0.2 ml/min per mmHg for K_{CW} has been reported (Gotch 1995). The distribution coefficient χ for urea was estimated to be 0.86 by (Colton et al. 1975), but a value equal to 1 resulted from measurements on uremic erythrocytes, implying concentration equilibrium between compartments (Nolph et al. 1978). In the latter case, χ may be ignored in pool calculations.

Example 19.1

Simulate the time course of plasma and intracellular urea concentration (U) in a patient on chronic extracorporeal treatment during HD and high-efficiency HDF and post-session rebound simulated using VVDP model, and comparative estimate (Kt/V) of the efficiency of the two sessions.

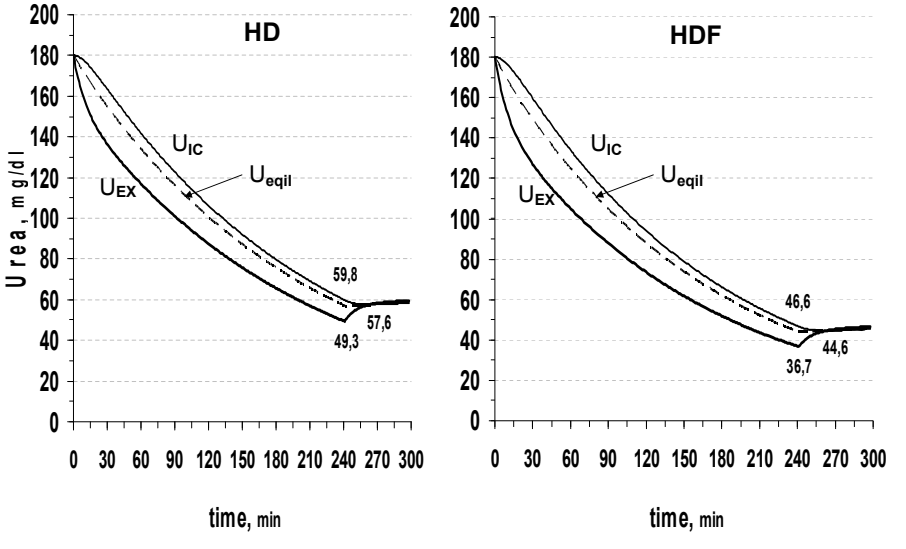
Known/measured patient parameters	*value*
Age, *years*	70
Height, *cm*	175
Dry BWt, *kg*	70.0
Hct , *%*	35.0
Tot Prot, *g/dl*	6.0
Urea start session , *mg/dl*	180

Treatment parameters	*value*	*note*
Session time, *min*	240	
Q_B , *ml/min*	400	
Q_{UF} (on HD), *ml/min*	10	
Q_{UF} (on HDF) , *ml/min*	122	Set to achieve FF= Q_{UF}/Q_{PW} = 0.5. Q_{PW} from Eq. (19.31).
$Q_{subs.fluid}$ (on HDF), *ml/min*	112	

Solution

Step 1: estimate of patient and treatment parameters to be included in calculations

Estimated Parameter	*value*	*method of estimate*
Urea G , *mg/min*	12.0	*Eq.(19.14) applied to a pilot session.*
K_{Renal} , *ml/min*	2.0	*Eq.(19.17) applied to a previous interdialytic interval.*
TBW (V_E +V_I)	39	*Watson equation (Watson 1980)*
V_I/V_E	2.0	*Assumed from Gotch (see Table 19.2)*
K_{IC} , *ml/min*	70	*Assumed from Gotch (see Table 19.2)*
K_D on HD, *ml/min*	230	*Nominal in vivo value from the Manufacturer*
K_D on HDF, *ml/min*	291	*From Eq. (19.13)*



HD	
U_{EX} *end-session, mg/dl*	49.3
U_{eq} *, mg/dl*	57.6
Rebound, %	14.4
Session time, *min*	240
TBW (V_E +V_I), *Liter*	39
K_D on HD, *ml/min*	230
Kt/V	1.42

HDF	
U_{EX} *end-session, mg/dl*	36.7
U_{eq} *, mg/dl*	44.6
Rebound, %	17.7
Session time, *min*	240
TBW (V_E +V_I), *Liter*	39
K_D on HD, *ml/min*	291
Kt/V	1.79

19.5.3 Kinetic Modeling of β2-microglobulin in HDF

In clinical practice, a simplified approach based on a single-pool kinetic was used in the past to quantify β2-m removal from its percent reduction (RR, %) in plasma concentration from the start to the end of the session (Floege et al. 1989; Jorstad et al. 1988).

$$RR = \left(\frac{1 - C_t}{C_o} \right) \times 100 \tag{19.30}$$

This approach entails significant imprecision given that it assumes a fixed single distribution space for β2-m (V_E) and but neglects its dimension, renal and non-renal clearance and generation rate of the solute, duration of the treatment (Leypoldt et al. 1997), and the effect of hemoconcentration on the end-session β2-m concentration (Bergstrom and Wehle 1987). Actually, a VVDP model is mandatory to simulate the actual β2-m kinetics during the dialysis cycle. A schematic representation of the β2-m VVDP model is depicted in Fig. 19.11. The VVDP-UKM model by Gotch (Gotch et al 2005) applies to β2-m kinetics with appropriate recognition of the inherent parameters and reciprocal relationships. However, problems with its clinical application are of the same nature as for urea, in that the necessary estimate of several unknown parameters is too cumbersome from only the time dependence of β2-m plasma concentration. Thus, values from the literature are often assumed for some key parameters (Clark et al. 1999b; Floege et al. 1991; Floege et al. 1988; Gotch et al. 1989; Kanamori and Sakai 1995; Karlsson et al. 1980; Maeda et al. 1990; Odell et al. 1991; Stiller et al. 2002; Ward et al. 2006), as reported in Table 19.2.

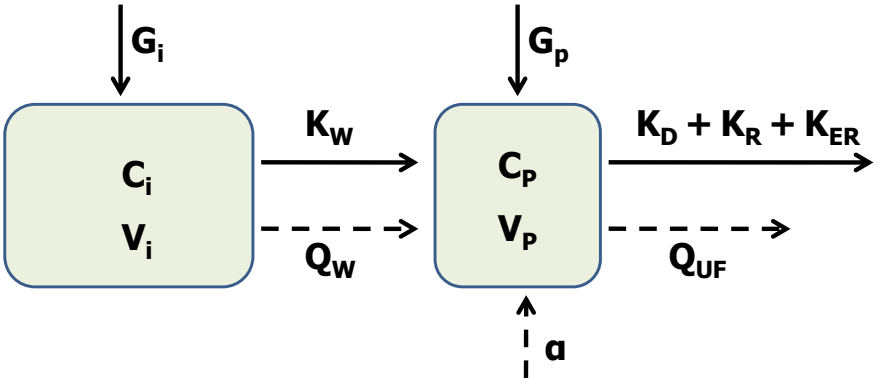


Fig. 19.11 Schematic representation of the VVDP kinetic model for β2-m. Explanation in the text.

The total distribution space for β2-m is V_E, divided in two homogeneous sub-compartments: V_P (plasma) and V_i (interstium). Resistance to β2-m transfer from V_i into V_P is large enough to generate substantial concentration disequilibrium between the two spaces during dialysis and a rapid increase in plasma concentration at its end, as an effect of the inter-compartmental re-equilibration (Leypoldt et al. 1999). Especially during convective treatments with high-flux filters, β2-m removal rate from plasma approaches and often exceeds the rate of diffusive transfer into V_P (K_{IC}) (Ward et al. 2006), and β2-m rebound after the sessions may last one to two hours with an increase in plasma concentration up to 50% (Leypoldt et al. 1999; Maeda et al. 1990). Fluid removal during dialysis is assumed to occur from V_E (Gotch et al. 1989), and distributes in both V_P and V_i proportionally to their size. Q_{UF} determines the rate of V_P changes while trans-capillary water shifts follow the osmotic gradient created by changes in plasma protein concentration and are limited by the trans-capillary water coefficient (K_W). Water removal from both V_I and V_E is assumed by other authors (Lian et al. 1993), based on the fact that Na is the most powerful osmotic agent in plasma and water shifts between compartments are mainly consistent with changes in its concentration/activity. Continuous β2-m G is assumed to occur at a constant rate. According to different views the site of G is the interstitial compartment (Gotch et al. 1989), the intravascular fluid (Kanamori and Sakai 1995; Karlsson et al. 1980), or both compartments (Ward et al. 2006). β2-m G may be independently measured in the interdialytic interval in analogy with urea generation by adapting the equation (19.14). Removal of β2-m occurs from plasma through three different pathways: residual renal (K_R) and extra-renal (K_{ER}) clearance

assumed to be continuous along the dialysis cycle, with values independently measured in the interdialytic interval in the former case (see Eq. 19.17) and measured (Xu et al. 2001) or assumed from the literature in the latter case, and dialyzer clearance (K_D) acting only during therapy. K_D can be measured at any time of the session by substituting the appropriate parameters into Eq. (19.9) and using the effective β2-m blood flow rate, which corresponds to plasma water flow rate (Q_{PW}):

$$Q_E = Q_{PW} = Q_B \left(\frac{1 - Hct}{100} \right) F_p \tag{19.31}$$

Table 19.2 Values for some key parameters of ß2-m VVDP model assumed from the literature.

Author	year	patients/method	G (mg/hr/kg)	K_{IC} (ml/min)	V_E = % TBW	V_i/V_p	K_{ER} (ml/min)
Karlson	1980	6 normal ^{125}I β2-m	**0.131** ± 0.023		**58.8** ml/kg normal **52.3** ml/kg IRC		**1.0**
Odell	1991	5 HD pts	**0.159** ± 0.041	**42.9** ± 6	**200** ± 30 ml/kg	**2.78** ± 0.8	**2.96** ± 0.35
Floege	1991	11 HD ^{131}I β2-m	**0.129** ± 0.033	**65.8** ± 12.8	**0.24** x BWt	**4.3**	**3.40** ± 0.7
		5 normal ^{131}I β2-m	**0.1** ± 0.028				
Kanamori	1995	simulation	**0.131** ± 0.023		**200** ml/kg		**1.64**
Maeda	1990	CKD pts	**0.130** ± 0.029				
		HD pts	**0.152** ± 0.016				
Gotch	1989	simulation	**0.131**	**5 ml x Lit VE**	**33%**	**3.0**	
Clark	1999	simulation	**0.170**	**40**	**33%**		**3.0**
Stiller	2002	8 HD pts	**0.104** ± 0.027 (0.065 - 0.155)	**56.3** ± 25.2 (26 -140)	**28.4** ± 3.1 (23.7 - 35.7)	**4.6** ± 1.8 (2.5 - 10)	**3.16** ±0.57
Ward	2006	10 HD pts	**0.113** ± 0.021 (0.0076 - 0.152)	**82.5** ± 21 (53 -108)	**14.3** ± 0.7%	**3.0**	**3.0**

An equation has been derived with the aim to provide a prompt quantification of the efficiency of a technique/dialyzer in removing β2-m. This approach was described by (Leypoldt et al. 1997), based on the observation that the normalized intra-dialytic reduction in β2-m plasma concentration depended primarily on β2-m Kt/V (K_D × treatment time / distribution volume V_E at end-treatment), and on the rate of fluid removal. Leypoldt's equation allows calculation of K_D for β2-m from the pre- and post-dialysis β2-m concentration, an estimate of V_E, treatment time, and the total amount of fluid removed during

therapy. Only β2-m G during dialysis, K_R and K_{ER} are not considered in this analysis. This equation was used to define the dialyzer clearance β2-m and the flux intervention in the HEMO study (Eknoyan et al. 2002).

$$K_D = Q_{UF}\left[\frac{1-\ln\left(\frac{C_t}{C_o}\right)}{\ln\left(1+Q_{UF}\,t\,V_{Et}\right)}\right] \tag{19.32}$$

As for urea, solution of the β2-m VVDP model is only possible by numerical integration of the model equations. However, this method is rather cumbersome to be applied in clinical practice as it requires several measurements of the solute concentration during and after the session and estimates of the parameters according to the best fit of the model curves. More practical approaches have been taken to solve the model equations by different authors, who reduced the number of the parameters left unknown. Gotch (Gotch et al. 1989) and Lian (Lian et al. 1993) left three parameters (G, K_D and K_{IC}) to be determined by fitting. Other authors evaluated β2-m G and K_{ER} in dialysis patients (Xu et al. 2001).

Based on the above relationships and assumptions, the equations of the β2-m VVDP model may be written in accordance to Ward (Ward et al. 2006) and with reference to other authors (Gotch et al. 1989; Kanamori and Sakai 1995). Change in β2-m mass in the two compartments as a function of time can be described as:

$$\frac{d\left(V_P C_P\right)}{dt} = V_P G + K_{IC}\left(C_i - C_P\right) - \Theta K_D C_P - \left(K_R + K_{ER}\right)C_P + \Theta V_i Q_{UF} C_i - \left(1-\Theta\right)V_i a C_P \tag{19.33}$$

$$\frac{d\left(V_i G\right)}{dt} = V_i G + K_{IC}\left(C_P - C_i\right) - \Theta V_i Q_{UF} C_i + \left(1-\Theta\right)V_i a C_P \tag{19.34}$$

where Θ is a constant which assumes the value of 1 during dialysis and 0 during the interdialytic period. β2-m G, calculated according to Eq. (19.14), is assumed to occur in both compartments in proportion to their volumes. Assumed values for the initial V_i/V_P ratio and for K_{ER} are those reported in Tab. 19.2.

Change in V_I and V_P are proportional to their relative volumes and can be described as:

$$\frac{d}{dt}\left(V_p\right) = -\Theta\, V_P\, Q_{UF} + \left(1-\Theta\right)V_P\, \alpha \tag{19.35}$$

$$\frac{d}{dt}(V_i) = -\Theta V_i \, Q_{UF} + (1-\Theta) V_i \, \alpha \tag{19.36}$$

Equations (19.33) to (19.36) may be solved with numerical methods (i.e. Runge-Kutta method) with the assumed parameters value and estimate of the unknown variables (i.e. KIC and V_P or V_i) by fitting the model equations to serial measured β2-m concentrations.

The time course of plasma and interstitial β2-m concentration during a HDF session and the post-session rebound as simulated by the VVDP model in a hypothetical patient is represented in Fig. 19.12

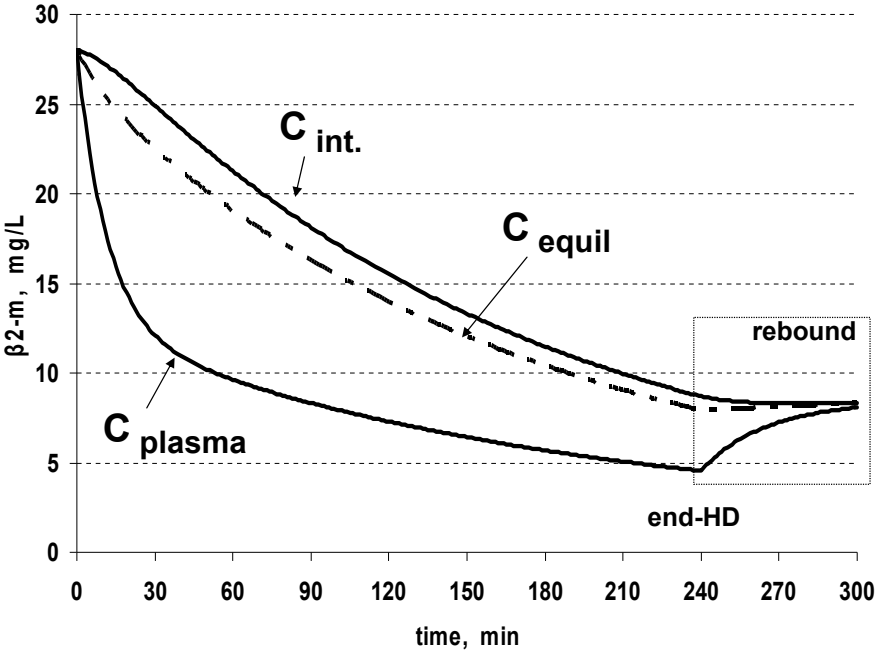


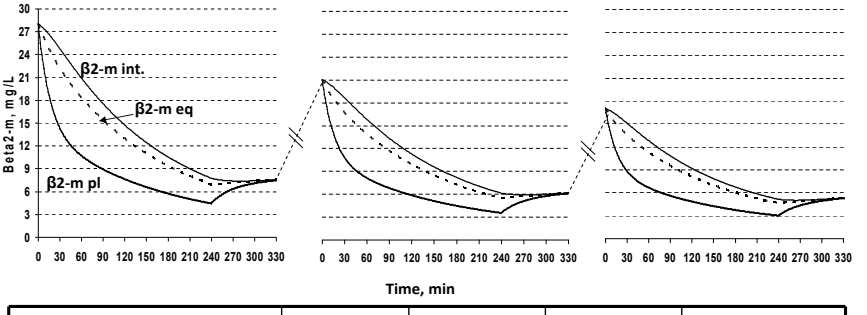
Fig. 19.12 The time course of plasma and interstitial β2-m concentration during a HDF session and the post-session rebound as simulated by the VVDP model.

Example 19.2

A patient on chronic HD treatment is shifted to high-efficiency HDF treatment with a substitution fluid rate set in order to achieve a FF of 50%. The pre-dialysis steady-state plasma β2-m concentration of the first session of the week on standard HD is 28 mg/L. Which will be the corresponding value on high-efficiency HDF according to the prediction of a 2-pool kinetic variable volume of β2-m ? The following parameters have been calculated/derived from the HD treatment.

Known/measured patient parameters	*value*	
Age, *years*	**70**	
Height, *cm*	**175**	
Dry BWt, *kg*	**70.0**	
Hct , *%*	**35.0**	
Tot Prot, *g/dl*	**6.0**	
β2-m start 1° HD , *mg/L*	**28**	
β2-m G , *mg/min*	**0.12**	*Eq.(19.14) applied to a pilot session.*
β2-m K_{Renal} , *ml/min*	**2.0**	*Eq.(19.17) applied to a pilot session*
β2-m $K_{ExtraRenal}$, *ml/min*	**3.0**	*Assumed (see Table 19.2)*
V_{EX} = 1/3 TBW , *L*	**13**	*TBW (Watson 1980), V_{EX} (Table 19.2)*
V_i/V_P	**4.3**	*Assumed from Gotch (see Table 19.2)*

HDF treatment parameters	*value*	*note*
Session time, *min*	**240**	
Q_B , *ml/min*	**400**	
Q_{UF} (Δ BWt), *ml/min*	**10**	
$Q_{UF\ TOTAL}$, *ml/min*	**122**	*Set to achieve FF= Q_{UF}/Q_{PW} = 0.5. Q_{PW} from Eq. (19.31).*
$Q_{subst.fluid}$, *ml/min*	**112**	$Q_{UF\ TOT}$ - *ΔBWt*
K_{IC} , *ml/min*	**82.5**	*Assumed (Ward 2006, see Table 19.2)*
β2-m K_D on HD, *ml/min*	**30**	*Nominal in vivo value from the Manufacturer*
β2-m K_D on HDF, *ml/min*	**99.6**	*Predicted from Eq. (19.13)*



B2-m concentr., mg/L		**1° session**	**2° session**	**3° session**	**Steady-state**
start		**28**	**20.7**	**17**	**19.8**
end	**plasma**	**4.4**	**3.4**	**3**	
	Interst.	**7.8**	**5.6**	**5.2**	
plasma equilibrated		**7.6**	**5.8**	**5.3**	
time of equilibrium		**88 min**	**90 min**	**85 min**	
% rebound		**42**	**41.3**	**43,3**	

19.5.4 Phosphate Kinetics

Phosphate (P) clearance is generally lower than urea clearance for any dialyzer membrane, due to a higher diffusive resistance for P in whole blood, with blood cells acting as diffusion barrier (Kuhlmann 2010). Past studies have shown that P removal is scarcely affected by increasing blood flow rates (Gutzwiller et al. 2003) and not significantly different in high-flux HD compared to low-flux HD with membranes of similar surface area (Chauveau et al. 1991; Kerr et al. 1999). Membrane surface area itself has a potentially important impact on phosphate mass removal, as reported by studies showing increasing P clearances with dialyzers with increasing membrane surface areas (Jindal et al. 1989; Zucchelli and Santoro 1987). More recently, several studies have demonstrated the ability of HDF to enhance P removal and reduce plasma P concentrations (Davenport et al. 2010; Lornoy et al. 2006; Minutolo et al. 2002; Pedrini et al. 2011; Penne et al. 2010; Vaslaki et al. 2006).

Phosphate has a molecular weight of 96 Da and falls into the category of water-soluble small toxins. However, due to its hydrophilic characteristics, P molecule is surrounded by an aqueous cover, which increases its effective molecular weight. Phosphate distribution volume is assumed to be TBW but it is mainly distributed in V_I and shows a slow intercompartmental transfer rate. These characteristics, which are more similar to those of middle molecules, determine the particular 2-phase kinetics of P during HD, with a steep decline of its concentration in the first half of the treatment and removal proportional to the initial concentration (Man et al. 1991; Sugisaki et al. 1982). Then, P concentration tends to level off or even to increase despite ongoing P removal during the second half of the treatment, and rebounds to almost pre-dialysis values after the end of the session (Gotch et al. 2003). The intradialytic decline of P concentration does not significantly change between HD and HDF despite the different removal (Minutolo et al. 2002). This behavior may be explained by the multi-compartmental kinetics of P, which is first removed predominantly from the extracellular plasma compartment and then from the intracellular space with a plasma P rate of change which is limited, in the second half of the session, by its transfer rate from the inner compartment(s) (Spalding et al. 2002).

HDF succeeds in enhancing P removal by convection in the first part of the treatment session. This leads to a greater reduction of P levels than during conventional HD, and a greater mobilization of phosphate from the inner compartment. This, in turn, results in a more pronounced rise of serum P levels in the second part of treatment and greater post-dialysis P rebound

in HDF compared to HD. However, cumulative P removal is greater in HDF and significant reduction of basal P levels is a possible long term effect of this convective technique (Minutolo et al. 2002).

For its characteristics, P kinetics during and after dialysis cannot be precisely simulated with the two-pool kinetic model of use in the case of most uremic marker solutes (Heaf et al. 1998). A comprehensive view of the limits of this model when applied to P kinetics has been provided by Spalding et al (2002), who compared the results of the application of different kinetic models, a two-pool, a three pool model and a four compartment model, to 29 patients on standard HD and HDF (see Fig. 19.13). In this study, the two pool model formulation was similar to the classical one, with a total distribution space for P coextensive to the TBW and divided into V_I and V_E. In the three-pool model, a third compartment was added and P transfer from this pool to V_E was supposed to occur when the intracellular P concentration dropped below an intracellular target concentration. In the four compartment model, the additional compartment released P in V_I when intracellular P concentration fell to a critically low concentration. In the author's experiments, the two- and three-pool models failed in most cases to explain P kinetics, while the four-compartment model was able to fit all experimental data of HD and HDF treatments.

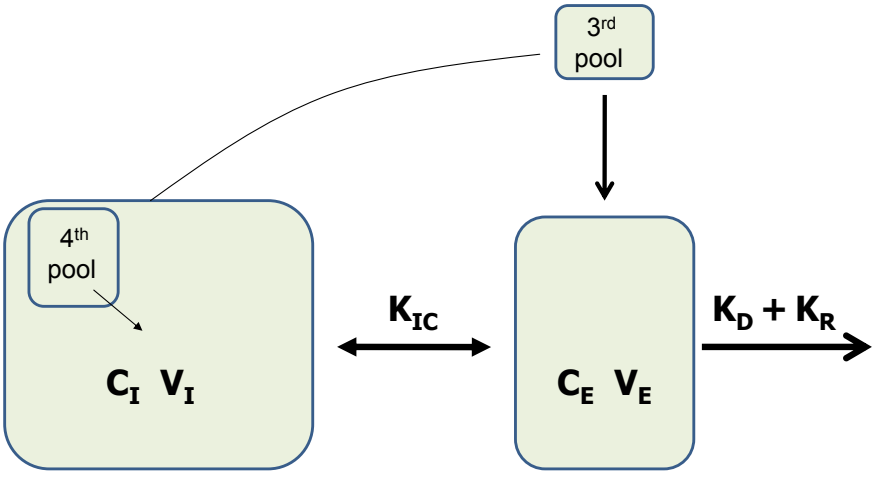


Fig. 19.13 Schematic representation of the four-compartment kinetic model of phosphate proposed by Spalding et al (2002). The perfused and non-perfused compartments are VE and VI, respectively. The third compartment releases P into VE when P in VI drops below an intracellular target concentration. The fourth compartment releases P in VI when P in VI falls to a critically low concentration.

19.6 BIOLOGICAL EFFECTS OF HDF

The uremic syndrome includes a constellation of symptoms and metabolic derangements attributed to the retention in the body of a large number of compounds which are normally excreted by the healthy kidneys and can be toxic per se or only at the high concentration found in uremia. These compounds are called uremic toxins, when they interact negatively with biologic functions. Knowledge of the dependence of uremic abnormalities on specific toxic solute concentrations is still incomplete, so it is difficult at this time to define the precise role of all compounds in uremic derangements. A systematic classification of uremic solutes has been compiled by the European Uremic Toxin Work Group (EUTox) according to their characteristics, molecular weight and/or electro-chemical binding that potentially influence their removal pattern during dialysis (Vanholder et al. 2008; Vanholder et al. 2003). Three main physico-chemicals group of uremic toxins have been recognized: 1) free water-soluble low-molecular-weight solutes (MW <500 D), such as urea, creatinine, uric acid and several guanidine compounds; 2) middle-molecular solutes, (MW >500 D up to 30 kD), among which several peptides such as β2-microglobulin, myoglobin, cystatin C, clara cell protein, retinol-binding protein and cytokines such as interleukins and tumor necrosis factor α are included; 3) protein-bound solutes, mostly characterized by a MW <500 D, such as pentosidine, homocysteine, hippuric acid, p-cresylate, indoxyl sulphate, and others.

19.6.1 Free Water-Soluble Low-Molecular-Weight Solutes

Urea (MW 60 D) is a recognized marker of this category of toxins for its biological and metabolic characteristics and easiness to be detected and measured in blood. The fractional excretion index of urea removal during dialysis (Kt/V) has become the most used index of adequacy of dialysis treatment (Gotch and Sargent 1985). Removal of urea and of all free small molecular weight solutes mainly occurs by diffusion and, thus, it is very effective during low- and high-flux HD. However, online HDF has been shown to further increase urea (Lin et al. 2001b; Maduell et al. 2002; Pedrini et al. 2003) and creatinine (Lornoy et al. 2000; Ward et al. 2000) removal, and higher Kt/V_{urea} has been reported on HDF treatment compared to HD at matched treatment duration and operational conditions (Lin et al. 2001b; Pedrini et al. 2011).

Phosphate molecule falls into the category of water-soluble low-molecular weight toxins (MW 96 D) but, for its hydrophilic characteristics, it is surrounded by an aqueous cover which considerably increases its

effective molecular weight. Moreover, P is mainly distributed within cells and is not freely diffusible into the extracellular space. For these reasons its elimination characteristics are different from those of urea and other small-molecular weight toxins and its intradialytic kinetics is more similar to that typical of middle molecules (Spalding et al. 2002).

HDF as compared to standard HD has been shown to increase P removal during single treatment sessions and to establish lower basal level in the medium-long term. This was demonstrated in several controlled studies and in large data base observational experiences (Davenport et al. 2010; Lornoy et al. 2006; Minutolo et al. 2002; Pedrini et al. 2011; Penne et al. 2010; Vaslaki et al. 2006) (see Table 19.3). Post-dilution HDF has been shown to be more effective than pre-dilution HDF and mixed-dilution HDF has shown a significant advantage over post-dilution HDF in regard of P removal (Feliciani et al. 2007).

Table 19.3 Studies comparing the effect of HDF on basal P levels versus low-flux HD

Author	year	comparison	study	n. of patients	follow-up	effect of high-flux HD	significance (p)
Minutolo	2002	low-flux HD vs HDF	RCT	12	3 months	reduced levels on HDF	0.05
Pedrini	2011	low-flux HD vs HDF	RCT	69	6 months	reduced levels on HDF	0.008
Penne	2010	low-flux HD vs HDF	RCT	493	6 months	reduced levels on HDF	0.001
Vaslaki	2006	low-flux HD vs HDF	RCT	70	6 months	reduced levels on HDF	<0.05
Davenport	2010	low-flux HD vs HDF	audit	5366	-	reduced levels on HDF	<0.001

19.6.2 Middle-Molecular Solutes

Beta2-microglobulin (β2-m, 11.800 D) has been recognized as the most suitable marker of middle molecular uremic toxins of similar molecular weight by the European Best Practice Guidelines Expert Group (The EBPG 2002). Its pre-dialysis level was shown to predict mortality in the randomized Hemodialysis (HEMO) study (Cheung et al. 2006) and in a Japanese prospective trial (Okuno et al. 2009).

It has been demonstrated that β2-m removal is greater during a session of HDF than on low-flux and high-flux HD (Floege et al. 1989; Lornoy et al. 2000; Maduell et al. 2002; Pedrini et al. 2003). On HDF, β2m removal correlates with the convection volume of the session (Lin et al. 2001b; Lornoy et al. 2000). While β2m basal level is reported to progressively increase with time in chronic patients on RRT with low-flux HD, observational and randomized studies have shown that β2m level remains stable (Locatelli et al. 2009) or may be reduced (Locatelli et al. 1996) in patients on high-flux HD, and even significantly decreases with time in patients switched to online HDF (Lin et al. 2001b; Locatelli et al. 1996; Pedrini et al. 2011) or HF (Beerenhout et al. 2005; Santoro et al. 2008). This effect is most pronounced when residual renal function is absent (Fry et al. 2007).

Besides β2-m, other uremic compounds of the larger molecular spectrum were removed to a greater extent in HDF with all the available highly permeable and biocompatible membranes. This was shown for myoglobin (17.2 kD) (Maduell et al. 2002), factor D (24 kD) (Beerenhout et al. 2005; Ward et al. 2000). A complement fraction abnormally elevated in patients with renal failure, other complement fractions, such as fraction Ba (33 kDa) (Kaiser et al. 1995), C3a (8,9 kD) and C5a (11 kD), (Jorstad et al. 1988). Online HDF has also been associated with increased removal and/or reduced production of pro-inflammatory cytokines such as TNF-α (17 kD)(Carracedo et al. 2006; Gil et al. 2003), interleukins 1-6-8 (17 kD) (Bouman et al. 1998; Carracedo et al. 2006; Gil et al.2003; Goldfarb and Golper 1994;Panichi et al. 2008) and proinflammatory CDl4+ CD16 + cells (Carracedo et al. 2006)., and with improvement of variables related to endothelial dysfunction (Ramirez et al. 2007), oxidative stress, and antioxidant capacity (Calo et al. 2007; Filiopoulos et al. 2008). Moreover, two randomized crossover studies demonstrated a potent effect of high-flux membranes on lipoprotein and lipid profiles (Wanner et al. 2004) and a significant reduction in triglycerides and increase in high-density lipoprotein concentration as a long-term effect of on-line HDF with high-flux membranes, not shown with standard HD (Pedrini et al. 2011).

19.6.3 Protein-Bound Solutes follow during dialysis a multicompartmental kinetics similar to that of the middle molecules in spite of their generally low molecular weight, as a possible consequence of their protein binding and metabolic transformation. Substantial part of removal of these compounds occurs by diffusion. As such, pentosidine (379 D) was removed to a similar extent (70%) with low-flux and high-flux membranes and long-term lower basal levels were only observed in patients on high-flux polysulfone, possibly as a consequence of reduced oxidative stress

promoted by this membrane (Jadoul et al. 1999). On the contrary, high-flux and low-flux polysulfone resulted in similar plasma level of homocysteine (135 D) in a 3-month longitudinal study, despite the greater removal per session obtained with the high-flux membrane (House et al. 2000). More recently, observational and randomized controlled studies have shown that internal HDF and on-line HDF applied in the long term were both able to reduce homocysteine level to a greater extent than low-flux HD (Beerenhout et al. 2005; Eiselt et al. 2010; Pedrini et al. 2011; Righetti et al. 2010). Variable reduction ratios have been reported for asymmetric dimethylarginine (ADMA, 202 D) during low-flux HD and HDF, but without significant long-term change of its basal level with both techniques (Beerenhout et al. 2005; Eiselt et al. 2010; Pedrini et al. 2011).

Convection was shown to positively impact protein-bound toxin removal because HDF was able to increase p-cresol clearance without leading to excessive albumin loss (Bammens et al. 2004). Similar removal (40% to 50%) of p-cresyl sulphate (MW 187 D, protein binding ±95%) and indoxyl sulphate (MW 212 D, protein binding ±90%) was reported during HD and HDF sessions with high-flux membranes (Krieter et al. 2010; Lesaffer et al. 2000) . On HDF, removal of different solutes was inversely proportional to the percentage of protein binding and ranging from 4% in the case of carboxy-methyl-propyl-furanpropanoic acid (CMPF, MW 240 D, protein binding ±100%) to 74% in the case of hippuric acid (MW 179 D, protein binding ±50%) (Meert et al. 2009). A clear effect of flux on such compounds, as well on homocysteine, was shown with the use of large pore "superflux" polysulfone and triacetate cellulose membranes (DeSmet et al. 2007; van Tellingen et al. 2001) at the expense, however, of significant albumin leakage. The longitudinal application of online post-dilution HDF was recently shown to result in consistent and progressive decline of the basal level of some protein-bound uremic solutes, particularly those with the strongest protein binding (p-cresylsulfate and CMPF), and this effect was not observed in the patients group on high-flux HD (Meert et al. 2010).

19.7 CLINICAL EFFECTS OF HDF

Several protein-bound and middle-molecular solutes have a pathogenic role or are markers of the most frequent long-term complications and causes of death in HD patients. Data from a number of clinical studies suggest that the use of online HDF may be associated with enhanced removal and reduced basal levels of these compounds that might be of relevance in the

pathogenesis of uremic and cardiovascular complications. So, HDF may promote a whole array of potential beneficial effects which individually are believed to improve clinical outcome.

Beta2-microglobulin accumulation and oxidation is retained as the main cause of dialysis related amyloidosis. Lower basal β2-m level, established in patients treated for long time with high-flux membranes and on-line HDF, not only resulted in lower incidence and progression of this invalidating systemic disease (Koda et al. 1997; Locatelli et al. 1999; Van Ypersele de Strihou 1996) but, outstandingly, it has been associated to a significant lower risk of mortality in HD patients, independent of treatment duration, diabetes, malnutrition and chronic inflammation (Cheung et al. 2006; Okuno et al. 2009). As well, lower phosphate level achieved in patients on long-term convective treatments (Davenport et al. 2010; Pedrini et al. 2011; Penne et al. 2010; Vaslaki et al. 2006) supported by appropriate pharmacological therapy may help to prevent the progression of mineral metabolic disorders caused by secondary hyperparathyroidism(Pedrini et al. 2011)., and of the accelerated athero- arteriosclerotic lesions which are the main cause of morbidity and mortality of uremic patients. Indeed, phosphate level has been associated with mortality in several authoritative studies (Block et al. 2004; Covic et al. 2009). Thus, online HDF may lead with time to a potentially improved outcome, given that the amount of β2-m and phosphate removal is greater than in high-flux therapy and leads with time to lower basal levels of these uremic toxins.

Several protein-bound solutes have been found to be toxic in vitro (Dou et al. 2004; Dou et al. 2007; Schepers et al. 2007)., and some of them have also been associated with adverse outcomes in dialysis patients, such as atherosclerosis (Taki et al. 2007)., cardiovascular disease (Meijers et al. 2008) , infectious disease (DeSmet et al. 2003), and neurological abnormalities (Deguchi et al. 2006). The free p-cresol serum concentration predicts overall mortality in HD patients group (Bammens et al. 2006). P-cresyl sulfate, the main in vivo metabolite of p-cresol, promotes vascular disease in uremia as a consequence of its pro-inflammatory effect on unstimulated leucocytes leading to oxidative stress and, consequently, atherosclerosis (Schepers et al. 2007). Since, convective strategies can result in significantly reduced plasma levels of these protein-bound compounds (Bammens et al. 2004; Meert et al. 2009), they may be beneficial for patients outcome.

Both uncontrolled and randomized studies have reported decreased erythropoietin resistance and reduced need for its administration in patients

treated with online HDF (Lin et al. 2002; Maduell et al. 1999; Pedrini et al. 2011; Vaslaki et al. 2006) possibly as an effect of the increased removal of middle molecular inhibitors of erithropoiesis (Bonomini et al. 2004; Le Meur et al. 2001). In this respect, also favored by the use of ultrapure dialysis fluid, HDF may play a role in the control of anemia in uremic patients by creating a more biocompatible environment with less toxic and inflammatory stimuli.

Intradialytic hypotension is frequently observed during HD and is associated with regional wall motion abnormalities of the left ventricle and myocardial stunning (McIntyre 2010). Repeated episodes can contribute to myocardial damage and cardiomyopathy. Online HDF and HF have been associated with improved hemodynamic stability and blood pressure control in some studies (Altieri et al. 2001; Lin et al. 2001a; Locatelli et al. 2010), but not in others (Karamperis et al. 2007). However, this effect, rather than to increased removal of unknown hypertensive factors, seems mainly due to the large amount of cooler substitution fluid infused in online HDF which causes thermal energy loss within the extracorporeal system and so avoids vasodilatation caused by heat accumulation (Donauer et al. 2003).

19.8 EFFECTS OF HDF ON OUTCOME

The hypothesis that the enhanced removal of larger solutes obtained with high-flux membranes might result in improvement of hard clinical end points, has been confirmed in a number of observational studies, and in two large data-base randomized trials. The HEMO study showed no difference in survival between low- and high-flux HD in the overall study population (Eknoyan et al. 2002). However, a reduced rate of death for cardiac causes (Eknoyan et al. 2002) or cerebrovascular disease (Delmez et al. 2006) in patients treated with high-flux membranes, as well as longer survival in patients undergoing high-flux HD for >3.7 years were observed in post hoc subgroups analyses. Similarly, a primary analysis of the European Membrane Permeability Outcome (MPO) study showed improved survival of high-flux HD patients with albumin level ≤4 g/dL and of diabetic patients in a secondary analysis (Locatelli et al. 2009). Moreover, a post-hoc analysis of the German 4D study (Krane et al. 2007) and a large observational French study (Chauveau et al. 2005) showed a superior survival in patients treated with high-flux as compared to low-flux HD (see Table 19.4).

Table 19.4 Studies comparing mortality risk in low-flux HD versus high-flux HD.

Author	year	comparison	study	n. of patients	follow-up, years	effect of high-flux HD
Eknoyan (HEMO Study)	2002	low-flux vs high-flux HD	RCT	1846	2.8 (mean)	reduced death risk 8% , n.s. (main outcome) reduced cardiac death risk 32% , p<0.05 (secondary outcome) reduced death risk for patients on high-flux for > 3.7 years, p<0.005 (secondary outcome)
Locatelli (MPO Study)	2009	low-flux vs high-flux HD	RCT	738	3.0 ± 1.9	reduced death risk 24% , ns (main outcome) reduced death risk with albumin < 4.0 g/dl 37%, p<0.01 (main outcome) reduced death risk diabetes 37%, p=0.056 (subgroup analysis)
Krane (4-D Study)	2007	low-flux vs high-flux HD	RCT	648	4 .0	reduced death risk 63% , p<0.001 (post-hoc)
Chauveau	2005	low-flux vs high-flux HD	observ.	650	2.0	reduced death risk 38% , p<0.01

The evaluation of the impact of HDF on hard clinical end points is still underway. However, the available evidence is suggestive for a definite benefit of convective treatments as compared to low- and high-flux HD at least in some categories of patients and/or treatment modalities (see Table 19.5). A small Italian randomized study showed better survival in patients on HF compared to low-flux HD over a 3-years period (Santoro et al. 2008). Some observational and registry studies reported similar findings: in a retrospective analysis of the European Dialysis Outcomes and Practice Patterns Study (DOPPS), Canaud et al. reported a significant 35% lower mortality risk in patients on high-efficiency HDF (volume exchange 15–25 liter per session), compared to low- and high-flux HD (Canaud et al. 2006). In a British study by Vilar et al., a reduced hazard for death of 0.66 was reported in 232 patients who were treated solely by HDF compared with 637 patients who solely used high-flux HD (Vilar et al. 2009). In the RISCAVID prospective study a survival benefit was associated with online HDF over standard HD; however, only 4.9% of the HD population used high-flux membranes (Panichi et al. 2008; Jirka et al. 2006) also reported similar results from data collected through the EuCliD network with a mortality reduction of 35.3% compared with an HD group (Jirka et al. 2006). It was not specified what proportion of the HD group used high-flux membranes.

Most recently, two large database prospective studies have been closed and results made public. The CONTRAST Study (Grooteman et al. 2011) did not show any benefit in terms of survival and fatal or not fatal cardiovascular events in 358 patients submitted to on-line HDF compared to a matched group of patients undergoing low-flux HD for a 3-years period. In analogy, the "Turkish HDF Study" (Ok et al. 2011), comparing high-flux HD and on-line HDF, found similar risk of death and composite cardiovascular risk in the overall study population (782 prevalent patients) after a 2-years follow-up. However, secondary subgroup analysis of both studies suggested benefit among patients treated with high convection volumes on cardiovascular and overall survival compared to HD. In the CONTRAST Study, HDF with over 20 liter/treatment was associated with a 34% reduction of mortality risk. In the Turkish Study, the subgroup of 195 HDF patients treated with a volume exchange of more than 17.4 liter/session showed better cardiovascular and overall survival than both the subgroups of HDF patients with substitution volume less than 17.4 liter session (p=0.03) and the HD patients (p=0.002). Even if secondary analyses entail reduced statistical power, the results obtained with high volume exchanges in HDF are impressing.

Table 19.5 Studies comparing mortality risk in low- and high-flux HD versus HDF

Author	year	comparison	study	n. of patients	follow-up years	reduced death risk with HDF , %	significance (p)
Grooteman	2011	low-flux HD vs HF	RCT	714	3.0	9.0	ns
Ok	2011	high-flux HD vs HDF	RCT	782	2.0	-	ns
Santoro	2008	low-flux HD vs HF	RCT	64	3.0	41.6%	<0.05
Canaud	2006	low-flux HD vs HDF	observ.	2165	3.0	35%	0.01
Vilar	2009	high-flux HD vs HDF	observ.	858	10	34%	0.014
Panichi	2008	low-flux HD vs HDF	observ.	757	2.5	22%	0.01
Jirka	2006	low-flux HD vs HDF	observ.	2564	1	35%	<0.05

19.9 CONCLUSION

Medium–long m term application of on-line high-efficiency HDF compared to low- and high-flux HD results in enhanced removal and lower basal levels of small, medium and protein-bound uremic solutes, some of which are retained as markers or causative agents of several uremic derangements, mainly inflammation, secondary hyperparathyroidism, dyslipidemia and cardiovascular disease. Probably, many of the benefits attributed to HDF potentially result from a general reduction of the uremic toxicity. This might be the link with the clinical benefits reported in patients undergoing chronic HDF which eventually contribute to improving patients' survival, as suggested by published studies. However, in the absence of, a definite evidence, it is reasonable to conclude that online HDF is a logical and safe therapy effective in maintaining the life and well-being of dialysis patients. Knowledge of the performance of materials, apparatus and devices used in HDF, and study of the solute transport mechanisms with the aid of modelling simulation will help to optimize this technique and obtain additional clinical benefits.

APPENDIX A: GLOSSARY

A	Surface Area Of A Membrane
BW	Body Weight
C	Concentration
D	Dialyzer Dialysance
ESRD	end-stage renal disease
FF	filtration fraction
F_P, F_R	fractions of plasma and red cell water
G	rate of solute generation
HD, HDF, HF	hemodialysis, hemodiafiltration, hemofiltration
Hct	hematocrit
KoA	overall mass transfer coefficient of the solute (per area)
$K_{UF}D$	ultrafiltration coefficient of a dialyzer
K_D, K_R, K_{ER}, K_T	dialyzer clearance, residual renal clearance, extra-renal clearance, total clearance ($K_D + K_R + K_{ER}$)
K_{IC}	solute inter-compartment mass transfer coeffi-cient (inter-compartmental clearance)
K_{CW} , K_W	Water transcellular and transcapillary coefficient
Lp	hydraulic permeability of the membrane for water
MW	molecular weight
MM	middle molecule
P	phosphate
P_B , P_D	hydraulic pressure within the blood/ dialyzer compartment
Q_B , Q_E, Q_D	whole-blood, effective blood and dialysate flow rate
Q_{UF}	ultrafiltration rate
R_D	Donnan factor
SF	super-flux (membranes)
S_C	sieving coefficient
t, t_d , t_{id}	time, duration of the dialysis session and the inter-dialytic period
TMP	trans-membrane pressure
UF	ultrafiltration
α	constant rate of change in V during the interdialytic period

APPENDIX A (Continued)

β2-m	beta2-microglobulin
Π	colloid osmotic pressure
χ	ratio of a substance in two compartments at equilibrium ($C_E = \chi C_I$)
γ	coefficient which expresses the resistance of a solute to trans-cellular transfer

APPENDIX B: Suffix

B, D, UF	blood, dialysate, ultrafiltrate
in, *out*	inlet and outlet ports of blood and dialysate compartments of the dialyzer.
o, t	start and end of the treatment session

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MULTIPLE CHOICE QUESTIONS

Choose the best answer

1. The scarce biocompatibility of cellulosic membranes was mainly related to…
   A. Their hydrophilic properties.
   B. The hydroxyl groups included in the chemical structure of these membranes.
   C. Their thin-walled structure.

2. Diffusion of small molecular weight solutes across a dialyzer membrane is favored by…
   A. The reduced thickness of the capillary wall and the porosity of the membrane.
   B. The large size of the pores.
   C. Low dialysate flow.

3. The hydraulic permeability of high-flux synthetic membranes is mainly related to…
   A. The pore size (diameter)
   B. Thickness of the inner layer of the membrane.
   C. Thickness of the spongy stroma of the membrane.

4. Earlier high flux membranes allowed high ultrafiltration rates but limited small solutes transfer by diffusion. What was the reason?
   A. The large pore diameter.
   B. Their chemical composition.
   C. The marked thickness of the whole hollow fiber wall.

5. The main characteristics of super-flux membranes are…
   A. They have pores with larger size than high-flux membranes.
   B. They provide greater clearances of low molecular weight proteins and small protein-bound solutes than do conventional high-flux membranes.
   C. They allow considerable amount of albumin loss in the dialysate.
   D. All of the above answers.

6. Plasma water ultrafiltration across a dialyzer membrane occurs as a consequence of…
   A. A pressure gradient established across the dialyzer membrane.
   B. A solute concentration gradient established across the dialyzer membrane.
   C. As an effect of the oncotic pressure of blood.

7. An index which expresses the ability of a dialyzer membrane to ultrafiltrate plasma water is…
   A. The Sieving coefficient for albumin.
   B. The ultrafiltration coefficient of the dialyzer ($K_{UF}D$, ml/hour/mmHg of TMP).
   C. The ultrafiltration rate in the absence of a pressure gradient across the membrane.

8. The ultrafiltration coefficient of the dialyzer ($K_{UF}D$)…
   A. Is the slope of the linear regression equation which relates the ultrafiltration rate (Q_{UF}) to the trans-membrane pressure (TMP) up to a certain TMP value (200-300 mmHg)
   B. Reduces progressively in vivo through a HDF session as a consequence of the protein layer formation on the inner surface of the membrane.
   C. Must be greater than 40 ml/hour/mmHg of TMP for high-flux dialyzers.
   D. Largely depends on the characteristics of the membrane (the pore radius).
   E. All of the above answers.

9. Removal of small solutes by diffusion is mainly influenced by…
   A. The blood flow rate (Q_B).
   B. The dialysate flow rate (Q_D).
   C. The trans-membrane pressure.

10. Removal of middle molecular solutes is mainly influenced by…
   A. The blood flow rate (Q_B).
   B. The overall surface area of the membrane.
   C. The dialysate flow rate (Q_D)

11. The sieving coefficient (S_C, dimensionless) is…
    A. Characteristic for a solute irrespective of the membrane.
    B. Characteristic for a membrane irrespective of the solute.
    C. Typical for a defined solute and a defined membrane.

12. The sieving coefficient (S_C)…
    A. Is a function of the membrane characteristics (electro-chemical properties and structure, pore radius and conformation.
    B. Is inversely related to the solute molecular weight and varies between 0 for a freely permeable molecule and 1 for a completely impermeable molecule.
    C. Reduces similarly to $K_{UF}D$ through the session in the case of middle molecular compounds and may approach zero in convective treatments at excessively high $Q_{UF.}$
    D. All of the above answers.
    E. None of the above answers.

13. Adsorption of solutes into the inner membrane surface…
    A. May occur when membranes not carrying electrical charges are used.
    B. Does not contribute to the overall solute removal from blood.
    C. Occurs to a greater extent on hydrophilic cellulosic membranes than on synthetic hydrophobic membranes.
    D. Albumin adsorption reduces the in vivo permeability of a membrane.

14. Whole-blood clearance of solutes not freely diffusible across the erythrocyte membrane…
    A. Underestimates the actual solute removal rate.
    B. Overestimates the actual solute removal rate.
    C. Determines the actual solute removal rate.

15. The Donnan factor (R_D), i.e. the ratio between the ionic concentration in dialysate and blood applies to…
    A. Positively charged solutes.
    B. Negatively charged solutes.
    C. Both of them.

16. During HDF, the total solute removed…

A. is the sum of diffusive and convective transfer.
B. Occurs by both transport mechanisms but it is lower than their algebraic sum due to negative interactions between them.
C. Only occurs by convection.

17. Internal filtration is a transport mechanism acting on…
A. Post-dilution HDF.
B. Mixed HDF.
C. Mid-dilution HDF.
D. high-flux HD.

18. During high-flux HD, water flow reverses its direction (internal filtration) within the dialyzer when…
A. The algebraic sum of hydrostatic and colloid osmotic blood pressure matches the hydrostatic pressure in the dialysate compartment.
B. The hydrostatic pressure in the dialysate compartment becomes positive.
C. The algebraic sum of hydrostatic blood and dialysate pressure becomes null.

19. During post-dilution HDF, very high ultrafiltration rates may result in…
A. Risky trans-membrane pressure.
B. Excessive haemoconcentration.
C. High blood viscosity.
D. Reduction of solute and water permeability of the dialyzer membrane.
E. All of them.
F. None of them.

20. When the above condition occur during post-dilution HDF, it is necessary to…
A. Reduce ultrafiltration rate.
B. Increase dialysate flow rate.
C. Stop the treatment session and substitute the dialyzer.
D. Reduce blood flow rate to the dialyzer.

21. At similar ultrafiltration rates pre-dilution HDF is less efficient than post-dilution HDF due to…
    A. Reduced convective power.
    B. Reduced diffusion of solutes.
    C. Dilution of blood entering the dialyzer and diluted concentration of solutes available for both diffusion and convection of solutes.

22. Middle molecular solutes are removed during HDF with endogenous reinfusion…
    A. By diffusion.
    B. By adsorption through the passage in a sorbent cartridge.
    C. By convection.
    D. All combined transport mechanisms.

23. Maximal infusion rate is maintained in mixed HDF by…
    A. Modulating the ratio between post- and pre-dilution.
    B. Increasing/decreasing the total infusion rate according to the expansion/contraction of circulating blood volume.
    C. Maintaing the trans-membrane pressure within an optimal range of values to get maximal filtration.
    D. All mechanisms.

24. Which of the following sentences is/are correct…
    A. The inter-compartment mass transfer coefficient ($K_{IC,}$ ml/min) of a solute is the inter-compartmental clearance of the solute.
    B. K_{IC} changes in accordance with the rates of blood and dialysate flow.
    C. K_{IC} depends on the resistance opposed by the cell membrane to the solute transfer.
    D. K_{IC} is null for large impermeable molecules and large for freely diffusible small molecules.

25. Which of the following sentences is/are correct…
    A. Post-dialysis rebound of a solute is mainly the expression of concentration re-equilibration between the distribution pools of the solute.
    B. Magnitude and duration of post-dialysis rebound are inversely proportional to the solute $K_{IC.}$
    C. Post-dialysis rebound of a solute is mainly the expression of the solute generation during the interval between dialyses.

D. Not accounting for post-dialysis rebound leads to an overestimate of the distribution volume for urea in single-pool urea kinetic model.

26. The distribution space assumed for sodium (Na) in two-pool model formulation is…
A. Total body water (TBW). Na is anatomically confined to the extracellular space but its osmotic power extends to the TBW.
B. The extracellular space.
C. The intracellular space.

27. The total distribution space for β2-microglobulin is…
A. The total body water (TBW).
B. The extracellular space (V_E).
C. The intravasculat space (V_P).

28. Which of the following sentences is/are correct…
A. Phosphate is a small molecular weight solute and its kinetics may be reliably simulated with a single-pool kinetic model.
B. HDF has scarce effect on phosphate removal and on its basal level.
C. Phosphate kinetics is more reliably simulated with a multiple-pool model.

29. The HEMO Study demonstrated that chronic HD patients treated with high flux membranes survive longer than those treated with low-flux membranes?
A. Yes, definitely.
B. No difference was shown in survival between low- and high-flux HD in the overall study population, but some sub-groups analyses were highly suggestive for longer survival of patients on high-flux HD.
C. No, definitely.

30. The European Dialysis Outcomes and Practice Patterns Study (DOPPS) reported a significant 35% lower mortality risk in patients on HDF compared to low- and high-flux HD when HDF was performed with volume exchange of…
A. At least 10 liter per session.
B. Between 15 and 25 liter per session.
C. Greater than 25 liter per session.
D. Irrespective of the amount of exchanged volume.