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The haemodialysis system: basic mechanisms of water and solute transport in extracorporeal renal replacement therapies

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Introduction

Since the very beginning of dialytic therapy, diffusion and convection have been combined in an attempt to replace renal function [1]. The knowledge of diffusive phenomena came from industrial chemistry, and dialysers were designed to be ideal counter-current exchangers [2]. Only later was convection used in clinical practice, showing potential depurative advantages [3,4]. At first, ultrafiltration was employed to treat overhydrated patients [5], but soon the removal of solutes by convection thanks to the 'solvent drag' phenomenon was utilized for blood purification [6–8].

Figure 1 summarizes some of the factors influencing solute transport across semi-permeable membranes. Blood flow greatly affects the clearance of small solutes such as urea, while the ultrafiltration rate affects mainly the removal of larger solutes such as inulin. Increases in dialysate flow rate become important only with large surface areas dialysers, and these affect mainly the clearance of small solutes. Finally, dialyser surface area determines the maximal solute clearance at a given blood flow. In addition, one must also consider the type of membrane utilized and the kinetics of water inside the entire unit.

Diffusion and convection

Diffusion is a process whereby molecules move randomly in all directions. Statistically, this movement results in the passage of solutes from a more concentrated to a less concentrated area. Besides the concentration gradient (driving force: $C1–C2 = dc$), the solute diffusive flux (Jd) through a semi-permeable membrane depends on the temperature (T), the surface area and the diffusivity coefficient (D) of the solute, while it is inversely proportional to the membrane thickness (dx).

$$Jd = D \cdot A \cdot T\,(dc/dx)$$

The convective process requires a fluid movement caused by a transmembrane pressure gradient. Therefore, the convective flux of a solute (Jc) will depend on the ultrafiltration rate (Qf), the solute concentration in plasma water (Cb) and the solute sieving coefficient (S),

$$Jc = Qf \cdot Cb \cdot S$$

being in ideal conditions: $S = 1–\sigma$, where σ is the reflection coefficient of the membrane. These definitions present convection and diffusion as two separate phenomena. However, it is impossible to define precisely the contribution of each single process to the removal of solutes because of their continuous interactions.

Membranes, diffusivity and sieving

Different membranes are utilized in extracorporeal therapy: some of them represent the earliest example of semi-permeable materials used for blood purification. The original polysulfone fibre had an internal skin layer surrounded by a macroporous structure with a total thickness of 100 μm. The polymer was hydrophobic and its efficiency in diffusion was poor. Cuprophane®, like all cellulosic membranes, is considerably hydrophilic and the wall thickness can be less than 10 μm. Such membrane offers remarkable diffusive performances, although solute sieving coefficients are rather low. Recently, partially hydrophilic synthetic membranes with a reduced wall thickness have been developed by the industry, and these have permitted the use of therapies such as haemodiafiltration, where diffusion and convection are conveniently combined.

Figure 2 reports the diffusivity coefficients of solutes in various media. As the solute molecular weight increases, the diffusivity coefficient tends to decrease. This underlines the fact that the characteristics of the solute are extremely important, and it may be useless to exploit the membrane permeability to remove solutes in the range of 5000–20 000 *D* solely by diffusion. In fact, for these solutes, diffusion is limited mainly by the low diffusivity coefficients rather than by the sieving characteristics of the membrane. Moreover, diffusion coefficients of smaller solutes in synthetic membranes

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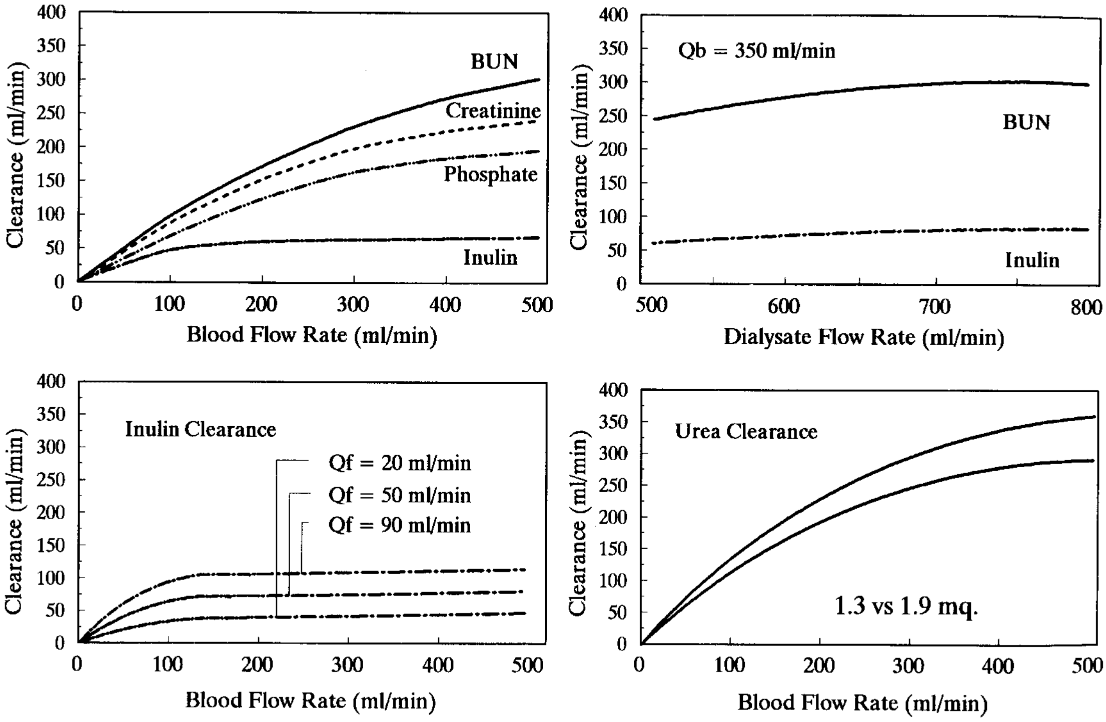

Fig. 1. Factors affecting solute clearances in extracorporeal treatments.

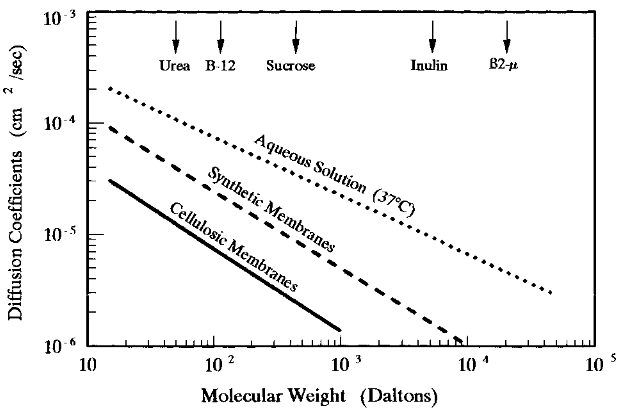

Fig. 2. Diffusion coefficients of different molecular weight solutes in various media.

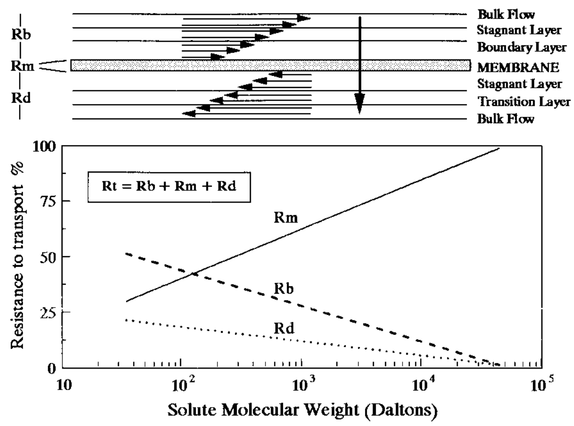

Fig. 3. Different percentage resistances to transport according to solute molecular weight.

are fairly good, and the diffusion process of these solutes should be faster, but this is not the case. Besides the hydrophobic nature of the membrane, the membrane wall thickness and the considerable amount of unstirred fluid inside the support structure slow down solute transport remarkably. The structure of the recently developed synthetic high-flux membranes partially avoids the above-mentioned problems by combining a relatively less hydrophobic nature with a reduced wall thickness and a more homogeneous structure.

In Figure 3, it is possible to see how the solute diffusivity plays an important role also in blood and dialysate compartments. The resistances generated by blood, dialysis fluid and membrane are reported as a percentage of the overall resistance to solute transport. At the cut-off value, the membrane represents 100% resistance. This resistance progressively decreases in terms of percentage for smaller solutes, while the resistance in the blood and dialysate compartments becomes more and more important. The resistance to the transport of larger solutes, due to their poor diffusive characteristics, can be overcome in treatments with a considerable amount of convection. The final convective flux is, in its turn, influenced by the permeability of the membrane, which is characterized by the observed sieving coefficient value. The sieving coefficient is given by the ratio between the solute concentration in the filtrate and the solute concentration in plasma water in the absence of a diffusion

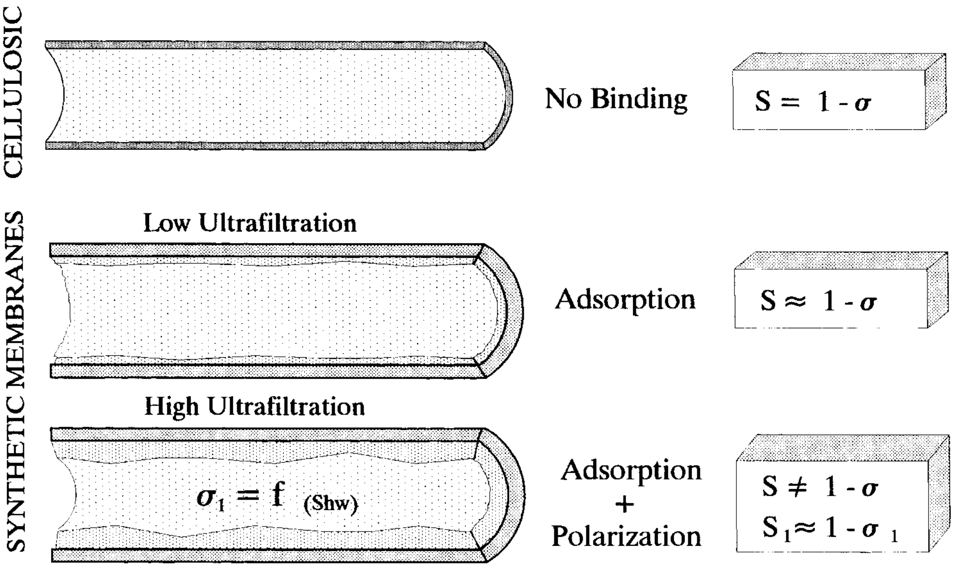

Fig. 4. Examples of possible interactions between the membrane and plasma proteins and effects on solute sieving coefficients.

gradient. However, solute distribution in the blood compartment is not homogeneous, being dependent on polarization and other phenomena. As ultrafiltration increases, part of the solute tends to accumulate at the blood–membrane interface, thus creating gradients for diffusion both towards the bulk region inside the hollow fibre and towards the dialysate compartment across the membrane. As a consequence, diffusion continuously interferes with convection and the sieving coefficient could be overestimated. In fact, the concentration in the bulk region (which is the value measured empirically) is generally lower than that at the blood–membrane interface. Therefore, the difference between the observed sieving coefficient (*So*) and the real one (*St*) can be affected significantly by this difference which, in turn, is affected by the amount of convection used. With low ultrafiltration values, *So* and *St* tend to be equal, while larger differences can be observed at high ultrafiltration rates.

The membrane and the blood compartment

The sieving value can be considered theoretically as the reverse of the actual reflection coefficient of the membrane. This, however, is only a theoretical consideration which is not always true in practice.

The observed sieving coefficient does not always correspond to the values expected from the theoretical porosity of the membrane, but it depends largely on the operational conditions of the system and on other membrane properties such as biocompatibility and interaction with plasma proteins.

In Figure 4, three examples are schematized. Cuprophan® membranes have minimal interactions with plasma proteins. This permits the sieving coefficient to be the inverse of the original reflection coefficient of the membrane. On the contrary, with synthetic membranes, two conditions may occur: in the presence of low ultrafiltration rates, an electrochemical link produces a thin protein layer deposit on the internal surface of the fibre. This characterizes the biocompatibility of the membrane that, once it has absorbed the protein layer, lets the blood flow on an autologus material surface. At the same time, this adsorption slightly reduces the membrane sieving coefficient with a rather constant trend. In the case of high ultafiltration rates, or better high filtration fractions, a thick protein deposit on the membrane is induced by the additional phenomenon of polarization. This progressively reduces the membrane permeability and the solute sieving becomes proportional to a new reflection coefficient (σ_1) of the membrane. This layer is a function of several variables, and above all, of the value of the 'shear rate' at the wall. As the blood enters the hollow fibre, the shear stress generates different layers of blood from the bulk phase to the membrane interface flowing at different velocities (Figure 5). The ratio

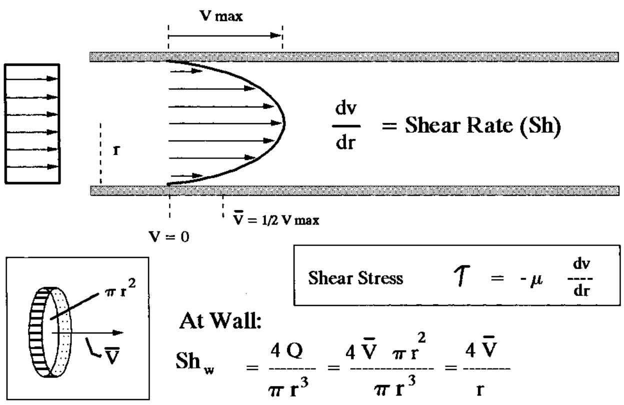

Fig. 5. Description of the shear stress and shear rate parameters, and typical velocity profile for a Newtonian fluid.

between the speed variations of the fluid threads in the fibre and the variation of the distance from the centre of the fibre ('shear rate' expressed in 1/s) is a function of blood viscosity and of the shear stress. The shear rate is also proportional to the blood flow per single fibre. The thickness of the protein layer at the blood–membrane interface depends on the wall's 'shear rate' value, and is extremely important for the membrane's performance. The shear rate value linearly correlates with the shear stess in the case of Newtonian fluids, and the velocity profile is regularly parabolic. Blood approaches Newtonian behaviour only at shear rates >200 1/s. Ultrafiltration and solute sieving coefficients are considerably influenced by the wall shear rate because this contributes to keeping the polarization layer very thin (Figure 6). This is particularly important for solutes in the middle–high range. Diffusion is also affected by the value of the shear rate since high shear rates contribute to maintaining the diffusion distance from blood to dialysate within minimal values (Figure 7). This is because concentration polarization and the secondary layer of proteins lead to the formation of a pseudo-membrane whose thickness is added to the thickness of the original membrane.

$$\sigma_1 \text{ and } \sigma_2 = f_{(wSh)}$$

At Low Shear Rates (a)

$$J = Qf \times (1 - \sigma_1)$$

At High Shear Rates (b)

$$J = Qf \times (1 - \sigma_2)$$

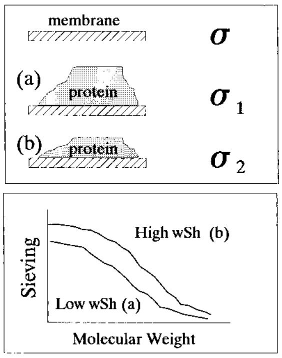

Fig. 6. Impact of wall shear rates on convective transport. σ_1 and σ_2 represent the different reflection coefficients of the functional membrane (membrane + protein layer) in the presence of low shear rates (**a**) and a consequent thick layer of plasma proteins, and high shear rates (**b**) and a thinner layer of proteins.

$$x \text{ and } x_1 = f_{(wSh)}$$

At Low Shear Rates

$$J = -DTA\frac{\delta c}{\delta x}$$

At High Shear Rates

$$J = -DTA\frac{\delta c}{\delta x_1}$$

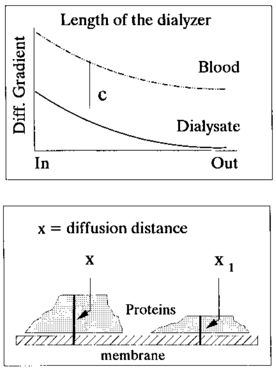

Fig. 7. Impact of wall shear rates on diffusion. In the presence of similar gradients for diffusion, the effect of different shear rates on the thickness of the protein layer affects the diffusion process, modifying the final diffusion distance (from x to x_1).

In clinical practice, high wall shear rates are obtained with high blood flows and adequate device geometry, and they result in higher ultrafiltration rates and solute clearance. In a recent study carried out with dye injection in the blood compartment of different hollow fibre dialysers, we could demonstrate that in peripheral fibres, blood flow and shear rates much lower than those in the central fibres of the bundle are observed (Figure 8). This is even more evident when the haematocrit is $>35\%$, increasing the viscosity of the blood. Accordingly, we could speculate that blood flow >350–400 ml/min must always be utilized in the presence of a 1.8–2.0 m^2 dialyser, if an optimal performance of all the fibres is to be achieved.

The dialysate compartment

While several attempts have been made to optimize the blood compartment, by creating adequate blood ports and flow distributors at the inlet of the dialyser, very little attention has been paid to the dialysate compartment. The dialysate distribution may in fact be asymmetrical inside the dialyser, causing non-homogeneous distribution within the fibre's bundle and the consequent phenomenon of channelling (i.e. the dialysate flows externally to fibres without reaching the space available within the fibres in the central region of the bundle). This may prevent the dialyser from operating properly, and may affect the final performance of the treatment.

Some attempts to increase the distance between adjacent fibres in the bundle and to avoid dialysate channelling have been made. For example, an increased fibre length permits the fibres to be packed more loosely once the bundle is fixed in the case. An external irregular surface avoids the perfect contact of adjacent fibres. Different systems of non-parallel orientation of the fibres or the use of tissue structures within the bundle may help further to maintain adequate distances between the external surface of adjacent fibres.

The most recent approach is the use of spacing filaments between the fibres in order to increase the distance between different fibres of the bundle and to permit a more homogeneous distribution of the dialysate flow (Figure 9). We have carried out a complex evaluation using a helical computerized tomography scan to achieve a detailed imaging of the dialysate distribution pattern after dye injection. The modified dialysate compartment with the spacing filaments between the fibres displayed a more homogeneous distribution of the dye, as compared with standard dialysers in which a typical channelling effect was displayed in the peripheral regions.

Further improvements could probably be achieved by optimizing the dialysate overflow ring placed at the inlet and outlet of the dialysate path, inside the dialyser case. Further modifications of the dialysate compartment have been proposed recently to increase the mechanism of internal filtration–backfiltration. These

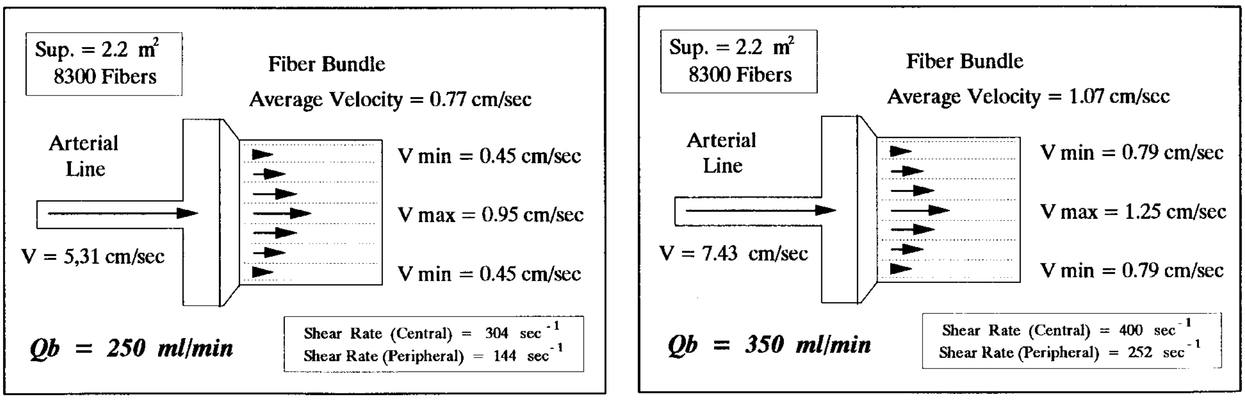

Fig. 8. Central and peripheral velocity of blood inside the fibres measured with dye injection in the blood compartment. Wall shear rates are also reported for the central and peripheral fibres in conditions of different blood flows.

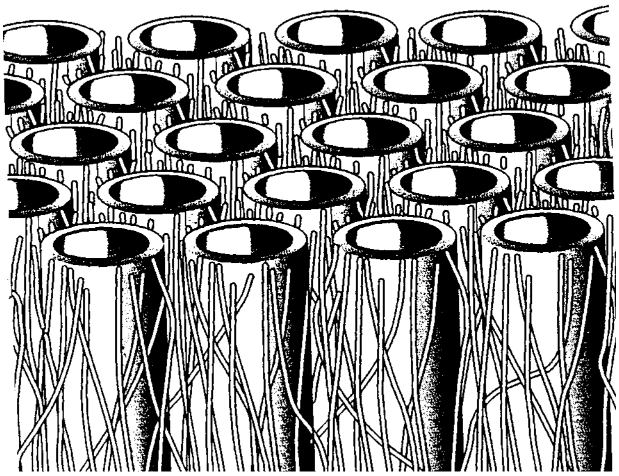

Fig. 9. Schematic representation of the new dialysate compartment designed by ASAHI Medical, including spacing filaments between adjacent fibres (courtesy of ASAHI).

studies are, however, still experimental and have not been applied to the clinical routine.

Interference between diffusion and convection

Although we describe convection and diffusion as two separate phenomena, in practice we cannot distinguish between the contributions of each of the two mechanisms. Moreover, especially in treatments that use a combinination of diffusion and convection, there is continuous interference between the two transport mechanisms [9]. In such circumstances, increasing one type of transport can produce effects on the other mechanism of transport that may have beneficial results but may also be detrimental.

In haemodiafiltration, solutes are carried across the membrane at the same concentration as in plasma water because of a high ultrafiltration rate. This phenomenon takes place mostly on the proximal side of the filter and reduces the driving force for diffusion. In this case, convection negatively affects diffusion, which becomes more important on the distal side of the filter where ultrafiltration approaches zero. This emphasizes the importance of the surface area for the diffusive performance in haemodiafiltration. However, in haemodiafiltration, the backdiffusion of substances, such as buffers, from dialysate into the blood may also be negatively affected, at least on the proximal side of the filter where ultrafiltration is higher. In high-flux dialysis, this is shown with the classic filtration–backfiltration profile. The minimal interference between convection and diffusion is achieved in the central part of the dialyser where the water flux in both directions is near zero. In the region near the blood ports, convection may interfere with diffusion in both the filtration and the backfiltration mode. It should be noted, however, that in the case of solutes with a sieving coefficient <1, the membrane might create an abnormally high concentration of these solutes at the blood–membrane interface. In this case, the driving force for diffusion might even increase and the final diffusive process could even be enhanced. A possible approach to utilize convection and diffusion separately is described in two-chamber haemodiafiltration or paired filtration–dialysis. The two processes of transport can therefore be optimized, making the reciprocal interference less important.

The hydraulic properties of the system

The dialyser must also be considered as a hydraulic unit, and therefore the water kinetics inside it should also be analysed carefully. At a given blood flow rate, each hollow fibre dialyser shows a typical value of obligatory ultrafiltration, depending on the dialyser geometry and the membrane hydraulic permeability. This is because, in such conditions, an average transmembrane pressure is created by the forces present in the system (blood hydrostatic pressure $= Pb$; dialysate hydrostatic pressure $= Pd$; plasma oncotic pressure $= \pi$).

Ultrafiltration can be reduced at values less than the obligatory ultrafiltration by adjusting the pressure in the dialysate compartment. This process may reach a

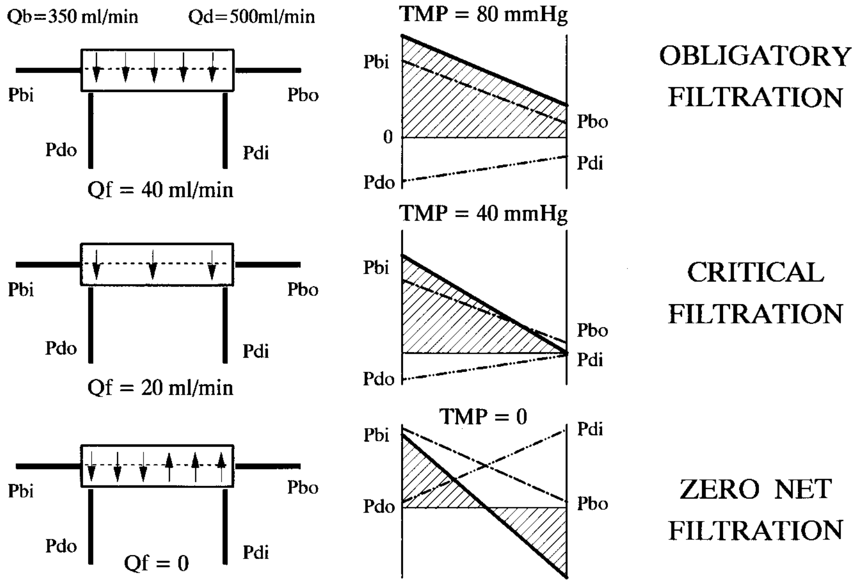

Fig. 10. Possible pressure profiles inside a hollow fibre dialyser. At zero net filtration, the amount of filtration equals the amount of backfiltration. Pressure profiles are reported schematically as a linear function.

point defined as 'critical filtration', in which transmembrane pressure at the dialyser outlet is zero. Each time ultrafiltration is set at a value lower than that of critical filtration, backfiltration will occur inside the filter (Figure 10). The mechanism is mainly a function of the membrane hydraulic permeability and the geometry of the blood and dialysate paths. Even on reducing the net ultrafiltration rate, the convective transport still occurs in the dialyser proximal portion. Indeed, in the case of a sterile dialysis fluid, an effective haemodiafiltration (internal haemodiafiltration) could be performed inside one filter without the need for replacement solutions. This would result in a greater removal of larger molecules with highly permeable membranes, not dependent on the membrane diffusive performance, but related to a remarkable convection hidden by relevant backfiltration rates. In this view, we have conducted experimental studies with modified hollow fibre dialysers in which internal filtration–backfiltration was enhanced. The transport of medium–large solutes was also improved, suggesting that this is a method that could be used in the future. However, the possibility of pyrogen transportation in the circulatory stream should not be disregarded, and this could be enhanced by larger amounts of backfiltration.

Conclusion

The haemodialysis system is comprised of three main components: the blood compartment, the membrane and the dialysate compartment. These three components are strictly linked into a final configuration that permits the optimal performance of the dialyser as a solute and water exchanger. Several factors are able to influence the two main mechanisms of solute transport: diffusion and convection. The two mechanisms are themselves continuously interfering in a complex phenomenon that leads to the final observed transport.

Once again, such analysis is schematic and represents phenomena which, even if well known and real, cannot be quantified easily as a single and separate contribution. Some other factors play an important role, such as the nature of the solute in terms of the Einstein–Stokes radius, protein binding, electrical charges and hydration status. The characteristics of blood in terms of haematocrit and viscosity may also influence the performance of the system. The increasing use of erythropoetin will undoubtedly cause a mean increase in haematocrit in dialysis patients with problems related to the increased blood viscosity. An increase in the plasma red cell percentage will also result in a smaller share of plasma water inside the filter at a given blood flow and will probably affect the dialytic efficiency. Improvements in dialysis efficiency and efficacy can be obtained with mixed diffusive–convective treatments. Knowledge of the basic chemical–physical mechanisms of solute transportation in such treatments will contribute to the optimization of the operative conditions and materials used in future forms of renal replacement therapy.

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