Problems related to backfiltration in hemodialysis

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Introduction

The clinical research towards highly efficient dialysis techniques, has encountered a series of problems related to the status of today's dialysis technology [1-4]. Despite recent advances in the development of needles, tubing, filters, membranes, dialysis machines and solutions, in the attempt to create materials adequate to the new operational ranges (high blood flows, high dialysate flows, high ultrafiltration rates, etc.), all of the highly efficient dialysis techniques are still far from complete optimisation [5-7]. Among various problems, the possible passage of dialysate across the dialysis membrane into the blood has represented in recent years one of the discussed issues. Therefore a need for a detailed study concerning the factors involved in backfiltration and the possible solutions to this problem became evident [8, 13, 14]. The aim of the present paper is to offer a quite complete summary of the problems involved in the hydraulic mechanisms occurring inside a hollow fiber dialyzer during hemodialysis.

Water flux in hollow fiber dialyzers

The water flux across dialysis membrane in each axial segment (dl) of the dialyzer may occur in either of two directions: from blood to dialysate, which is termed filtration, or from dialysate to blood which is termed backfiltration.

Backfiltration may occur inside any kind of filter, and during any kind of treatment, when the transmembrane pressure gradient (ΔP) at a given point becomes negative (i.e. when the hydraulic pressure of dialysate [Pd] together with the oncotic pressure exerted by plasma proteins [π] exceeds the hydraulic pressure of the blood inside the fibres [Pb]). This condition may happen occasionally during the treatment or for the entire duration of the session, depending on the technique and materials utilized. TMP is generally expressed in average values with the simplified formula:

$$\overline{TMP} = \frac{Pbi + Pbo}{2} - \frac{Pdi + Pdo}{2} - \frac{\pi i + \pi o}{2} \qquad [1]$$

where $\overline{TMP}$ is the average transmembrane pressure, i = inlet, o = outlet of the filter, and the overall water flux (Qf) is calculated from the final balance at the outlet of the filter. However this representation only describes and average phenomenon and does not define the actual pressure profile inside the filter. Although the average TMP is positive, the local ΔP is not necessarily positive at every point along the length of the dialyzer. Equation 1 also assumes that the pressures drop inside the fibres of the dialyzer is linear with distance, which, according to the Hagen-Poiseuille law, is only true under specific conditions. As depicted in figure 1, the pressure drop is linear only when blood viscosity remains constant along the fibres, and this only occurs when no ultrafiltration takes place. When water is removed by ultrafiltration, increases in hematocrit and plasma protein concentration cause the blood viscosity to increase along the length of the device, which results in a non-linear pressure drop.

The overall water flux in a single fiber of the dialyzer is described in detail in figure 2. ds represents a single surface unit and dl represents a single unit of the fiber length. Expanding this concept to the whole dialyzer, the overall water flux in a given dialyzer will be expressed by the formula

$$Qf = \iint_{o}^{s} \Delta P \cdot Kf \cdot dS \qquad [2]$$

where: $\underline{\Delta P} = \underline{\Delta P1} + \underline{\Delta P2}$, where $\underline{\Delta P1}$ is the difference of hydrostatic pressure between blood and dialysate and
$\underline{\Delta P2}$ is the difference of oncotic pressure between the two compartments.

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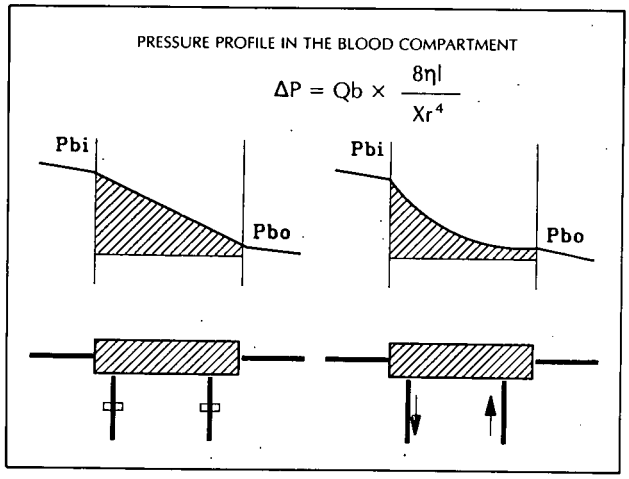

Fig. 1.—Pressure profiles in the blood compartment according to the Hagen-Poiseuille Law in absence or in presence of ultrafiltration. In the latter case the change in blood viscosity causes a non-linear pressure drop inside the fibres.

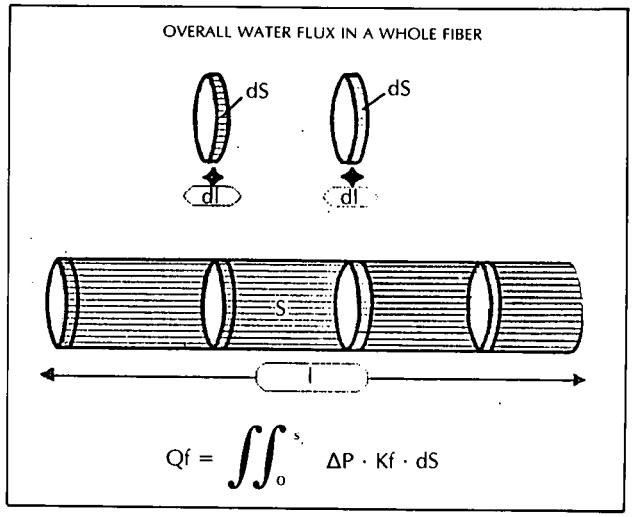

Fig. 2.—Water flux in a whole fiber. dS is a single surface element. Considering the P equally distributed on the entire circumpherence, we can consider dl as a single length unit of the whole fibre. The same condition could be transposed to the entire dialyzer.

Kf is the ultrafiltration coefficient of the membrane.
dS is a single surface element of the dialyzer.
S is the surface of the dialyzer.

Arbitrarily assuming Kf to be constant on the whole surface area S, and ΔP to be identical in any point of a cross sectional segment of the dialyzer, equation #2 can be simplified as follows:

$$Qf = Kf \int_0^l \Delta Px \cdot dl \qquad [3]$$

where: *l* is the length of the dialyzer and
ΔPx is the local ΔP in a cross sectional segment of the dialyzer (dl).

For simple calculations we can use the formula:

$$Qf = DKf \cdot \int_0^l \Delta Px \cdot dl/l \qquad [4]$$

where: $\int_0^l \Delta Px \cdot dl/l$ = average transmembrane pressure ($\overline{TMP}$) and therefore the overall water flux will be:

$$Qf = DKf \cdot \overline{TMP} \qquad [5]$$

where for practical purposes, assuming a linear pressure drop along the fibres (which is not the case), TMP can be calculated using equation #1.

The above equations describe the water flux across the membrane as the net result of two opposing fluxes, filtration and backfiltration.

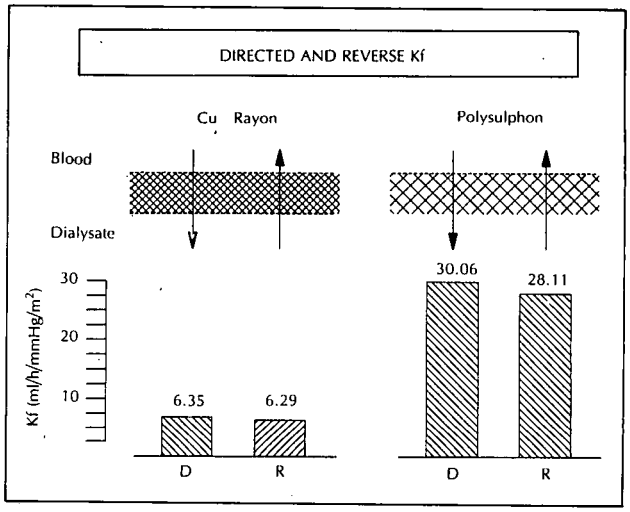

Fig. 3.—Coefficients of ultrafiltration measured in two different membranes in both directions.

A more accurate analysis would require a detailed characterisation of this phenomenon in which the final flux is defined as a sum of the opposing water fluxes:

$$Qf = Qf1 - Qf2 = (Kf1 \cdot \int_0^y \Delta Px \cdot dl) - (Kf2 \cdot \int_y^l \Delta Px \cdot dl) \qquad [6]$$

Where:

Qf = total water flux.
Qf1 = direct water flux (filtration).

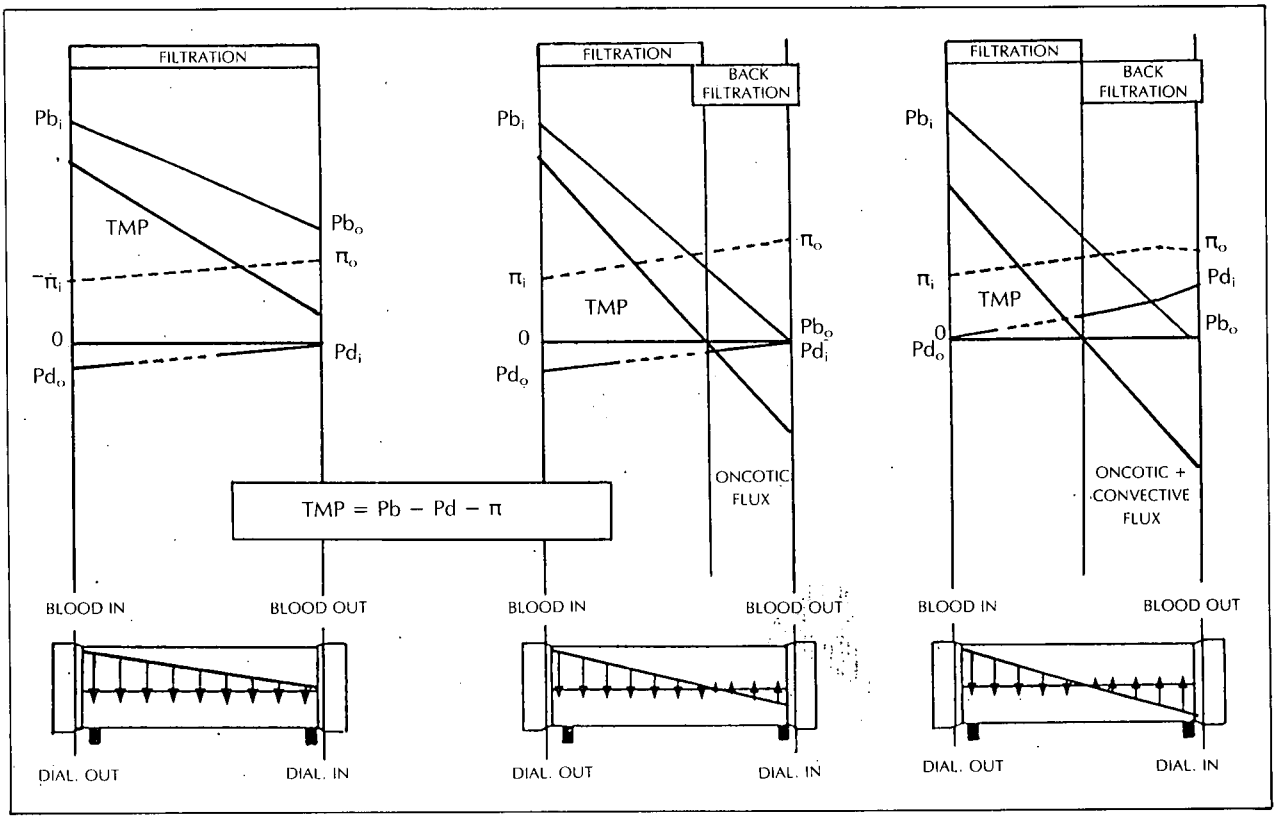

Fig. 4.—Three typical pressure profiles in a dialyzer: a) TMP constantly positive and no backfiltration. b) TMP negative at the end of the dialyzer with a small amount of backfiltration due to oncotic flux. c) TMP negative in the second half of the dialyzer with a significant amount of backfiltration due both to an oncotic and a convective water flux.

Qf2 = reverse water flux (backfiltration).
Kf1 = membrane direct ultrafiltration coefficient.
Kf2 = membrane reverse ultrafiltration coefficient.
y = point of inversion of ΔPx and water flux.

It should be noted that Kf1 and Kf2 can be slightly different in vitro and even more different in vivo because of the protein boundary layer in the blood compartment, and the structure of the membrane. As shown in figure 3, the direct Kf and reverse Kf of the membrane are almost identical with cellulosic symmetric membranes, while some differences can be noted with synthetic asymmetric membranes like polysulphon.

One additional factor which can influence the pressure profile in the blood compartment is the variation of the diameter of the fibres along the length of the dialyzer, being smaller in the segment surrounded by the potting and larger in the segment surrounded by dialysate. This may affect the pressure drop inside the fibres, which in turn will affect the final water flux across the membrane.

In conclusion, backfiltration may occur during dialysis whenever the sum of the dialysate pressure plus the oncotic pressure exceeds the hydrostatic pressure of the blood, and the amount of backfiltration will be dependent on the coefficient of permeability of the membrane.

Mechanisms of backfiltration

Figure 4 demonstrates the mechanisms of backfiltration during dialysis. Transmembrane pressure (ΔP or TMP) varies with axial position and depends on the pressure profile of blood and dialysate along the fibres. We will neglect the effect of axial variation in viscosity on axial pressure drop and assume, for simplicity that the pressure decreases linearly from Pbi to Pbo.

Pbi is primarily dependent on the speed of the pump and on the resistance of the filter, while Pbo is a function of three factors: Pbi, the pressure drop inside the fibres and the venous resistance. For a given blood flow, dependence of the pressure drop inside the fibres on the geometry of the filter, is given by the Hagen-Poiseuille law:

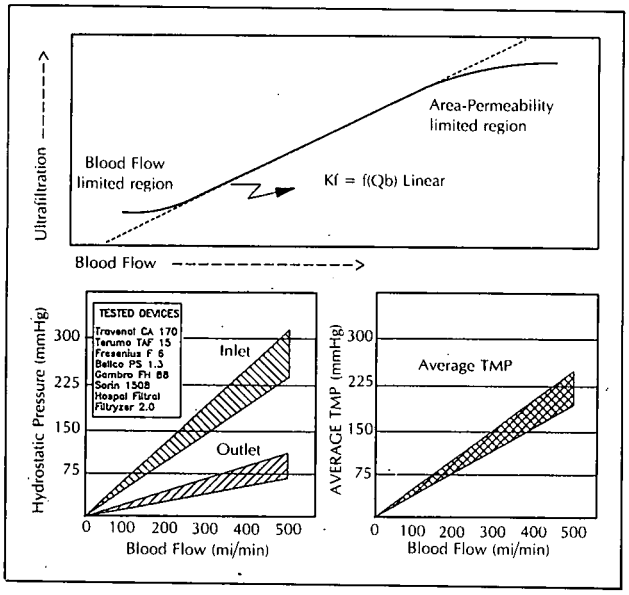

Fig. 5.—Relationship between blood flow and ultrafiltration in a general dialyzer. The function is linear in a wide range of flows being limited by low blood flows or by the surface area-permeability at high blood flows. The explanation is in the lower panels where the relationship between blood flow and pressure inside the devices is reported. From this observation the concept of «critical filtration» at a given blood flow in a dialyzer is derived.

$$\text{Pressure drop} = Qb \times \frac{8 \cdot \eta \cdot l}{n \cdot \pi \cdot r^4} \qquad [7]$$

where *Qb* is the blood flow, η is the viscosity of blood, *l* is the length of the fibres, *n* is the number of the fibres and *r* is the inner radius of the fibres.

It is therefore evident that the length of the filter and its total cross sectional area, together with hematocrit and total protein concentration of the inlet blood, will influence the pressure drop inside the filter. Furthermore, the permeability of the membrane plays an important role in the pressure profile for two reasons: a) As the blood moves inside the filter, water is removed by ultrafiltration with a consequent increase in hematocrit and plasma proteins. This causes a significant increase in blood viscosity and further reduces the hydrostatic pressure of blood in the fibres; b) The higher the permeability of the membrane and the intrinsic resistance of the filter are, the larger the amount of ultrafiltration at a given plasma flow will be, and therefore the higher the filtration fraction will be. This will cause a significant increase of the oncotic pressure in the distal segment of the filter that further reduces the overall transmembrane pressure. Finally, dialysate solution is pumped inside the filter at a certain pressure which is generally low because of the lower resistance of the dialysate compartment. In the absence of ultrafiltration control systems the spontaneous pressure can be positive or negative depending on the position of the pump and the setting of the manometric regulation. When ultrafiltration control systems are utilized, dialysate pressure may rise significantly in response to a required reduction of filtration rate.

Figure 4 shows examples of three different pressure profiles that may be encountered inside a dialyzer which employs a countercurrent configuration. Part (A) shows the ideal situation in which the entire surface and length of the filter is utilized for filtration, and no backfiltration occurs. The TMP is always positive because of the hydrostatic pressure drop in the blood compartment is low and Pbo is slightly greater than πo + Pdi (where Pdi = inlet dialysate pressure). Part (B) shows the case in which, for any of a number of possible reasons (higher resistance of the filter, higher permeability of the membrane and higher ultrafiltration in the proximal segment of the filter) the pressure drop in the blood compartment is larger and the increased pressure generated by plasma proteins causes an oncotic flux of dialysate into the blood in the distal segment of the filter. The amount of backfiltration in this condition is self limited because of a simultaneous decrease of the oncotic pressure as blood is diluted by the backfiltration flux. Part (C) shows the case in which the pressure drop inside the blood compartment is even greater because of the above mentioned reasons as well as higher ultrafiltration rates in the proximal segment of the filter. This is likely to occur in case of high blood flows, filters with high surface area and high flux membranes. Under these conditions, it would be impossible to maintain the scheduled weight loss of the patient in that session and, unless fluid reinfusion in the venous line is scheduled, an ultrafiltration control apparatus would be required. Ultrafiltration control systems limit fluid withdrawal from the patient by increasing the hydrostatic pressure in the dialysate compartment. Whenever Pdi exceeds Pbo, dialysate flows into the blood as a result of a hydraulic pressure difference as well as an oncotic pressure difference, and the extent of backfiltration is greater than in the case of a purely oncotically-driven flux.

These phenomena largely result from the fact that the dialyzers available today were originally designed to rely on diffusion (like multi pipe heat exchangers) rather than convection (like hydraulic units) to transfer molecules across dialysis membrane. Satisfactory operation was achieved under standard conditions of dialysis with low blood flows, low pressures, and membranes with low hydraulic permeability. Furthermore, in the absence of ultrafiltration control systems, fluid reinfusion, rather than positive manometric regulation of dialysate pressure was generally employed in cases of high spontaneous filtration rates.

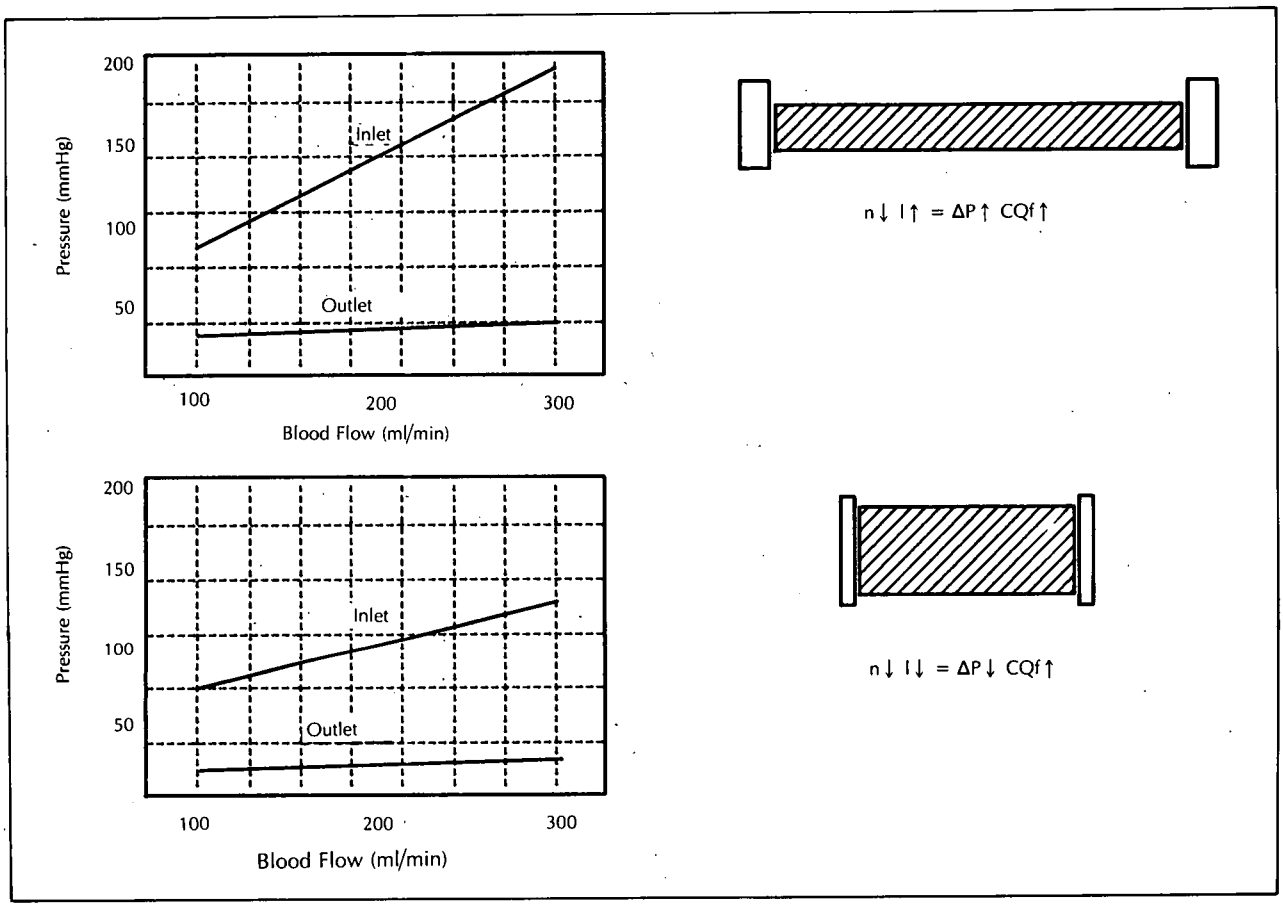

Fig. 6.—At a given Kf the geometry of the filter determines the rate of «obligate filtration» or «critical filtration». A long thin dialyzer, shows a greater resistance with a significant pressure drop (P), and a higher critical ultrafiltration (CQf).

Today we are facing the problem of backfiltration more frequently because of a dramatic change in the operational ranges of our treatments and the clinical introduction of new membranes and equipment.

Determinants of backfiltration

Backfiltration is a physical phenomenon that strictly depends on the intrinsic characteristics of the dialyzer. As depicted in figure 5, there is a direct relationship between ultrafiltration rate and blood flow. At intermediate blood flows, this relationship is linear because the hydrostatic pressure inside the filter increases linearly as blood flow increases. At low blood flows the relationship is non-linear because the axial pressure drop becomes negligible. At high blood flows, surface area-permeability cause further non-linearity. In the lower panels the ranges of pressures recorded in different dialyzers at various blood flows are reported. From these values the average hydrostatic pressure inside each dialyzer can be calculated. If Kf is known, the corresponding filtration rate required to avoid backfiltration can also be calculated. This concept is commonly defined as obligate or critical filtration at a given blood flow, and describes the minimal filtration rate that must be achieved during treatment to avoid backfiltration. The value of critical filtration is strictly dependent on the geometry of the dialyzer and the permeability of the membrane. In figure 6 the pressure profiles and obligate filtration rates in two different dialyzers are summarised. It is evident that at a given permeability of the membrane, the device with higher resistance will present a higher hydrostatic pressure inside the fibres and a significant pressure drop in the blood compartment with a parallel higher obligate filtration. The opposite phenomenon will take place in a shorter filter with larger cross sectional area.

For similar blood path geometries, the filtration rate will be a function of membrane Kf, which is much higher in synthetic asymmetric membranes. In figure 7 a series of examples are reported. The upper panel shows that at a given blood flow and its corresponding average TMP, the filtration rate is significantly different

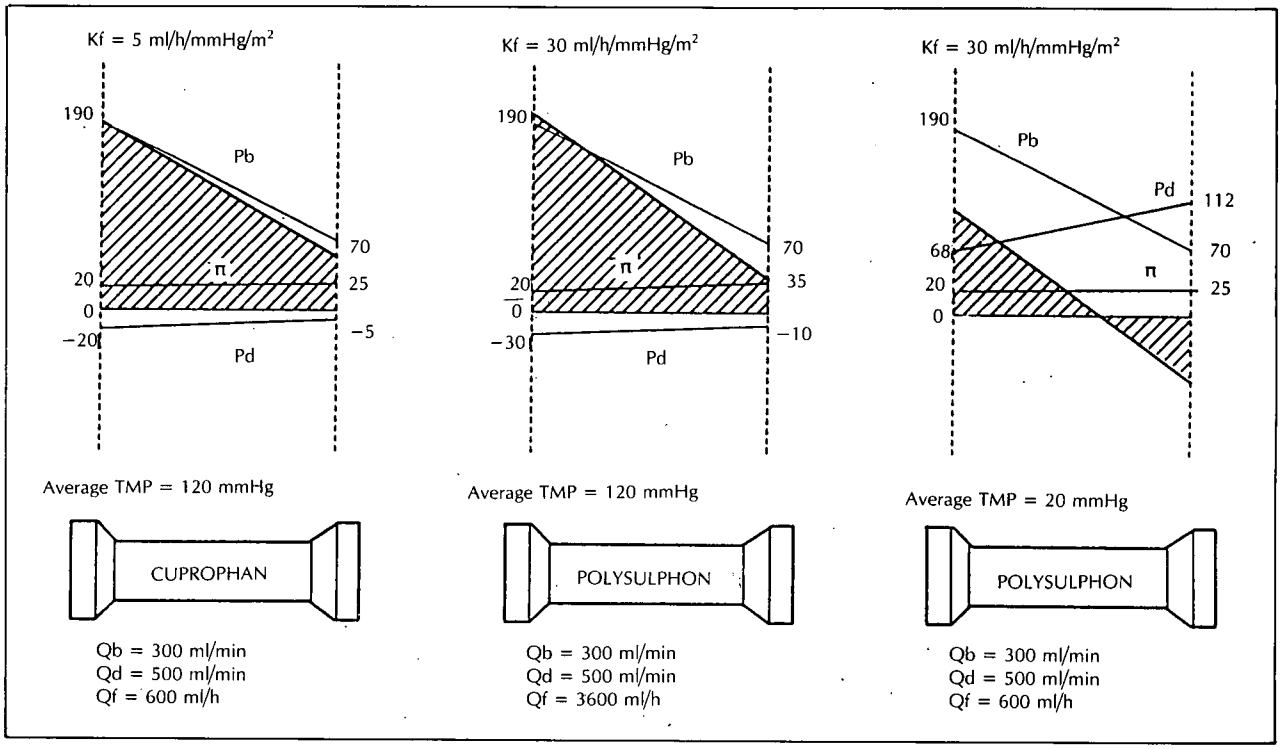

Fig. 7.—At a given geometry of the filter the membrane Kf determines the obligate filtration. In the first panel a cuprophan dialyzer 1 m² large has a critical filtration of 600 ml/h at 300 ml/min of Qb. The same conditions gives an ultrafiltration of 3600 ml/h in a polysulphon device. To achieve in the same device an ultrafiltration similar to the first filter, a significant rise in the dialysate pressure must be obtained and a remarkable amount of backfiltration takes place.

in the two dialyzers. In the lower panel a second situation is shown. When lower ultrafiltration rates are required with highly permeable membranes, a positive pressure in the dialysate compartment must be applied in order to reduce the obligate filtration at a given blood flow; this produces significant amounts of backfiltration.

Backfiltration modelling

Several approaches have been proposed to model backfiltration and therefore to predict the amount of dialysate infused into the blood during a given treatment. We have developed a simple calculation based on the concept of obligate filtration. Once blood and dialysate pressures are estimated at the inlet and outlet of the filter, and reverse Kf and surface area of the membrane are known, the extent of backfiltration can be calculated by noting that, at 0 ultrafiltration, reverse filtration will approximately equal direct filtration and the amount will be given by the formula:

$$BF = \frac{(Pbo - Pdi - \pi) \times SA}{2} \times rKf \qquad [8]$$

The value of BF will be negative because of the reverse direction of the flux and it will correspond approximately to 1/2 of the obligate filtration at a given operating condition.

Considering conditions different from 0 ultrafiltration, backfiltration can be calculated from the difference between the actual filtration and the critical filtration value at the present operative condition. The critical filtration (CF) in a dialyzer can be calculated by the formula

$$CF = \overline{TMP} \times Kf \times SA \qquad [9]$$

when the TMP at the outlet of the filter = 0.

Dialysate quality

The question that arises from the above mentioned observations is whether we can accept backfiltration or not in our dialysis treatments and eventually how we could try to avoid it.

It has been demonstrated that tap water, bicarbonate concentrate solutions and dialysate fluids may contain several types of undesired particles[8-10]. Bacterial fragments, chemical pyrogens or endotoxins may

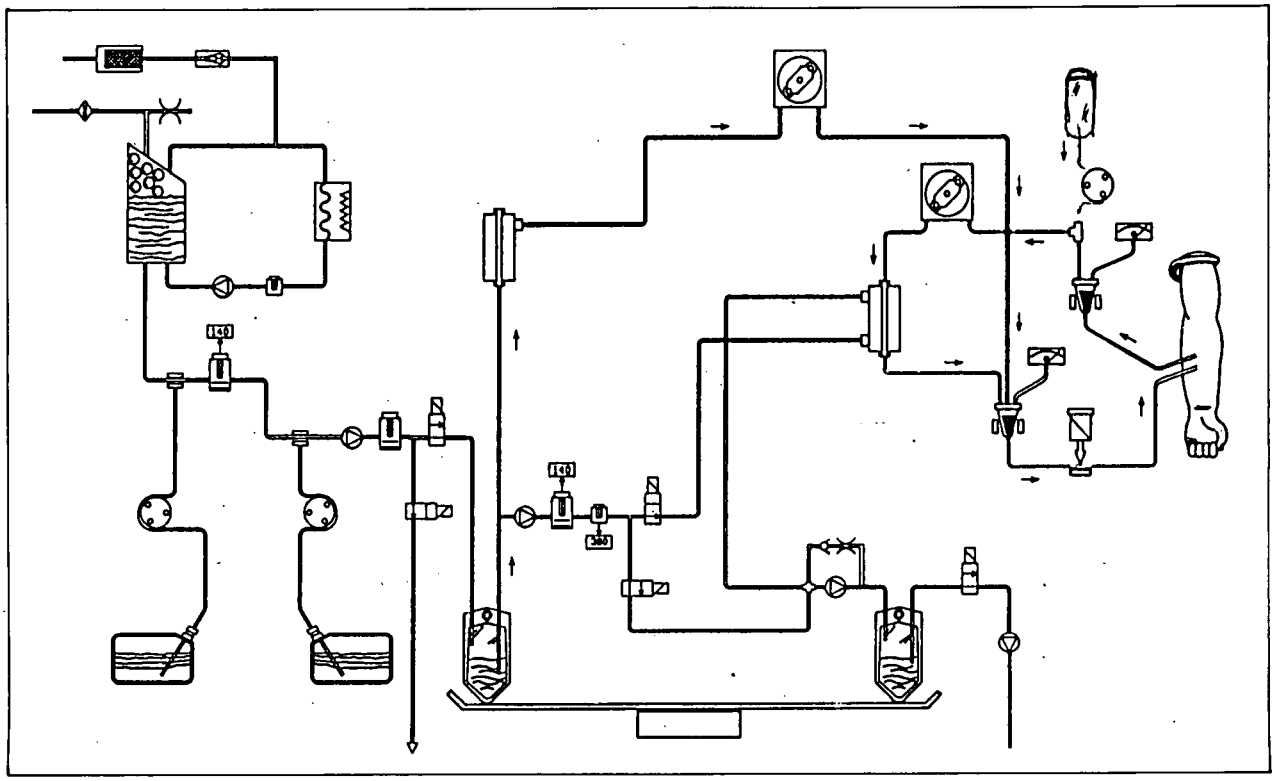

Fig. 8.—Schematic representation of the new apparatus for hemodiafiltration designed by Frigato et al. The focal point is represented by the gravimetric control of ultrafiltration regulating the TMP. When TMP approaches 0, the backfiltration risk is signalized by an alarm an, on demand, TMP is rised to avoid backfiltration with a reinfusion in the venous line of fresh, on line sterilized dialysate.

cause pyrogenic reactions in the patient during treatment [11].

While bacteria are generally absent in well treated water and well sterilized circuits, several pyrogens with molecular weight varying from 1,000 to 15,000 Daltons may be present at various concentrations even in high quality dialysis solutions. Once they have reached the dialysate compartment in the dialyzer, the smallest endotoxins or muramyl peptides can easily diffuse to the blood compartment across the membrane at a relatively high rate [12]. This process is highly influenced by the permeability of the membrane and it may be significantly enhanced by a certain amount of backfiltration and the consequent increase of convective flux of dialysate into the blood.

Several contributions have demonstrated the importance of reducing at the minimum the immunostimulation of the patient during dialysis to make the treatment more compatible and therefore tolerated [13, 14]. Since the standard level of preparation of dialysate in the dialysis routine does not now guarantee a safe, pyrogen-free solution, we believe that attempts should be made to avoid or, at least to reduce, the amount of backfiltration in our treatments.

Approaches to backfiltration

Different solutions could be proposed to reduce or avoid the problem of backfiltration and we will briefly summarise them:

a) *Pre-postdilution:* Backfiltration often occurs when the average transmembrane pressure is maintained low in order to reduce the amount of fluid withdrawal from the patient. This is generally achieved by increasing the hydrostatic pressure of dialysate or by reducing the blood flow, thus reducing the obligate filtration imposed by the resistance of the filter. One possible solution to avoid this mechanism of backfiltration would be to maintain a positive local transmembrane pressure constantly positive for the entire length of the filter. This can be achieved with high blood flows and/or a negative pressure applied to the dialysate compartment. However, such an approach does not guarantee a complete absence of backfiltration inside the filter unless one calculates the critical filtration for each device, and it introduces the problem of controlling the weight loss of the patient. The maintenance of the scheduled weight loss in fact can only be obtained by the infusion of replacement

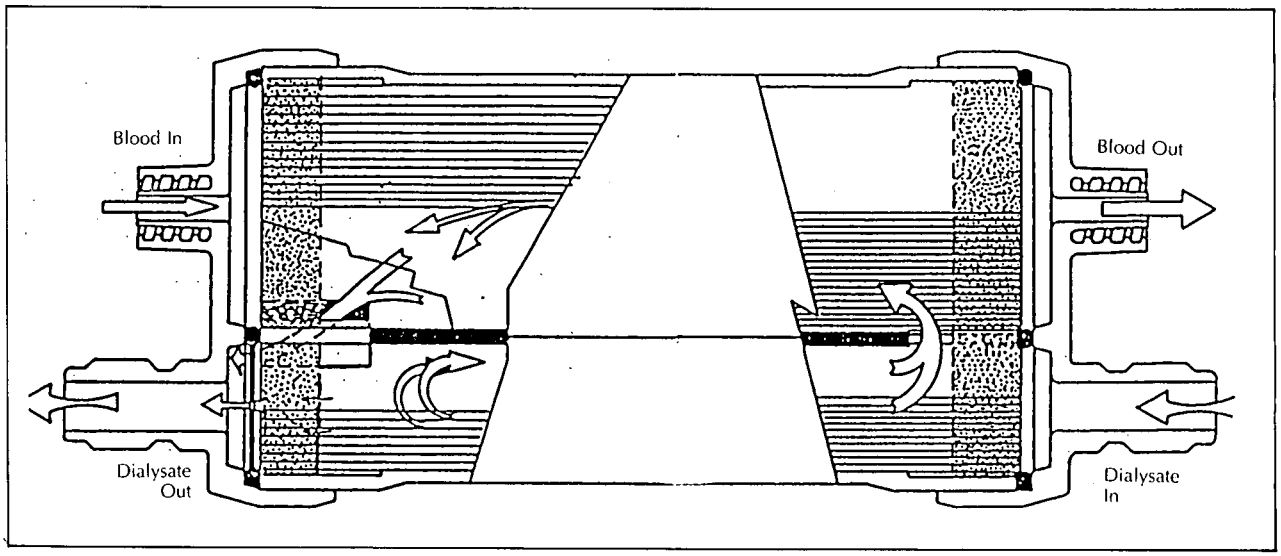

Fig. 9.—Prototype designed by Fecondini et al. to filter the dialysate in a second chamber, before it enters in contact with the fibres of the dialyzer. In this unit backfiltration is wanted to increase the convective transport of solutes.

solutions in the arterial or the venous line. The use of replacement solutions in predilutional mode offer the advantage of reducing the protein cake formation inside the filter because of a significant decrease in filtration fractions, but decreases the efficiency of the treatment by reducing the solute plasma concentrations and therefore the diffusive gradients for solutes across the membrane. Postdilution is more commonly utilized but again it is not completely free of problems. The quality of substitution fluids can be different and variable depending on preparation and storage procedures. In some countries the infusion of commercially prepared solutions stored in plastic bags is not allowed by the law and alternative procedures are required. Only recently, machines equipped with a system for on-line production of sterile solution for replacement have been introduced in the clinical practice. Such machines are not yet widely utilized. Finally, the rate of postdilution must be governed by a system strictly under control of the dialysis machine and its ultrafiltration control module. This again introduces financial problems linked to the necessary technological investments in the dialysis centres for the acquisition of new dialysis machines. An interesting approach to this problem has been proposed by Frigato et al. who created a new dialysis machine equipped with ultrafiltration control and an alarm for backfiltration. As reported in figure 8, the system operates a gravimetric control on ultrafiltration that regulates the final TMP to achieve the desired weight loss. As Pdi approaches Pbo and backfiltration is likely to occur, two responses are available: one is just a blinking alarm telling the operator that backfiltration is occurring; the other consists of a sudden adjustment of TMP to higher values and a consequent reinfusion in the venous line of a certain amount of fresh dialysate previously sterilised on line. The advantages of this system include a free choice by the operator with respect to backfiltration control and eventually a sterilising procedure that only concerns small amounts of fluid and not the entire dialysate pool.

In conclusion pre or post-dilution may represent a possible solution for backfiltration when highly permeable membranes are utilized and large amounts of ultrafiltration are scheduled. This approach has been found to be practical in treatments such as hemodiafiltration in which quantities of exchanged

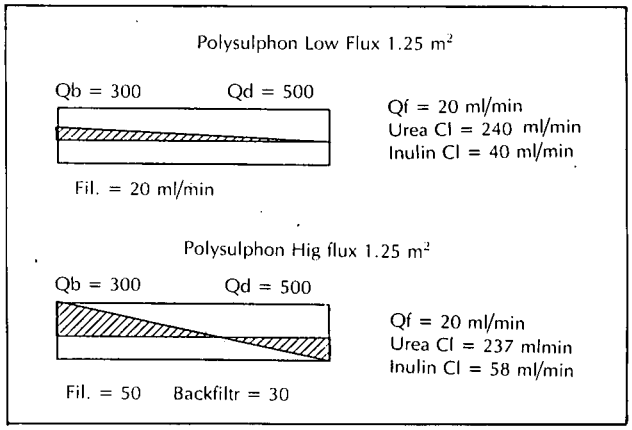

Fig. 10.—The importance of convection in removing large solutes such as inulin is shown. At a given sieving coefficient and net filtration, the clearance is much higher with higher ultrafiltration rates in the proximal end and backfiltration in the distal segment than in conditions of constantly positive TMP and lower water exchange. This condition shows as backfiltration could be usefully utilized once the dialysate is made sterile and pyrogen free.

fluid are sufficient to overcome the critical filtration volumes imposed by the dialyzer.

b) *Geometry of the filter:* The blood pressure drop inside the fibres is strictly dependent on the length and the cross sectional area of the filter. The shape of the dialyzer influences its resistance to the blood flow and consequently the rate of obligate filtration. In any case, the pressure drop inside a long thin dialyzer will be so large that it renders the net TMP in the distal part of the fibres negative, causing backfiltration. Changes of the blood path geometry of the dialyzer might therefore contribute to reducing this mechanism of backfiltration. An increase of the number of the fibres, an enlargement of the their inner diameter, and/or a reduction of their effective length would reduce the resistance of the filter making it more compliant to high blood flows and reducing the obligate filtration in the proximal segment of the filter. In addition to the high cost of re-designing dialyzers, new problems related to the reduction of the diffusive performance of such a dialyzer would be introduced. The shape of the re-designed filter in fact would reduce diffusive mass transport rates significantly for various reasons. Hollow fiber dialyzers were originally designed as multipipe diffusive exchangers rather than optimised hydraulic units. This configuration resulted from the use of membranes with low hydraulic permeability that could be quite safely utilized without serious risks of excessive ultrafiltration. The introduction of highly permeable membranes and treatments with large convective components has therefore created the necessity for devices based on a good compromise between convective and diffusive capacities. The ideal diffusive unit would have an adequate length, surface area and flow distribution to take the maximal advantage from the blood and dialysate countercurrent flows utilized in a given treatment. The ideal convective units, on the other hand, would make the pressure inside the filter less dependent on blood flow thus dissociating ultrafiltration rate from the blood flow rate. The low resistance of such unit would result in low pressure drops inside the fibres and low obligate filtrations at a given blood flow. At the same time, the use of high flux membranes would permit a significant increase in the rate of ultrafiltration when desired, by increasing the overall transmembrane pressure. In this field, an interesting solution comes from the new treatment called Paired filtration dialysis where convection and diffusion are achieved in two separate units during the treatment. Blood is reconstituted by reinfusion of replacement solution after the first unit (polysulphon hemofilter), where ultrafiltration occurs, and diffusion is then optimised in the second unit (dialyzer), where the risk of backfiltration is limited by the low hydraulic permeability of the membrane (hemophan). As was discussed above, changes of the geometry of the filter may represent another possible solution of the backfiltration problem (by changing the flow dependent pressure profiles in the filter), although such an approach will require large investments and long development times. Changes in pressure profiles could also be obtained by utilizing the present filters with blood and dialysate cocurrent flows. This again would reduce the risk of backfiltration, but would also reduce the efficiency of the system for diffusive mass transfer.

We have recently proposed a new configuration of the dialysate path with the inlet in the middle of the filter and the outlet at the two ends. In this configuration part of the flow is cocurrent and part of it is countercurrent. Some tests carried out with this configuration showed that it behaves in between co and countercurrent configurations with satisfactory purification performance and reduction of critical filtration rates. On the other hand, when high dialysate flows are utilized, the cocurrent configuration could also be adequate in terms of solute removal. An interesting prototype designed by Fecondini et al., is reported in figure 9. The unit consists on two sections: the blood compartment is a simple hemodiafilter with polysulphon hollow fiber membrane; the dialysate compartment consists of a group of fibres that are used to filter the dialysate before it enters the space between the blood fibres. The dialysate is therefore treated and backfiltration could even be promoted to enhance the convective transport of substances. Figure 10 in fact reports the increased clearance of large solutes like inulin utilizing backfiltration. When membranes with the same sieving coefficient for inulin but different Kf are utilized (F6-F60 Fresenius), the higher convection is, the higher the clearance for such a large molecule will be.

c) *Membrane:* The permeability of the membrane plays an important role in two different ways. The higher the hydraulic permeability of the membrane is, the higher the ultrafiltration in the proximal segment of the filter will be with a remarkable pressure drop in the blood compartment. The consequent hemoconcentration and the possible positive pressure of the dialysate in the distal segment of the filter will generate a negative TMP with consequent backfiltration. The flux of dialysate into the blood will be much higher with highly permeable membranes depending on their ultrafiltration coefficients (Kf). Since it has been pointed out that high flux membranes are useful to achieve a better removal of large solutes such as β_2-microglobulin, the use of these membranes would be preferable not only for convective treatments but also for the so-called «High flux dialysis» where low ultrafiltration rates are employed. In this last technique however low ultrafiltration rates are achieved using an UF control apparatus, and large quantities of backfiltration may occur. An interesting compromise between high permeability to large solutes and low

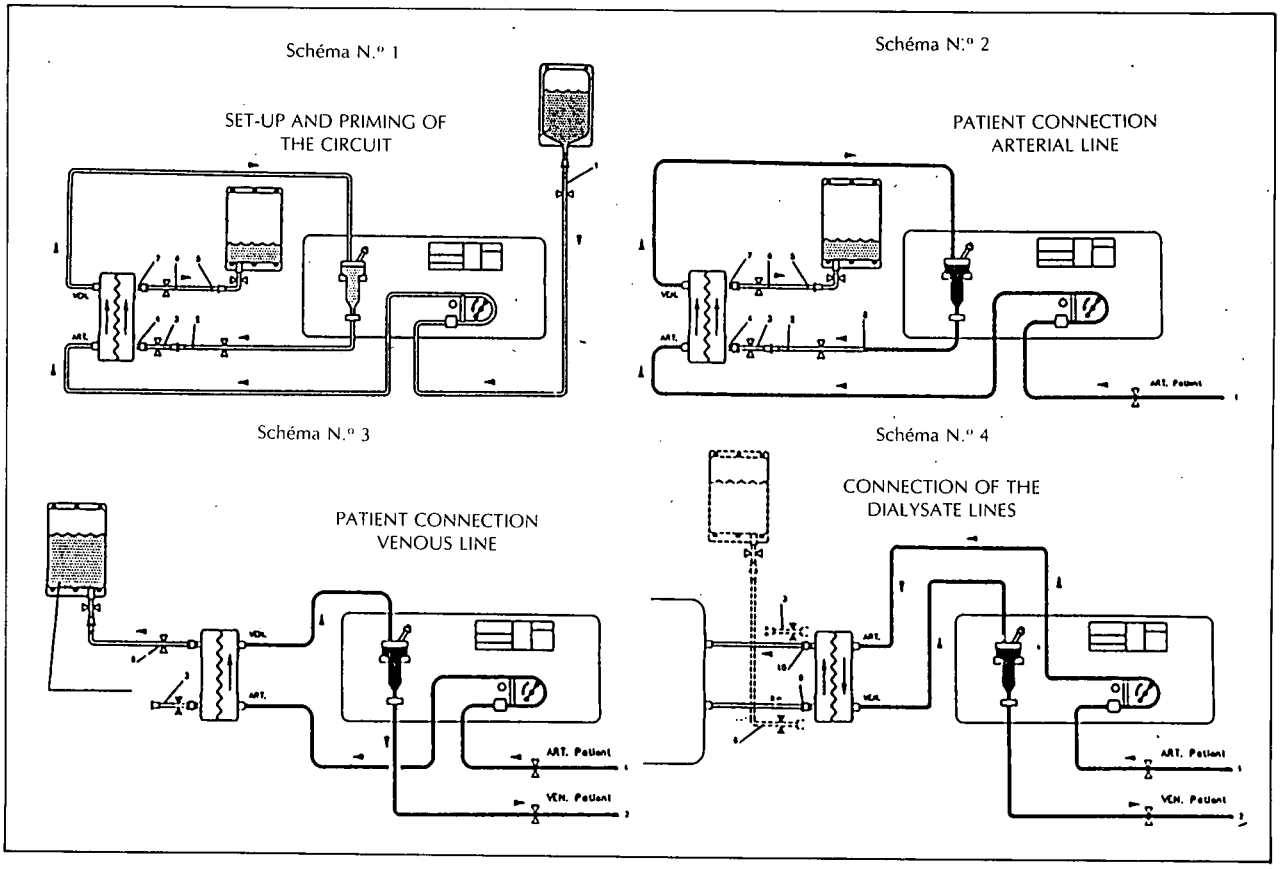

Fig. 11.—A new system for filter priming and washing is reported. The bioprime system (Hospal) consists on a sterile closed loop of heparinized saline solution that remains in the dialysate compartment until the blood flow is at regimen. Since the risk of backfiltration is greater in the first minutes of the session, in case of backfiltration a sterile solution will be transferred into the blood without risks of adverse reactions.

hydraulic permeability seems to be offered by the new synthetic membrane created in Europe by Fresenius defined «High perm. Low flux». In this low flux polysulphon membrane (F6) the structure has been modified in order to achieve high permeability to medium-large solutes but low Kf (as low as 5-6 ml/hr/mmHg/m^2). This approach, although still experimental, may permit significantly reduction of the amount of backfiltration without decreasing the clearance of medium-large solutes during treatment. Other methods have been used to modify the performance of the membrane by changing its hydrophylic or hydrophobic sites or varying its electrical charge in different points of the structure. Finally, we should remember that the higher the permeability of the membrane is, the larger the number of particles which are not rejected by the membrane and can be transferred from dialysate into the blood will be.

d) *Dialysate cleaning procedures:* The quality of water and dialysate treatment does not guarantee today a complete sterilization and elimination of pyrogen contamination. Several companies have therefore proposed dialysate cleaning procedures in order to make the treatment safer and even to make possible the on-line production of replacement fluid for i.v. reinfusion. The «conditio sine qua non» for a safe sterile, pyrogen free dialysate is a cascade of filtration procedures that begins from a RO treatment of water, followed by filtration of the concentrate and of the final dialysate prior to enter the dialyzer. These procedures attempt to avoid any contamination of dialysate by the liquid bicarbonate concentrate and they must be accompanied by a thorough sterilization of the dialysis machine and avoidance of any stagnation of fluid inside. Some other approaches have been proposed such as a mixing of dry bicarbonate with the dialysate as realized with the Gambro Bichart. On the contrary, other approaches have proposed to clean up only the small amount of dialysate that can be infused into the blood and this has been achieved in the above mentioned Miren Machine. In this machine only small amounts of dialysate are sterilized and infused as replacement solution to maintain ultrafiltration above

the critical values for backfiltration. Another possibility is offered by the Hospal Bioprime Kit. This is just a special priming procedure of the filter before use that allows for a complete lavage of the blood and dialysate compartment with sterile solution. As depicted in figure 11, in the first minutes of dialysis the system permits the blood to be in contact only with the sterile solution of the bioprime, making backfiltration less dangerous. This approach is based on the observation that backfiltration generally occurs during the first minutes of dialysis, when the blood flow is not yet at the established regimen. To ensure a better quality of dialysate during the whole treatment, this company has also proposed to achieve a self-sterilizing dialysate using a complete buffer-free concentrate. This strategy, defined as acetate-free biofiltration consists of hemodiafiltration with reinfusion of large quantities of bicarbonate via the replacement solution and a buffer-free dialysate. In this way, a sterile fluid is achieved reducing the risks in case of backfiltration.

Conclusion

In summary we may conclude that backfiltration is an entity inherent to the nature of extracorporeal therapies as they are today conceived. The real impact of this phenomenon in the treatment tolerance and in patients clinical condition has still to be clarified. The recent introduction of highly permeable membranes and high flux dialysis treatments has certainly contributed to identifying the mechanisms that may cause backfiltration. Several factors may influence the amount and direction of fluid flux inside the filters and the knowledge of these details at least permits definition of when and why backfiltration occurs. Several possible solutions have been summarized in this paper but the real question whether backfiltration should be avoided remains still open.

We personally think that changes in the geometry of the filters and fibres, in the structure of the membranes and in the strategy of dialytic treatments may not only solve the problem of backfiltration but will certainly contribute to increase the efficiency and the efficacy of the treatments at lower blood flows, clinical risks, rate of complications and costs. At the present time, backfiltration is one of the problems that we may encounter during dialysis but at least today we are aware of a process that for years has been unknown or neglected. Since none of the possible proposed solutions guarantee a 100 % backfiltration-free treatment, we strongly suggest that a strict control of the quality of dialysate should be the rule. RO treatment, deionization, short periods of storage and possible filtration of bicarbonate solutions can offer a certain safety in our treatments. New machines equipped with on line preparation of sterile pyrogen-free dialysate and replacement solutions will certainly contribute to increasing the clinical reliability and safety of any extracorporeal therapy of the coming years. All these observations, together with a careful analysis of the patient's clinical behavior during dialysis will further contribute to reducing the number of adverse reactions and to better define what biocompatibility means in a comprehensive attempt for a personalised renal replacement therapy.

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