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Backfiltration: Past, Present and Future

Armando Vazquez Rangel · Jeong Chul Kim · Manish Kaushik · Francesco Garzotto · Mauro Neri · Dinna N. Cruz · Claudio Ronco

Department of Nephrology, San Bortolo Hospital and International Renal Research Institute Vicenza (IRRIV), Vicenza, Italy

Abstract

Backfiltration has been recognized to be present in most diffusive-convective therapies. Although initially considered an inconvenience due to its implications in transport of contaminants in dialysate to the blood compartment, the availability of ultrapure dialysate has prompted a fresh look at the phenomenon of backfiltration with the possibility of exploiting it to further enhance the convective clearance of middle and large molecules. This review discusses the historical aspects of backfiltration, its mechanisms and influencing factors, and subsequently the different hemodialysis techniques in relation to increasing or diminishing this phenomenon.

Backtransport in a hollow-fiber hemodialyzer is defined as the movement of water and substances from the dialysate to the blood. This includes two mechanisms: (1) backdiffusion: movement of substances along a concentration gradient, and (2) backfiltration: a convective mechanism dependent upon the local pressure gradient across the membrane. This gradient, called transmembrane pressure (TMP), is defined by the formula:

$$TMP = P_b - (P_d + \pi_b),$$

where P_b is the hydrostatic pressure in the blood, P_d is the hydrostatic pressure in dialysate, and π_b is the oncotic pressure in blood. When TMP is positive, the hydraulic flow is from the blood to the dialysate side (filtration); nevertheless, if at any point the TMP becomes negative, backfiltration occurs [1]. This constitutes a dynamic process along the filter, where factors related to patient characteristics, dialysis prescription, filters and membranes properties,

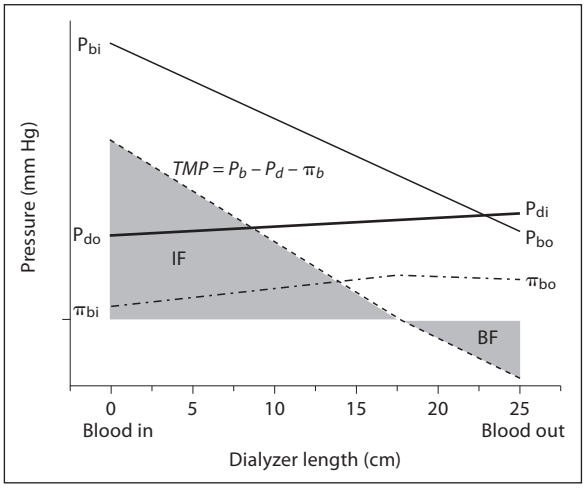

Fig. 1. Pressure profiles along the dialyzer contributing to internal filtration (IF) and backfiltration (BF). TMP = Transmembrane pressure; P_{bi} = inlet hydrostatic blood pressure; P_{bo} = outlet blood pressure; P_{di} = inlet hydrostatic dialysate pressure; P_{do} = outlet dialysate pressure; π_{bi} = inlet oncotic blood pressure; π_{bo} = outlet oncotic blood pressure.

and dialysis modality, play a role in promoting or ameliorating backfiltration. Basically, starting with a high hydrostatic pressure in the blood compartment, the filtration process is favored in the proximal part of the filter; this happens in proportion to the ultrafiltration (UF) rate allowed by the membrane. This initial UF, together with the geometrical properties of the fibers, will produce a hydrostatic pressure drop in the blood compartment along the filter, promoting hemoconcentration and a consequent progressive increase in the oncotic pressure. Both factors reduce the TMP in the distal part of the filter and, together with the incoming dialysate pressure, can contribute to backfiltration (fig. 1).

While backtransport of chemical impurities and microorganisms from contaminated dialysate to the blood compartment has been a concern since the inception of hemodialysis (HD), the existence of backfiltration during high-flux HD was first empirically demonstrated by Schmidt et al. [2]. These investigators showed that the dialysate inflow hydraulic pressure did indeed exceed the blood outlet hydraulic pressure minus the blood outlet oncotic pressure, establishing the existence of this driving force. Therefore, having a higher pressure in the blood compartment is not enough to prevent backfiltration, since the oncotic pressure in the blood plays a major role possibly starting from the second third of the filter.

Direct measurements of backfiltration are few. Leypoldt et al. [3] developed a method for determining backfiltration rates by measuring the changes

in local concentrations of a marker molecule along the dialyzer length. Ronco [4], on the hand, measured radiolabeled albumin macroaggregates added to the blood using a gamma camera. The increase in marker macromolecule concentration indicated internal filtration, and a decrease indicated backfiltration.

Historical Importance of Backfiltration

Clinical appreciation of this entity regained importance with the evolution from using predominantly diffusive clearance to using mixed diffusive-convective clearance with higher permeability membranes. In an attempt to improve clearance of middle and large molecules, and reduce bioincompatibility, modified cellulose and eventually asymmetrical thick-walled synthetic membranes were developed. These membranes exhibit higher solute and water permeability (β_2-microglobulin clearance >20 ml/min and UF coefficient >20 ml/h/mm Hg) [5–7], which by themselves increased the risk of backfiltration of endotoxins and bacteria from suboptimal quality dialysate. Besides, with the reintroduction of bicarbonate buffered dialysate in the 1980s (justified by better blood pressure and cardiopulmonary outcomes compared to acetate-based dialysate), an increased risk of contamination and pyrogenic reactions was observed. The reason is that bicarbonate solution is an excellent medium for propagation of bacteria [8, 9].

Clinical impact of backfiltration became evident from observations of these pyrogenic reactions in high-flux HD patients, the incidence of which was directly proportional to the degree of dialysate contamination [10]. Antibodies specific to dialysate-derived endotoxins have been more commonly identified in high-flux HD than in low-flux HD patients [11]. Laude-Sharp et al. [12] first demonstrated in vitro the passage into the blood compartment of intact lipopolysaccharides capable of inducing IL-1 in dialyzers with acrylonitrile, polysulfone and cuprophan membranes. Panichi et al. [13] evaluated the long-term effects of backfiltration on cytokine production in a multi-center study. They demonstrated that post/pre ratios of IL-1 receptor antagonist and IL-1β were higher in patients receiving hemodiafiltration (HDF) with backfiltration compared to those on HDF without backfiltration.

In context of the above, the use of ultrapure dialysate is a prerequisite for the safe delivery of mixed diffusive-convective therapies with high water permeability membranes. The minimum quality requirement of dialysate as defined by ISO standards is <100 CFU/ml for viable microbial count and <0.5 EU/ml for endotoxin concentration [14], while the ERA-EDTA best practice guidelines and Swedish Pharmacopoeia have stricter definitions for the endotoxin levels (<0.25 EU/ml) [15]. For ultrapure dialysate, the definition has been established as <0.1 CFU/ml for bacteria and as <0.03 EU/ml for endotoxins [14].

Patients treated with ultrapure dialysis fluid have shown a decrease in serum β_2-microglobulin concentrations and related amyloidosis, a decrease in markers of inflammatory response and oxidant stress, an increased responsiveness to erythropoietin, better preservation of residual renal function, and improved nutritional status [14, 16]. These observations have led to the recommendation that ultrapure dialysis fluid should be used for high-flux HD, although it has been recognized that obtaining this level of purity on a routine basis might not yet be feasible in all dialysis settings [14, 16].

A practical approach to achieve good water quality has been to equip dialysis machines with polysulfone ultrafilters as part of the water treatment process [17, 18]. In vitro studies have shown that polysulfone membranes have considerable capacity to adsorb pyrogens from contaminated dialysate [19]. Ronco et al. [17] have explained this adsorption by the interaction of negatively charged lipopolysaccharide with hydrophobic domains of these membranes.

Factors Influencing Backfiltration

As previously mentioned, backfiltration is directly determined by pressures in the blood and dialysate compartments. Pressures at the inlet and outlet of the blood compartment are mostly dependent on the speed of the blood pump and the resistance of the filter. The latter is directly influenced by the number, length and inner radius of the fibers, and the viscosity of blood associated with the water permeability of the membrane [20].

Water Permeability

In low water permeability membranes, the lower total internal filtration might not produce the required drop in TMP for backfiltration to occur. However, in high permeability membranes, the higher water total internal filtration generates a more significant drop in hydrostatic pressure and a more pronounced hemoconcentration raising the oncotic pressure. This results in a lower TMP in the second half of the filter and consequent backfiltration by 'oncotic flux'. This last process could be self-limited since the amount of water entering from the dialysate to the blood decreases the oncotic and increases the hydrostatic pressures. But given the actual use of volume control systems in HD machines, the restriction in net UF generates an increase in hydrostatic pressure in the dialysate, and therefore a higher degree of backfiltration. This 'convective flux' overrides the self-limiting mechanism of the 'oncotic flux' [20]. In this sense, low UF or absence thereof does not avoid internal filtration using high water permeability membranes; moreover, if this filtered plasma water does not match a corresponding UF rate, backfiltration will be produced. This leads to the concept of critical or obligate UF as the minimum required UF rate to avoid backfiltration [21].

Experimental modifications have been described to manipulate water permeability. While membranes might not show the same permeability to water flux in both directions because of the formation of a protein layer, new membranes could be designed having low resistance for water towards the dialysate but high resistance towards the blood compartment [20]. Soltys et al. [22] reported the use of a dual-skinned filter membrane allowing convective solute transport in blood to dialysate direction but not in dialysate to blood direction. Finally, membranes with low water permeability but high solute permeability have been created, although these are still just in the experimental stage [20].

Blood and Dialysate Flows

It has been previously observed that backfiltration generally occurs during the first minutes of dialysis, when the blood flow has not yet reached the established regimen [21]. In general, the increase in blood flow represents not only a higher potential clearance for uremic toxins, but also an increase in TMP that could prevent backfiltration. Using high-flux filters, blood flows as high as 500 ml/min have been used without major complications. However, in high water permeability membranes, increasing blood flow might not be enough for maintaining a high TMP along the whole length of the filter. In computer simulations, Yamashita [23] estimated that when increasing blood and dialysate flow to more than 300 and 500 ml/min, respectively, internal filtration can increase from a baseline value of 10 to 40 ml/min. Moreover, the increase of the dialysate flow from 500 to 800 ml/min practically doubles the hydrostatic pressure at the inlet of the dialysate compartment, generating a higher pressure change through the filter which promotes backfiltration [24].

Hematocrit

An increase of hematocrit from 20 to 33% can increase backfiltration from 10 to 15 ml/min/m^2. Of course, at any hematocrit, the increase in the pressure drop associated with higher blood flow rates increases backfiltration further [25].

Fiber Geometry

By maintaining the same total surface area, increasing the inner diameter of the fibers from 200 to 220 μm decreases backfiltration from 15.7 to 11.8 ml/min/m^2. This corresponds to a similar decrement if the length of fibers is shortened from 25 to 21 cm [25]. In this sense, increasing the number of fibers or enlarging their inner diameter while reducing their length would reduce the overall resistance of the filter, producing a reduction of both filtration in its proximal segment and backfiltration in the distal segment [20]. Accordingly, dialysate flow in co-current direction instead of counter-current to blood flow would reduce crossfiltration in general. Of course, all these previously mentioned adjustments would have a negative impact in overall clearance.

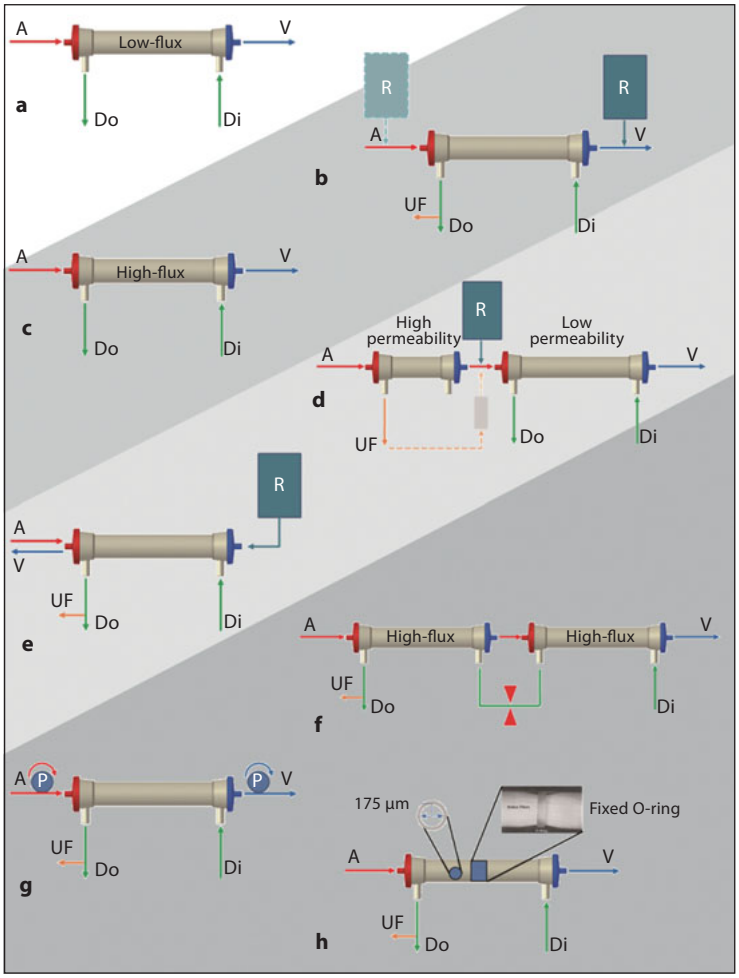

Fig. 2. Different hemodialytic techniques involving backfiltration: (**a**) low-flux HD, (**b**) hemodiafiltration, (**c**) high-flux HD, (**d**) paired filtration dialysis/hemofiltration with reinfusion, (**e**) mid-dilution HDF, (**f**) double high-flux HDF, (**g**) push-pull HDF, and (**h**) enhanced internal filtration HD. White = Minimum backfiltration, Dark gray = maximum backfiltration.

Evolution of Hemodialytic Techniques in Terms of Backfiltration

Low-Flux HD

Backfiltration has a different weighting among the diverse HD techniques (fig. 2). Initially, with low-flux HD, the low water permeability membranes prevented a significant drop in hydrostatic pressure in the blood compartment, maintaining a more constant TMP, less hemoconcentration, and resulted in very low or no probability of backfiltration (although this does not mean no backdiffusion).

High-Flux HD

The introduction of high-flux HD with high water permeability membranes increased the crossfiltration from the blood to the dialysate in the first part of the filter, due to the high TMP obtained by increasing blood flow, and backfiltration in the second part, due to the drop in TMP and hemoconcentration. In contrast to HDF (see below), the UF rate was considerably lower, with an increase in the hydrostatic pressure in the dialysate compartment secondary to the volumetric control by the dialysis machine contributing to backfiltration. This obviously pointed out the erroneous concept that high-flux HD was mostly a diffusive technique.

Hemodiafiltration

The availability of replacement solutions (initially sterile exogenous fluids in a range of 5 to 15 liters per session used in classical HDF and later on-line ultrapure prepared fluids infused at a rate of more than 20 liters per session), allowed an increase of the hydrostatic pressure in the blood compartment and the TMP, promoting more total UF. In the post-dilution modality, a considerable hemoconcentration was generated in the distal part of the filter, favoring backfiltration. Its magnitude again depends upon the water permeability of the membrane. On the other hand, replacement fluid infused in pre-dilution mode could theoretically reduce backfiltration by reducing hemoconcentration inside the hollow fibers [26].

Mid-Dilution HDF

Having mentioned the differences between pre- and post-dilution, a new technique was created to combine both approaches, called mid-dilution HDF. The technique comprises special filters with two longitudinal compartments. The blood passes through the first producing a certain amount of UF. At the end of this, the replacement fluid is added so that hemoconcentration is corrected. Subsequently, blood is redirected to exit in the same entry port. The blood flow in this last section is co-current with the dialysate. The first compartment reproduces post-dilutional HDF and allows backfiltration. Backfiltration is limited in the second, pre-dilutional, compartment. Despite the co-current flow configuration of latter section, high clearances can be obtained due to high convective volumes [26].

Paired Filtration Dialysis and Hemofiltration with Reinfusion

In order to avoid backfiltration, mostly because of concern about water quality, a two-chamber system was conceived by Ghezzi et al. [27] called *paired filtration dialysis*, and was later modified by Ronco et al. [28]. In the first unit, plasma water is removed by UF without the use of dialysate. A sterile replacement solution is reinfused after the first convective filter, and the blood is dialyzed in the second filter equipped with a low-flux low-permeable membrane

[29]. Years later, to avoid an exogenous fluid infusion before the second filter, a new technique called *hemofiltration with reinfusion* was developed in which the ultrafiltrate from the first filter is passed through a sorbent-containing cartridge to retain uremic toxins and then used as replacement fluid. These techniques improve HDF performance by separating the diffusive and convective processes and thus avoiding any interference between them during treatment. Hemofiltration with reinfusion additionally avoids loss of vital molecules during the convective process, such as nutrients, hormones, amino acids or vitamins [29].

Having achieved better standards for water quality, the idea of using backfiltration instead of avoiding it started to be tested. If ultrapure dialysate is employed, substantial amounts of internal filtration and backfiltration could lead to increased convective solute transport across the membrane and to increased dialyzer clearance of middle molecules.

Push-Pull HDF

In push-pull HDF the rotation of a pre-filter blood pump produces filtration (while a post-filter blood pump is stopped), and the rotation of the post-filter pump produces a negative pressure in the blood compartment and thus backfiltration (while the pre-filter pump is stopped). With this system, the blood is concentrated and diluted approximately 25 times before it leaves the hemofilter. It has been reported that up to 120 liters of fluid can be moved in a 4-hour session with high water permeability membranes by this technique [30].

Double High-Flux HDF

In double high-flux HDF, two high-flux dialyzers are placed in series, with the same dialysate flowing through both of them counter-current. By placing a flow restrictor in the dialysate line between the two filters, the first filter which has the arterial port shows a low dialysate pressure favoring filtration. The second filter shows a high dialysate pressure which, together with hemoconcentration, favors fluid substitution by backfiltration under volumetric control. This high efficiency technique was originally created for shortening treatment time down to 2 h per session [31].

Enhanced Internal Filtration HD

Since the beginning of the use of high-flux filters, diverse constructions have been described to enhance the internal filtration in high water-permeable membranes. Yamashita [23] showed that enhancing internal filtration and backfiltration can effectively remove small and middle molecules (cytochrome *c*) in vitro.

Ronco et al. [24] tested a filter modified by a fixed O-ring in the dialysate compartment. This generates a pronounced differential in dialysate pressure,

increasing the peaks of positive and negative TMP along the length of the dialyzer. A pronounced drop in the arterial inlet side contributes to filtration, while the increased dialysate pressure in the venous outlet side favors backfiltration. It was estimated that crossfiltration was enhanced by approximately 50% compared to the standard high-flux dialyzer. While clearance for small molecules remained unchanged, inulin and β_2-microglobulin clearances were significantly improved (by 30%).

Applying the Hagen-Poiseuille formula, it is expected that even small changes of the inner diameter of the fiber may result in dramatic changes in its performance [7]:

$$\Delta P = Q_b \times (8\eta l/\pi r^4),$$

where ΔP is the pressure drop along the filter, Q_b is the blood flow, η is the blood viscosity, l is the length of the fiber, and r is the inner radius of the fiber. Dellanna et al. [32] compared β_2-microglobulin removal with 175- and 250-μm diameter fibers. Both had equivalent urea clearance, but a higher flow resistance and TMP produced a higher internal filtration and backfiltration in the filter with the smaller inner diameter, leading to a higher middle molecule removal. In a similar experiment, Ronco et al. [33] compared polysulfone hemodialyzers with fibers of 175 and 200 μm inner diameter. The pressure drop in the blood compartment was higher in the 175-μm fiber dialyzer, leading to an increase in the internal filtration-backfiltration rate from 23.1 to 48.2 ml/min. This resulted in a significant increase of in vivo clearances of vitamin B_{12} and inulin of more than 30%. Moreover, the reduction of the inner diameter increases the average flow velocity per fiber with a consequent increase in wall shear rates; theoretically, this should produce an additional 'cleaning' effect at the blood/membrane interface by reducing the thickness of the protein boundary layer, and therefore improve membrane permeability [7].

Tomo et al. [34] tested a modified 'high fiber density' polysulfone dialyzer as an alternative to enhance internal filtration. At the same time, they improved the structure of the dialyzer housing using a complete surrounding baffle and a slope to allow the uniform diffusion of the dialysate. The results were, again, a clearance of small and middle molecules equivalent to 10 liters of post-dilutional HDF. This equivalence has been confirmed by other authors [33, 35], pointing out the possibility of achieving a good dialytic performance with less complex equipment, no use of replacement solutions, and with an extra barrier for endotoxins and bacteria represented by the polysulfone membrane of the dialyzer itself.

Koda [36] reported a better cost-effectiveness profile for internal filtration-enhanced HD compared to HDF. However, it must be emphasized that loss of proteins, amino acids and water-soluble vitamins can be exacerbated by increasing crossfiltration, so this has to be further evaluated [34, 36].

Conclusions

Backfiltration is a phenomenon that deserves attention as it frequently occurs with the use of high permeability dialysis membranes. First of all, every effort must be made to ensure optimal dialysate and water quality. The availability of ultrapure dialysate has permitted testing of a new paradigm, namely that of using filtration/backfiltration to improve clearance of middle and large molecules. Patient characteristics, dialysis prescription, treatment modality and future modifications in filter and hollow-fiber designs may help us manipulate backfiltration to meet clinical requirements. Backfiltration could become a key factor in performing on-line HDF, with reverse crossfiltration as a mechanism for reinfusion

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Dr. Claudio Ronco
Department of Nephrology, San Bortolo Hospital
Viale Rodolfi, 37 36100 Vicenza (Italy)
Tel. +39 444 753650
E-Mail cronco@goldnet.it