Ultrafiltration and convective-based dialysis modalities: new trends and applications for renal replacement therapy in ESRD patients

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Introduction

Ultrafiltration (UF) is a membrane filtration process based on a molecular sieving exclusion [1]. The use of UF in renal replacement therapy (RRT) has been reported in various fields including dialysis therapy, the sterilization of dialysate and the bloodless access to the internal milieu of the patient. Occurring naturally in the native kidney, UF is the basis of glomerular filtration, the first step of the detoxification process. When mechanically induced through an artificial membrane, UF ensures convective removal of solutes and excess extracellular fluid volume. High UF volume adequately compensated with a physiological electrolyte solution is the common process of convective-based renal replacement modalities [haemofiltration (HF), haemodiafiltration (HDF)]. As solute convective fluxes are only restricted by the sieving properties of the membrane and the operative conditions, it was assumed several years ago that the use of a highly permeable membrane with a large UF volume was an interesting option to enhance dialysis performance [2]. Dialysis-related pathology increasingly observed in long-term dialysis patients marks the boundary limits of long-term RRT by dialysis and must be perceived as a direct consequence of the low performance of conventional diffusive-based modalities [3] and/or the haemoincompatibility of the dialysis system. The new perspectives offered by the use of highly permeable membranes have favoured the development of convective-based RRT options. Ultrafiltration capacity and enhanced convective removal capacities have stimulated interest for clinicians and opened the way for new RRT modalities with the hope of best preventing dialysis-related pathology.

We summarize here the recent applications of UF in extracorporeal RRT. The UF and convective capacities of a highly permeable membrane will serve to illustrate several fields of application to optimize the treatment of patients with end-stage renal disease (ESRD). (i) The sieving exclusion capacity of UF is used to produce an ultrapure dialysate. An ultrafilter placed on the dialysate line provides a simple, safe and economical way of producing an on-line pharmaceutical grade solution (sterile and non-pyrogenic) used for substitution fluid. In this case, UF acts as a ‘cold sterilizing’ process. (ii) The enhanced blood purification capacities of convectively based modalities is illustrated through the performance of high flux HDF [4,5]. (iii) A high UF concentrates the protein at the blood–membrane interface and contributes to passivate the membrane [6]. (iv) The blood separating capacity of UF gives direct access to a protein- and cell-free solution. Continuous production of pure ultrafiltrate gives simple access to the patient’s ‘internal milieu’. On-line dialysis efficacy monitoring is illustrated using urea as a marker.

Ultrafiltration, on-line ‘cold sterilizing’ process

Following the pioneering work of Henderson proving the retentive capacity of ultrafilters for microbiological contaminants of water and biological fluids, it has been shown that UF could be used as a sterilizing process to produce extemporaneously sterile and non-pyrogenic fluid from the dialysate [7–9]. The retentive capacity of ultrafilters depends upon the chemical composition of their membrane, the nature of the biological fluid filtered and the chemical agent employed to disinfect the filter [10–12]. On-line production of ultrapure dialysate from standard dialysate by UF has been confirmed in several studies to be an effective and a competitively priced process [13,14]. Production of pharmaceutical quality i.v. fluid from dialysate was recognized later on and proposed as a substitution fluid in convective-based methods and related modalities. On-site batch preparation of infusate for high flux haemofiltration (pre- or post-dilutional) has been proved safe and effective for the economical production of large amount of substitution fluid [15]. Based on a similar concept, the on-line production of infusate directly from dialysate was used for high flux HF [16] and HDF modalities [17]. On-line production of sterile and non-pyrogenic electrolytic
solution has also been proposed to facilitate handling and self-treatment of home haemodialysis patients [18].

On-line production of substitution fluid from dialysate clearly appears to be the only viable and economically affordable method required for further development of both high flux HF and HDF modalities [19]. Instantaneous production of infusate in a closed circuit without storage is an efficient way to prevent contamination and the growth of bacteria. Extemporaneous production virtually unlimited amounts of infusate at low cost was the rationale for applying this process to the on-line high flux HDF methods. Providing there were adequate technical modifications of the existing HD equipment, it was possible to introduce a new treatment modality called on-line HDF in the armamentarium of RRT options [20].

Until now, several convective-based dialysis modalities of the HDF type using the fresh dialysate as substitution fluid have been reported (Figure 1). Schematically, they fall into two categories: one is based on direct dialysate internal backfiltration occurring in the haemodiafilter device itself under a certain pressure regimen; the other is based on an external infusion of the substitution fluid via the venous bubble trap into the blood of the patient in post-dilutional mode (or the arterial bubble trap in the pre-dilutional mode). On one hand, internal substitution of fluid, as occurs in the first option, is of course invisible and is associated with the hidden hazard of contaminated dialysate. On the other hand, external substitution of fluid, as occurs in the second option, is associated with a visible and appraisable risk.

Internal substitution of ultrafiltrate has been used in three HDF modalities: (i) The push–pull HDF was first described by Shinzato et al. [21–23]. In this case, UF and backfiltration occur alternatively in the same device according to the change in transmembrane pressure profiles. Both the UF and backfiltration phenomena occur perpendicularly to the membrane. (ii) High flux HDF using two chambers was described by Von Albertini et al. [24,25]. In this case, HDF used two haemodiafilters placed in-series while a pressure restriction is maintained on the intermediary dialysate line. The first filter (arterial side) submitted to high positive transmembrane pressure is responsible for the UF, while the second filter (venous side) submitted to a negative transmembrane pressure due to the action of the UF pump and the balancing chamber ensures the fluid substitution by dialysate backfiltration. (iii) Finally, internal HDF properties have been used in a new haemodiafilter designed to induce a high convective UF rate. Such a peculiar pressure profile was achieved by lengthening the fibres, and reducing the internal lumen of the fibres and their wall thickness. In this way, the increased blood flow resistance was associated with an increase in the UF rate of the first part of the device. In the second part of the device, the fluid balancing system of the haemodialysis machine compensates the UF by an equivalent amount of infusate infused via backfiltration.

External substitution fluid infusion is usually performed post-filter directly into the blood of the patient, i.e. in the post-dilutional mode. HDF can also be performed by substituting the infusate pre-filter, i.e. in the pre-dilutional mode. In either case, the safety and reliability of the on-line HDF depend upon strict and permanent rules of hygiene for handling. Compliance with these rules is the only way to prevent serious adverse effects and to ensure long-term success of the modality. Such guidelines have been described in detail elsewhere to which we refer the interested reader. The use of ultrapure water to feed the machine is standard practice for on-line HDF [26,27]. Specifically designed on-line HDF machines are necessary for safety reasons. Redundancy of the filters ensures safety. Two ultrafilters currently are installed: one is on the fresh dialysate to produce the ultrapure dialysate; the other is on the infusate line to ensure the production of the ultrapure infusate. Ultrafilters belonging to the on-line HDF machine are a fixed component of the dialysis system which are disinfected each time along with the HDF machine. Hygienic handling is crucial to ensure the permanent safety of the on-line HDF system. Disinfection procedures involve both the water treatment system and the HDF machine itself. The periodicity and type of disinfectant should be designed to

![Internal and External HDF modalities](image-url)
reduce bacterial contamination and to prevent biofilm formation. Frequent disinfection, descaling and cleaning procedures are necessary to optimize the results. Ultrafilters must be changed periodically to prevent any failure. The integrity of their membrane may be checked automatically on the new generation of HDF machines with an on-line air pressure test.

The water treatment system is an essential component in this chain of treatment. As an example, the water treatment system used in our unit is presented in Figure 2. Such a system operating for >10 years has been shown to be highly efficient in producing and delivering ultrapure water to all dialysis machines at our facility, providing strict hygiene and disinfection rules are followed.

A typical on-line HDF machine used by our group is presented in Figure 3. The infusate module consists of a pump with a flow rate counter diverting a certain amount of fresh dialysate which is finally infused into the blood venous bubble trap. An equivalent amount of ultrafiltrate is obtained from the patient’s blood by means of the UF pump and the fluid-balancing chamber of the dialysis machine. Sterilization of the infusate is obtained by a series of filters. As shown, the first ultrafilter (UF₁) placed on the inlet dialysate line ensures a cross-flow filtration of dialysate and sterilization of the dialysate that reaches the patient’s haemodialyzer. A second ultrafilter (UF₂) installed on the infusate line guarantees the ultrapurity of the infusate by a dead-end filtration. A third disk microfilter (0.45 µm) placed at the final point of the infusate line just before the blood infusion has a double function: first, it is used for an a posteriori quality control through the culture of the membrane which is performed after each session; second, it also has a safety role in preventing the contamination of blood by the infusate.

Microbiological follow-up of the dialysate and the infusate contamination over the last 3 years is summarized in Figure 4 and Table 1. Note that the bacteriometry of the dialysate and infusate are expressed per litre (c.f.u./l) due to the low contamination of our system. Six pyrogenic reactions were noted during this 3-year follow-up, giving a session incidence of 0.3%, a value lower than that observed in high-flux haemodialysis [28]. At this stage, it is clearly shown that on-line production of infusate by UF is a safe and economical way to produce i.v. quality fluid for high flux HF and HDF options [29]. Long-term and extensive quantified monitoring of the bacterial contamination of the infusate has proved the efficacy and the reliability of the UF
Ultrafiltration and convective clearance, a way to enhance dialysis performance and to enlarge the spectrum of uraemic toxins removed

HDF efficacy relies on the treatment schedule, effective operational conditions and the metabolic characteristics of the patient. The combination of enhanced convective fluxes with large diffuse fluxes in the same device through a high flux membrane contribute to good HDF performances [30–32]. Convective clearances increase the removal of larger molecular weight substances [33], post-dilution more effective than predilution in high flux HDF [34]. The contribution of convection to the overall efficacy of the dialysis is illustrated in Figure 5. As shown, HDF increased the molecular weight spectrum of uraemic toxins removed, while not altering the performance for small solutes such as urea.

The overall efficacy of on-line post-dilutional HDF may be illustrated from our experience [35]. On-line HDF is performed routinely in two separate dialysis units using the same technical conditions. Fifty-five to 60 ESRD patients are treated regularly. The dialysis schedule consists of three weekly sessions lasting 3–4 h each (9–12 h per week). The duration of the HDF session is determined according to each patient’s metabolic needs and cardiovascular stability. No selection of patients is carried out. Vascular access is as follows: native arteriovenous fistula in 70%; PTFE graft in 20%; and permanent silastic double catheters inserted in the internal jugular vein in 10%. Mean dry weight was 62.7 ± 11.9 kg. The blood flow set between 300 and 400 ml/min was 361 ± 29 ml/min. Dialysate produced by the HDF machine was 650 ± 25 ml/min. The infusate flow was 100 ± 10 ml/min (6 l/hr) and the net ultrafiltration rate to control extracellular fluid volume was 2.4 ± 0.7 l/session. Dialysate flowing through the haemodiafilter was 550 ± 20 ml/min.

Dialysis adequacy based on standard clinical and biochemical parameters is achieved in all cases. Haemodynamic tolerance was considered excellent. The incidence of symptomatic hypotension is estimated at 0.3% per session. Arterial pressure control was considered satisfactory. Pre-HDF mean arterial pressure was 90 ± 10 mmHg. Antihypertensive drugs were used in 20% of patients as the single medication in 96%.

‘Dialysis dose’, evaluated using a double-pool...
equivalent urea Kt/V model, is $1.55 \pm 0.27$ which is equivalent to a solute removal index (SRI) of $73 \pm 3\%$. The percentage reduction for several solutes such as urea, creatinine and phosphorus were $78 \pm 4$, $72 \pm 4$ and $59 \pm 8\%$, respectively. The normalized protein catabolic rate (nPCR) obtained from the urea generation rate was $1.12 \pm 0.25$ g/kg/day. Enlarged solute removal capacity may be illustrated using $\beta_2$-microglobulin ($\beta_2$M: 11800 Da) as a clinically relevant marker for a large molecular weight uraemic toxin. The percentage reduction of $\beta_2$M per HDF session was $78 \pm 2\%$, equivalent to a $\beta_2$M Kt/V value of $0.90 \pm 0.10$. The $\beta_2$M time-averaged concentration ($\beta_2$MTAC), a value that reflects better the exposure risk in HDF patients, was $17.2 \pm 7.5$ mg/l. Such results are in good agreement with previous studies showing that HDF was superior to high flux haemodialysis in removing medium and large molecular weight solutes [36–38].

More recently, it also has been shown that high flux HDF performed using a superflux polysulfone membrane was able to remove significant amount of advanced glycosylation end-products (AGEs), a novel class of uraemic toxins that have been implicated in the pathogenesis of ageing, accelerated atherosclerosis and $\beta_2$M-amyloidosis of the ESRD patient [39–41]. If confirmed, such a preliminary observation would appear to be of major importance clinically for the prevention or reduction of the risk of vascular disease and $\beta_2$M-amyloidosis in long-term dialysis patients [42]. Convective clearance has been shown to be able to remove vasoactive mediators such as NO synthase inhibitor [43]. Here again, if confirmed, such a clearing capacity of HDF would partially explain the better haemodynamic stability usually reported with the convective-based modalities.

On-line HDF using a bicarbonate-buffered infusate facilitates the control of acidosis of ESRD patients [44]. Pre- and post-HDF bicarbonate concentrations were $21 \pm 2.1$ and $25.4 \pm 2.1$ mmol/l respectively. Calcium and phosphorus control was satisfactory, being $2.36 \pm 0.12$ and $1.63 \pm 0.25$ mmol/l in pre-dialysis, respectively. Calcium carbonate was used as phosphate binder in all patients. Mean daily dose was 2.5 g/day. Anaemia correction was achieved with a target haematocrit of 30–33\%. rHu-EPO was used in 50% of patients at a mean weekly dose of 4800 IU. Such results are in agreement with those indicating that HDF was reducing the requirement for rHu-EPO [45].

**Ultrafiltration and convection, a step further towards a fully haemocompatible concept**

Today, on-line HDF provides the most haemocompatible system for extracorporeal RRT. Several factors are combined to reduce the haemoreactivity of the HDF system [46,47]. High flux synthetic membranes used in HDF have a reduced blood reactivity. Ultrapure dialysate reduces the priming effect of dialysate contaminants on the protein and blood cell systems. UF of blood has also some additional beneficial effects illustrated in Figure 6: first, it tends to concentrate the proteins at the surface of the membrane favouring ‘protein coat’ formation; second, it prevents backfiltration phenomena occurring [48,49]; third, it reduces the albumin loss [50]. In addition, the ‘protein coat’ of the membrane has two other beneficial effects: one, is to ‘passivate’ the membrane with an autologous protein layer [51]; the other, is to prevent backdiffusion of potential remnant dialysate contaminants [52,53].

Finally, by enhancing the spectrum of molecular weight solutes cleared and by reducing the patient–dialysis system interaction, on-line HDF provides the best potential for preventing complications in long-term dialysis patients.

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**Fig. 6.** High flux HDF prevents backfiltration and minimizes backdiffusion of the dialysate.
Ultrafiltration, an easy access to the internal milieu of dialysis patients

Ultrafiltration availability will suppress most of the needs for blood sampling. Permanent and easy access to the ultrafiltrate provides a good opportunity to monitor dialysis efficiency. The solute concentration in the ultrafiltrate is determined mainly by the sieving property of the membrane. Small solutes, such as urea, freely passing the membrane have a concentration in the ultrafiltrate virtually superposable on that of the plasma water. Based on this concept, continuous access to pure ultrafiltrate, as is obtained in HF, offers a simple and easy way to monitor the ‘internal milieu’ of a dialysis patient.

This approach is used in the double-chamber HDF technique (paired filtration dialysis, PFD), developed by the Bellco-Sorin group [54]. In this modality, convective and diffusive clearances are split: the first filter made of high flux polysulfone is responsible for the convective clearance with the production of a pure unmixed ultrafiltrate; the second filter, made from a low flux membrane (polysulfone or hemophane) ensures the standard haemodialysis based on a pure diffusive mechanism. The double-chamber HDF method and urea monitoring system (UMS) are depicted in Figure 7.

Following the National Cooperative Dialysis Study (NCDS), it was shown that urea kinetic analysis (UKM) was a powerful tool to search for dialysis adequacy. Urea was then considered as a surrogate of uraemic toxins. In addition, urea was recognized as a multipurpose marker providing information on the dialysis efficiency, the degree of uraemic intoxication and the protein nutritional status of the dialysis patient. From a kinetic modelling approach, urea is a quite convenient marker: it is a small solute distributed in the body water; it has a rapid diffusion within the different compartments of the body appearing as a well mixed solution; its determination in biological fluid is relatively easy. Urea determination in the ultrafiltrate is based on conductivity changes induced by use of urease. Conductivity changes recorded in the ultrafiltrate are recorded continuously in a microcomputer system and converted into urea concentration by an appropriate algorithm. Typical urea traces obtained with the UMS from Bellco-Sorin are presented in Figure 8. Continuous monitoring of the urea concentration in the ultrafiltrate permits the Kt/V slope to be calculated precisely, a value reflecting the effective ‘dialysis dose’ delivered to the patient [55]. More refined mathematical modelling of urea kinetics permits prediction of post-dialysis rebound and calculation of the effective urea Kt/V incorporating post-dialysis re-equilibrium. The urea mass removed which can be calculated from a time integration of the instantaneous urea fluxes may be used also to calculate the urea generation rate and the nPCR equivalent.

Other solute markers dragged into the ultrafiltrate may be monitored potentially providing appropriate sensors are developed. Sodium fluxes using conductivity cells have already been explored and are under current investigation. Acidosis status may be explored by monitoring pH or bicarbonate with an appropriate sensor. Creatinine sensors have not yet been developed but their use would be suitable and useful to evaluate the lean body mass of ESRD patients.

Continuous production of ultrafiltrate may be considered as an equivalent of patient plasma water sampling, which offers an interesting way for permanent on-line internal milieu monitoring.

In conclusion UF and convective-based dialysis modalities have clearly opened up new RRT strategies in ESRD patients. On-line HDF, a treatment modality combining several of these technical advances, has emerged as the most desirable modality [56, 57]. Online HDF provides an economical solution for a treatment dialysis modality which is associated with the highest clearances both for small and large solutes,

![Fig. 7. HDF with a double chamber method (PFD) splits the convective and diffusive phenomena. The ultrafiltrate produced in the first haemofilter give direct access to the ‘internal milieu’ of the dialysis patient. Urea monitoring system (UMS) as developed by the Bellco-Sorin group.](image1)

![Fig. 8. Urea kinetic traces obtained from the UF with the UMS during and after an HDF session according to three different Kt/V values.](image2)
providing the most haemocompatible option and preserving the cardiovascular stability tolerance.

References

Ultrafiltration and convective-based dialysis modalities