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The Early Years of On-Line HDF: How Did It All Start? How Did We Get Here?

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Abstract

In the mid-1980s, limits and side effects of contemporary hemodialysis were basically due to short treatment time, use of low-flux membranes and employment of acetate-buffered dialysate. These were already associated with a relatively high morbidity and cardiovascular mortality as part of diaysis-related pathology. Based on these considerations, the concept of on-line hemodiafiltration (HDF) was proposed as an innovative solution. By combining diffusive and convective clearances, HDF offered the most efficient modality to clear small and middle-sized uremic toxins. Furthermore, by using ultrapure dialysis fluid and high-flux synthetic membranes, HDF also offered the most biocompatible dialysis system, thereby going a long way towards preventing inflammation. Through provision of virtually unlimited amounts of sterile dialysis fluid by cold sterilization of fresh dialysate, on-line HDF offered an economical and viable method of conducting high-efficiency HDF (high volume exchange) therapy. By keeping the hemodialysis machine with all built-in technical options (e.g. adjustable blood pump, fluid-balancing system, conductivity meter, flow and pressure monitoring, bicarbonate-buffered dialysate), HDF benefited from being associated with the use of dialysis machines with excellent technology as well as highest safety standards. Use of ultrapure water made it then possible to produce dialysis fluid of intravenous grade quality with these machines. The first on-line HDF clinical trial was performed with a modified A2008C dialysis machine in 1984–85. This confirmed the feasibility and potential of the on-line HDF method. Some 25 years later, on-line HDF has proven to be safe, efficacious and with clinical benefits that justify it becoming a new standard for high-quality care of chronic kidney patients.

After three decades of rapid and impressive technical development in renal replacement therapy, dialysis patients were still faced with a high morbidity and mortality risk. Morbidity was reflected in frequent hospitalizations for solving

vascular access dysfunction, infection-related problems, cardiovascular events and other dialysis-related pathologies, including β_2-microglobulin amyloidosis. Mortality was high, averaging 17% per year worldwide with large inter-country variations (Japan 7%, Europe 15% and USA 25%). Causes of mortality were predominantly cardiovascular diseases (ischemic cardiac, stroke, arrhythmia, sudden death, etc.) in about 50% of patients, followed by infection, cachexia and various other causes. Several reports identified that, despite multiple adjustments for age, case-mix and comorbidity, the main source of morbidity and mortality in chronic kidney disease patients was the practice of conventional three times weekly, short sessions with low-flux hemodialyzers and acetate-buffered dialysate.

Why Was High-Efficiency Hemodiafiltration Needed in the 1980s to Complete the Armamentarium of Renal Replacement Therapy?

Several hypotheses were proposed to explain the shortfalls in renal replacement therapy. It is not our intention to review the details of the pathophysiological pathways elaborated to elucidate these findings. However, it is important to mention the putative causes and barriers of conventional hemodialysis in order understand the need for designing a more efficient and physiological renal replacement modality. Briefly, the term 'dialysis-related pathology' addresses five main pathophysiological features of the earlier dialysis therapy. First, the incomplete correction of uremic abnormalities by dialysis, this led to the chronic retention of particular toxic compounds [1] and was the focus of attention of the 'uremic toxin group'. In fact, two theories were being followed at that time: the 'small molecule hypothesis' and the 'middle molecule hypothesis'. The 'small molecule hypothesis' was supported by the US nephrology community that uniformly used the 'dialysis dose' concept based on urea Kt/V ratio [2–4]. The 'middle molecule hypothesis', on the other hand, was supported by the European nephrology community that postulated that chronic accumulation of larger molecular size toxins, which are poorly cleared by conventional hemodialysis, were implicated in the high mortality of dialysis patients [5]. The second pathophysiological feature was the 'bioincompatibility' of the hemodialysis system. The generation of bioactive byproducts from protein and cell activation systems led to repetitive inflammation and immune-mediated insults. In this context, two components of the hemodialysis system were identified as triggers for biologic reactions: the biochemical composition of the dialysis membrane (cellulosic versus synthetic polymers) and the microbial contamination of the dialysis fluid [6]. The third pathophysiological aspect of dialysis was the 'hemodynamic instability' of short treatment schedules, accounting for maltolerance in 30–40% of dialysis sessions. Hypotensive episodes induced by dialysis sessions were soon recognized as repetitive cardiac ischemic insults leading, potentially,

to myocardial lesions. Apart from high ultrafiltration rate, another factor implicated was the sodium acetate buffering of the dialysate; this was finally proven to play a major role by its vasodilatory and negative inotropic roles in the maltolerance of dialysis sessions [7–9]. The fourth pathophysiological facet was the 'unphysiology' of intermittent therapy that maintained dialysis patients in a permanent unstable situation by creating a 'peak-and-valley' profile of the patient's internal milieu [10]. Finally, the fifth characteristic was the inability to correct 'metabolic abnormalities' of chronic kidney patients, such as anemia, vitamin D deficiency, lipid disorders and mineral and bone disorders [11].

Following reports stressing the limits and side effects associated with short hemodialysis, several technical improvements were proposed for routine clinical practice. This time period led to an intense and fruitful research that contributed to our knowledge and substantially ameliorated outcomes of dialysis patients. In the following, major advances introduced over a short period of time in the dialysis field are briefly reviewed.

Uremic toxins benefited from particular attention. Intense research aimed at their biochemical identification and kinetic characterization, development of specific dosing assays, and proving their toxicity (either in vitro or in animal experiment models) [12]. According to the EUTOX group, uremic toxins are now best classified in three categories based on their molecular size and protein-binding affinity [13]. Although not perfect, this classification has the advantage of underlining difficulties in efficiently clearing middle sized and protein-bound uremic toxins in the clinic setting. As a result, knowledge of uremic toxins is now more comprehensive and strong links to uremic pathology were established. Furthermore, dialyzer manufacturers were prompted to increase membrane permeability and hemodialyzer performances in order to enhance removal of these toxic compounds. Subsequently, high-flux, high-performance, synthetic hemodialyzers (polyacrylnitrile, polysulfone, polyamide, etc.) were developed. Thanks to bioengineering and nanotechnological progress, their performances were optimized. Clinical results were so convincing that their use increased regularly over time so that they are now generally the more prevalent dialzer type worldwide [14–16].

Bicarbonate-buffered dialysate was introduced after the original study from Graefe et al. [17] demonstrated its clear superiority compared to acetate in terms of dialysis tolerance and incidence of hypotensive episodes. Beneficial effects of bicarbonate have been confirmed over time to the point that bicarbonate is nowadays universally the most accepted buffer for dialysate.

Systems for better control of ultrafiltration were developed simultaneously to highly permeable membranes. These systems ensured fluid volume control in dialysis patients during treatment [18]. Beneficial clinical effects were confirmed soon after implementation in hemodialysis machines. This technical option was able to achieve a precise and predictable weight loss associated with a significant improvement in hemodynamic tolerance. Ultrafiltration control systems based

on volumetric or flowmetric devices were progressively implemented into the dialysate circuits of all hemodialysis machines, ensuring precise fluid volume balance during highly efficient hemodialysis sessions [19].

Microbiological contamination of water and dialysis fluids was later identified as harmful for dialysis patients. The incidence of fever reactions (pyrogenic reactions) increased significantly after the introduction of bicarbonate-buffered dialysate and high-flux membranes [20]. The link with bicarbonate was soon established and dialysis fluid filtration has since proved to be efficient in preventing fever reactions [21]. More subtly, it was also shown that even low-grade microbial contamination was implicated in monocyte/macrophage activation, resulting in cytokine production and inflammatory reactions [22]. Ultrapurity of water and dialysis fluids was proposed to prevent inflammation and related reactions during hemodialysis sessions [23, 24]. Correcting microinflammation associated with contaminated dialysate is now known to be of paramount importance in preventing the deleterious role of a ubiquitous pathogenic amplifying factor in dialysis patients.

Considering these facts, it became clear to us and others in the mid-1980s that a more effective, gentle and economically viable dialysis modality was required in order to improve outcomes. Ideally, the best suitable treatment modality to achieve this objective had to fulfill several pre-requirements: regular use of highly permeable synthetic membrane hemodialyzers; increased diffusive dialysis dose and maximum convective dose for removal of middle and larger uremic toxins; optimal blood and dialysate flow rates to maximize solute mass transfer; regular use of ultrapure dialysis fluid, and employment of safe and flexible hemodialysis machines capable of mastering balance of fluid volume exchange with multipurpose options for customizing treatment.

Based on these considerations, the concept of on-line hemodiafiltration (HDF) was proposed as an innovative solution. By combining diffusive and convective clearances, HDF offered the most efficient modality to clear small and middle-sized uremic toxins. In vitro and in vivo studies confirmed the superiority of HDF compared to high-flux hemodialysis and high-flux hemofiltration (HF) for removing small and middle-sized uremic toxins [25]. By using ultrapure dialysis fluid and high-flux synthetic membranes, HDF offered in addition the most biocompatible dialysis system. In vitro and in vivo studies showed the beneficial effects in reducing activation of circulating cells and protein systems, and of preventing the induction of inflammation [26]. By providing virtually unlimited amounts of sterile dialysis fluid by cold sterilization of fresh dialysate, on-line HDF offered an economical and viable method to achieve high-efficiency HDF (high volume exchange) therapy. Production of ultrapure dialysis fluid, namely sterile and non-pyrogenic fluid, by ultrafiltration was first reported by Henderson et al. [27, 28] and later successfully applied in a clinic setting, essentially with HF methods. The 'on-line' term was taken from the HF methods that were developed for supply of large volumes of

substitution. By keeping the hemodialysis machine with all built-in technology (adjustable blood pump, fluid-balancing system, conductivity meter, flow and pressure monitoring, bicarbonate-buffered dialysate), HDF would rely on the best technical options and most safe dialysis machines.

How Did It All Start?

Discoveries are frequently the fruit of chance and/or personal communications. The birth of on-line HDF may be considered an example of fruitful chance. In the mid-1980s, HF, confusingly named hemodiafiltration by Henderson [29], was presented as the most innovative and promising renal replacement therapy proposed to enhance middle molecule removal and improve chronic kidney disease patient outcomes. Initial clinical studies performed in the USA by Henderson and in Germany by Quellhorst [30, 31] clearly identified the beneficial effects of HF, namely improvement in cardiovascular tolerance and reduction of patient mortality. Due to the gravimetric fluid-balancing system of HF monitors and the bag presentation of substitution electrolyte fluid, the volume of exchange per session was usually limited to 20–25 liters. Low-volume HF appeared insufficient for adequate control of uremia in heavy or non-compliant dialysis patients. In addition, the bag HF method was cumbersome for nurses or technicians, and costly when large volumes of substitution fluid (>40 liters per session) were used. On-line batch preparation was proposed by Shaldon et al. [32, 33] to overcome these difficulties. The feasibility and safety of large volume HF based on on-line batch preparation was assessed in several studies, including a study conducted by our group [34]. Microbiological safety of the batch method was proved in routine clinical practice by applying strict hygiene rules of preparation [35]. Safety of the on-line batch preparation of infusate for HF was also proved using specific HF monitors that included production of ultrapure water from reverse osmosis water [36]. The efficacy of HF with on-line batch substitution fluids was proved to be directly correlated with the substitution volume administered to patient. With the use of on-line batch preparation of substitution fluid, the amount of fluid was no longer limited and the volume of substitution (either in post- or predilutional mode) could be tailored to the metabolic needs of the patient [37]. In order to facilitate the clinical implementation of the batch HF method on a large scale, we developed a central system for producing massive amounts of substitution fluid in closed plastic bags (30 liters). After having overcome the barrier of large volume of infusate, the maximal ultrafiltration rate achievable in clinical practice became the new limiting factor. Despite the use of high blood flow rates (>400 ml/min) and highly permeable hemodialyzers (Kuf >50 ml/mm Hg/h), the mean ultrafiltration rate could not exceed 150 ml/min. This meant that the length of the treatment session needed to be 4–6 h in order to exchange 40–60 liters per

session (equivalent to water or urea distribution volume, V) and attain a Kt/V of 1 to 1.2.

Interestingly, during this period, Leber et al. [38] in Germany first reported a new dialysis modality combining diffusive and convective clearances in a high-flux hemodialyzer that they named 'hemodiafiltration'. The term hemodiafiltration, HDF, was well suited to describing the dual action of diffusion (for dialysis) and convection (filtration) occurring within the same filter. In their first clinical experience, the authors underlined the high efficacy and the excellent cardiovascular tolerance of this method. In their original report, which describes the external addition of an infusion pump into the hemodialysis monitor, the sterile electrolyte substitution fluid was delivered in plastic bags (5 liters) and fluid balance was ensured by a gravimetric balancing system that continuously adjusted the ultrafiltration rate to the infusion rate by means of an ultrafiltration pump and a fluid-balancing system in the dialysis machine.

While looking for a more efficient and user-friendly dialysis machine, we were approached by Fresenius to evaluate their new 2008 hemodialysis machine. The A2008C HD machine delivering bicarbonate-buffered dialysate, equipped with a volumetric fluid-balancing module and providing all technical options, was ideally designed to perform HDF. Based on our long experience of producing ultrapure dialysate and infusate, we decided to adapt the 2008 machine to produce on-line substitution fluid. In cooperation with the research and development department of Fresenius and with the help of highly specialized engineers, the 2008 machine was modified: a cold sterilizing ultrafilter was placed in the fresh dialysate circuit ensuring delivery of ultrapure dialysis fluid, an additional infusion module was implemented on the 2008 HD machine consisting of an adjustable infusion pump, and a second sterilizing ultrafilter was placed in the infusate line. The fluid diverted from the fresh dialysate by the infusion pump and infused in the blood drip chamber was isovolumetrically compensated by the ultrafiltrate taken from the patient's blood by the ultrafiltration pump and the fluid-balancing module of the A2008C dialysis machine. A scheme of this original hydraulic circuit modification is given in figure 1. On-line production of substitution fluid from fresh dialysate was born and immediately applied in the clinical treatment of chronic kidney disease patients. The original picture of on-line HDF 2008 machine is presented in figure 2. The first feasibility and safety clinical trial was performed in Montpellier with 4 patients over a 6-week period and reported at the Bad Homburg meeting in 1985 [39]. After this initial trial, the on-line HDF method was progressively expanded to all dialysis patients in our dialysis facilities [40]. Several technical improvements performed on the HDF monitors (2008, 4008 and 5008 series) clearly contributed to geographical spreading of the method. These facilitated clinical handling, enhanced safety, optimized performances by introducing new options for quantifying such, improved cardiovascular tolerance, and developments in substitution

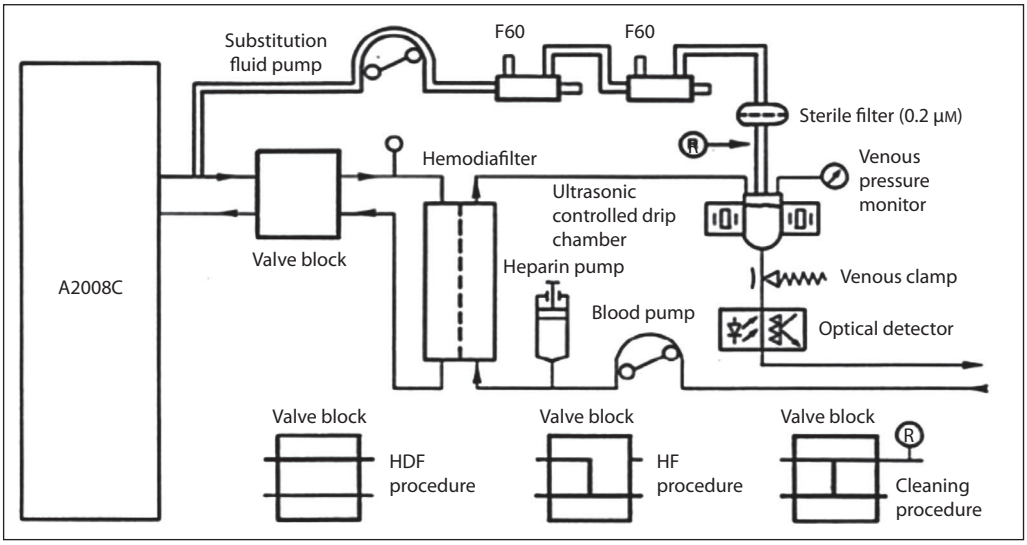

Fig. 1. Modifications of the hydraulic circuit of the A2008C HD machine to perform online HDF as originally done.

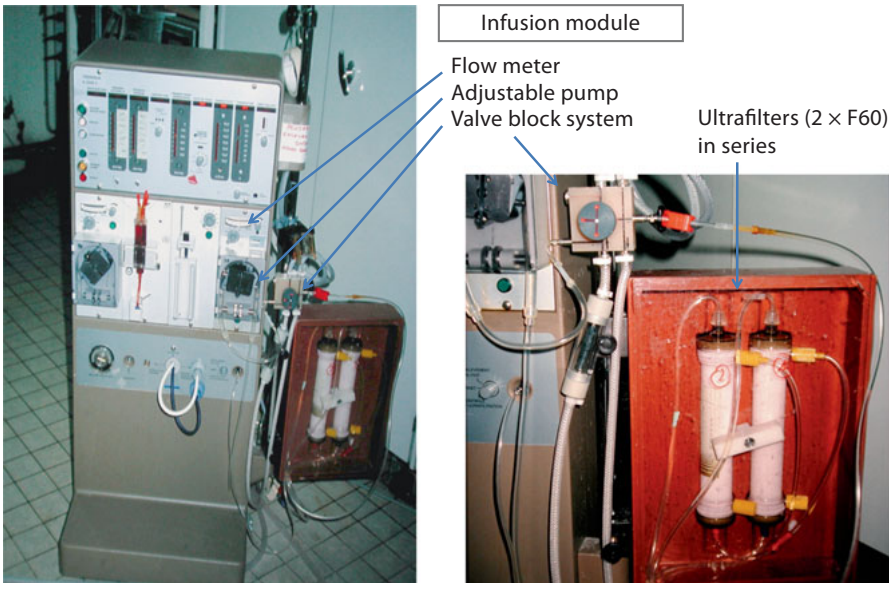

Fig. 2. A2008C HDF machine with its online infusion module and side-kick ultrafilters system.

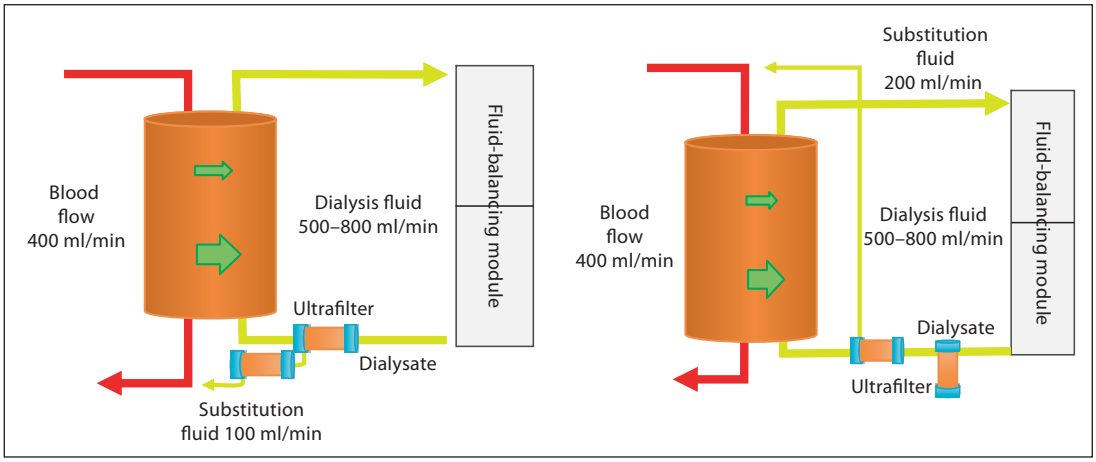

Fig. 3. Configurations of online HDF machines to perform post- or pre-dilution modalities.

possibilities (fig. 3). The evolution of the on-line HDF machines is presented in figures 4 and 5.

How Did We Get Here?

Over the last three decades, on-line HDF has gained in popularity. Such an increase in prevalent use (now more than 1 million HDF sessions have been performed worldwide) has largely confirmed the safety, efficiency and reliability of the method.

On-line production of substitution fluid based on cold sterilization processing of fresh dialysate by ultrafiltration has been proven efficient and safe both in experimental and clinical conditions [41]. Safety and reliability of on-line HDF machines has also been largely proven in routine clinical use over long-term periods, provided the purity of the water feeding into the HD machine is ensured and best clinical practices of hygiene are followed [42]. In addition, on-line techniques have proven to be the only economically viable model, giving access to unlimited amounts of sterile non-pyrogenic fluid [43]. Based on this concept, several alternatives to the post-dilution modality were proposed for optimizing performances of HDF, e.g. pre-dilution HDF, mixed dilution (combined pre- and post-dilution) HDF, or mid-dilution HDF. Interestingly, these options were mainly developed to match the volume of substitution to the metabolic needs of the patient, taking into account the hemorheological changes induced by high hematocrit levels. High hematocrit levels can result from use of erythropoietic-stimulating agents as well as from

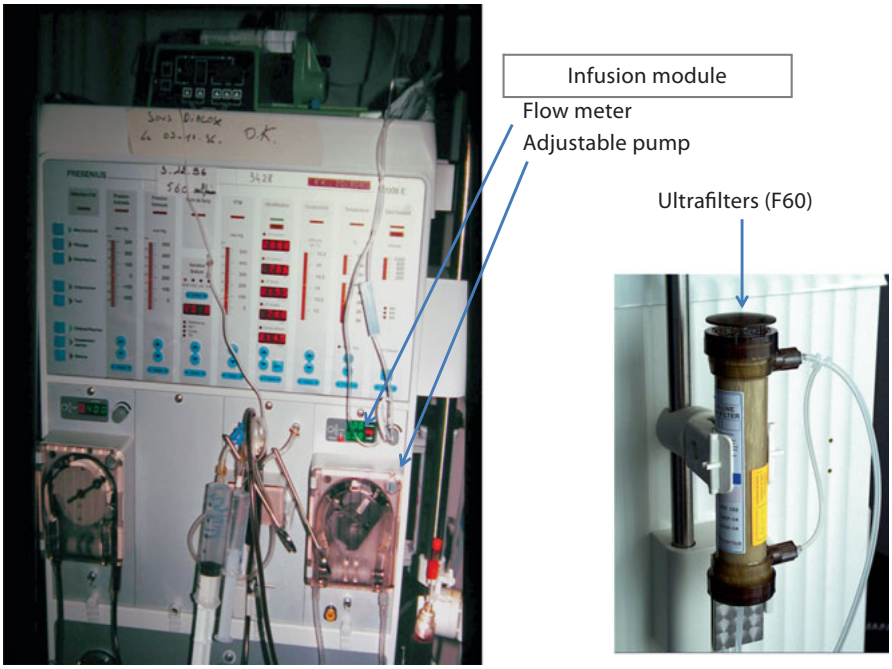

Fig. 4. Evolution of the online HDF machine with the 2008E series.

the phenomenon of hemoconcentration (increase protein concentration) following ultrafiltration.

Best practice guidelines have also been developed to ensure the quality of on-line HDF methods. Best practices incorporate basic hygienic rules of maintenance and disinfection for water treatment systems, fluid distribution systems and the HDF machines themselves in order to prevent microbial contamination and biofilm formation, also within the hydraulic tubings of the machines [44]. This regulation has been reinforced in some specific countries where the on-line methods were particularly applied. A specific working group (EUDIAL) has recently been created within the ERA-EDTA to evaluate and give preferentiality to safe development of on-line methods.

Over the last decade, tremendous technical progress has been made in HDF machines by manufacturers. This ensures safety, reliability and high performance, while simultaneously adding new options to quantify efficacy and to increase the tolerance of sessions. On-line HDF machines now benefit from a specific certification and CE marking by regulatory bodies in the European Community (EC) [45]. This official recognition of CE marking for on-line methods was a major advance in the field of renal replacement therapy. Indeed, it is the first time that a medical device was approved and certified for intravenous infusion of a sterile and non-pyrogenic pharmaceutical product prior to any

Fig. 5. Evolution of the online HDF machine with the 4008 series.

laboratory testing. By the way, on-line HDF techniques opened a new approach in the regulatory field of pharmacopoeia regarding intravenous fluids and solutions; acceptance of this approach is a matter which is not yet solved everywhere today. Water treatment systems representing a key and sensitive component for on-line methods clearly benefited from this dynamic and now deliver improved end-products. Ultrapure water is a recognized prerequisite for on-line methods but is also strongly recommended for all hemodialysis modalities by most international best practices guidelines [46]. Interestingly, water treatment and distribution systems, as a part of dialysis treatment chain, may be certified by European Community.

Several studies have shown that HDF provides significantly higher clearances than high-flux HD, both for small and middle molecule solutes [47–50]. *Phosphate* removal is increased by 15–20% over a weekly mass balance, allowing a reduction in the required amount of oral phosphate binders

[51–54]. *β_2-Microglobulin* is also more effectively removed by HDF therapies [55–57]. Due to the significantly enhanced clearance of middle molecule, HDF achieves a significant decline of circulating β_2-microglobulin concentrations over a mid-term period [58, 59]. *Leptin* (16 kDa) is a protein-bound uremic toxin that accumulates in chronic kidney disease and is implicated in malnutrition and anorexia [60]. Free leptin is effectively removed by HDF, resulting in reduced circulating concentrations in HDF-treated patients [61, 62]. *Cytokine* removal has been reported with high-flux convective therapies, both in acute and chronic ESRD patients [63]. Anti-inflammatory effects of on-line HDF have been shown in several prospective studies and are characterized by reductions in the number of pro-inflammatory monocytes and acute phase proteins [64–66]. Circulating concentrations of *oxidation-derived products (AGEs and AOPPs)* are reduced in diabetic and non-diabetic CKD patients treated by high-efficiency HDF [67]. *3-Carboxy-4-methyl-5-propyl-2-furanpropionic acid* (CMPF), a protein-bound erythropoietic inhibitor, can be reduced in HDF, particularly when using protein-leaking high-flux membranes [68, 69]. Free *p-cresyl sulfate or indoxyl sulfate*, protein-bound endothelial toxin compounds [70], are poorly removed during high-efficiency HDF [71, 72].

Clinical benefits of HDF have been underlined in treated patients in several studies. Improvement of clinical tolerance is frequently reported with convective therapies. The incidence of hypotensive episodes is reduced in HDF and HF therapies [73]. Maltolerance (nausea, vomiting, cramps, headache, etc.) of sessions is also reduced with high-efficiency HDF. Post-dialysis fatigue is less frequently observed with convective therapies. These properties are particularly advantageous for the treatment of elderly, diabetic and cardiovascular 'high-risk' patients. Better blood pressure control with reduced occurrence of cardiac events has been reported in two observational studies [74, 75]. Recent studies have shown that high-flux therapy and HDF modalities contributed to better preservation of residual renal function over time than conventional HD [76]. Anemia appears to be more easily corrected in HDF-treated patients. Although this fact remains still controversial [77], anemia correction tends to be facilitated in HDF-treated patients while the weekly EPO dose is reduced [78]. In the context of inflammatory cachexia, enhancing convective clearances is associated with an improvement of nutritional parameters (dry weight) and somatic proteins (albumin) [79, 80]. β_2-Microglobulin amyloidosis was a major concern in long-term HD therapy 20 years ago, but has virtually vanished with the regular use of new high-flux convective therapies and ultrapure dialysis fluid [81]. More interestingly, it has been recently shown that daily HDF promotes children growth, catching up to normal growth curve in this population [82]. To our knowledge, this was the first study to show that growth in CKD children could be recovered, virtually to the normal growth curve, by renal replacement therapy.

Reduced mortality of HDF-treated patients is more difficult to ascertain. Large cohort studies indicate that mortality is reduced by about 35% in HDF-treated patients even accounting for confounding factors (age, Kt/V, comorbidities, etc.), while small prospective studies did not find significant differences [83–85]. This will probably be solved in the near future by prospective, randomized, controlled studies. Two recent randomized, controlled studies (the Turkish HDF and the Contrast studies) were reported at the last ERA-EDTA congress. Both indicated significant survival benefits only for HDF-treated patients receiving large volumes of substitution fluid (17–20 liters per session) [86, 87]. This observation is of particular interest for two reasons: on the one hand, it confirms the previous findings of the DOPPS study that identified the major role of large volumes of substitution in patient survival, and on the other it raises concern regarding the true convective dialysis dose required to influence patient survival. According to findings of these studies, the concept of convective dialysis dose should be seriously considered as an add-on in the quest for dialysis adequacy.

What Does the Future Hold for On-Line Hemodiafiltration?

Despite the fact that there are still open questions, today on-line HDF offers the best option available for renal replacement therapy in chronic kidney disease patients [88]. On-line HDF is a safe and very efficient treatment modality that is associated with better patient outcomes. On-line HDF is an economically viable alternative treatment modality providing unlimited fluid replacement possibilities. Furthermore, it is a technique that is quite open for the development of new therapeutic strategies. On-line HDF has anti-inflammatory effects that are beneficial and protective for dialysis patients. Daily or nocturnal on-line HDF treatment schedules offer appealing new avenues for more physiological treatment. In addition, the access to sterile, apyrogenic, electrolytic fluid may facilitate development of automated dialysis machines for self-care or home therapy. Automated priming, rinsing of the blood circuit and volume repletion during dialysis sessions would be clearly facilitated by this option. New technical developments in HDF machines will also probably contribute to optimizing volume of substitution and favoring delivery of higher convective dialysis doses.

Conclusions

On-line HDF today offers the best renal replacement therapy option for chronic kidney disease patients, virtually at the same cost of contemporary high-flux HD. So why not offer on-line HDF to all end-stage kidney disease patients? It

is a promising wager on a future of renal replacement therapy with improved patient survival and enhanced quality of patient life.

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