Krick G, Ronco C (eds): On-Line Hemodiafiltration: The Journey and the Vision.
Contrib Nephrol. Basel, Karger, 2011, vol 175, pp 1–14

Historical Milestones of a Long Pathway

Thomas Roy

Fresenius Medical Care Deutschland GmbH, R&D International, Bad Homburg, Germany

Abstract

Hemodiafiltration (HDF), developed from the combination of hemodialysis and hemofiltration, is considered to be the most effective current procedure to remove uremic toxins from the blood of kidney patients. Historically, the clinical use of HDF was for many years limited due to the cost burden related to the large amount of sterile volume replacement fluid needed. The solution offered was on-line preparation of replacement fluid from standard dialysate by means of membrane filtration. Industry opened to this concept quite early and worked on various technical solutions between the early 1980s and the late 1990s before real state-of-the-art systems became commercially available on a broad basis. This article reviews in particular the activities of initially Fresenius and later Fresenius Medical Care in this field and identifies major concepts and prototypes up to today's commercially available high-end product – the 5008 therapy system – where on-line HDF finally became integrated as a standard component.

From 'Ultrafiltration' to 'Diafiltration' and 'Hemofiltration'

To review the historical pathway from the early days to modern on-line hemodiafiltration (HDF) necessarily requires starting with hemofiltration (HF) as developed and carefully introduced into clinical practice during the late 1960s/early 1970s. To the author's knowledge and as referenced by other sources, the first paper reporting preclinical trials to correct the uremic conditions of dogs by means of 'ultrafiltration' dates from 1947. There, Mailonov and Korzon [1] describe an 'ultrafiltration' procedure in normal and nephrectomized dogs where the gained ultrafiltrate volume was manually replaced by a standard Ringer-lactate solution. Due to the high hydraulic resistance of the

used tubular cellophane membrane assemblies, the achieved filtrate volume was so discouraging low (50–70 ml/h at effective pressures between 760 and 900 mm Hg) that the authors concluded that the '. . .procedure with the apparatus employed (is) unsuitable for man. . .' and clearly favored the Kolff drum dialyzer approach.

Retrospectively, it seems fair to say that the lack of membrane materials with low hydraulic resistances over the following two decades prevented repetition and expansion of these early experiments. A paper by Henderson et al. [2] from 1967 on the in vitro evaluation of the newly developed Amicon Diaflo membrane is considered to mark the resumption of ultrafiltration for extracorporeal detoxification purposes. The process used for removing toxins from blood by convective transport in this paper was termed 'diafiltration', which caused some confusion in later years before the name was finally converted to 'hemofiltration' by Dr. Benjamin Burton from the NIH during the historic Braunlage Conference in 1976 [see 3].

The transfer of the rediscovered HF procedure to clinical routine proceeded with extreme caution during the following years, moving in several steps from animal experiments to humans and by scaling up the amount of required fluid exchange. An impressive description of this really pioneering work and the inherent risks and uncertainties was given retrospectively by Henderson [4] himself in 2003. In fairness, it must be acknowledged here that the first reliable clinical data for patients on long-term maintenance HF were generated by German researchers such as Quellhorst and others in the years after 1971.

Due to the early interest of German nephrologists in HF, it was not by chance that some of the first commercially available systems for HF were developed by German companies such as Sartorius/Göttingen and Dialysetechnik/Karlsruhe [5]. This clinical and technical progress in Europe was certainly influenced by the availability of membranes with high hydraulic permeabilities, such as the famous AN69 [6, 7] or the disc filters by Sartorius [see 8]. It should be mentioned that, unlike early hemodialysis (HD), HF was supported from the very beginning by thorough theoretical analyses regarding solute transport, and this finally led to a very straightforward approach in terms of clinical application [9, 10].

HF, however, was burdened from the start by two different factors: financially, by the high cost for large amounts of intravenous replacement fluids, and medically, compared to HD, by the lower efficacy of the procedure in terms of low molecular weight clearances [e.g. 11]). Compensation for the HF-related increase in systemic urea concentration required larger amounts of substitution fluid (given in predilution mode to increase convective fluxes) and further exacerbated the cost aspect of maintenance HF. The author remembers that it needed some courage and 'acclimatization' in the first maintenance HF patients in the light of their otherwise improved status to simply tolerate these

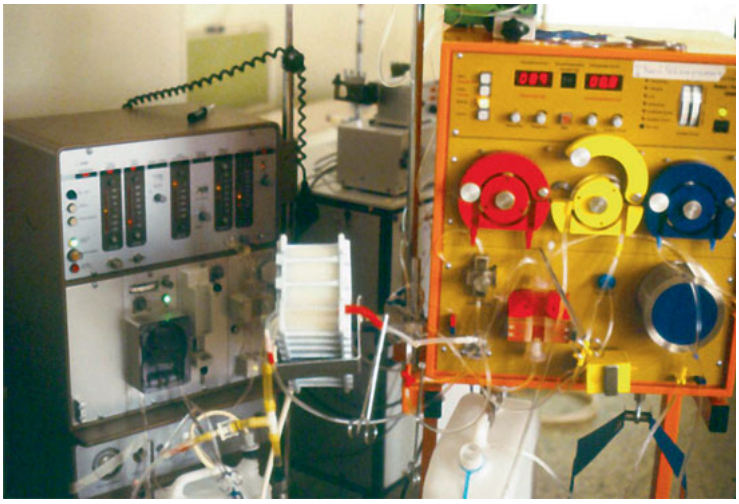


Fig. 1. Fresenius A2008C (left) and Sartorius Haemoprocessor (right) in Giessen (Germany) simultaneously performing HD and HF via a shared RP-6 high-flux dialyzer. Courtesy of Prof. Volker Wizemann, Giessen.

elevated urea levels for the sake of reasonable expenditure for substitution fluid.

Hemodiafiltration as the Ultimate Modality

It seems to be impossible to retrospectively determine the source of the idea of combining HD and HF in a single procedure. Definitely the working group of Prof. Leber from the University Hospital Giessen/Germany in 1976 [12] started with a procedure where HD and HF were performed within one single RP-6 filter in order to maximize solute removal over the whole sieving range of the filter. The paper reporting these experiments was published in 1978 and is commonly considered to be the birth certificate of HDF [13]. Therein, the authors describe a procedure where fluid removal by ultrafiltration and fluid reinfusion from an intravenous fluid reservoir was performed by means of manual control of the respective pumps under the guidance of the patient's bed scale in order to achieve the desired fluid balance. The HD circuit of the treatment was operated in parallel by a standard Drake Willock HD machine. This cumbersome way of performing HDF was improved in later years by using the volumetric fluid-balancing feature of a Fresenius A2008C HD system in conjunction with a gravimetric fluid-balancing system to control the convective flux conditions in an automated way [14]. Fortunately, a remarkable photograph of one of these early HDF set-ups is available from Giessen (see fig. 1).

Fresenius and Hemodiafiltration

The Fresenius R&D archive documents that some of the company's interest in the mid-1970s was focused on equipment for HF while, in parallel, a new-generation HD system – the later A2008 – was under development. Since the HD project began earlier and certainly was the more challenging one (not less challenging than the development of the first single-pass HD machine with volumetric UF control in an autoclavable stainless steel version), the company's HF activities never led to anything more than a combination of various components for performing HF in a manually controlled way. However, other companies developed dedicated HF equipment at this time (Sartorius/Göttingen, Dialysetechnik/Karlsruhe or Gambro/Lund).

Due to contacts with the Giessen group of Leber and Wizemann, we became aware of their very successful and convincing developments regarding HDF and saw the possibility of combining the meanwhile ready A2008 dialysis machine with a Sartorius Haemoprocessor. In a resulting cooperation between Fresenius and Sartorius, the first commercially available system for HDF, the so-called ABG-1, was developed and introduced to the market. As described in figure 2, the closed hydraulic circuit of the A2008 provided a perfect platform for extension towards HDF, a feature from which even today's Fresenius HD machines still benefit. The final device (shown in figure 3) was a slightly modified A2008 equipped with a substitution fluid heater and pump, and with the Sartorius-manufactured ABG (i.e. the German abbreviation for automatic balancing device) on top. The ABG was produced in two different versions (the later ABG-II without cooperation with Sartorius) for all Fresenius 2008 series HD machines.

All Fresenius activities regarding HDF benefited from a strong and enduring support from the top level management. This was first provided by the person of Gerd Krick and later by Emanuele Gatti. Gerd Krick, then the board member responsible for the Medical Devices Division, clearly recognized the potential of the new treatment modality and the advantageous technical position of Fresenius in this context. This position was further improved by the upcoming polysulfone high-flux dialyzer, the well-known Fresenius F-60, which became the yardstick for synthetic, high-performance, biocompatible dialyzers for many years.

The Need to Go 'On-Line'

As promising as the clinical results of the newly introduced technique were its expansion into the field of treating maintenance dialysis patients clearly remained below expectations and below the potential of the method. In Europe, typical HDF countries were France, Germany and Italy, but even in these

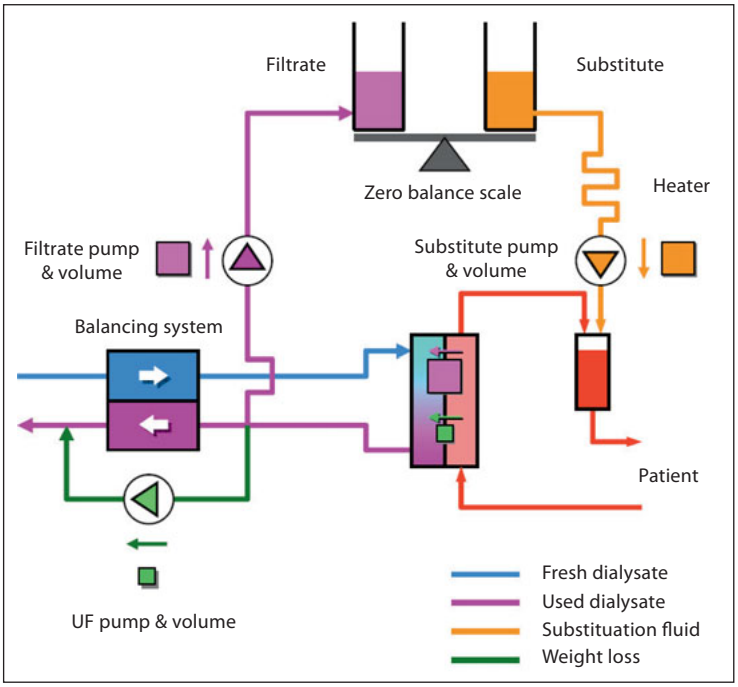


Fig. 2. This schematic diagram shows why the hydraulic circuit of an A2008 machine was ideal for retrofitting with a HDF module: an added filtrate pump removed fluid from the spent dialysate stream. Due to the closed hydraulic system of the A2008, exactly this amount of fluid was removed from the patient (compare squares indicating volumes). Under control of a zero balance scale, an equal amount of substitution fluid was given back to the patient. The desired weight loss was achieved with the machine's standard UF pump.

countries HDF was not common practice and remained fairly isolated in the hands of some convinced and enthusiastic medical doctors. Among the different reasons for the hesitant application of HDF, financial constraints always played a major role due to the required large volumes of intravenous grade electrolyte solution.

However, a solution (again by Henderson et al.) for the financial dilemma appeared in 1978 when they successfully produced large amounts of intravenous grade electrolyte solution from standard dialysate by cold filtration in a batch-like mode [15] and in a true 'on-line' mode [16] through Amicon XP-50 filters. In batch mode, filter integrity was demonstrated by means of blue dextran challenging (MW 2×10^6 daltons) and 'classic' tests of the product fluid (culturing, LAL). In on-line mode, pretreatment integrity testing using blue dextran was combined with sufficient filter redundancy (two filters). This filter redundancy strategy is still in use in today's state-of-the-art on-line systems.

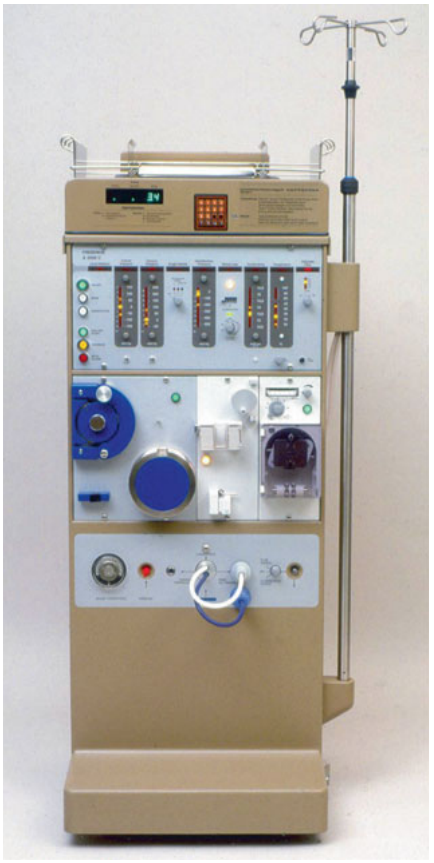


Fig. 3. The first commercially available system for HDF: a Fresenius A2008C with the ABG-1 Hemodiafiltration Module, a joint development of Fresenius AG (Bad Homburg, Germany) and Sartorius AG (Göttingen, Germany). Source: FMC R&D archive.

Thus, Henderson's ASAIO paper [16] can be considered the birth document of modern on-line HF/HDF technology. This is somewhat ironical in medical devices history considering the fact that for regulatory reasons this type of technology in the USA is virtually still unused.

Which Membranes for On-Line Filters?

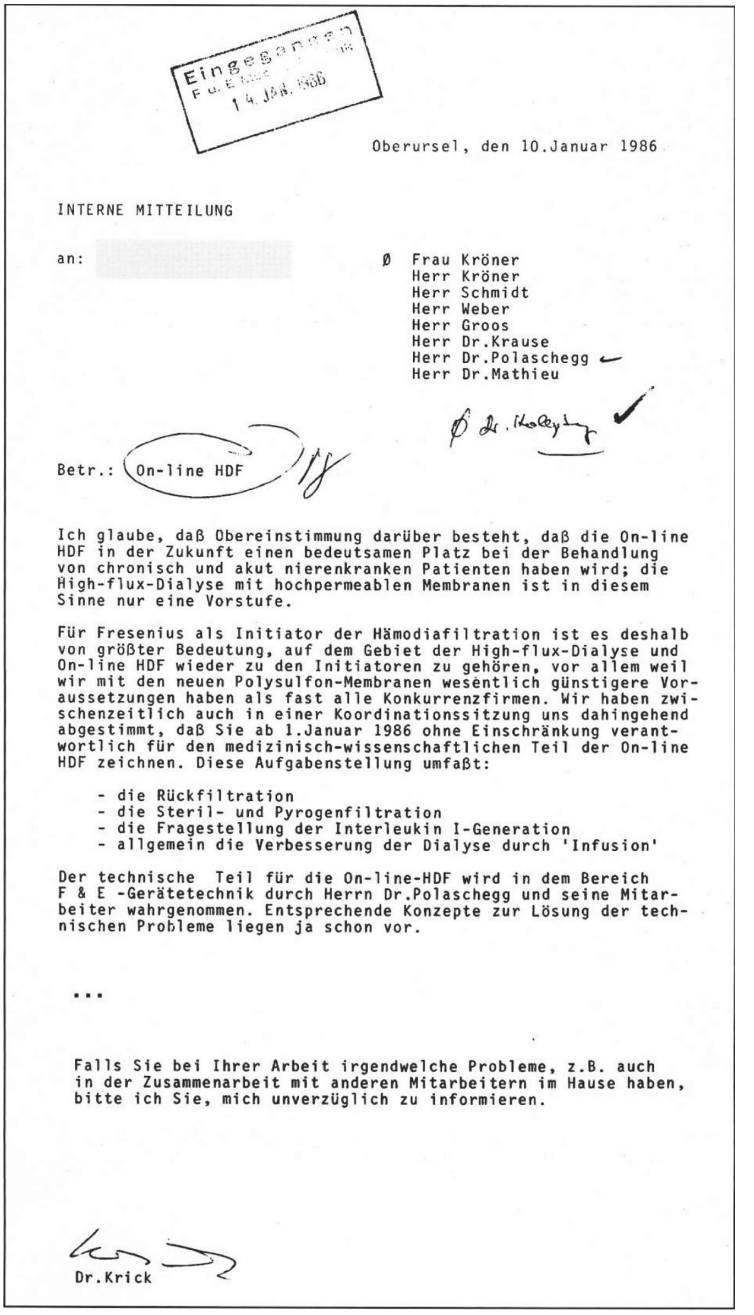
Interest in on-line substitution fluid preparation fortunately developed in parallel to the introduction of new synthetic capillary filter membranes such as polysulfone (PSu) and polyamide (PA). Filters with these new membranes were high-flux types with corresponding high clearances and low hydraulic resistances. The high water permeability of these membranes, combined with the standard pressures and pressure drops in an extracorporeal circuit containing a dialyzer, caused a new phenomenon called 'backfiltration' [see 17]. This term describes a

situation where, due to local pressure gradients from the dialysate compartment towards the blood compartment of the filter, fluid from the dialysate side enters the patient's blood. This potential hazard prompted a careful investigation of these membranes regarding rejection and adsorption of various microbiological contaminants normally present in standard dialysate. Although there was early evidence that especially asymmetric synthetic polymers, such as PSu and PA, provided excellent barriers against the relevant microbiological burdens [see e.g. 18] the concern regarding the safety of high-flux membranes was kept alive by various corporate marketing departments for many years. However, medical science and industry quickly recognized the potential of these new membranes not only as a safe barrier against microbiological dialysate contamination but – even more important – to serve as suitable dialysate filters and to allow the desired production of intravenous grade fluid from standard dialysate. It was certainly not by chance that the industrial corporations focusing on PSu (Fresenius AG, Bad Homburg, Germany) and PA (Gambro AB, Lund, Sweden) were the pioneers and the drivers when it came to equipment for HF/HDF with on-line preparation of substitution fluid.

Fresenius and On-Line Fluid Preparation

The meanwhile available A2008C HD machine with its volumetric fluid-balancing systems offered a perfect platform for integration of not only a HF/HDF procedure but also the feature of on-line fluid preparation. The respective activities inside Fresenius were primarily driven by Gerd Krick, at that time CEO of the Medical Devices Division, and Hans Dietrich Polaschegg, the Director for R&D Medical Devices. Figure 4 shows the facsimile of a 1986 order from Gerd Krick to enforce and finish the development and the market introduction of a system for on-line HDF. The letter perfectly describes the far-sighted attitude and future intention of Fresenius as started by Gerd Krick and continued by Emanuele Gatti until today.

However, the early prototypes of on-line HDF systems were far from being elegant and user-friendly as they included a lot of time-consuming and essential manual handling steps. Figure 5 – without further details being discussed here – shows the flow path of a 1984 system which was clinically tested in Giessen, Germany. Apart from all the manual elements in this system, it already represents the configuration Fresenius followed from the beginning until today: volume control is provided by the balancing system of the HD machine, and fluid preparation is done by means of two redundant large-surface-area, multiple-use PSu filters. For safety reasons, this configuration requires a predialysis functional test for filter integrity [19]. This follows from the adopted concept of two redundant filters as a safeguard against a first fault as required by the various safety standards for medical devices. For a detailed analysis of the safety concept



Eingegangen
F. u. E. Abt.
14. JAN. 1986

Oberursel, den 10.Januar 1986

INTERNE MITTEILUNG

an:

Ø Frau Kröner
Herr Kröner
Herr Schmidt
Herr Weber
Herr Groos
Herr Dr.Krause
Herr Dr.Polaschegg
Herr Dr.Mathieu

Ø Dr. Krick

Betr.: On-line HDF

Ich glaube, daß Obereinstimmung darüber besteht, daß die On-line HDF in der Zukunft einen bedeutsamen Platz bei der Behandlung von chronisch und akut nierenkranken Patienten haben wird; die High-flux-Dialyse mit hochpermeablen Membranen ist in diesem Sinne nur eine Vorstufe.

Für Fresenius als Initiator der Hämodiafiltration ist es deshalb von größter Bedeutung, auf dem Gebiet der High-flux-Dialyse und On-line HDF wieder zu den Initiatoren zu gehören, vor allem weil wir mit den neuen Polysulfon-Membranen wesentlich günstigere Voraussetzungen haben als fast alle Konkurrenzfirmen. Wir haben zwischenzeitlich auch in einer Koordinationssitzung uns dahingehend abgestimmt, daß Sie ab 1.Januar 1986 ohne Einschränkung verantwortlich für den medizinisch-wissenschaftlichen Teil der On-line HDF zeichnen. Diese Aufgabenstellung umfaßt:

- die Rückfiltration
- die Steril- und Pyrogenfiltration
- die Fragestellung der Interleukin I-Generation
- allgemein die Verbesserung der Dialyse durch 'Infusion'

Der technische Teil für die On-line-HDF wird in dem Bereich F & E -Gerätetechnik durch Herrn Dr.Polaschegg und seine Mitarbeiter wahrgenommen. Entsprechende Konzepte zur Lösung der technischen Probleme liegen ja schon vor.

...

Falls Sie bei Ihrer Arbeit irgendwelche Probleme, z.B. auch in der Zusammenarbeit mit anderen Mitarbeitern im Hause haben, bitte ich Sie, mich unverzüglich zu informieren.

Dr.Krick

Fig. 4. Written order and rationale by Fresenius AG Board Member Dr. G. Krick to boost and finish development of the scientific, medical and technical basis for a commercial on-line HDF system. Source: FMC R&D archive, permission G. Krick (author's translation): *'. . .I believe there is agreement that on-line HDF in future will play an important role in the treatment of acute or chronic kidney patients; in this sense high-flux dialysis with highly permeable*

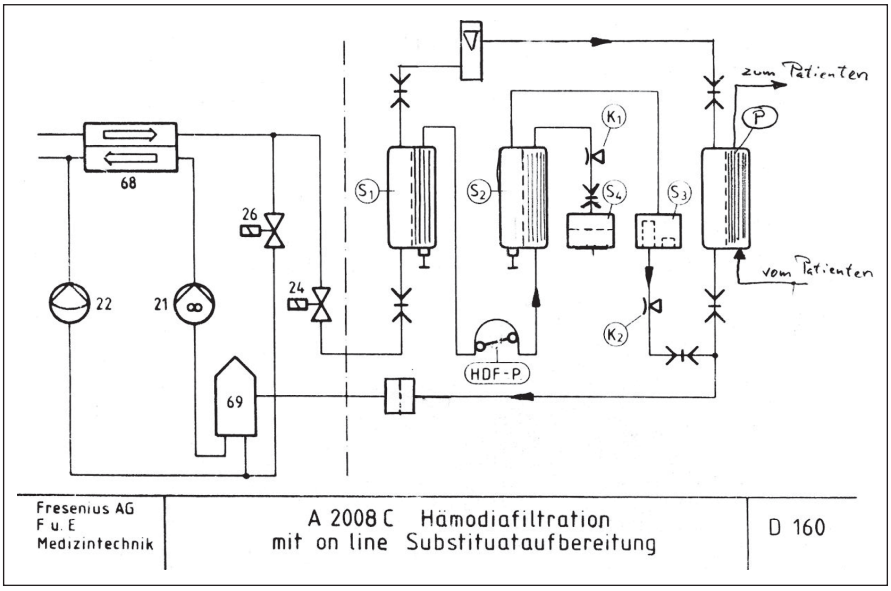


Fig. 5. Experimental on-line HDF system for the A2008C HD machine from 1984, including redundant fluid filters, various additional filters and clamps for manual filter integrity testing. Source: FMC R&D archive.

for HDF systems comprising on-line fluid preparation, see Polaschegg and Roy [20].

Apart from the need for dialysate ultrafilters as major elements for on-line HDF, we were always convinced about the benefit of having ultrafiltered dialysate in every standard HD treatment. Consequently, early R&D activities, in parallel to the development of on-line systems, led to the introduction of special dialysate filters. These filters (later known under the brand name 'Diasafe®') were optimized in several steps for their intended use together with Fresenius HD machines. The process included membrane adaptation, fiber potting, resistance to damage during chemical and thermal procedures, connection

membranes is just a preliminary stage. For Fresenius as initiator of hemodiafiltration it is of outermost importance to belong to the pioneers of high-flux dialysis and on-line HDF again, especially because we have a much better position compared to nearly all competitors due to the new polysulfone membrane. . . .We meanwhile agreed that – effective January 1st, 1986 and without any constraints – you will be responsible for the medical and scientific concept of on-line HDF. This task includes (a) backfiltration, (b) sterile and pyrogen filtration, (c) the question of IL-1 generation, (d) the general improvement of dialysis by means of 'infusion'. The technical part of on-line HDF is addressed already in R&D Medical Devices by Dr. Polaschegg and his co-workers. Concepts to solve the technical problems already are available. . . . In case you face any problems during your work, including problems regarding cooperation with in-house employees, you are asked to inform me immediately. . .'

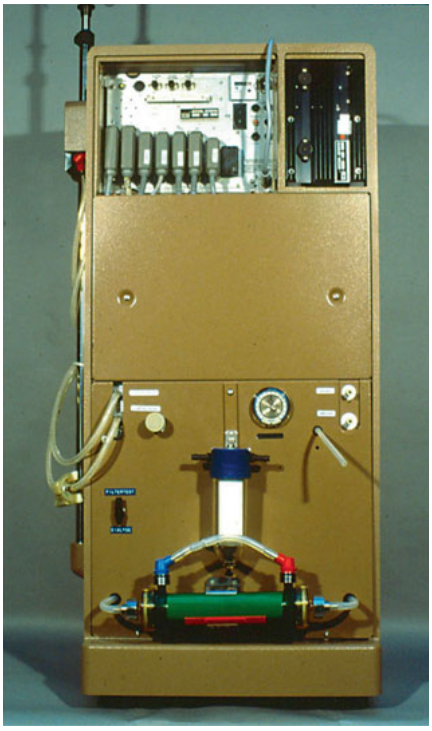


Fig. 6. The A2008C HD machine with early Diasafe® dialysate ultrafilter installation (1986). Source: FMC R&D archive.

technology and, most importantly, a sufficiently sensitive and finally automated filter integrity test. Figure 6 shows an early A2008C machine from 1986 with one of these specially adapted filters.

The first approved and commercially available on-line HDF system by Fresenius (fig. 7) was ready in 1987, when it was approved by the German TÜV according to the Medical Devices Act ('Medizingeräteverordnung' MedGV) in its 1985 version. This particular approval procedure was a new challenge for the manufacturer as well as for the test house since the existing relevant standards (VDE DIN 0750 part 1/05.1982 and VDE DIN 0750 part 206/09.1984) did not contain any explicit statements about procedures or safety measures for the on-line preparation of intravenous infusion fluid. A positive result, however, could be achieved by an appropriate interpretation of existing standards in the light of their general intention to provide first fault safety as required for this type of equipment.

The A2008 on-line HDF system comprised two special filters, a dialysate filter and a so-called HDF filter. The HDF filter could be vented via a GoreTex membrane to allow the required initial filter integrity test. The test procedure was partly automated although it had to be manually started and the results had to be checked and judged by the operator. In an improved version, which

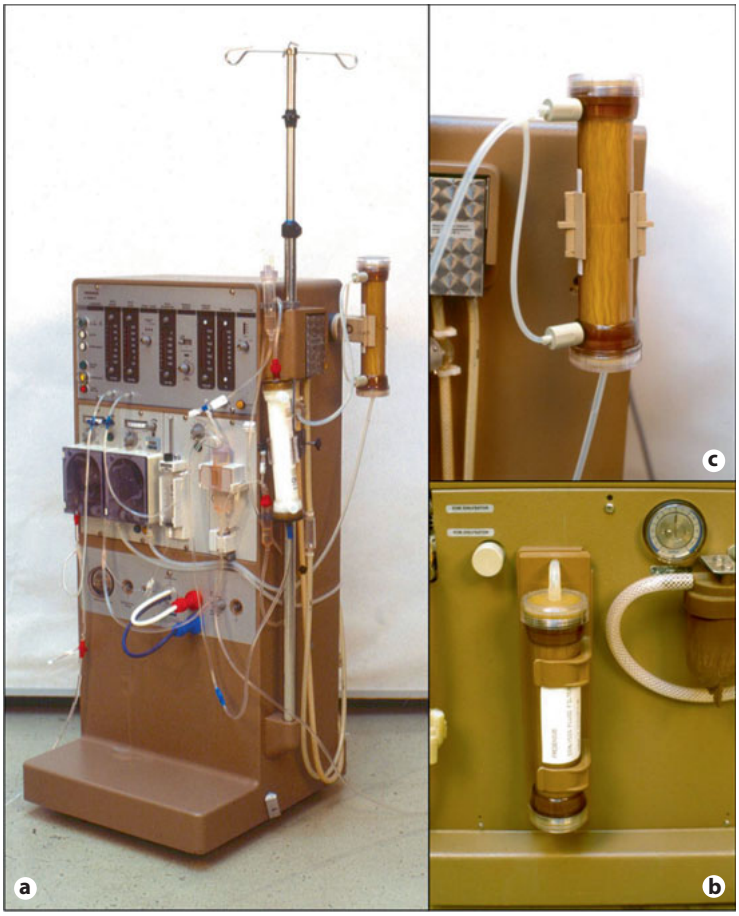


Fig. 7. First approved and commercially available Fresenius on-line HDF system for the HD machine A2008C/D/E (1987): (**a**) overall view, (**b**) Diasafe® dialysate ultrafilter, and (**c**) on-line HDF-filter. Source: FMC R&D archive.

included a fully automated filter integrity test, the system also was used in the FMC 4008 HD machine before it was replaced by the current Online plus™ system (see further down).

Retrospectively, one has to admit that these early systems still were quite cumbersome and had a high potential for further improvement and automation. Nevertheless, they opened the way towards a cost-efficient, high-performance renal replacement therapy. Sales figures, mostly on the basis of individual prescriptions by a physician for a particular patient, remained low and the systems stayed in the hands of few interested nephrologists. However, looking back, one must say that this period of subdued and limited use provided the required basis for gathering data and experiences with this new kind of technology.

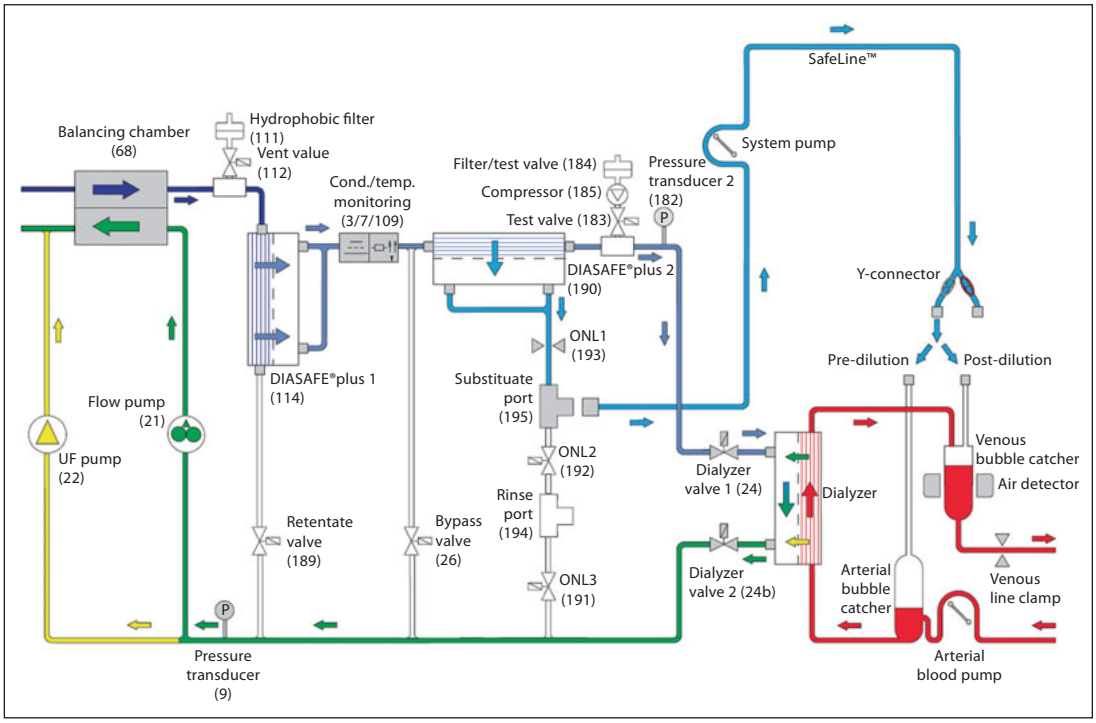


Fig. 8. Flow path for the Fresenius Online plus® hemodiafiltration system. Source: FMC product documentation.

Our Standard in On-Line HDF: Online plus™

In 1998, after summarizing all the experiences collected over more than 10 years with a newly designed system, Fresenius introduced the basis of the current technology under the brand name 'Online plus™'. The required approval procedure for on-line fluid preparation systems at that time had been clarified on the basis of the so-called 'Medical Devices Directive' [21] and a detailed interpretation given by Pirovano [22] in 1998. These virtually cleared the last hurdles for broad clinical use of on-line HDF in Europe.

Apart from fully automated procedures implemented in the Online plus™ system at the machine side (filter testing, monitoring of proper connections, etc.), a new filter generation under the name 'Diasafe® plus' came on the market. While earlier filters had a certain heritage from standard dialyzer technology, the Diasafe® plus, a 2.2-m^2 PSu filter, comprised special, new technologies (potting, connector design, etc.) to ensure handling comfort, excellent hygiene and maximum filter lifetime. The hydraulic flow path of the system is shown in figure 8. The new arrangement of the two Diasafe® plus filters in dead-end

(filter 1) and in cross-flow mode (filter 2) provides effective use of the freshly prepared dialysate and – in parallel – prevents potentially dangerous build-up of microbiological burdens at the retentate side of the filters [see 23] by cyclic rinse procedures performed at the inlet side of filter 1.

To achieve cost-effective operation of the system, both filters are designed for multiple use over a life period of 3 months or 100 treatments (whichever comes first); a third disposable filter element, as used in other systems [see 20], is not necessary. This set-up requires a functional pretreatment filter integrity test as is always used in Fresenius systems. This test, based on the unique hydraulic configuration of Fresenius HD machines and the properties of the PSu membranes used in the filters, could be further improved [24] and fully automated. The growing experience with the new technology even allowed the defined exposure of the filter membranes to an otherwise critical substance such as bleach – this was urgently required by the dialysis clinics for cleaning purposes [25]. Since on-line prepared fluid was proven to be safe, it was consequently also considered for application in other steps of the dialysis procedure, such as priming of the extracorporeal circuit, applying volume boli and return of blood at the end of the treatment. These features of modern on-line HDF/HF systems further improve the financial footprint of these highly effective treatment modalities.

Exciting New Technologies One Day Become Common Standards

In 2005, after nearly 20 years of research, development and gathering experience, it was decided that, rather that just being an option, on-line HDF would be a standard procedure of the newly introduced Fresenius HD machine.

On this historical path towards today's therapy systems, the Lister Renal Unit from Stevenage was (among others) a much appreciated partner over many years. The author remembers a conversation with Roger Greenwood about on-line HDF from that time, where one of Dr. Greenwood's answers was that HDF (and for financial reasons on-line HDF) would just '. . .be common sense. . .'.

Sometimes it is as simple as this.

References

1 Malinow MR, Korzon W: An experimental method for obtaining an ultrafiltrate of blood. J Lab Clin Med 1947;32:461–471.

2 Henderson LW, Besarab A, Michaels A, Bluemle LW: Blood purification by ultrafiltration and fluid replacement (diafiltration). Trans ASAI0 1967;13:216–226.

3 Quellhorst E: Geschichte der Hämofiltration. Nieren- und Hochdruckkrankheiten (in German), Jahrgang 38, Nr 2/2009, pp 43–47.

4 Henderson LW: The beginning of clinical hemofiltration: a personal account. ASAIO J 2003;49:513–517.

5 Kramer P, Wigger W, Matthaei D, Langescheid C, Rieger J, Fuchs C, Rumpf KW, Scheler F: Clinical experience with continuously monitored fluid balance in automatic hemofiltration. Artif Organs 1978;2:147–149.
6 Funck-Brentano JL, Sausse A, Vantelon J, Granger A, Zingraff J, Man NK: A new disposable plate-kidney. Trans Am Soc Artif Intern Organs 1969;15:127–130.
7 Man NK, Granger A, Rondon-Nucete M, Zingraff J, Jungers P, Sausse A, Funck-Brentano JL: One year follow-up of short dialysis with a membrane highly permeable to middle molecules. Proc Eur Dial Transplant Assoc 1973;10:236–246.
8 Nussbaumer D, Perl H: Einflussgrössen bei der Hämofiltration (in German). Wissenschaftliche Informationen Fresenius, Nephrologie, Heft 2/1078, 145–155.
9 Colton CK, Henderson LW, Ford CA, Lysaght MJ: Kinetics of hemodiafiltration. I. In vitro transport characteristics of a hollow-fiber blood ultrafilter. J Lab Clin Med 1975;85:355–371.
10 Henderson LW, Colton CK, Ford CA: Kinetics of hemodiafiltration. II. Clinical characterization of a new blood cleansing modality. J Lab Clin Med 1975;85:372–391.
11 Baldamus CA, Schoeppe W, Koch KM: Comparison of haemodialysis and post-dilution haemofiltration on an unselected dialysis population. Proc Eur Dial Transplant Assoc 1978;15:228–235.
12 Wizemann V, Rawer P, Schmidt H, Techert F, Schuetterle G: Efficiency of hemodialysis, hemofiltration and hemodiafiltration; in Schuetterle G, Wizemann V, Seyffart G (eds): Hemodiafiltration. Proceedings 1. Symposion Giessen 1981. Oberursel/Ts, Verlag Hygieneplan, 1982.
13 Leber HW, Wizemann V, Goubeaud G, Rawer P, Schütterle G: Simultaneous hemofiltration/hemodialysis: an effective alternative to hemofiltration and conventional hemodialysis in the treatment of uremic patients. Clin Nephrol 1978;9:115–121.
14 Leber HW, Wizemann V, Techert F: Simultaneous hemofiltration/hemodialysis: short- and long-term tolerance. Introduction of a system for automatic fluid replacement. Artif Organs 1980;4:108–112.
15 Henderson LW, Beans E: Successful production of sterile pyrogen-free electrolyte solution by ultrafiltration. Kidney Int 1978;14:522–525.
16 Henderson LW, Sanfelippo ML, Beans E: 'On line' preparation of sterile pyrogen-free electrolyte solution. Trans Am Soc Artif Intern Organs 1978;24:465–467.
17 Stiller S, Mann H, Brunner H: Backfiltration in hemodialysis with highly permeable membranes. Contrib Nephrol. Basel, Karger, 1985, vol 46, pp 23–32.
18 Bommer J, Becker KP, Urbaschek R, Ritz E, Urbaschek B: No evidence for endotoxin transfer across high-flux polysulfone membranes. Clin Nephrol 1987;27:278–282.
19 Polaschegg HD, Mathieu B: EP 0189 561, priority 05.12.1985.
20 Polaschegg HD, Roy T: Technical aspects of online hemodiafiltration. Contrib Nephrol. Basel, Karger, 2007, vol 158, pp 68–79.
21 Community Directive 93/42/EEC on Medical Devices: Official Journal of the European Communities, No L169, 12 July 1993.
22 Pirovano D: Regulatory issues for on-line haemodiafiltration. Nephrol Dial Transplant 1998;13(suppl 5):21–39.
23 Nederlof B: European Patent EP 0692 268, priority 13.07.1994.
24 Wamsiedler R, Mathieu B: European Patent EP 0763 367, priority 16.09.1995.
25 Weber C, Groetsch W, Schlotter S, Mitteregger R, Falkenhagen D: Novel online infusate-assisted dialysis system performs microbiologically safely. Artif Organs 2000;24:323–328.

Dr. Thomas Roy
Fresenius Medical Care Deutschland GmbH
R&D International, Daimlerstrasse 15
DE–61352 Bad Homburg (Germany)
Tel. +49 6172 609 2397, E-Mail thomas.roy@fmc-ag.com